NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Final Scope and Final Matrix of Consultees and Commentators

Contents:

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

NICE National Institute for Health and Care Excellence

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis

Pre-meeting briefing

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Key issues for consideration: clinical

- At what point in the treatment pathway would fluocinolone acetonide ocular implant (FAc) be used?
- Is limited current practice ((L)CP) in the trial representative of UK clinical practice?
- Are the relevant comparators included?
- Does the clinical trial provide evidence of the efficacy of FAc compared with the most appropriate comparator?
- Is FAc effective in preventing recurrence of uveitis?

Key issues for consideration: cost

Intervention and comparators

- After 3 years, what is the likely effectiveness of fluocinolone acetonide?
- Should the model include an option to receive multiple implants?
- Is dexamethasone a relevant comparator?
  - If so, what is the likely comparative effectiveness of dexamethasone?

Model structure

- Should a ‘remission’ health state be included in the model?
- Should a transition between ‘on treatment’ and ‘permanent blindness’ be possible?
  - What should be used as the rate of blindness?

Utility values

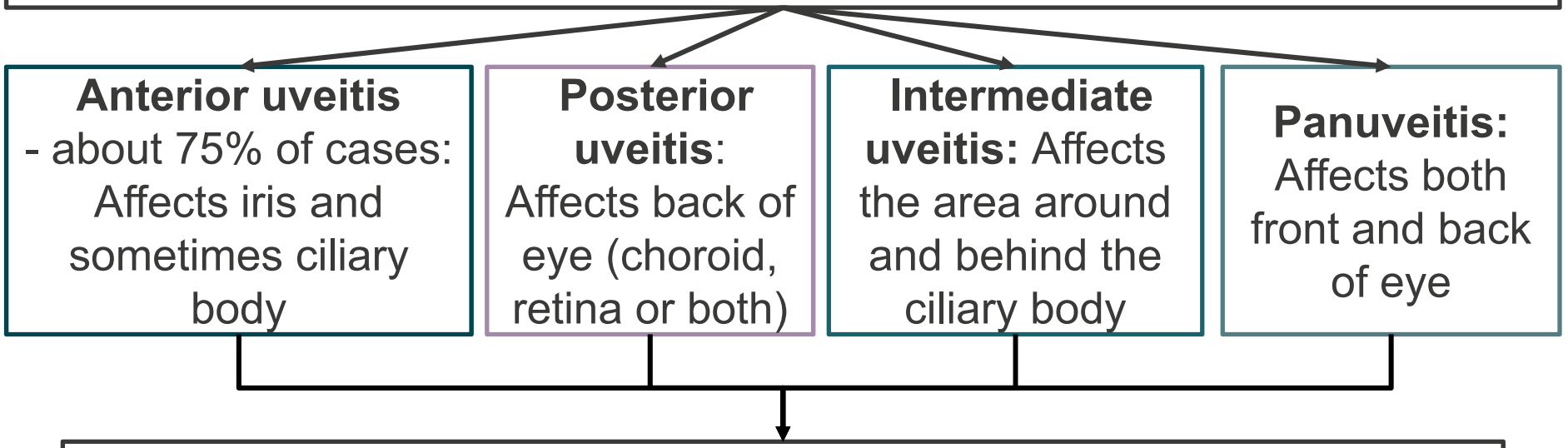
- What utility values should be used for the ‘on treatment’ and ‘subsequent therapy’ health states?
- Should disutilities for adverse events be included in the modelling?
  - If so, what disutility should be included?

General

- Is the model suitable for decision-making?
- Is fluocinolone acetonide cost-effective compared with the most relevant comparator?

Uveitis background

- Intraocular inflammation that may arise from various causes
- Around 2-5 in 10,000 people affected each year in the UK
- Can be caused by infection or trauma but more commonly associated with underlying autoimmune disorder
- Symptoms include eye pain, problems with vision, sensitivity to light



Complications of uveitis such as retinal damage and glaucoma may be irreversible and result in loss of vision

- Uveitis is one of the leading causes of visual impairment in UK

Related NICE guidance

TA460

Adalimumab is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults with inadequate response to corticosteroids:

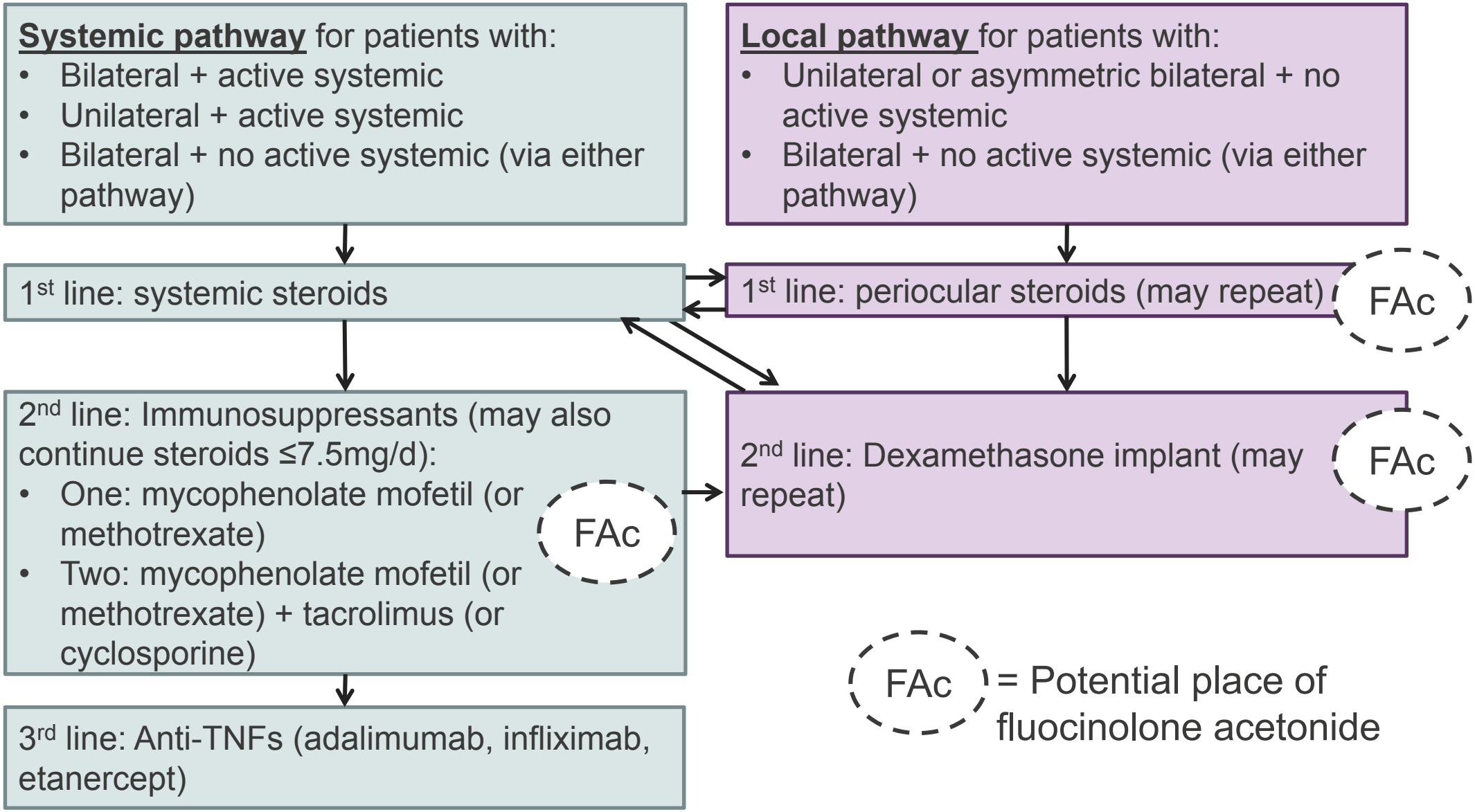
- active disease (that is, current inflammation in the eye) and
- inadequate response or intolerance to immunosuppressants and
- systemic disease or both eyes are affected (or 1 eye is affected if the second eye has poor visual acuity) and
- worsening vision with a high risk of blindness (for example, risk of blindness that is similar to that seen in people with macular oedema).

Dexamethasone intravitreal implant is recommended as an option for treating non-infectious uveitis in the posterior segment of the eye in adults, only if there is:

- active disease (that is, current inflammation in the eye) and
- worsening vision with a risk of blindness.

Current UK treatment pathway

Non-infectious uveitis



Adapted from TA460

Comments from patient and professional groups

- People with uveitis experience fear of worsening vision or blindness, may have to stop work or study, emotional impact may affect relationships
- Control of inflammation can prevent sight loss – important for working age population
- Current treatments cause burden of physical and mental side effects which can be long term (systemic corticosteroids)
- Unmet need for a long acting adjunct to adalimumab, alternative to repeated short term dexamethasone implant is needed, or when disease is not eligible for or does not respond to current systemic treatments (immunosuppression and adalimumab)
- Expect fluocinolone implant would mostly be used when response has been shown to dexamethasone implant but recurrence requires longer acting treatment
- Side effects include cataracts, which may require surgery, and raised pressure
  - Not expected to be worse than with 4-6 dexamethasone implants over 3 years
- Implant in trial (0.18mg fluocinolone) different to implant considered in this appraisal (0.19mg fluocinolone) but expected to be similar in efficacy and side effects
- Long-acting nature of treatment means patients don’t need multiple hospital visits

Fluocinolone acetonide intravitreal implant (Alimera Sciences)

Anticipated marketing authorisation	[redacted]
Mechanism of action	Fluocinolone acetonide is a corticosteroid used in uveitis for reduce inflammation and macular oedema.
Administration and dosage	Administered through intravitreal injection. Each ocular implant contains 0.19 mg of fluocinolone acetonide and is designed to release 0.2 micrograms per day for up to 36 months. The implant is made of polyimide and is expected to remain inert inside the eye. It is not biodegradable.
List price	£5500 for a single implant. A simple discount patient access scheme (PAS) has been approved.

Decision problem [1]

	Final scope issued by NICE	Decision problem in the company's submission	Rationale if different
Population	Adults with recurrent non-infectious uveitis	[redacted]	In line with expected marketing authorisation.
Intervention	FAc intravitreal implant in applicator	FAc intravitreal implant in applicator	N/A

Decision problem [2]

	Final scope issued by NICE	Company's submission	Rationale if different
Comparators	• Periocular or intravitreal corticosteroid injections • Intravitreal corticosteroid implants including dexamethasone intravitreal implant • Systemic corticosteroids • Systemic immunosuppressive therapies, including but not limited to, azathioprine, methotrexate, cyclophosphamide, ciclosporin, tacrolimus, mycophenolate mofetil (and mycophenolic acid) • TNF-alpha inhibitors including adalimumab • Best supportive care (when all other treatment options have been tried)	• Current practice / limited current practice ((L) CP)	As in TA460, defined active control arm in trial as current clinical practice in the UK. In the event of a recurrence of uveitis both FAc and control arm patients could receive: • periocular or intravitreal corticosteroid injections; or • topical corticosteroids as first line treatment. Systemic immunosuppressants or systematic steroids could also be provided. Best supportive care not considered a comparator as due to the risk of sight loss associated with uveitis, standard practice is active treatment, rather than supportive only.

Decision problem [3]

	Final scope issued by NICE	Decision problem in the company's submission	Rationale if different
Outcomes	• Recurrence of uveitis (the affected eyes) • Visual acuity (the affected eyes) • Visual acuity (both eyes) • Need for further corticosteroid treatment • Mortality • Adverse effects of treatment • Health-related quality of life	• Recurrence of uveitis in study eye • Recurrence of uveitis in fellow eye • Time to recurrence • Number of supplemental treatments required to treat recurrences of uveitis • Mean change from baseline in BCVA letter score in the study eye • Resolution of macular oedema (possible complication of uveitis)	Measures of efficacy against uveitis and its complications that were included in the PSV-FAI-001 trial. Health-related quality of life data not available from the PSV-FAI-001 trial or the PSV-FAI-005 trial.

ERG comments on decision problem

Population

- Population in the trial is 'chronic' [redacted]. Company states that 'chronic disease relapses promptly when therapy is discontinued', while the 'key feature of recurrent acute disease is the presence of episodes of active inflammation separated by periods of no inflammation when not on therapy'
- Number of patients with [redacted] in the trial is unclear

Comparators

- None of the comparators in the scope included in the submission
- ERG considers searches for all comparators in scope should have been performed
- Company considered not appropriate to compare HURON trial (dexamethasone implant vs (L)CP) and PSV-FAI-001 because of different patient populations and because HURON trial did not report outcomes specifically [redacted]
  - ERG considers dexamethasone is most relevant comparator and comparison should be performed

PSV-FAI-001 Study

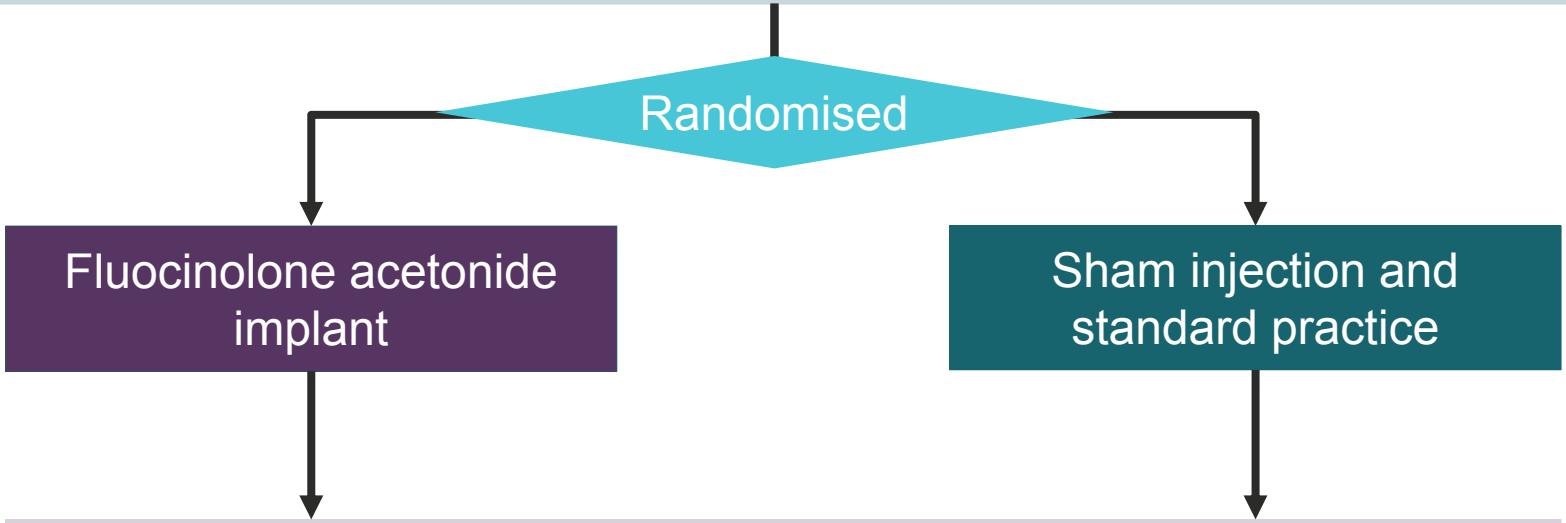
Adults with one or both eyes having a history of [redacted] with or without anterior uveitis (≥1-year duration) who had

treatment in the 12 months before enrolment with

- systemic corticosteroid or other systemic therapies given for at least 3 months, and/or
- at least 2 intra- or peri-ocular injections of corticosteroid for management of uveitis

OR the study eye had experienced recurrence:

- at least 2 separate recurrences of uveitis requiring systemic, intra- or peri-ocular injection of corticosteroid



Primary outcome:

- Proportion of patients who had a recurrence of uveitis in study eye within 6 months after receiving study treatment

PSV-FAI-001 Study

Baseline characteristics

	FAc (n=87)	(L)CP (n=42)	Total (n=129)
Age ≤20 years, n (%)	1 (1.10)	2 (4.8)	3 (2.3)
Age 20 to<40 years, n (%)	24 (27.6)	8 (19.0)	32 (24.8)
Age 40 to<60 years, n (%)	40 (46.0)	22 (52.4)	62 (48.1)
Age ≥60 years, n (%)	22 (25.3)	10 (23.8)	32 (24.8)
Male, n (%)	37 (42.5)	13 (31.0)	50 (38.8)
Female, n (%)	50 (57.5)	29 (69.0)	79 (61.2)
Mean duration of uveitis, years (standard deviation)	7.8 (6.69)	5.6 (6.82)	7.1 (6.79)
Lens status, n (%)			
- Phakic	42 (48.3)	21 (50.0)	63 (48.8)
- Cataract present	25 (59.5)	9 (42.9)	34 (54.0)
- Aphakic	0	0	0
- Pseudophakic	45 (51.7)	21 (50.0)	66 (51.2)

Trial results

Recurrences of uveitis in study eye (ITT population)

	Number of people		Odds ratio (95% CI)	P value
Time point	FAc implant (n=87), n (%)	(L)CP (n=42), n (%)		
6 months	24 (27.6)	38 (90.5)	24.94 (8.04, 77.39)	<0.001
Observed	1 (1.1%)	12 (28.6)	–	–
Imputed	23 (26.4)	26 (61.9)	–	–
12 months	33 (37.9)	41 (97.6)	67.09 (8.81, 511.05)	<0.001
Observed	3 (3.4)	12 (28.6)	–	–
Imputed	30 (34.5)	29 (69.0)	–	–
36 months	[redacted]	[redacted]	[redacted]	[redacted]
Observed	[redacted]	[redacted]	–	–
Imputed	[redacted]	[redacted]	–	–

Recurrence assumed if patient without previously recorded recurrence:

- had missing data for the required eye examinations (due to study discontinuation, visit occurring outside of the visit window, or missed visit)
- received prohibited local or systemic medication

⟶ **Recurrence rates likely overestimated**.

Trial results

Time to recurrence in study eye (ITT population)

Trial results

Supplemental treatments

Number of supplemental treatments within 36 months by type of treatment

Outcome	Study eye	
	FAc (n=87) n, %	(L)CP (n=42) n, %
Systemic steroid or immunosuppressant		
Total no. of supplemental treatments	[redacted]	[redacted]
No. of patients with ≥1 supplemental treatment	[redacted]	[redacted]
Intra/peri-ocular steroid (study eye)		
Total no. of supplemental treatments	[redacted]	[redacted]
No. of patients with ≥1 supplemental treatment	[redacted]	[redacted]
Topical steroid (study eye)		
Total no. of supplemental treatments	[redacted]	[redacted]
No. of patients with ≥1 supplemental treatment	[redacted]	[redacted]

ERG comment: No between group statistical significance tests reported

Trial results

Visual acuity

Mean best-corrected visual acuity (BVCA) change from baseline in the study eye up to 36 months

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ERG comment: No between group statistical significance tests reported

Adverse events

	FAc implant (N=87) n, %	(L)CP (N=42) n, %	Total (N=129) n, %
Any ocular TEAE (study eye, 36 months)	[redacted]	[redacted]	[redacted]
Any serious ocular TEAE (study eye, 36 months)	[redacted]	[redacted]	[redacted]
Increased intraocular pressure	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]
Cataract (study eye, 36 months)	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]

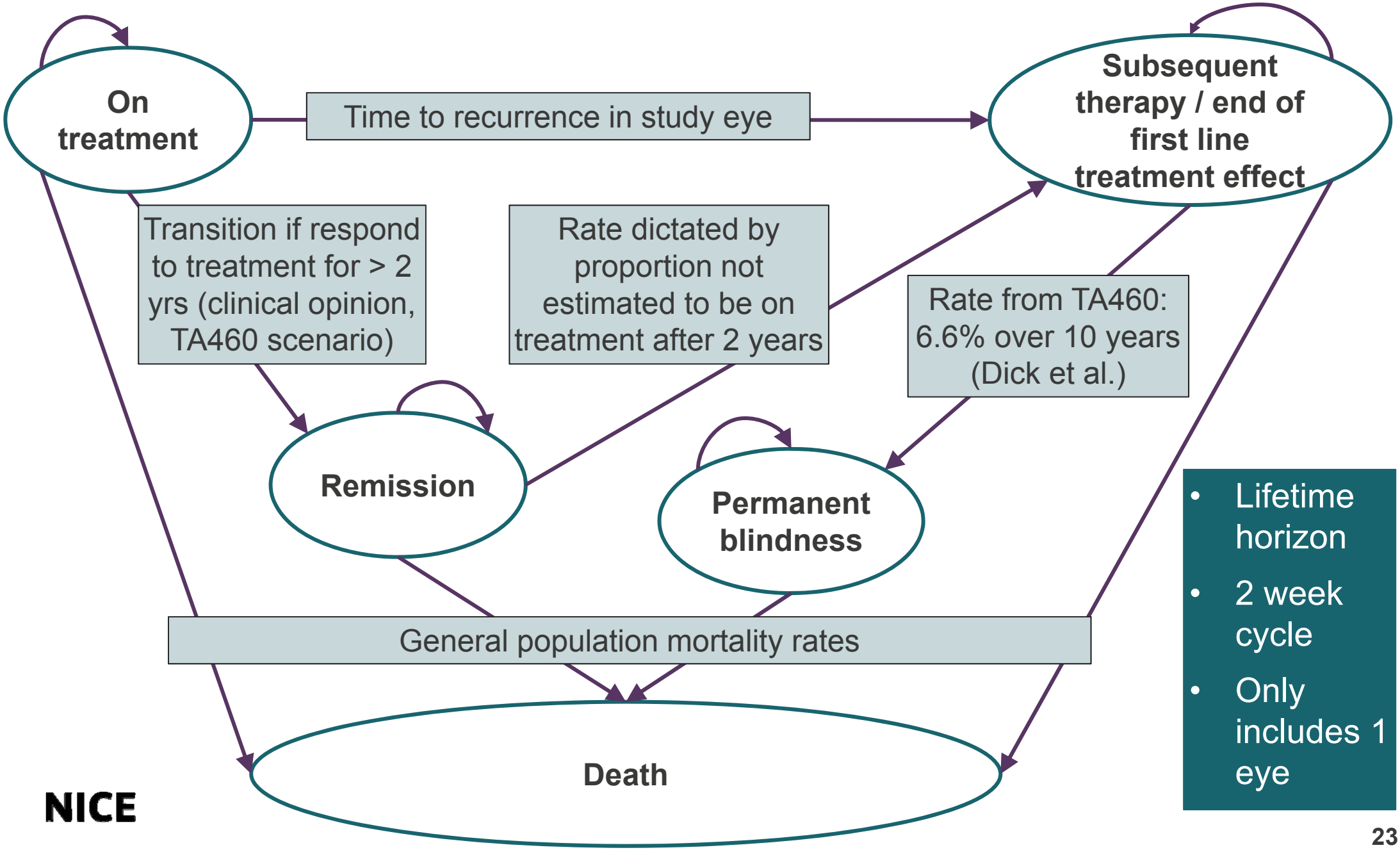
The most frequently reported ocular TEAEs in the study eye were [redacted] in the FAc implant group and [redacted] in the (L)CP group.
[redacted]

ERG comments on trial

- Size of the effect of FAc is unclear due to the high rate of imputation and the comparator used in the trial
  - Recurrence was imputed when prohibited local or systemic medication given, but reasons why treatment needed not recorded. Could be for other reasons e.g. recurrence in fellow eye or underlying autoimmune condition.
- PSV-FAI-001 trial does not provide evidence for use of FAc as first line treatment – all patients had received previous treatment with a systemic therapy
- Not clear which treatments patients in the control arm of the trial received
- Patients in intervention group could receive same treatments as patients in control group, so the trial actually compares FAc+(L)CP and (L)CP
- In both groups, systemic and local steroids or systemic immunosuppressants were tapered off after 3 months
  - After 3 months, comparison is FAc versus no treatment until recurrence
  - More likely that patients in control group will have recurrence after 3 months because they are receiving no treatment (not representative of UK clinical practice)
- In UK practice, bilateral disease may be treated with systemic therapy – this was not allowed in the trial unless local treatment failed

Cost effectiveness

Company's Markov model



- Lifetime horizon
- 2 week cycle
- Only includes 1 eye

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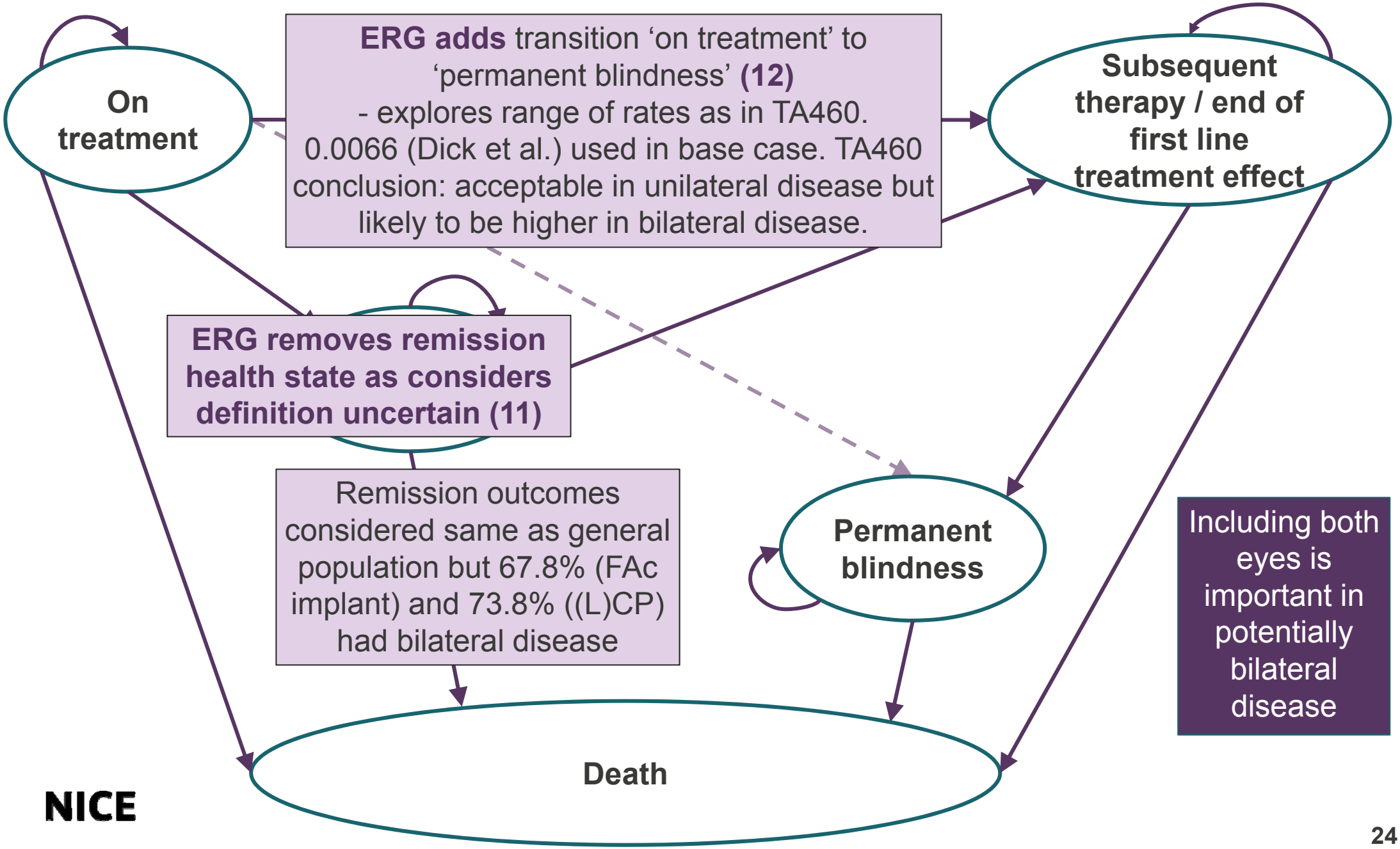
ERG comments: model structure



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Treatment effectiveness in the model

Time to recurrence

FAc group

- Parametric curves fitted from day 120 of observed period in trial. **Exponential** distribution chosen as base case based on visual inspection and AIC/BIC fit statistics.

(L)CP group

- Parametric curves fitted from beginning of observed period. **Log logistic** distribution chosen as base case based on visual inspection and AIC/BIC fit statistics.

ERG comments: treatment effectiveness

Time to recurrence

- Recurrence data in the trial imputed – rates likely overestimated
- [redacted]
- Company digitised Kaplan-Meier curves of both arms of trial to reconstruct individual patient level data
  - used individual patient data in response to clarification: → **ERG uses in base case (amendment 6)**
- FAc implant does not release active substance after 3 years
  - → **ERG base case: effectiveness equal to (L)CP after 3 years (amendment 13)**
  - ERG scenario analysis: no treatment effectiveness after 3 years
- ERG also explored the possibility of patients receiving more than 1 FAc implant **(amendment 18)**

Utility values in the model

- Health-related quality of life not recorded in PSV-FAI-001 trial
  - Data sourced from literature review
  - MUST trial investigated 0.59 mg FAc implant in same indication

Health state	Mean utility value	Source
On treatment	0.818	VFQ-25 data from MUST trial mapped to EQ-5D
Subsequent therapy	0.607	VFQ-25 data from MUST trial mapped to EQ-5D
Permanent blindness		
Company base case	0.38	Czoski-Murray et al (TA460)
Company scenario	0.57	Brown et al (TA460 scenarios – committee preferred)

Remission utility

- Not considered to experience any quality of life detriment so utility values based on age-matched values for the general population

ERG comments – utility values

- Key differences between MUST and PSV-FAI-001 trials:

MUST trial	PSV-FAI-001 trial
0.59 mg FAc implant	0.18* mg FAc implant
20% patients received systemic treatment	Systemic treatment before recurrence prohibited*
Bilateral FAc treatment allowed	Unilateral treatment only
Lower proportion with oedema at baseline	Higher proportion

- Utility values for 'on treatment' and 'subsequent therapy' mapped from MUST trial – different population
  - EQ-5D data based on the US tariff is available from MUST → ERG explored in scenario analysis
- Disutilities for adverse events not included → **ERG included in base case 2 & 4 (amendment 17)** and explored different assumptions in scenario analyses
  - Company stated this would be double counting
  - ERG disagrees because 'on treatment' utility based on the utility at 24 months of follow-up in MUST trial and 'remission' utility based on general population values
- Utility in remission health state overestimated
  - Patients may have bilateral disease, autoimmune disease, adverse events

**corrected at committee meeting*

Costs and resources in the model

Monitoring costs:

- Patients taking subsequent treatment assumed to receive monitoring every 6 weeks (in line with TA460)
- Patients with FAc implant and no systemic treatment assumed to have observation every 12 weeks

Supplemental therapy costs:

- Patients in both groups assumed to be taking supplemental therapy
  - Proportions of patients taking supplemental therapies taken from trial

Blindness:

- Sourced from TA460, inflated to 2017 costs

Adverse events:

- Costed from NHS reference costs, PSSRU and MIMS

Subsequent therapies:

	Proportion taking	Total cost
Immunosuppressants	19%	£2.29
Corticosteroids	31%	£0.16
Total cyclical cost of subsequent therapy	-	£2.45

ERG comments: costs and resources

- Costs of permanent blindness sourced from population with age-related macular oedema, and included costs of hip replacement, community care and residential care → **ERG base case excluded these costs for people under 65 (amendment 14) based on clinical opinion**
- Costs of monitoring not included in 'remission' state → no remission state in ERG base case but **includes costs of monitoring (part of amendment 11)** every 6 months after 2 years in 'on treatment' state
- **ERG base case includes** costs of blood tests every 12 weeks while receiving immunosuppressants **(amendment 15)**
- Because the ERG base case assumes that the probability of recurrence after 3 years is the same in both treatment groups, it also assumes that **upon transition into the 'subsequent treatment' state, patients receive the same treatments (amendment 16)**

Company's base case results (deterministic)

All results include PAS for FAc

- In company submission

	Total costs	Total QALYs	Inc. cost	Inc. QALYs	ICER (£/QALY)
L(CP)	[redacted]	[redacted]			
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£7,183

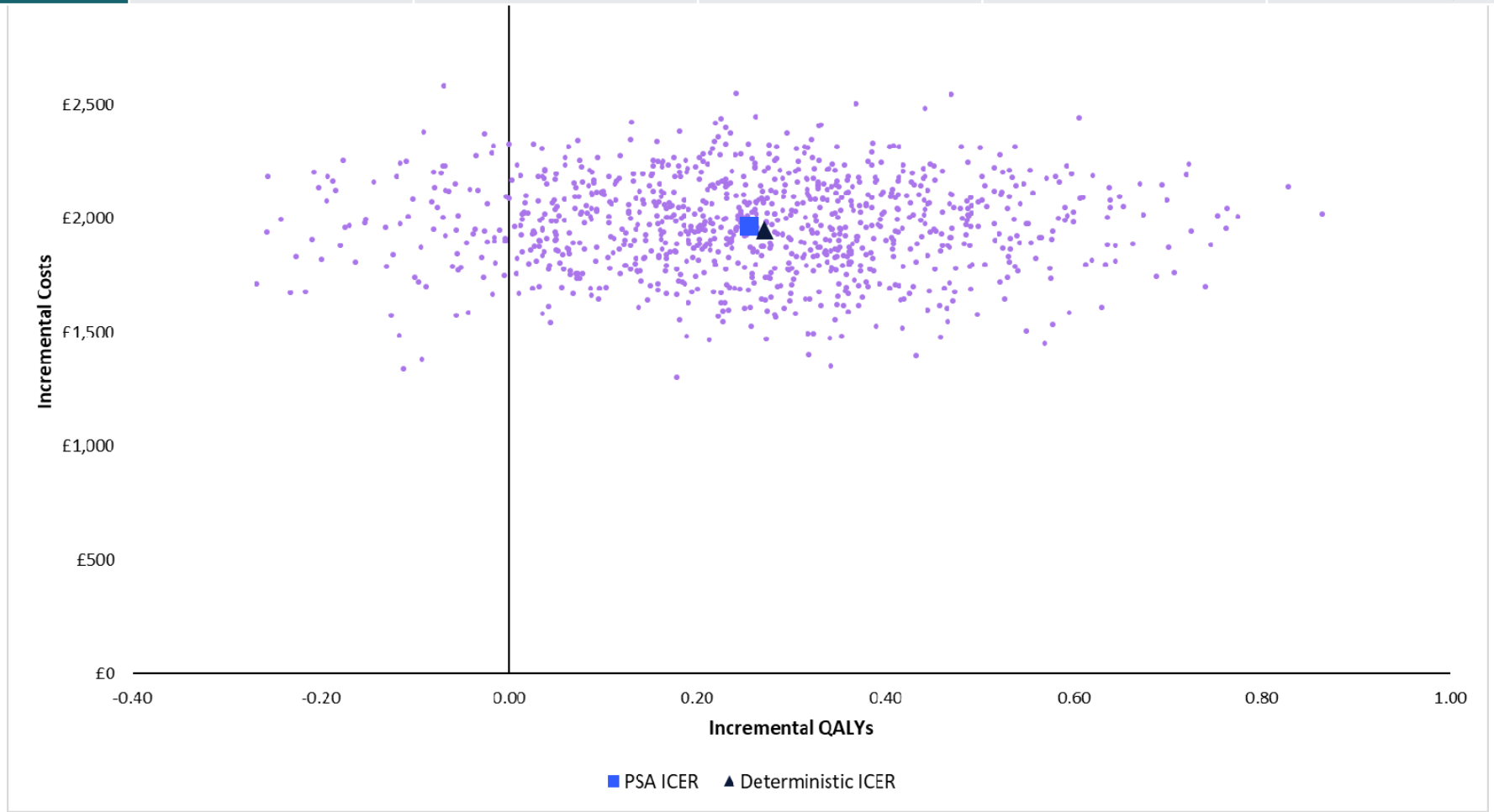
- Revised after clarification
  - Errors corrected, time to recurrence estimated from patient level data

	Total costs	Total QALYs	Inc. cost	Inc. QALYs	ICER (£/QALY)
L(CP)	[redacted]	[redacted]			
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£1,072

Company's probabilistic sensitivity analysis

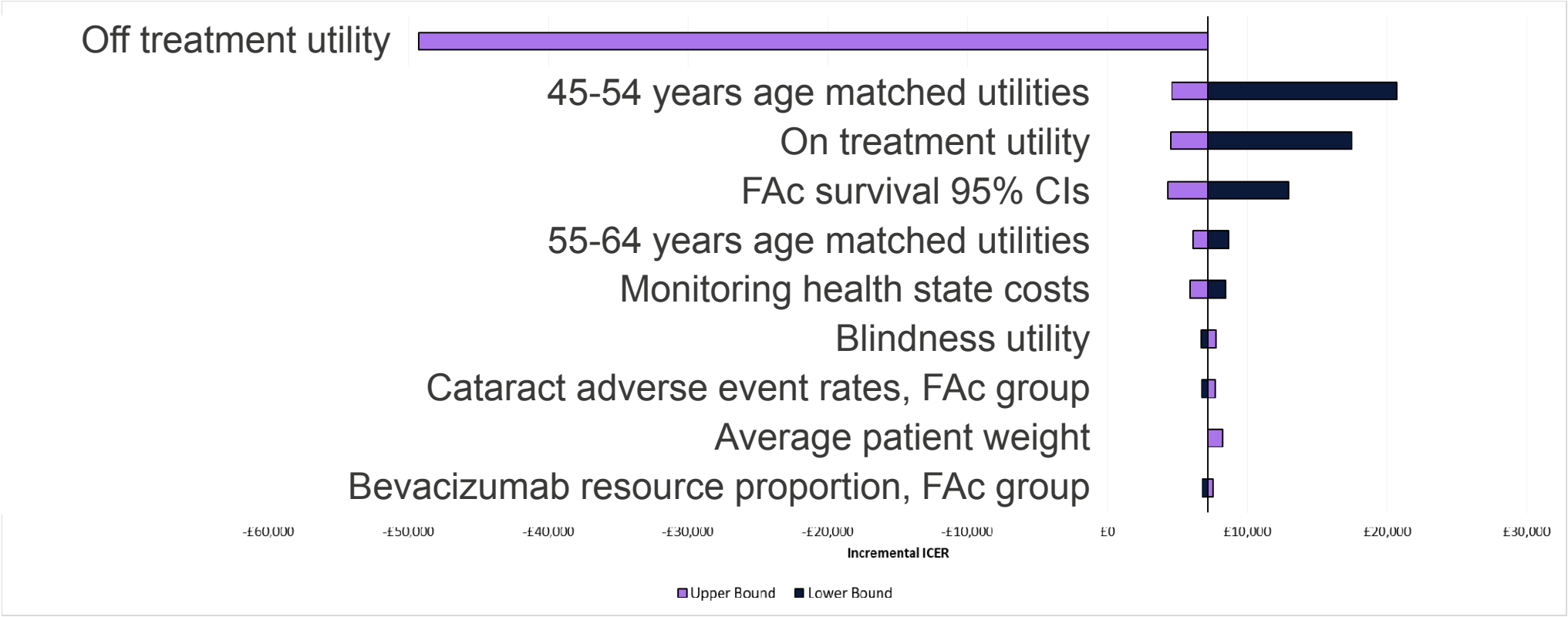
On base case included in submission

Mean results	Total costs	Total QALYs	Inc. cost	Inc. QALYs	ICER (£/QALY)
L(CP)	[redacted]	[redacted]			
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£7,702



Company's deterministic sensitivity analysis

On base case included in submission



ERG comments: comparators

- A formal indirect comparison with dexamethasone was not possible because different outcomes were reported in the trials → **ERG considered it an important comparator so estimated effectiveness relative to other treatments**

TA460 reported an incremental QALY gain of 0.029 for dexamethasone vs (L)CP

ERG's assumptions in calculating relative effectiveness
- QALY gain of 0.029 over the whole time horizon
- Patients receive 1 dexamethasone implant, effective for only 30 weeks

To obtain an incremental QALY gain of 0.029 in ERG base case 1, ERG calculated that hazard ratio of 0.456 for dexamethasone versus (L)CP would be needed

Limitations
- Different assumptions in TA460 model and ERG base case model
- Likely different utility values
- The 2 trials included a different mix of treatments

Therefore ERG included **sensitivity analyses** with hazard ratios of 1 and 0.7 compared with FAc

ERG exploratory analyses

1-4	Error corrections
5	Include dexamethasone as a comparator
6	Individual patient data for time to recurrence
7	Capped health state utility values to age-adjusted general population values
8	Supplemental treatment costs equal in both treatment arms
9	Corrected doses for subsequent and supplemental treatments
10	Used empirical standard error (when available) for probabilistic results
11	Removed remission health state
12	Included transition between ‘on treatment’ and ‘blindness’
13	Effectiveness of FAc after 3 years made equal to (L)CP
14	Cost components of permanent blindness removed before 65 years of age
15	Included cost of blood test every 12 weeks when receiving immunosuppressants
16	After 3 years, upon transition into ‘subsequent therapy’ state, both groups receive same treatments
17	Included disutility for adverse events (0.05)
18	Included possibility of receiving multiple FAc implants (effectiveness after 3 years maintained)

ERG exploratory analyses: results [1]

Assuming hazard ratio of 0.456 for dexamethasone vs (L)CP

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Fully inc. ICER (£/QALY)	ICER FAc vs comparator
Company base-case						
(L)CP	[redacted]	[redacted]				£7,183
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£4,906
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£7,183	-
Errors corrected (1-4)						
(L)CP	[redacted]	[redacted]				£2,510
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£716
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£2,510	-
Corrections for NICE reference case, scope or best practice (1-10)						
(L)CP	[redacted]	[redacted]				£1,502
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£1,502	-
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	FAc dominates*	FAc dominates

ERG = Evidence Review Group; FAc = fluocinolone acetonide implant; ICER = incremental cost effectiveness ratio; (L)CP = (limited) clinical practice; QALY = quality-adjusted life year, ext. dominated = extendedly dominated

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**corrected after committee meeting*

ERG exploratory analyses: results [2]

Assuming hazard ratio of 0.456 for dexamethasone vs (L)CP

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Fully inc. ICER (£/QALY)	ICER FAc vs comparator
Removing the remission health state (1-4, 11)						
(L)CP	[redacted]	[redacted]				£3,513
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£240
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£3,513	-
Create transition from on treatment to permanent blindness (annual rate 0.0066) (1-4, 12)						
(L)CP	[redacted]	[redacted]				£3,644
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£2,165
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£3,644	-
Effectiveness of FAc after 3 years equal to (L)CP (1-4, 13)						
(L)CP	[redacted]	[redacted]				£4,221
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£540
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£4,221	-
Cost components of permanent blindness removed before 65 years of age (1-4, 14)						
(L)CP	[redacted]	[redacted]				£5,354
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£3,595
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£5,354	-
Cost of blood test every 12 weeks when receiving immunosuppressants (1-4, 15)						
(L)CP	[redacted]	[redacted]				£2,500
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£707
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£2,500	-

ERG base-case results (deterministic)

Assuming hazard ratio of 0.456 for dexamethasone vs (L)CP

Technology	Total costs	Total QALYs	Fully inc. costs	Fully inc. QALYs	Fully inc. ICER (£/QALY)	ICER of FAc versus comparator
ERG base case 1 (1-16)						
(L)CP	[redacted]	[redacted]	-	-		£12,325
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£5,335
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£12,325	-
ERG base case 2 (1-17) (include 0.05 utility decrement for adverse events)						
(L)CP	[redacted]	[redacted]	-	-		£21,531
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£9,457
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£21,531	-
ERG base case 3 (1-12, 14-16, 18) (include possibility of receiving multiple FAc implants)						
(L)CP	[redacted]	[redacted]	-	-		£19,049
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£13,856
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£19,049	-
ERG base case 4 (1-12, 14-18) (BC3 plus 0.05 utility decrements for adverse events)						
(L)CP	[redacted]	[redacted]	-	-		£30,153
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£22,810
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£30,153	-

FAc, fluocinolone acetonide implant; ICER, incremental cost effectiveness ratio; (L)CP, (limited) clinical practice; QALY, quality-adjusted life year; inc., incremental; ext., extendedly.

ERG base-case results (deterministic)

Varying hazard ratio for dexamethasone

- Results for ERG base case 1 to 4, dexamethasone compared to FAc:

Hazard ratio 1 (equal efficacy)	Dexamethasone dominates FAc
Hazard ratio 0.7 (dexamethasone is more effective than FAc)	Dexamethasone extendedly dominates FAc

ERG base-case results (deterministic)

Assuming hazard ratio of 1 for dexamethasone vs FAc

Technology	Total costs	Total QALYs	Fully inc. costs	Fully inc. QALYs	Fully inc. ICER (£/QALY)	ICER of FAc versus comparator
ERG base case 1						
(L)CP	[redacted]	[redacted]	-	-		£12,325
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	£12,283	Dominated
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
ERG base case 2						
(L)CP	[redacted]	[redacted]	-	-		£21,531
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	£21,457	Dominated
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
ERG base case 3						
(L)CP	[redacted]	[redacted]	-	-		£19,049
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	£18,710	Dominated
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
ERG base case 4						
(L)CP	[redacted]	[redacted]	-	-		£30,153
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	£29,617	Dominated
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-

FAc, fluocinolone acetonide implant; ICER, incremental cost effectiveness ratio; (L)CP, (limited) clinical practice; QALY, quality-adjusted life year; inc., incremental; ext., extendedly.

ERG base-case results (deterministic)

Assuming hazard ratio of 0.7 for dexamethasone vs FAc

Technology	Total costs	Total QALYs	Fully inc. costs	Fully inc. QALYs	Fully inc. ICER (£/QALY)	ICER of FAc versus comparator
ERG base case 1						
(L)CP	[redacted]	[redacted]	-	-		£12,325
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	-
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	£10,412	£2,297
ERG base case 2						
(L)CP	[redacted]	[redacted]	-	-		£21,531
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	-
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	£17,843	£3,643
ERG base case 3						
(L)CP	[redacted]	[redacted]	-	-		£19,049
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	-
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	£17,239	£12,911
ERG base case 4						
(L)CP	[redacted]	[redacted]	-	-		£30,153
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	-
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	£25,074	£15,730

FAc, fluocinolone acetonide implant; ICER, incremental cost effectiveness ratio; (L)CP, (limited) clinical practice; QALY, quality-adjusted life year; inc., incremental; ext., extendedly.

ERG scenario analyses based on base case 1	Technology	Fully incremental ICER (£/QALY)	ICER of FAc versus comparator
ERG base-case 1	(L)CP		£12,325
	Dexa 700	Ext. dominated	£5,335
	FAc	£12,325	-
FAc and dexamethasone are not effective anymore after 3 years, all patients switch to subsequent treatment	(L)CP		£24,443
	Dexa 700	Ext. dominated	£15,627
	FAc	£24,443	-
Use utility based on the US tariffs (MUST trial) for the 'on treatment' and 'subsequent treatment' health states	(L)CP		£22,679
	Dexa 700	Ext. dominated	£10,303
	FAc	£22,679	-
‘Permanent blindness' health state utility value from Brown et al. (0.57)	(L)CP		£14,565
	Dexa 700	Ext. dominated	£6,194
	FAc	£14,565	-
Inclusion of disutility for adverse events (assumed all AEs incur a disutility value of 0.1)	(L)CP		£85,084
	Dexa 700	Ext. dominated	£41,574
	FAc	£85,084	-
Rate for blindness (Durrani et al. 0.0374 annual)	(L)CP		£4,465
	Dexa 700	Ext. dominated	£934
	FAc	£4,465	-
Rate for blindness (Tomkins-Netzer 0.0038 annual)	(L)CP		£15,072
	Dexa 700	Ext. dominated	£6,903
	FAc	£15,072	-

Innovation

Company comments

- Long-lasting design with sustained release leads to
  - reduced risks from frequent intravitreal injections
  - improved adherence
  - decreased fluctuation in disease control
  - reduction of treatment burden

Professional/expert comments

- Promise of up to 3 years of disease control with a single application
- FAc implant could be an option for people for whom systemic treatment is contraindicated or whose disease does not respond to conventional treatment

Equality considerations

- Long-lasting design of the FAc implant could improve adherence to treatment for some people e.g. people with dementia or mental health problems

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

November 2018

File name	Version	Contains confidential information	Date
ID1039 Iluvien Alimera Company Submission Document B ACIC.docx	**FINAL-1.1**	**Yes**	**06/12/2018**

Contents

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Abbreviations

AE	Adverse Event
BCVA	Best corrected visual acuity
CFT	Central foveal thickness
DMO	Diabetic macular oedema
EQ-5D	EuroQol 5-dimensions
FAc	Fluocinolone acetonide
HRQoL	Health related Quality of life
HTA	Health Technology Appraisal
ICER	Incremental Cost Effectiveness Ratio
IOP	Intraocular pressure
MHRA	Medicines and Healthcare Products Regulatory Agency
NICE	National Institute for Health and Care Excellence
[redacted]	[redacted]
PAS	Patient access scheme
PICOS	Population – Intervention - Comparators - Outcomes- Study
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
QALY	Quality Adjusted Life Year
SAE	Serious Adverse Event
SLR	Systematic literature review
TA	Technology Assessment
TEAE	Treatment-Emergent Adverse Event
TNF	Tumour Necrosis Factor
WTP	Willingness-to-pay

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

1.1 *Decision problem*

This submission addresses the clinical efficacy and safety, and cost-effectiveness of an injectable 0.19 mg fluocinolone acetonide intravitreal implant (ILUVIEN®) within the expected licensed indication of [redacted]. The decision problem addressed in this submission deviates from the final NICE scope for this appraisal, as outlined in Table 1.

Table 1. The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with recurrent non-infectious uveitis	[redacted]	The proposed marketing authorisation for the fluocinolone acetonide (FAc) 0.19 mg implant (ILUVIEN®) is restricted to [redacted]
Intervention	FAc intravitreal implant in applicator	FAc intravitreal implant (ILUVIEN) in applicator	N/A
Comparator(s)	• Periocular or intravitreal corticosteroid injections • Intravitreal corticosteroid implants including dexamethasone intravitreal implant (in line with NICE technology	• Current practice / limited current practice ((L) CP)	The company model assesses ILUVIEN versus (L) CP, using the pivotal trial comparator (active sham arm with corticosteroids and immunosuppressants for treatment of recurrences). In the event of a recurrence of uveitis both the ILUVIEN and the sham arm patients were allowed to receive: • periocular or intravitreal corticosteroid injections; or • topical corticosteroids as first line treatment. Additionally, systemic immunosuppressants or systematic steroids could also be provided on first-line therapy failure. A previous MTA conducted by NICE recognised the challenges in defining current clinical practice in the UK, given the absence of national treatment guidelines and heterogeneity in both the patient population and subsequent therapies. The nature of the pivotal trial's active sham arm is reflective of the various treatment options in the UK. Therefore, in

	appraisal 460) • Systemic corticosteroids • Systemic immunosuppressive therapies, including but not limited to, azathioprine, methotrexate, cyclophosphamide, ciclosporin, tacrolimus, mycophenolate mofetil (and mycophenolic acid) (with the exception of ciclospori		common with the previous MTA, we have defined our active sham arm comparator as current clinical practice in the UK. We propose not to include best supportive care as a comparator for ILUVIEN. We recognise that best supportive care may also be considered a comparator; however, due to the risk of sight loss associated with uveitis, standard practice is active treatment, rather than supportive only. Indeed, patients in both arms of the pivotal PSV-FAI-001 trial could receive standard practice, including corticosteroids and immunosuppressants, in case of uveitis recurrences. Furthermore, due to the lack of a nationally agreed clinical pathway, it remains a challenge to adequately characterise and quantify best supportive care.

	n, none of the listed immunosuppressive therapies currently have a marketing authorisation in the UK for this indication) • TNF-alpha inhibitors including adalimumab (in line with NICE technology appraisal 460) • Best supportive care (when all other treatment options have		

	been tried)		
Outcomes	The outcome measures to be considered include: • recurrence of uveitis (the affected eyes) • visual acuity (the affected eyes) • visual acuity (both eyes) • need for further corticosteroid treatment • mortality • adverse effects of treatment • health-related	The company presents evidence on the measures of efficacy against uveitis and its complications that were included in the PSV-FAI-001 trial at 6, 12 and 36 months. The comparator arm was active sham with corticosteroids and immunosuppressants for treatment of recurrences. The primary outcome measure was: • Proportion of subjects who have a recurrence of uveitis in the study eye within 6 months after receiving study treatment. Additional exploratory outcomes presented include: • Proportion of subjects who have a recurrence of uveitis in the study eye within 12 or 36 months • Proportion of subjects who have a recurrence of uveitis in the fellow eye (within 6, 12 and 36 months) • Number of recurrences of uveitis (within 6, 12 and 36 months) • Time to recurrence of uveitis (within 6, 12 and 36 months) • Number of supplemental treatments (local or systemic corticosteroids, or systemic immunosuppressants) required to treat recurrences of uveitis (within 6, 12 and 36 months) • Mean change from baseline in BCVA letter score in the study eye (at 6, 12 and 36 months) • Resolution of macular oedema, as measured by OCT imaging (at 6, 12 and 36 months)	As the relevant data from the PSV-FAI-001 trial is available, the company presented a detailed analysis on recurrence of uveitis (including recurrence rate, time to recurrence and number of recurrences per patient). The data on resolution of macular oedema, based on measurement of CFT, is also presented to demonstrate the efficacy of ILUVIEN against one of the possible complications of uveitis. In addition to the need for further corticosteroid treatment (local or systemic), the use of systemic immunosuppressive medication was also captured in the PSV-FAI-001 trial and is presented in this submission. Health-related quality of life data was not available from the PSV-FAI-001 trial or the PSV-FAI-005 trial and is not presented in the clinical effectiveness section; however, it is incorporated into the economic model.

	quality of life		
Subgroups to be considered	If evidence allows, consideration will be given to subgroups according to: • Type of uveitis (acute or chronic; single incident or recurrent; posterior segment, posterior, intermediate or pan uveitis) • Baseline visual acuity • Previous treatment history Guidance will only be issued in accordance with the marketing	No subgroup analyses performed	The description of clinical effectiveness and base-case cost effectiveness model aligns with the expected marketing authorisation for ILUVIEN; [redacted]. Therefore, subgroup analysis based on the type of uveitis as described in the final NICE scope (acute or chronic; single incident or recurrent; posterior segment, posterior, intermediate or pan uveitis) is not considered appropriate. While the manufacturer acknowledges that the subgroups analysis for: • Baseline visual acuity • Previous treatment history are potentially relevant to the decision problem, there is insufficient clinical data available to consider them in the appraisal. Nonetheless, descriptive analysis of the primary PSV-FAI-001 endpoint only (proportion of subjects with recurrence of uveitis at 6 months) is presented in this submission (prior treatment history) and Appendix E (baseline visual acuity)

	authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.		

BCVA: best corrected visual acuity; FAc: fluocinolone acetonide; MTA: multiple technology assessment; N/A: not applicable; NICE: National Institute for Health and Care Excellence; [redacted]; NHS: National Health Service; (L) CP: limited current practice; OCT: optical coherence tomography; PAS: patient access scheme

1.2 *Description of the technology being appraised*

ILUVIEN implant is a unique and innovative intravitreal implant containing 0.19 mg fluocinolone acetonide (FAc) that over 36 months continuously releases a micro-dose (0.2 µg/day) of FAc to the posterior segment of the eye. It is currently indicated in the UK and 16 other European countries, as well as in the US, for the treatment of diabetic macular oedema (DMO). Currently, the company is in the process of seeking regulatory approval for indication extension to include the use of ILUVIEN [redacted]. This is being conducted through the mutual recognition procedure with the UK as the reference state. Appendix C includes three documents – the current Summary of Product Characteristics (SmPC) and Public Assessment Report (PAR) for ILUVIEN pertaining to its use in DMO, and a draft SmPC incorporating the proposed indication extension; the corresponding PAR is not yet available. Of note, recently (12 Oct 2018, NDA 210331) the same implant technology was approved by the US Food and Drug Administration (FDA) for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye[1].

Since [redacted] is often a chronic condition, most patients require long-term treatment to reduce inflammation and decrease the number of uveitis recurrences. The aim of treatment is to protect the ocular tissues from cumulative damage associated with recurrences of chronic inflammation and, ultimately, preserve vision. ILUVIEN implant is injected through a 25-gauge injector system in the outpatient setting and provides sustained release of FAc (on average 0.2 µg per day) for up to 36 months. Therefore, ILUVIEN allows to maintain a continuous , stable low dose of FAc for as long as 36 months, without the need for repeated intravitreal injections and their inherent risks. It may also decrease or eliminate the need for systemic steroids or immunosuppressants, which have burdensome side-effect profiles. Further details of ILUVIEN are provided in Table 2.

Table 2.Technology being appraised

UK approved name and brand name	Fluocinolone acetonide intravitreal implant (ILUVIEN)
Mechanism of action	ILUVIEN contains fluocinolone acetonide, a corticosteroid used in uveitis to reduce both inflammation and macular oedema. A single ILUVIEN implant contains 0.19 mg of the active ingredient and delivers a continuous, low dose of the medication into the vitreous humour over 36 months.
Marketing authorisation/ CE mark status	ILUVIEN does not currently have a marketing authorisation in the UK for the treatment of uveitis. [redacted]
Indications and any restriction(s) as described in the summary of product cha	[redacted]

ract eris tics (Sm PC)	
Met hod of adm inist rati on and dos age	Administered through intravitreal injection. Each ILUVIEN implant contains 0.19 mg of FAc and is designed to release 0.2 µg of FAc per day for up to 36 months.
Add itio nal test s or inve stig atio ns	Following ILUVIEN injection, patients should be monitored for potential initial complications related to the injection procedure, such as endophthalmitis, increased IOP, retinal detachments, and vitreous haemorrhages or detachments. Biomicroscopy with tonometry should be performed between two and seven days after the implant injection. Immediate IOP measurement may be performed at the discretion of the treating ophthalmologist. Thereafter it is recommended that patients are monitored at least quarterly for potential complications, due to the extended duration of FAc release. Patients who have ILUVIEN implanted in a phakic eye should be closely monitored for cataract development and may require cataract surgery with intraocular lens implantation.
List pric e and aver age cost of a cou rse of trea tme nt	The list price for ILUVIEN is £5500.00[2] and a single implant lasts up to 36 months. [redacted]
Pati ent acc ess sch eme (if appl icab le)	[redacted]

FAc: fluocinolone acetonide; IOP: intraocular pressure; MHRA: Medicines and Healthcare products Regulatory Agency; PAS: patient access scheme

1.3 *Health condition and position of the technology in the treatment pathway*

Uveitis is a potentially sight-threatening condition, which involves intraocular inflammation that may arise from various causes[3]. In the developed world, uveitis and its complications are the cause of approximately a fifth of all legal blindness[3] and around 2–5 in every 10,000 people in the UK are affected each year[4]. The condition is among the leading causes of visual impairment in the UK, being responsible for 1 in every 10 cases[5].

Uveitis occurs as a result of inflammation of the uvea, which includes the iris, the ciliary body and the choroid[6]. Standardization of Uveitis Nomenclature, introduced in 2005, divides uveitis into distinct types based on the anatomic eye structures affected[7] (see Figure 1). The most common form of the condition is anterior uveitis (about 75% of cases), which affects the iris and may also affect the ciliary body[5]. Intermediate uveitis affects the area around and behind the ciliary body and is focused on the vitreous. Posterior uveitis affects the back of the eye – the choroid, the retina or both[5,8]. Inflammation of retinal blood vessels (retinal vasculitis) may also be present, especially in patients with an underlying systemic disease[9]. Uveitis affecting both the front and the back of the eye is termed panuveitis[5] and this type of uveitis is particularly predisposing to visual loss[10]. Complications of uveitis, such as retinal damage and glaucoma, may be irreversible and can result in loss of vision[4,5]. These are more common in uveitis that affects the intermediate and posterior segments of the eye, and in patients with repeated uveitis episodes[5]. Intermediate, posterior, and pan-uveitis are the most severe and highly recurrent forms of the condition that often cause blindness if left untreated[6]. Compared with anterior uveitis, posterior and pan-uveitis have been reported to cause visual loss that is both more common and more severe[11].

[redacted] comprises [redacted]; however, some cases of [redacted], where the posterior segment of the eye is also affected (e.g. if macular oedema is present), can also be considered a form of NIU-PS. In terms of

the epidemiology of [redacted], no single estimate for England has been identified. In terms of prevalence, a recent estimate comes from the 2018 Orphanet report which states that 3.8 per 10,000 people in Europe have uveitis[12]; however, this does not separate uveitis by the eye segment affected, or by aetiology (infectious vs non-infectious). In the US, non-infectious uveitis has been reported to account for 91% of uveitis cases[13], and this proportion may be considered applicable to the UK as well. In terms of anatomical location of uveitis, a retrospective review of referrals to the Manchester Uveitis Clinic suggested posterior uveitis is responsible for 21.8% of uveitis cases, intermediate uveitis for 11.1% and panuveitis for 21.1%[14]; suggesting that the posterior segment of the eye is affected in approximately 54% of uveitis cases. Thus, based on the adult population size of England, there are approximately 8,500 prevalent cases of [redacted] in England, with an estimated 51 new cases diagnosed per year (see Section **Error! Reference source not found.**). Importantly, most patients affected by uveitis are of working age at onset (16–65 years old) and over a third are young adults aged 16–35[14].

In the response to consultee and commentator comments in relation to the draft remit and draft scope for NICE TA460, Santen estimated that across England between 1,500 and 5,000 people per year are diagnosed with non-infectious intermediate or posterior uveitis each year[15,16]. While restricted to non-infectious causes, this does not consider panuveitis, which, according to the data from the Manchester Uveitis Clinic presented above, is nearly as common as posterior uveitis[14]. Therefore, the estimate of 8,500 prevalent cases of [redacted] appears plausible.

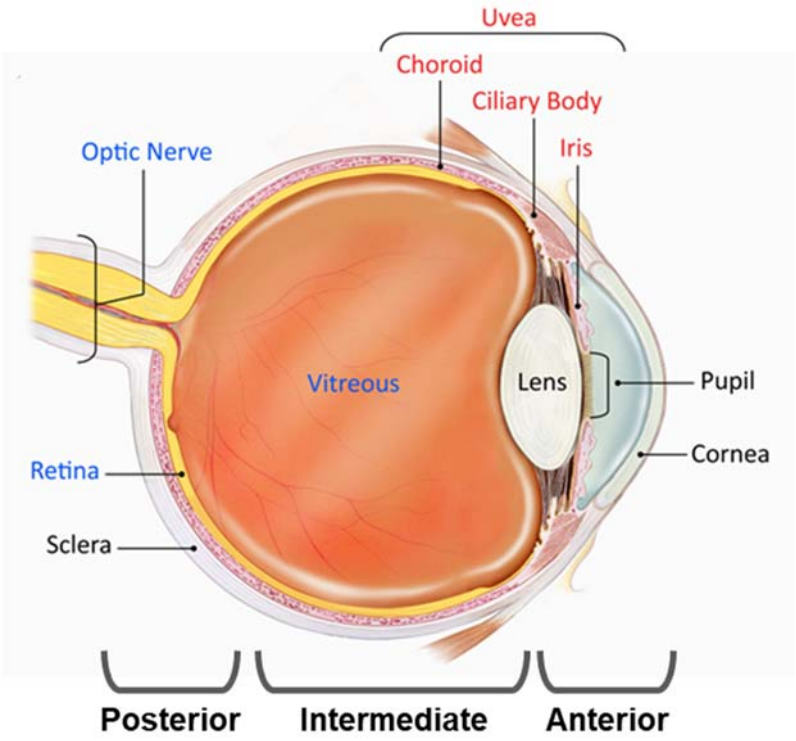


Figure 1. Schematic of the eye[6], including anatomical structures affected by different uveitis types[5,8]

Management of uveitis is based on whether uveitis is related to an infection or arises from a non-infectious cause[17,18]. Several autoimmune conditions can be associated with uveitis[4], including:

- ankylosing spondylitis;
- reactive arthritis;
- Crohn's disease and ulcerative colitis;
- psoriasis and psoriatic arthritis;
- multiple sclerosis;
- Behçet's disease;
- sarcoidosis and juvenile idiopathic arthritis

Thus, treatment choices depend largely on whether patients have an underlying active systemic disease and whether one or both eyes are affected.

A further aspect that should be taken into account when making treatment-related decisions is whether uveitis is chronic (i.e. relapses promptly when therapy is

discontinued) or if the patient experiences recurrent episodes of acute uveitis (where periods of active ocular inflammation are separated by periods of no inflammation despite the patient being off-treatment)[19]. While the latter uveitis type may only require treatment of acute attacks[19], particularly if they are infrequent and associated with little pain or visual loss, chronic disease is likely to require prolonged therapy[19], as is uveitis resenting with frequent recurrences.
Currently, no national guidelines for the treatment of [redacted] exist in the UK and the clinical knowledge summary from NICE[20] does not include a detailed management pathway; however, the treatment pathway presented in TA460 (Figure 2) was based on clinical expert opinion and considered by NICE to be representative for the treatment of non-infectious uveitis in England[16].

Local treatment is generally preferred in patients with inflammation restricted to the eye (i.e. no active systemic disease that could prompt a systemic treatment approach), especially if the disease is unilateral or highly asymmetric.
Corticosteroids are considered first-line treatment in non-infectious uveitis and aim to reduce inflammation by lowering the activity of the immune system, which is critical to minimise vision loss. These may be administered systemically (via oral or parenteral routes) or locally (via periocular or intravitreal routes, which includes intravitreal implants[7,21]). Systemic corticosteroids are associated with substantial adverse events (AEs), such as osteoporosis and fractures, susceptibility to infections, depression, skin conditions, hyperglycaemia and weight gain, leg oedema, cushingoid appearance, and ocular conditions such as glaucoma and cataract[22,23]. This adverse event profile is particularly important given that patients often initially require high doses of systemic steroids to deliver therapeutic doses of the drug across the blood–brain/eye barrier to the retina and vitreous. In a clinical setting, the high systemic dose of the corticosteroid is gradually tapered down in an attempt to lower the dose whilst maintaining control of the uveitis. However, this clinical strategy is not always successful, meaning that patients may be maintained on higher systemic steroid doses or instead receive immunosuppressive drugs (see below), both of which may be considered to have a burdensome adverse effect profile.

When systemic corticosteroid treatment proves to be ineffective (i.e. is contraindicated, not tolerated or long-term use at a high dose is required), immunosuppressive drugs (i.e. methotrexate, ciclosporin, mycophenolate mofetil or azathioprine) may be considered as off-label therapies especially alongside a low-dose of a corticosteroid. Nevertheless, treatment with immunosuppressants is also linked to substantial AEs[24,25]. If the disease does not respond to these treatments, or if they are not tolerated, biological tumour necrosis factor (TNF)-alpha inhibitors may be used as third-line treatments.

The local administration of steroids potentially reduces the frequency and type of adverse effects through their localised action and their use reduces the potential frequency of systemic adverse effects[26]. Periocular and intravitreal steroid injections are effective but provide only short-term control, often requiring repeated injections every three to six months; however, the injection procedure may cause issues related to the invasive nature of this approach, and these may include retinal tears, haemorrhage, endophthalmitis, ptosis and fibrosis[27,28]. In addition, intravitreal injections may be associated with substantial anxiety and it is well documented that patients would like good treatment outcomes but with fewer injections and hospital appointments[29].

The use of sustained-release intravitreal implants offers an alternative to periocular and intravitreal steroid injections and are designed to deliver corticosteroids over a prolonged period of time (i.e. up to 36 months in the case of ILUVIEN). ILUVIEN has several clinical advantages compared with current standard practice (represented by the sham arm of the PSV-FAI-001 trial (see Section 2.6) including:

I. [redacted].

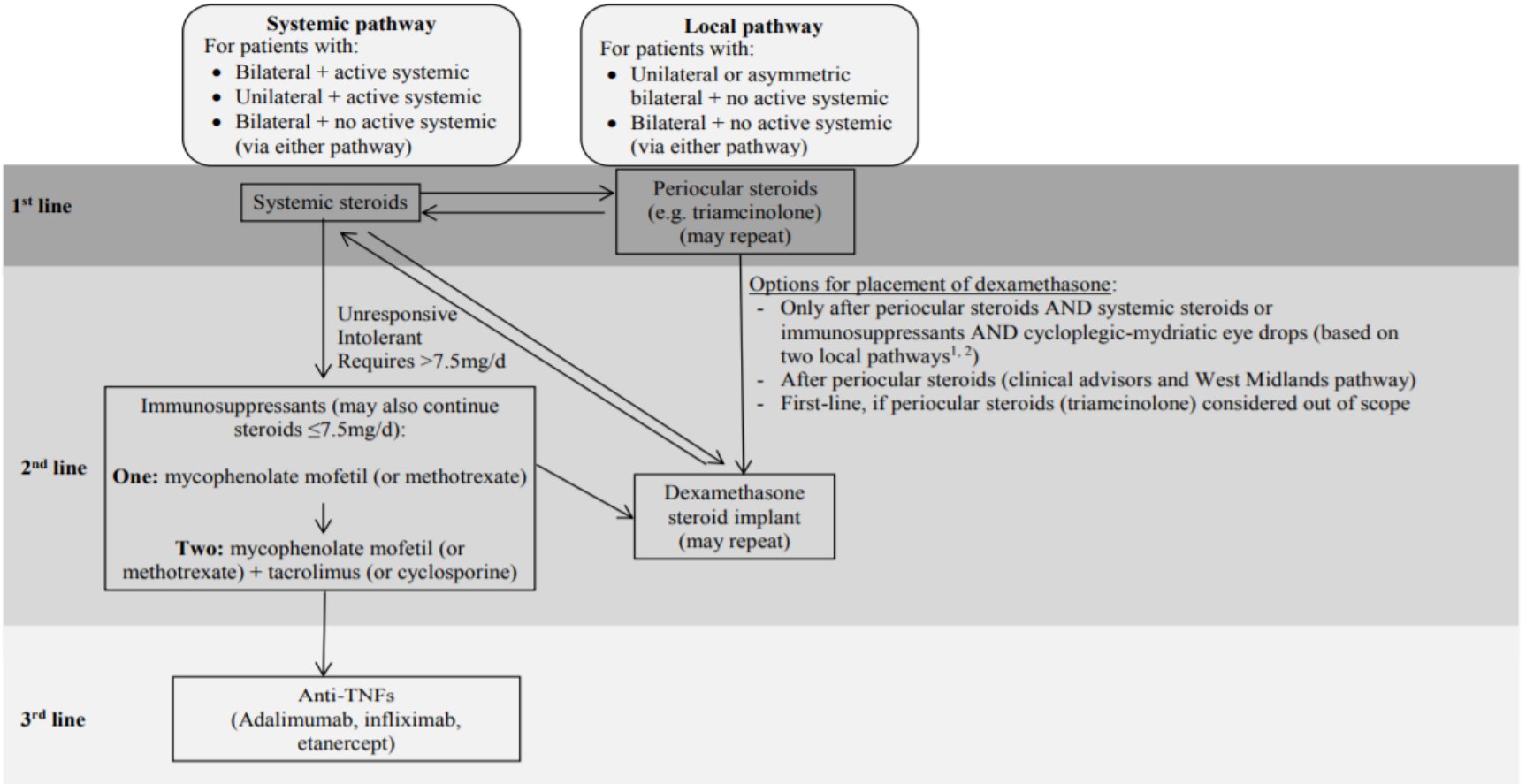
II. [redacted].

III. [redacted].

The dexamethasone (Ozurdex®) implant is another intravitreal implant and indicated for use within the National Health Service (NHS) in patients with active disease (that

is, current inflammation in the eye) and worsening vision with a risk of blindness[16]. The dexamethasone implant is effective for up to 6 months[30], although the efficacy of the implant begins to decline after 3 months, which results in approximately a quarter of patients requiring rescue medication (systemic corticosteroids or immunosuppressants, or local corticosteroids) from 3 months onwards[31]. ILUVIEN has a significantly longer duration of action (up to 36 months) than the dexamethasone implant (up to 6 months) and in patients with [redacted] it is anticipated this will reduce healthcare appointments and treatment-related burden. Furthermore, ILUVIEN may offer an alternative for patients who may benefit from the dexamethasone implant without the worry of rapid recurrence every 3 to 6 months. Indeed, the treatment effect of ILUVIEN lasts longer than the dexamethasone implant and so that there are less fluctuations over time in parameters such as macular oedema and visual acuity over time. This has been confirmed in the DMO patient case reported by Singh *et al*.[32] where multiple dexamethasone implants had been administered prior to treatment with ILUVIEN.

Figure 2. Treatment of non-infectious uveitis in England[16]



TNF: tumour necrosis factor

Systemic pathway: Treatment pathway proposed for patients with uveitis in one or both eyes in the presence of an active systemic disease or those with severe bilateral uveitis with or without an underlying active systemic condition. Local pathway: Treatment pathway proposed for patients with unilateral uveitis or asymmetrically 'severe' bilateral uveitis with no active systemic condition. Unilateral uveitis may be a first episode or a re-activation of a previous inflammation (flare).

1.4 *Equality considerations*

The manufacturer does not perceive the use of ILUVIEN as likely to raise any equality issues.

2 Clinical effectiveness

Key points

- Over a 36-month period, [redacted] as represented by the active sham arm of the PSV-FAI-001 trial). Treatment with ILUVIEN [redacted] Treatment with ILUVIEN (delivering a localised low dose of fluocinolone acetonide) may reduce patient exposure to systemic corticosteroids and immunosuppressants, which are associated with a range of burdensome AEs.
- Patients who received ILUVIEN had a [redacted] over the entire 36-month period, [redacted] The safety profile of ILUVIEN is well-documented and consistent with reported use in DMO indication, and no new or unexpected safety findings have been identified.

2.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify relevant evidence on the efficacy and safety of the ILUVIEN for the treatment of [redacted] The SLR also included potentially relevant comparators, for the purposes of allowing the application of the most appropriate evidence synthesis methodology. The SLR was conducted in September 2018. See appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

The systematic literature review (SLR) was inspired by TA460 and conducted to identify relevant evidence. In contrast to TA460, however, this search was limited to patients with uveitis affecting the posterior segment of the eye as compared with TA460 where the search strategy had a broader scope and included patients with intermediate, posterior and panuveitis. TA460 represents a multiple technology appraisal (TA) of adalimumab and dexamethasone and took account of the potential need to make simultaneous comparisons between interventions. This justifies taking up a broader scope for the eligible patient population.

Within this appraisal, the search was focused on the effectiveness of a single product, ILUVIEN for patients with [redacted], which resulted in the exclusion of the

relevant studies identified in TA460 due to the heterogeneity of the analysed patient populations.

This SLR identified four publications which included ILUVIEN pivotal study PSV-FAI-001. It was not possible to conduct additional evidence synthesis among these publications due to the non-standardised outcome measures for trials in uveitis.

Please note, that at the time this SLR was conducted, 12-month results of PSV-FAI-001 had not been published and the SLR only identified a relevant conference proceeding. Since then, the 12-month data has been published[33] and 24-month data has been presented at the American Academy of Ophthalmology 2018 Annual Meeting in Chicago, Illinois between 26th and 30th October, 2018[34]. The following evidence is derived from the associated clinical study report as well as the publication.

2.2 *List of relevant clinical effectiveness evidence*

Two Phase 3 studies have been initiated to assess the safety and efficacy of ILUVIEN compared to sham injection over a 36-month period in patients with [redacted]. These two studies are both prospective, randomised, controlled, double-blind, multicentre studies, with PSV-FAI-001 enrolling patients in the United States, Europe, the Middle East and India and PSV-FAI-005 enrolling patients in India only. The primary outcome in both studies was recurrence of uveitis at six months and secondary outcomes included recurrence of uveitis at three years.

An overview of the PSV-FAI-001 and PSV-FAI-005 trials is provided in Table 3 and Table 4, respectively. As noted above, PSV-FAI-001 enrolled patients from USA, Israel, India and Europe (including the UK), whereas PSV-FAI-005 enrolled patients solely from Asia (India). Furthermore, 3-year results are already available from the PSV-FAI-001 trial compared with only 12-month results for the PSV-FAI-005 trial. Hence, PSV-FAI-001 provides patient outcomes over the full duration of action of a single ILUVIEN implant. Overviews of both trials are provided for completeness, but only clinical efficacy outcomes from PSV-FAI-001 are used to support this submission and PSV-FAI-005 is not considered further as it has not completed 36 months of follow-up.

Table 3. Overview of clinical effectiveness evidence: PSV-FAI-001[35]

Study	**PSV-FAI-001 (completed)**				
Study design	Phase 3, randomised, sham-controlled, double-blind, multi-centre study conducted in 49 study centres in the US, India, Israel, UK, Germany and Hungary				
Population	Patients with chronic [redacted]				
Intervention(s)	FAc Intravitreal Implant with 0.19 mg fluocinolone acetonide releasing 0.2 µg/day				
Comparator(s)	Sham injection				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓
	No			No	
Rationale for use/non-use in the model	PSV-FAI-001 is the pivotal study supporting the European marketing authorisation of ILUVIEN in uveitis and is therefore the primary source of efficacy and safety data used in the economic model				
Reported outcomes specified in the decision problem	• Proportion of subjects who had a recurrence of uveitis in the study eye within 6, 12 and 36 months following treatment • Mean change from baseline in BCVA letter score in the study eye (at 6months, 12 months, or 36 months) • Number of supplemental treatments required to treat recurrences of uveitis (within 6 months, 12 months, or 36 months) • Mortality • Ocular and non-ocular adverse effects of treatment				
All other reported outcomes	• Proportion of subjects who had a recurrence of uveitis in the fellow eye (within 6, 12 or 36 months following treatment) • Number of recurrences of uveitis (within 6, 12 or 36 months) • **Time to recurrence of uveitis (within 6, 12 or 36 months)** • Resolution of macular oedema, as measured by optical coherence tomography imaging (at 6, 12 or 36 months)				

BCVA: best corrected visual acuity; FAc: fluocinolone acetonide; [redacted]

Table 4. Overview of clinical effectiveness evidence: PSV-FAI-005[36]

Study	**PSV-FAI-005 (ongoing)**
Study design	Phase 3, randomised, sham-controlled, masked, multi-centre study conducted in 15 study sites in India
Population	Patients with [redacted]
Intervention(s)	FAc Intravitreal Implant with 0.19 mg fluocinolone acetonide releasing 0.2 µg/day

<table>
<tr><td>Comparator(s)</td><td colspan="5">Sham injection</td></tr>
<tr><td rowspan="3">Indicate if trial supports application for marketing authorisation</td><td>Yes</td><td>✓</td><td rowspan="2">Indicate if trial used in the economic model</td><td>Yes</td><td></td></tr>
<tr><td>No</td><td></td><td>No</td><td>✓</td></tr>
<tr><td colspan="5">As per the US FDA requirement, two parallel clinical trials were designed to support the marketing authorisation of the FAc implant in the US. In Europe, PSV-FAI-001 is the pivotal trial supporting the marketing authorisation for the treatment of uveitis.</td></tr>
<tr><td>Rationale for use/non-use in the model</td><td colspan="5">The PSV-FAI-001 trial offers more mature data compared to PSV-FAI-005 and was conducted internationally (also in the UK), while PSV-FAI-005 was conducted solely in India.</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td colspan="5">• Proportion of subjects who had a recurrence of uveitis in the study eye within 6, 12 and 36 months following treatment
• Mean change from baseline in BCVA letter score in the study eye (at 6 months, 12 months, or 36 months)
• Number of supplemental treatments required to treat recurrences of uveitis (within 6 months, 12 months, or 36 months)
• Mortality
• Ocular and non-ocular adverse effects of treatment</td></tr>
<tr><td>All other reported outcomes</td><td colspan="5">• Proportion of subjects who had a recurrence of uveitis in the fellow eye (within 6, 12 or 36 months following treatment)
• Number of recurrences of uveitis (within 6, 12 or 36 months)
• Time to recurrence of uveitis (within 6, 12 or 36 months
• Resolution of macular oedema, as measured by optical coherence tomography imaging (at 6, 12 or 36 months)
• Safety: Pregnancies, laboratory test abnormalities (screening only), vital signs, physical examination (screening only), and concomitant medications</td></tr>
</table>

BCVA: best corrected visual acuity; FAc: fluocinolone acetonide; FDA: Food and Drug Administration; [redacted]

2.3 *Summary of methodology of the relevant clinical effectiveness evidence*

A summary of the methodology of the PSV-FAI-001 is provided in Table 5, followed by a more detailed description.

Table 5. Summary of methodology of PSV-FAI-001[35]

Study	PSV-FAI-001

Location	USA, India, Israel, UK, Germany, and Hungary
Trial design	Phase 3, randomised, sham-controlled, double-blind, multi-centre study over 36 months
Eligibility criteria for participants	Eligible patients were males or females aged at least 18 years, who had been diagnosed with unilateral or bilateral chronic [redacted] for at least 12 months prior to randomisation. During the 12 months prior to enrolment, the study eye should have received treatment with systemic corticosteroid or other systemic therapies given for at least 3 months, and/or at least 2 intra- or peri-ocular administrations of corticosteroid for the management of uveitis, or the study eye experienced at least 2 separate recurrences of uveitis requiring systemic, intra- or peri-ocular injection of corticosteroid. At the time of enrolment, the study eye was to have <10 anterior chamber cells/high powered field, vitreous haze ≤grade 2 and visual acuity of at least 15 letters on the early treatment diabetic retinopathy study chart.
Settings and locations where the data were collected	49 study centres in the following six countries: the US, India, Israel, UK, Germany, and Hungary; 39 study centres screened patients and 33 centres randomly assigned patients to treatment.
Trial drugs **Permitted and disallowed concomitant medication**	<u>ILUVIEN (intervention, n=87):</u> Patients were administered 0.19 mg FAc delivered as an intravitreal implant injected into the vitreous humour. ILUVIEN was administered to the study eye by injection through the pars plana using a preloaded applicator with a 25-gauge needle. Each implant was implanted on day 1 of the study and delivered a constant dose of 0.2 µg/day of FAc over 36 months. <u>Sham injection (comparator, n=42):</u> The sham applicator consisted of an empty 1ml syringe attached to a blunt 14-gauge needle without ILUVIEN. On day 1 of the study the sham applicator was gently pressed against the study eye to provide the subject with the perception that an intravitreal injection was being performed <u>Concomitant medications:</u> The following concomitant medications were not permitted during the study, other than during the initial 3-month tapering-off period or in case of uveitis recurrences: • Oral, systemic, injectable or topical steroids • Systemic immunosuppressants
Primary outcomes (including scoring methods and timings of assessments)	The primary efficacy endpoint was defined as the proportion of patients who had a recurrence of uveitis in the study eye within 6 months following treatment. For subjects with unilateral uveitis, the study eye was the affected eye. For subjects with bilateral uveitis, the study eye was the more severely affected eye meeting the inclusion/exclusion criteria and for subjects with symmetrical uveitis, the study eye was the right eye. The protocol permitted any local ocular treatment of the non-study (fellow) eye at the discretion of the investigator.

	Recurrence of uveitis was defined as: • A ≥2-step increase in the number of cells in the anterior chamber per high powered field (1.6 × using a 1 mm beam), compared with baseline or any visit time point prior to Month 6 (or Month 12, or Month 36 for assessments of recurrence at these time points, which were evaluated as exploratory endpoints) OR • An increase in the vitreous haze of ≥ 2 steps, compared with baseline or any visit time point prior to Month 6 (or Month 12, or Month 36 for assessments of recurrence at these time points) OR • A deterioration in visual acuity of at least 15 letters, compared with baseline or any visit time point prior to Month 6 (or Month 12, or Month 36 for assessments of recurrence at these time points) Any criterion used to define recurrence was required to be attributable only to non-infectious uveitis. To prevent post-procedural inflammatory reactions from being reported as uveitis recurrences, assessments for recurrence of uveitis began after the Day 7 visit. Recurrence was also imputed in the following circumstances: • A subject who had not previously experienced a recurrence and did not complete the required eye examinations at Month 6 (or Month 12, or Month 36 for assessments of recurrence at these time points) for any reason was considered as having a recurrence. • A subject who had not previously experienced a recurrence and took a prohibited systemic concomitant medication or a prohibited local concomitant medication in the study eye at any time during the study prior to Month 6 (or Month 12, or Month 36 for assessments of recurrence at these time points) was considered as having a recurrence.
Other outcomes used in the economic model/specified in the scope	See Table 3
Pre-planned subgroups	Subgroup analyses, using descriptive statistics only, were performed on the primary efficacy endpoint for the ITT population at Month 6. Analyses were performed to determine the treatment effect within specific subgroups of interest, and to determine if the treatment effect is consistent across different subgroup levels. See Section 2.7 for details.

BCVA: best corrected visual acuity; FA: fluocinolone acetonide; FAc: fluocinolone acetonide; ITT: intention-to-treat; [redacted]

2.3.1 Study Design

PSV-FAI-001 (NCT01694186) is a recently completed 36-month Phase 3, multinational, randomised, double-blind, sham-controlled trial initiated by pSivida Corp in June 2014 to assess the efficacy and safety of a fluocinolone acetonide (FA) intravitreal implant in the management of patients with chronic [redacted][35]. [redacted] while 12- and 24-month data are now publicly available.

The trial followed a parallel group design and the treatment arms were:

- 0.19 mg ILUVIEN implant which delivers FAc into the vitreous humour for 36 months
- Sham injection followed by standard practice which is an established control for the indication.

The multi-centre study comprises of 49 study locations across USA, India, Israel, UK, Germany and Hungary.

Three study periods were defined as follows:

- Screening: (within 30 days prior to Day 1)
- Treatment: (Day 1)
- Follow-up: (Day 7, Day 28, Months 2, 3, 6, 9, 12, 18, 24, 30, and 36)

Additional examinations could have been conducted as necessary, as unscheduled follow-up visits, to ensure the safety and well-being of patients during the study period.

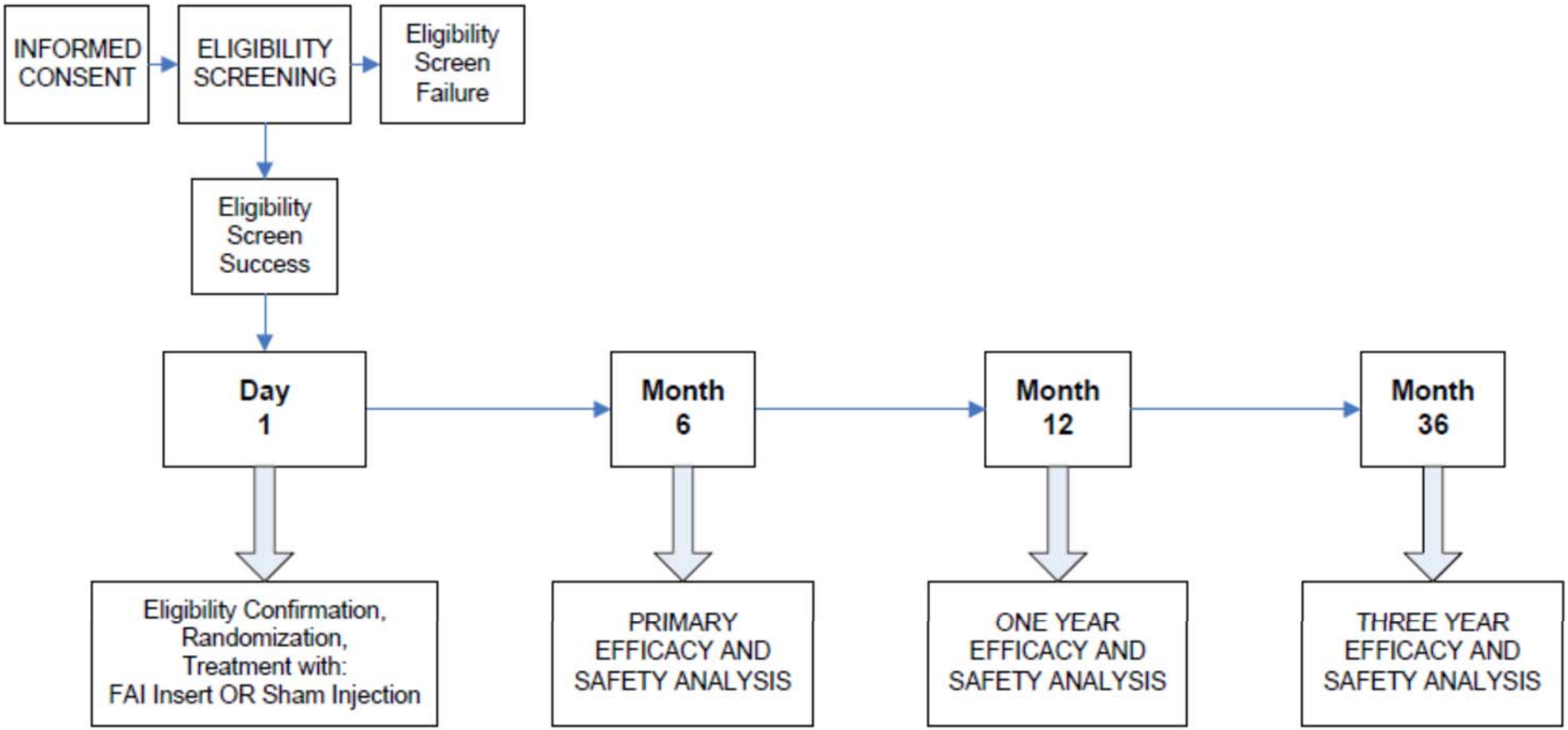
For patients with unilateral uveitis, the study eye was the affected eye. For patients with bilateral uveitis, the study eye was the more severely affected eye meeting the inclusion/exclusion criteria. For patients with symmetrical uveitis, the study eye was the right eye. The protocol permitted any local ocular treatment of the non-study (fellow) eye at the discretion of the investigator.

Following confirmation of eligibility at Day 1, patients were randomly assigned to receive ILUVIEN or sham injection via a central interactive voice response system. Patients who failed to meet the inclusion/exclusion criteria during the screening period or on Day 1 could have been rescreened.

To minimise bias, two investigators participated at each site. One unmasked investigator administered study treatments and performed Day 1 assessments. The second investigator was masked to the assigned treatment and performed all study assessments after Day 1.

A flow chart of the study design is presented in Figure 3.

Figure 3. Study design of PSV-FAI-001[35]



FAI: fluocinolone acetonide intravitreal

2.3.2 Eligibility criteria

Each patient had to meet the following criteria to be enrolled in this study:

- Male or non-pregnant female at least 18 years of age at time of consent
- One or both eyes having a history of [redacted] with or without anterior uveitis (≥1-year duration)
- During the 12 months prior to enrolment (Day 1), the study eye had either received treatment:
    - systemic corticosteroid or other systemic therapies given for at least 3 months, and/or
    - at least 2 intra- or peri-ocular injections of corticosteroid for management of uveitis
- OR the study eye had experienced recurrence:
    - at least 2 separate recurrences of uveitis requiring systemic, intra- or peri-ocular injection of corticosteroid
- At the time of enrolment (Day 1), study eye had <10 anterior chamber cells per high power field and a vitreous haze ≤grade 2
- Visual acuity of study eye was at least 15 letters on the early treatment diabetic retinopathy study (ETDRS) chart
- Patient was not planning to undergo elective ocular surgery during the study
- Patient had the ability to understand and sign the informed consent form
- Patient was willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures

A patient meeting any of the following criteria was excluded from the study:

- Allergy to FAc or any component of ILUVIEN

- History of posterior uveitis only, that was not accompanied by vitritis or macular oedema
- History of iritis only and no vitreous cells, anterior chamber cells, or vitreous haze
- Uveitis with infectious aetiology
- Vitreous haemorrhage
- Intraocular inflammation associated with a condition other than non-infectious uveitis (e.g., intraocular lymphoma)
- Ocular malignancy in either eye, including choroidal melanoma
- Toxoplasmosis scar in study eye; or scar related to previous viral retinitis
- Previous viral retinitis
- Current viral diseases of the cornea and conjunctiva including epithelial herpes simplex, keratitis (dendritic keratitis), vaccinia, varicella, and mycobacterial infections of the eye or fungal diseases of ocular structure
- Media opacity precluding evaluation of retina and vitreous
- Peripheral retinal detachment in area of implantation
- Diagnosis of any form of glaucoma or ocular hypertension in the study eye at screening, unless study eye had previously been treated with an incisional surgery procedure that resulted in stable intraocular pressure (IOP) in the normal range (10–21 mmHg)
- IOP >21 mmHg or concurrent therapy at screening with any IOP-lowering pharmacologic agent in the study eye
- Chronic hypotony (<6 mmHg)
- Ocular surgery on the study eye within 3 months prior to Day 1

- Capsulotomy in study eye within 30 days prior to Day 1
- Prior intravitreal treatment of study eye with Retisert within 36 months prior to Day 1
- Prior intravitreal treatment of study eye with Ozurdex within 6 months prior to Day 1
- Prior intravitreal treatment of study eye with Triesence or Trivaris within 3 months prior to Day 1
- Prior peri-ocular or subtenon steroid treatment of study eye within 3 months prior to Day 1
- Patients requiring chronic systemic or inhaled corticosteroid therapy (>15 mg prednisone daily) or chronic systemic immunosuppressive therapy
- Excluding certain skin cancers (specifically, basal cell carcinoma and squamous cell carcinoma), any malignancy receiving treatment, or in remission less than 5 years prior to Day 1
- Patients who tested positive for human immune deficiency virus (HIV) or syphilis
- Mycobacterial uveitis or chorioretinal changes of either eye which, in the opinion of the investigator, resulted from infectious mycobacterial uveitis
- Systemic infection within 30 days prior to Day 1
- Any severe acute or chronic medical or psychiatric condition that could have increased the risk associated with study participation or could have interfered with the interpretation of study results and, in the judgment of the investigator, could have made the Patient inappropriate for entry into this study
- Any other systemic or ocular condition which, in the judgment of the investigator, could have made the Patient inappropriate for entry into this study

- Treatment with an investigational drug or device within 30 days prior to Day 1
- Pregnant or nursing females; females of childbearing potential who were unwilling or unable to use an acceptable method of contraception from at least 14 days prior to Day 1 until the Month 12 Visit
- Patients unlikely to comply with the study protocol or who were likely to be lost to follow-up within 36 months

2.3.3 Study medications

2.3.3.1 Intervention

ILUVIEN is an injectable intravitreal sustained-release implant preloaded into an injection device (Figure 4). Each implant contained a drug core of FAc as the active ingredient within a cylindrical polyimide polymer tube 3.5-mm long with an external diameter of 0.37 mm. One end of the tube was capped with an impermeable polymer (silicone adhesive); the other end was capped with a permeable polyvinyl alcohol membrane. Release of FAc occurred through the permeable end of the cylinder. Each ILUVIEN implant contained 0.19 mg FAc and delivered FAc into the vitreous humour on day 1 of the study, releasing 0.2 µg/day for 36 months. ILUVIEN was designed to be injected through the pars plana into the vitreous.

Figure 4. ILUVIEN implant within its injection device

2.3.3.2 Sham Injector

The sham applicator was an empty 1 ml syringe attached to a blunt 14-gauge needle; it did not contain an ILUVIEN implant. During study Day 1, the sham applicator was gently pressed against the study eye to provide the patient with the perception that an intravitreal injection was being performed. This procedure was performed to mask study patients to their assigned treatment.

2.3.3.3 Concomitant medications

2.3.3.3.1 Tapering/Ending Systemic or Topical Uveitis Treatment Following Day 1

The protocol allowed investigators to treat subjects prior to entry to meet study inclusion criteria. The objective of prior treatment was to obtain a relatively quiet eye prior to enrolment. If a subject was receiving systemic corticosteroids or immunosuppressants, or topical steroids to control uveitis prior to study enrolment, that subject had such treatment discontinued within 3 months following Day 1, in a manner that followed the standard practice for discontinuing the specific treatment. For example, some systemic treatment regimens may have been ended immediately, while others may have required a period of gradual dose reduction (tapering). Systemic medications or topical steroids administered as part of tapering-off were not considered prohibited medications.

2.3.3.3.2 Prohibited Medications

Other than during the initial tapering-off or in case of uveitis recurrence (see below), the following concomitant medications were not permitted during the study:

- Oral, systemic, injectable, or topical steroids
- Systemic immunosuppressants

Systemic medications or topical steroids administered as part of gradual dose reduction (tapering) were not considered prohibited medications. Additionally, topical steroids administered as short-term standard treatment following an ocular surgical procedure were not considered prohibited medications. The investigators were advised to discuss treatment with the medical monitor before administering any prohibited medication unless it was an emergency.

2.3.3.3.3 Intraocular Pressure Reduction Therapy

Pharmacologic treatment (eye drops) for elevated IOP was required whenever IOP exceeded 30 mmHg, and could have been instituted at lower IOP levels at the discretion of the investigator and in accordance with local standard practice. Treatment could have included referral to another ophthalmologist. If the patient did not adequately respond to pharmacologic treatment, an alternative treatment could

have been considered (e.g., laser, trabeculectomy). The investigator should have obtained information on the treatment administered by any non-study ophthalmologists for inclusion in the study records.

2.3.3.3.4 Cataract Removal and Other Elective Ocular Surgery

Cataracts were recommended to have been removed by extra-capsular extraction with phacoemulsification. A cataract could have been removed prior to a subject's enrolment. Because of the importance of visual acuity evaluations in this study, the timing of cataract removal or any elective surgery during the post-treatment follow-up period should have been scheduled at least 4 weeks prior to any study visit involving visual acuity assessment.

2.3.3.3.5 Treatment of Recurrences of Uveitis

In the event of a uveitis recurrence in either eye, intra- or peri-ocular corticosteroid injections, or topical medications would have been administered as first-line local therapy in accordance with the protocol. Investigators would have considered treatment with topical steroids as first-line therapy for a recurrence that involved only an increase in anterior chamber cells with no increase in vitreous opacity. Systemic treatment with immunosuppressants or steroids was only to be used if local therapy failed.

Subjects who experienced a recurrence of uveitis were able to continue participation in the study. Once the subject's recurrence was controlled, the treatment regimen (local or systemic therapy) was ended in a manner that followed the standard practice for ending that specific treatment regimen. Details of each recurrence and its treatment were documented in the eCRF.

2.3.4 Study endpoints

2.3.4.1 Primary endpoint

The primary efficacy endpoint was defined as the proportion of subjects who had a recurrence of uveitis in the study eye within 6 months after receiving study treatment defined as:

- A ≥2-step increase in the number of cells in the anterior chamber per high powered field (1.6 × using a 1 mm beam), compared with baseline or any visit time point prior to Month 6

OR

- An increase in the vitreous haze of ≥ 2 steps, compared with baseline or any visit time point prior to Month 6

OR

- A deterioration in visual acuity of at least 15 letters, compared with baseline or any visit time point prior to Month 6

Any criterion used to define recurrence was required to be attributable only to non-infectious uveitis. To prevent post-procedural inflammatory reactions from being reported as uveitis recurrences, assessments for recurrence of uveitis began after Day 7 visit.

Recurrence was also imputed in the following circumstances:

- A subject who had not previously experienced a recurrence and did not complete the required eye examinations at Month 6 for any reason was considered as having a recurrence.

- A subject who had not previously experienced a recurrence and took a prohibited systemic concomitant medication or a prohibited local concomitant medication in the study eye at any time during the study prior to Month 6 was considered as having a recurrence.

Systemic medications or topical steroids administered as part of gradual dose reduction (tapering) were not considered prohibited medications. Topical steroids administered as part of short-term standard treatment following an ocular surgical procedure were also not considered prohibited medications.

2.3.4.2 Secondary and exploratory endpoints

The exploratory efficacy endpoints included:

- [redacted]
- [redacted]
- [redacted]

2.3.5 [redacted]Baseline characteristics of patients included in the PSV-FAI-001 trial

The demographics and baseline disease characteristics of patients enrolled in PSV-FAI-001 are summarised in Table 6. Patients in the ILUVIEN and sham injection arms had comparable median age (48.0 years in both groups) with the majority of patients aged between 40 and 60 years (46% and 52.4% in the ILUVIEN and sham injection arms, respectively). The patients were primarily white (69% and 61.9%, respectively) and female (57.5% and 69%, respectively).

At baseline, approximately half of the patients were receiving systemic treatments to control active/ persistent uveitis, while the other half (49.4% and 50% of patients in the ILUVIEN and sham injection arms, respectively) were not receiving systemic treatment for their uveitis. Mean duration of uveitis was slightly longer in the ILUVIEN arm (7.8 years) compared to patients treated with sham injection (5.6 years). The majority of patients experienced 2 or fewer recurrences of uveitis in the year prior to screening (74.4% and 81% in the ILUVIEN and sham injection arms, respectively). More patients receiving ILUVIEN presented with cataract than patients receiving sham injection (59.5% and 42.9%, respectively). The patients in the two treatment arms had similar mean BCVA (66.9 (SD: 15.49) letters and 64.9 (SD: 15.53) letters in the ILUVIEN and sham injection groups, respectively).The most frequently reported vitreous haze score was 1+ (33.3% and 45.2% in the ILUVIEN and sham

injection groups, respectively) while the most frequently reported anterior chamber cell score was 0 (62.1% and 47.6% in the ILUVIEN and sham injection groups, respectively). The majority of subjects in each treatment arm had a central subfield thickness (CSFT) greater than or equal to 300 microns (55.2% and 64.3% in the ILUVIEN and sham injection treatment groups, respectively). Patients in both treatment arms showed similar mean IOP (13.9 (SD: 3.12) mmHg and 13.6 (SD: 3.15) mmHg in the ILUVIEN and sham injection treatment groups, respectively).

Table 6. PSV-FAI-001 study (ITT population): Baseline demographics and disease characteristics for PSV-FAI-001[35]

PSV-FAI-001	**ILUVIEN** (n=87)	**Sham** (n=42)	**Total** (n=129)
Age (years)			
Mean (SD)	48.3 (13.90)	48.3 (13.71)	48.3 (13.79)
Median (range)	48.0 (20,77)	48.0 (18,73)	48.0 (18,77)
Age categories (years), n (%)			
≤20	1 (1.10)	2 (4.8)	3 (2.3)
20 to<40	24 (27.6)	8 (19.0)	32 (24.8)
40 to<60	40 (46.0)	22 (52.4)	62 (48.1)
≥60	22 (25.3)	10 (23.8)	32 (24.8)
Sex, n (%)			
Male	37 (42.5)	13 (31.0)	50 (38.8)
Female	50 (57.5)	29 (69.0)	79 (61.2)
Race, n (%)			
White	60 (69.0)	26(61.9)	86(66.7)
Black	4 (4.6)	3 (7.1)	7 (5.4)
Asian	21 (24.1)	12 (28.6)	33(25.6)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	2 (2.3)	1 (2.4)	3(2.3)
Ethnicity, n (%)			
Hispanic or Latino	3 (3.4)	3 (7.1)	6(4.7)
Not Hispanic or Latino	84 (96.6)	39 (92.9)	123 (95.3)
Study Eye, n (%)			
Right eye	46 (52.9)	19 (45.2)	65(50.4)
Left eye	41 (47.1)	23 (54.8)	64 (49.6)
Systemic treatment to control uveitis, n (%)			
Not receiving systemic treatment	43 (49.4)	21 (50.0)	64 (49.6)
Receiving systemic treatment			
Corticosteroid therapy	27 (31.0)	13 (31.0)	40 (31.0)

Immunosuppressive therapy	17 (19.5)	8 (19.0)	25 (19.4)
Duration of uveitis (years)[a]			
Mean (SD)	7.8 (6.69)	5.6 (6.82)	7.1 (6.79)
Median (range)	5.9 (1,28)	2.8 (1, 30)	4.0 (1, 30)
Duration of uveitis categories (years), n (%)			
<2	15 (17.2)	14 (33.3)	29 (22.5)
2 to 5	25 (28.7)	16 (38.1)	41 (31.8)
>5	47 (54.0)	12 (28.6)	59 (45.7)
Number of recurrences in the study eye within 12 months prior to screening, n (%)			
≤2	65 (74.7)	34 (81.0)	99 (76.7)
>2	21 (24.1)	8 (19.0)	29 (22.5)
Lens status, n (%)			
Phakic	42 (48.3)	21 (50.0)	63 (48.8)
Cataract present[b]	25 (59.5)	9 (42.9)	34 (54.0)
Aphakic	0	0	0
Pseudophakic	45 (51.7)	21 (50.0)	66 (51.2)
History of vitrectomy, n (%)			
Yes	8 (9.2)	7 (16.7)	15 (11.6)
No	79 (90.8)	35 (83.3)	114 (88.4)
History of incisional surgery to control elevated IOP, n (%)[c]			
History collected[c]	56 (64.4)	24 (57.1)	80 (62.0)
Yes[d]	5 (8.9)	0	5 (6.3)
History not collected	31 (35.6)	18 (42.9)	49 (38.0)
BCVA (letters)			
Mean (SD)	66.9 (15.49)	64.9 (15.53)	66.3 (15.47)
Median (range)	70.0 (19, 89)	65.0 (21, 99)	68.0 (19,99)
Vitreous haze			
Absent (0)	22 (25.3)	8 (19.0)	30 (23.3)
Trace (0.5)	26 (29.9)	13 (31.0)	39 (30.2)
1+	29 (33.3)	19 (45.2)	48 (37.2)
2+	10 (11.5)	2 (4.8)	12 (9.3)
3+	0	0	0
4+	0	0	0
Anterior chamber cells			
0	54 (62.1)	20 (47.6)	74 (57.4)
0.5+	23 (26.4)	13 (31.0)	36 (27.9)
1+	10 (11.5)	8 (19.0)	18 (14.0)
2+	0	1 (2.4)	1 (0.8)
3+	0	0	0
4+	0	0	0
IOP (mmHg)			
Mean (SD)	13.9 (3.12)	13.6 (3.15)	13.8 (3.12)

Median (range)	14.0 (6, 21)	13.0 (8, 20)	14.0 (6, 21)
Severity of oedema, n (%)			
CSFT<300 microns	37 (42.5)	14 (33.3)	51 (39.5)
CSFT >300 microns	48 (55.2)	27 (64.3)	75 (58.1)

BCVA: best-corrected visual acuity; CSFT: central subfield thickness; IOP: intraocular pressure; ITT: intention-to-treat; SD: standard deviation

a For partial uveitis onset dates, a missing month was imputed as January, and a missing day was imputed as the first of the month.
b Only assessed for eyes with a lens status of phakic. Percentages were based on the number of phakic eyes.
c Incisional surgery history was collected following the approval of protocol version 5.0 and was not collected for subjects that enrolled in the study prior to the amendment's approval.
d Percentage is based on the number of subjects with incisional surgery history collected.

2.4 *Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence*

2.4.1 Statistical analysis

2.4.1.1 Primary analysis

The primary efficacy analysis was performed on the ITT population at 6 months and compared the proportion of subjects, in the treatment and control groups, who did not have a recurrence of uveitis in the study eye (as defined in Section 2.3.4.1) in the 6 months following Day 1. The primary efficacy analysis was conducted after all subjects in the study have completed 6 months of treatment or have discontinued study participation.

The number and percentage of subjects with no recurrence of uveitis in the study eye was presented by treatment group. A continuity-corrected Chi-square test was used to assess the statistical significance of a difference between treatment groups in the primary efficacy analysis. Mathematically stated:

H_0: 6 Month Recurrence-Free $Rate_{ILUVIEN}$ = 6 Month Recurrence Free $Rate_{Sham}$

H_1: 6 Month Recurrence-Free $Rate_{ILUVIEN}$ ≠ 6 Month Recurrence Free $Rate_{Sham}$

The odds ratio for no recurrence (ILUVIEN/sham) and 95% confidence interval based on Mantel-Haenszel are also presented.

The US FDA requested the sponsor to conduct the primary efficacy analyses using a definition of recurrence that differed from the protocol-specified definition of

recurrence. Specifically, FDA requested the sponsor to remove the following criterion from the primary endpoint: “a >2-step increase the number of cells in the anterior chamber”. In addition, for the purpose primary endpoint analysis, the FDA did not consider topical steroids to be a prohibited medication which use would prompt a recurrence to be imputed. Since the regulatory authorities in other regions in which the study was being conducted had not requested the changes recommended by the FDA, the sponsor did not revise the primary efficacy endpoint in protocol for PSV-FAI-001 and instead prepared two statistical analysis plans: one for US regulatory submissions and one for submissions in the rest of the world. The two analyses were independently evaluated, so that no adjustment of type I error was performed. The analyses presented in this submission are based on the protocol-specified (rather than FDA-requested) definition of recurrence.

The same inferential analysis employing the same methods as for the primary analysis was performed for the per-protocol (PP) population to assess recurrence at Month 6. Additionally, the same analysis was performed for both the intention-to-treat (ITT) and PP populations to assess recurrence in the exploratory analyses conducted at Months 12 and Month 36. No adjustment of type I error was performed as these analyses were considered supportive to the primary analysis.

2.4.1.2 Sample size and power calculation

A 2-group continuity-corrected Chi-square test with a 0.05 two-sided significance level had 89% power to detect the difference between a sham-treated group recurrence-free rate of 0.600 and an FA-treated group recurrence-free rate of 0.880 (odds ratio of 0.205) when the sample sizes were 40 and 80, respectively (a total sample size of 120).

2.4.1.3 Interim, subgroup and sensitivity analyses

2.4.1.3.1 Interim analyses

No interim analysis was planned for this study. Primary efficacy analysis, and all other efficacy and safety analyses, were conducted after the 6-month database lock, i.e. after all subjects have completed the Month 6 visit or have been discontinued from the study prior to this visit. Similarly, the 12- and 36-month analyses were

completed only after all patients completed the relevant follow-up or discontinued the study.

2.4.1.3.2 Sensitivity analyses

For the primary endpoint, data on recurrence of uveitis was imputed in a conservative manner, as follows:

- A subject who had not previously experienced a recurrence and did not have the required eye examination data for assessing recurrence at Month 6 (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) for any reason was considered as having a recurrence.

- A subject who had not previously experienced a recurrence and takes a prohibited concomitant medication (systemic or local in the study eye) at any time during the study prior to Month 6 (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) was considered as having a recurrence. See Section 2.3.3.3.2 for details of these treatments.

Two sensitivity analyses were performed around the aforementioned data imputation:

1. Rather than being considered as having a recurrence, a subject who had not previously experienced a recurrence and did not have the required eye examination data was considered as NOT having a recurrence.

2. A tipping point analysis was performed, whereby ILUVIEN-treated subjects with missing data were considered as having a recurrence, while sham-treated subjects with missing data were considered as NOT having a recurrence.

Additionally, for missing data due to any reason, sensitivity analyses were conducted using multiple imputation methods.

The primary efficacy endpoint was also analysed with logistic regression with recurrence as the dependent term and treatment as the independent term and including systemic treatment at study entry (stratification factor) as a covariate.

2.4.1.3.3 Subgroup analyses

Subgroup analyses, using descriptive statistics only, were performed on the primary efficacy endpoint for the ITT population at Month 6. Analyses were performed to determine the treatment effect within specific subgroups of interest, and to determine if the treatment effect is consistent across different subgroup levels. Subgroups were defined on the basis of study eye baseline characteristics, including:

- Severity of macular oedema (CSFT < 300 microns, CSFT >= 300 microns)
- Duration of disease (< 2 years, 2 to 5 years, > 5 years)
- Lens status (Phakic, Aphakic, Pseudophakic)
- Intraocular pressure (10 to 15 mmHg, >15 to 21 mmHg)
- History of incisional surgery to control elevated IOP (History, No History)
- Presence/absence of vitrectomy
- BCVA (≤49 letters, >49 letters)
- Randomization strata (Not receiving systemic treatment, Receiving systemic treatment – corticosteroid therapy, Receiving systemic treatment – immunosuppressive therapy)

Subgroup analyses were also performed based on region (US, EMEA, India). Additionally, subgroups were defined based on IOP lowering medication or surgery received in the study eye, as follows:

- Use of IOP lowering medication (No IOP lowering medication, Required IOP lowering medication)
- Surgical Intervention to Control Elevated IOP (No surgical intervention, Required surgical intervention)

IOP lowering medication status was based on a subject's use of any IOP lowering medication in the study eye up to the time point of interest (Month 6, 12 or 36). Surgical intervention status was defined in a similar manner.

2.4.2 Study populations

The ITT and Safety populations included all randomised subjects, who were analysed according to the treatment they were randomised to receive (ITT) or treatment actually received (Safety). In this specific study, all subjects included in the safety population were also included in the ITT population, i.e. the two populations were the same.

Analysis on the PP population was supplementary to the ITT analysis and was performed for all efficacy endpoints. The PP population was defined separately for Month 6, Month 12 and Month 36 analyses and excluded all subjects in the ITT population who:

- Received systemic treatment for recurrence of uveitis in the fellow eye
- Experienced an imputed endpoint at 6 months (or 12 or 36 months)
- Failed screening, without exemption, but received ILUVIEN
- Had a major protocol deviation

Analysis population are summarised in Table 7.

Table 7. Analysis populations in the PSV-FAI-001 trial[35]

Analysis Population	ILUVIEN (n=87), n (%)	Sham (n=42), n (%)	Total (n=129), n (%)
Safety	[redacted]	[redacted]	[redacted]
ITT	[redacted]	[redacted]	[redacted]
PP at Month 6	[redacted]	[redacted]	[redacted]
PP at Month 12	52 (59.8)	13 (31.0)	65 (50.4)
PP at Month 36	[redacted]	[redacted]	[redacted]

ITT: intention-to-treat; PP: per-protocol

2.4.3 Summary of statistical methodology of PSV-FAI-001

A summary of the methodology for statistical analysis applied in the PSV-FAI-011 trial is presented in Table 8.

Table 8. Statistical analysis and definition of study groups in PSV-FAI-001[35]

Study	PSV-FAI-001
Hypothesis objective	To test the hypothesis that ILUVIEN delivering micro-doses of FAc for 36 months can reduce recurrence of [redacted]
Statistical analysis	Continuous data were described using descriptive statistics (i.e., n, mean, standard deviation, median, minimum, and maximum). Categorical data were described using the subject count and percentage in each category A continuity-corrected Chi-square analysis was used to assess the statistical significance of a difference between study groups in the primary efficacy analysis. Descriptive statistics were provided for all TEAEs. All analyses were conducted using SAS Version 9.2 or higher.
Sample size, power	A 2-group continuity-corrected Chi-square test with a 0.05 two-sided significance level had an 89% power to detect the difference between a sham group recurrence-free rate of 0.600 and an ILUVIEN-treated group recurrence-free rate of 0.880 (odds ratio of 0.205) at sample sizes of 40 and 80, respectively (a total sample size of 120).
Study groups	ITT: All patients randomly assigned to the study treatment. The ITT population was used for all efficacy analyses. PP: Patients within the ITT population remaining after excluding patients who met the following criteria: • received systemic treatment for recurrence of uveitis in the fellow eye • received an imputed endpoint at Months 6, 12 or 36 endpoint of the study • failed screening, without exemption, but received ILUVIEN had a major protocol deviation. The PP population was defined separately for the Months 6, 12 and 36 analyses. Safety: All randomly assigned patients into the study.
Data management, patient withdrawals	Data management The following steps were taken to ensure the accuracy, consistency, completeness and reliability of the data: • routine study centre monitoring • eCRF review against source documents • data management quality control checks

	• medical review by the manufacturer • quality assurance audit Patient withdrawals Patients had the right to withdraw from the study at any time and examples of criteria considered for study withdrawal include: • withdrawal of patient consent • intercurrent illness including death that prevented continuation of regular follow-up visits. Patients who withdrew for any reason from the study following randomisation and administration of treatment were not replaced. All patients randomly assigned to treatment were followed for as long as they agreed to return for visits.

eCRF: electronic case report form; FA: fluocinolone acetonide; FAc: fluocinolone acetonide; ITT: intention-to-treat; PP: per-protocol; [redacted]; TEAE: treatment-emergent adverse event

2.5 *Quality assessment of the relevant clinical effectiveness evidence*

Quality assessment of PSV-FAI-001 was conducted using the checklist developed by Downs and Black (1998)[37]; the results of which are provided in Table 9.

Table 9. Quality assessment of the PSV-FAI-001 trial

Study name	PSV-FAI-001
Reporting	
Is the hypothesis/aim/objective of the study clearly described?	Yes
Are the main outcomes to be measured clearly described in the Introduction or Methods section?	Yes
Are the characteristics of the patients included in the study clearly described?	Yes
Are the interventions of interest clearly described?	Yes
Are the distributions of principal confounders in each group of Patients to be compared clearly described?	Unable to determine
Are the main findings of the study clearly described?	Yes
Does the study provide estimates of the random variability in the data for the main outcomes?	Yes
Have all important adverse events that may be a consequence of the intervention been reported?	Yes
Have the characteristics of patients lost to follow-up been described?	No
Have actual probability values been report- e.g. (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	Yes

External validity	
Were the Patients asked to participate in the study representative of the entire population from which they were recruited?	Yes
Were those Patients who were prepared to participate representative of the entire population from which they were recruited?	Yes
Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	Yes
Internal validity - bias	
Was an attempt made to blind study Patients to the intervention they have received?	Yes
Was an attempt made to blind those measuring the main outcomes of the intervention?	Yes
If any of the results of the study were based on “data dredging”, was this made clear?	Yes
In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Yes
Were the statistical tests used to assess the main outcomes appropriate?	Yes
Was compliance with the intervention/s reliable?	Yes
Were the main outcome measures used accurate (valid and reliable)?	Yes
Internal validity - confounding (selection bias)	
Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	Yes
Were study Patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	Yes
Were study Patients randomised to intervention groups?	Yes
Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?	Yes
Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Yes
Were losses of patients to follow-up taken into account?	Yes
Power	
Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Yes

2.6 *Clinical effectiveness results of the relevant trials*

Twelve-month results of the PSV-FAI-001 have only recently been published[33] and two-year results presented at the American Association of Ophthalmology Annual Meeting[34]; 36-month results are provided as academic in confidence. All data presented in sections 2.6, 2.7 and 2.8 is based solely on Month 6[38], Month 12[39] and Month 36[35] Clinical Study Reports for the PSV-FAI-001 trial.

2.6.1 Recurrence of uveitis

2.6.1.1 Recurrence rate in the study eye

Recurrence of uveitis in the study eye, assessed in the intention-to-treat (ITT) population at 6 months following ILUVIEN or sham injection was the primary endpoint of the PSV-FAI-001 study, while recurrence of uveitis in the study eye at 12 and 36 months were exploratory endpoints. At 6 months, the proportion of patients who had uveitis recurrence was significantly [redacted] in the ILUVIEN arm than the sham arm [redacted] By 12 months, more patients in both trial arms experienced a recurrence; however, at this was still significantly lower in the ILUVIEN arm, where 37.9% of patients had a recurrence, than the sham arm where nearly all patients (97.6%) were affected (p<0.001). The number of patients with uveitis recurrence [redacted] by 36 months in [redacted] in the ILUVIEN than the sham arm [redacted] The numbers of patients experiencing uveitis recurrence at 6, 12 and 36 months are presented in Table 10.

Table 10. PSV-FAI-001 study (ITT population): Patients experiencing recurrence of uveitis in the study eye up to 36 months

Time point	ILUVIEN arm (n=87), n (%)	Sham arm (n=42), n (%)	Odds ratio (95% CI)	P value (continuity corrected Chi-square test)
Recurrence at 6 months	[redacted]	[redacted]	[redacted]	[redacted]
Observed	[redacted]	[redacted]	[redacted]	[redacted]
Imputed	[redacted]	[redacted]	[redacted]	[redacted]
12 months	33 (37.9)	41 (28.6)	67.09 (8.81, 511.05)	<0.001
Observed	3 (3.4)	12 (28.6)	–	–
Imputed	30 (34.5)	29 (69.0)	–	–
36 months	[redacted]	[redacted]	[redacted]	[redacted]

Observed		[redacted]			[redacted]			[redacted]			[redacted]	
Imputed		[redacted]			[redacted]			[redacted]			[redacted]	

CI: confidence interval; ITT: intention-to-treat

Since recurrence of uveitis could be observed on ophthalmological examination or inputted in case of the patient not completing the required examination or receiving prohibited medication, Table 10 provides a breakdown of recurrence by type. The [redacted] of imputed recurrences were due to the [redacted] None of the imputed recurrences in the sham arm were due to [redacted] In the ILUVIEN arm, there were [redacted] imputed recurrences due to missing data at 6 months, 1 (1.1%) at 12 months and [redacted] at 36 months. It is worth noting that when only observed (i.e. protocol-defined) recurrences are considered, the proportion of patients with recurrence is clearly [redacted] in the sham than the ILUVIEN arm, although statistical analysis was not performed.

In the per-protocol population, which at 6 months included a total of [redacted] in the ILUVIEN arm and [redacted] in the sham arm), uveitis recurrence in the study eye within 6 months was significantly [redacted] in the ILUVIEN arm [redacted] than in the sham arm [redacted] A similar result was observed at 12 months, by which time 3 of 53 patients (5.7%) in the ILUVIEN arm and 12 of 13 patients (92.3%) in the sham arm had experienced a recurrence of uveitis (OR: 200.0 [95% CI: 19.09, 2095.51], p<0.001). By 36 months, [redacted] in the ILUVIEN arm and [redacted] in the sham arm remained in the per-protocol population. The rate of recurrence was again significantly [redacted] in the ILUVIEN arm [redacted] than the sham arm [redacted]

2.6.1.2 Recurrence rate in the fellow eye

In theory, the natural history of patients' uveitis, as well as the treatment itself could affect recurrence rate and, indeed, [redacted] patient remained free of recurrence in the study eye at 36 months. However, the design of the PSV-FAI-001 study, where only one eye per patient was randomised to receive ILUVIEN, mean that the fellow eye (i.e. the eye untreated with ILUVIEN or sham) could serve as an intrinsic control. Including only patients whose fellow eyes were affected by uveitis at

baseline, in the ITT population slightly [redacted] in the ILUVIEN arm [redacted] than the sham arm [redacted] experienced recurrence of uveitis in the fellow eye throughout the study duration: [redacted] at 6 months, 86.4% vs 74.2% at 12 months [redacted] at 36 months. This could be explained by the [redacted] in the ILUVIEN arm than the sham arm [redacted] as these would affect both the study and the fellow eye.

2.6.1.3 Number of recurrences per study eye

In the ITT population, the mean number of uveitis recurrences per study eye was consistently [redacted] 2.5 at 12 months [redacted] At 36 months, [redacted] remained recurrence-free. Importantly, among those patients who did have a recurrence, a single recurrence was most frequent in the [redacted] during the course of the study (Table 11).

Table 11. PSV-FAI-001 study (ITT population): Number uveitis recurrences in the study eye up to 36 months

	ILUVIEN arm (n=87)	Sham arm (n=42)
Number of recurrences per subject at 6 months		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Number of recurrences per subject at 12 months		
Mean (SD),	0.7 (1.22)	2.5 (1.67)
Median (min, max)	0.0 (0,7)	2.0 (0,8)
Number of recurrences per subject at 36 months		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Number of recurrences per subject at 36 months, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
>5	[redacted]	[redacted]

ITT: intention-to-treat; max: maximum; min: minimum; SD: standard deviation

2.6.1.4 Time to first uveitis recurrence in the study eye

At 36 months, that is over the entire study duration, the median time to first recurrence of uveitis in the ITT population was [redacted] in the ILUVIEN group compared with [redacted] in the sham group. The Kaplan-Meier plot of time to first uveitis recurrence in the study eye, calculated as the number of days between the date of injection (Day 1) and the visit date of the first reported recurrence of uveitis in the study eye or the Month 36 visit date for subjects who did not experience a recurrence, is shown in Figure 5. Note that the graph extends beyond 36 months (1085 days), and recurrences of uveitis can be observed in the ILUVIEN arm beyond 1140 days as FAc in the ILUVIEN implant runs out.

Figure 5. PSV-FAI-001 study (ITT population): Time to first Recurrence of uveitis in the study eye (up to 36 months and beyond)

[redacted]FAI: fluocinolone acetonide intravitreal; ITT: intention-to-treat

2.6.2 Supplemental systemic, topical and intra-ocular treatments for managing uveitis recurrence

Throughout the 36-month study duration, the proportion of patients receiving at least one systemic steroid or immunosuppressant treatment was lower in the [redacted] Similarly, the proportion of patients requiring study eye treatment with intra- or per-ocular steroids [redacted] and topical steroids [redacted] was [redacted] in the ILUVIEN arm compared to the sham arm.

[redacted] A summary of supplemental treatments administered for inflammation control over the 36-month follow-up is presented in

Table 12.

Table 12. PSV-FAI-001 study (ITT population): Number of supplemental treatments within 36 months by type of treatment

Outcome	Study eye	
	ILUVIEN arm	Sham arm (n=42)

	(n=87)	
Systemic steroid or immunosuppressant		
Total no. of supplemental treatments		
No. of patients with ≥1 supplemental treatment		
No. of supplemental treatments per patient		
0, n (%)		
1, n (%)		
2, n (%)		
3, n (%)		
4, n (%)		
5, n (%)		
>5, n (%)		
Intra/peri-ocular steroid (study eye)		
Total no. of supplemental treatments		
No. of patients with ≥1 supplemental treatment		
No. of supplemental treatments per patient		
0, n (%)		
1, n (%)		
2, n (%)		
3, n (%)		
4, n (%)		
5, n (%)		
>5, n (%)		
Topical steroid (study eye)		
Total no. of supplemental treatments		
No. of patients with ≥1 supplemental treatment		
No. of supplemental treatments per patient		
0, n (%)		
1, n (%)		
2, n (%)		
3, n (%)		
4, n (%)		
5, n (%)		
>5, n (%)		

CI: confidence interval; ITT: intention-to-treat

2.6.3 Visual acuity

Mean BCVA (expressed as ETDRS letters) in the study eye at baseline and at 6, 12 and 36 months is shown in Table 13 and presented visually in Figure 6 (mean BCVA) and Figure 7 (change from baseline BCVA). While mean BCVA could be considered comparable between the ILUVIEN and sham injection arms at baseline (66.9 and 64.9 letters, respectively), there was a rapid and sustained improvement in BCVA in the and the change in BCVA from baseline to Month 36 was in the ILUVIEN arm compared with the sham injection arm Furthermore, by Month 36 substantially patients in the ILUVIEN arm experienced an ≥15-letter gain in BCVA compared with the

sham arm [redacted] conversely, the number of patients with an ≥15-letter loss in BCVA was substantially [redacted] with ILUVIEN than with sham [redacted]

Table 13. PSV-FAI-001 study (ITT population): BCVA (ETDRS letters) in the study eye at baseline and Months 6, 12 and 36

Visit	ILUVIEN arm (n=87)	Sham injection arm (n=42)
	Value	Value
Baseline^		
n	87	42
Mean (SD)	66.9 (15.49)	64.9 (15.53)
Median (range)	70.0 (19,89)	65.0 (21,99)
Month 6		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Month 12		
n	85	39
Mean (SD)	72.8 (13.25)	69.2 (18.35)
Median (range)	76.0 (33,90)	73.0 (0,97)
Month 36		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

BCVA: best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; ITT: intention-to-treat; SD: standard deviation

Figure 6. PSV-FAI-001 study (ITT population): Mean BCVA in the study eye up to 36 months

[redacted]

BCVA: best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; ITT: intention-to-treat
Error bars represent standard deviation.

Figure 7. PSV-FAI-001 study (ITT population): Mean BCVA change from baseline in the study eye up to 36 months

[redacted]

BCVA: best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; ITT: intention-to-treat
Error bars represent standard deviation.

2.6.4 Macular oedema

In the ITT population, [redacted] in the ILUVIEN arm and [redacted] in the sham arm had macular oedema in the study eye at baseline; [redacted] in the ILUVIEN arm was not evaluable. By the end of the 36-month study period, resolution of macular oedema in the study eye was observed in [redacted] in the ILUVIEN arm and [redacted] in the sham arm. [redacted] in the ILUVIEN

arm and [redacted] in the sham arm did not have macular oedema at baseline but developed it by Month 36. In terms of the degree of macular thickening, at baseline, mean central foveal thickness (CFT) in the safety population was [redacted]). A [redacted] in CFT was observed in the ILUVIEN arm [redacted] and this was sustained throughout the 36-month study period. In the [redacted] the reduction in macular thickness was slower. Mean change in CFT from baseline at Months 6,12 and 36 is illustrated in Figure 8.

Figure 8. PSV-FAI-001 study (Safety population): Mean change in CFT from baseline in the study eye up to 36 months

[redacted]

CFT: central foveal thickness; ITT: intention-to-treat
Error bars represent standard deviation.

2.6.5 Vitreous haze and anterior chamber cell count

Vitreous haze and the presence of anterior chamber cells are established markers of inflammation in uveitis. *Table 14 presents the number of patients in the safety population with absent, trace or 1+ vitreous haze and anterior chamber cell count grades in the study eye. Patients in the ILUVIEN arm attained [redacted] over 36 months; in the sham arm, [redacted] Table 14. PSV-FAI-001 study (Safety population): Vitreous haze and anterior chamber cell count in the study eye at baseline and Months 6, 12 and 36

Arm	ILUVIEN arm, n (%)			Sham arm (n=42), n (%)		
Grade	**Absent**	**Trace**	**Grade ≥1+**	**Absent**	**Trace**	**Grade ≥1+**
Anterior chamber cells						
Baseline (n= 86 for ILUVIEN and n= 42 for sham)	53 (61.6)	23 (26.7)	10 (11.6)	20 (47.6)	13 (31.0)	9 (21.4)
Month 6 (n= 87 for ILUVIEN and n= 42 for sham)	[redacted]					
Month 12 (n= 85 for ILUVIEN and n= 39 for sham)	73 (85.9)	10 (11.8)	2 (2.4)	28 (71.8)	5 (12.8)	6 (15.4)
Month 36 (n= 72 for ILUVIEN and n= 34 for sham)	[redacted]					
Vitreous haze						
Baseline (n= 87 for ILUVIEN and n= 42 for sham)	22 (25.3)	26 (29.9)	39 (44.8)	8 (19.0)	13 (31.0)	21 (50.0%)
Month 6 (n= 87 for ILUVIEN and n= 42 for sham)	[redacted]					
Month 12 (n= 85 for ILUVIEN and n= 39 for sham)	70 (82.4)	12 (14.1)	3 (3.5)	27 (69.2)	6 (15.4)	6 (15.4)

Month 36 (n= 72 for ILUVIEN and n= 34 for sham)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

ITT: intention-to-treat

2.7 *Subgroup analysis*

Subgroup analyses, using descriptive statistics only, were performed on the primary efficacy endpoint, that is recurrence of uveitis at 6 months for the ITT population. Subgroups were defined based on the baseline characteristics of the study eye, randomisation strata, region and use of IOP-lowering medication or surgery to control IOP in the study eye by 6 months on study and are listed below.

- Baseline characteristics of the study eye
    - Severity of macular oedema (CSFT < 300 microns, CSFT ≥ 300 microns)
    - Duration of disease (< 2 years, 2 to 5 years, > 5 years)
    - Lens status (phakic, aphakic, pseudophakic)
    - IOP (10–15 mmHg, >15–21 mmHg)
    - History of incisional surgery to control elevated IOP (history, no history)
    - Presence/absence of vitrectomy
    - BCVA (≤ 49 letters, > 49 letters)
- Randomisation strata (not receiving systemic treatment, receiving systemic corticosteroid therapy, receiving systemic immunosuppressive therapy)
- Region (United States, Europe, the Middle East and Africa (EMEA), and India)
- Use of IOP-lowering medication (no IOP lowering medication, required IOP lowering medication)
- Surgical intervention to control elevated IOP (no surgical intervention, required surgical intervention)

The recurrence of uveitis in the study eye was [redacted] in the ILUVIEN arm than the sham arm [redacted] according to baseline characteristics of the study eye, or the use of IOP lowering medication or surgery. The rates of uveitis recurrence in the study eye within 6 months for

subgroups based on region and randomisation strata is presented in Table 15, while results in the remaining subgroups are shown in Appendix E.

Table 15. PSV-FAI-001 study (ITT population): Proportion of subjects with recurrence of uveitis in the study eye at 6 months by region and randomisation strata[38]

Subgroup	ILUVIEN arm	Sham arm
US	[redacted]	[redacted]
EMEA	[redacted]	[redacted]
India	[redacted]	[redacted]
Not receiving systemic treatment	[redacted]	[redacted]
Receiving systemic corticosteroid therapy	[redacted]	[redacted]
Receiving systemic immunosuppressive therapy	[redacted]	[redacted]

EMEA: Europe, the Middle East, and Africa; ITT, intention-to-treat, US: United States
Data are presented as the number patients with recurrence within 6 months / the number of all patients in the subgroup (%)

2.8 *Adverse reactions*

2.8.1 Treatment-Emergent Adverse Events

2.8.1.1 Ocular Treatment-Emergent Adverse Events

General ocular and non-ocular TEAEs are described below. TEAEs of special interest, i.e. IOP increases and cataract development, are described in more detail in Sections 2.8.3 and 2.8.4, respectively.

2.8.1.1.1 Study Eye

Of 129 enrolled patients, [redacted] experienced at least one ocular treatment-emergent adverse event (TEAE) in the study eye during the 36-month study period. The proportion of patients in the ILUVIEN treatment group [redacted] who experienced any ocular TEAE [redacted] compared to patients in the sham injection group [redacted]

Of all 129 patients, [redacted] experienced a serious ocular TEAE in the study eye, although patients in the ILUVIEN group were [redacted] Considering relationship with study treatment, [redacted] of patients experienced a treatment-related ocular TEAE in the study eye [redacted] in the ILUVIEN arm [redacted] being affected compared to the sham arm [redacted] Similarly, serious treatment-related ocular TEAEs in the study eye were [redacted] in the ILUVIEN arm, with

[redacted] of patients affected in the ILUVIEN and sham arms, respectively [redacted] A summary of TEAEs affecting the study eye is shown in Table 16.

[redacted] patients in this study experienced ocular TEAEs in the study eye leading to treatment discontinuation or study discontinuation, [redacted] of the patients die due to an ocular AE through Month 36 [redacted]).

Table 16. PSV-FAI-001 study (Safety population): Overall Summary of Ocular Treatment-Emergent Adverse Events for the Study Eye Through Month 36 Visit

Number of patients with:	ILUVIEN (N=87), n (%)	Sham (N=42), n (%)	Total (N=129), n (%)
Any TEAE	[redacted]	[redacted]	[redacted]
Any serious TEAE	[redacted]	[redacted]	[redacted]
Any study treatment- related TEAE	[redacted]	[redacted]	[redacted]
Any study treatment- related serious TEAE	[redacted]	[redacted]	[redacted]
Any TEAE leading to treatment discontinuation	[redacted]	[redacted]	[redacted]
Any TEAE leading to study discontinuation	[redacted]	[redacted]	[redacted]
Any AE leading to death	[redacted]	[redacted]	[redacted]

AE: adverse event; TEAE: treatment-emergent adverse event.

Overall, the most frequently reported ocular TEAEs affecting the study eye in both treatment groups were [redacted] in the ILUVIEN and sham injection treatment groups, respectively) and [redacted] in the ILUVIEN group experienced treatment-related eye disorders than in the sham group [redacted] as well as [redacted]

The most frequently reported ocular TEAEs in the study eye were [redacted] in the ILUVIEN group and [redacted] in the sham group. The most frequently reported treatment-related ocular TEAEs in the study eye were also [redacted] in the ILUVIEN group and [redacted] in the sham group.

[redacted] of study eye ocular TEAEs and treatment-related ocular TEAEs were mild or moderate in both treatment groups. [redacted] in the ILUVIEN

group than the sham group experienced severe ocular TEAEs affecting the study eye [redacted] However, when relationship to study treatment was considered, treatment-related serious TEAEs were reported [redacted] in the ILUVIEN group [redacted] than the sham group [redacted] A detailed summary table of ocular TEAEs and treatment-related ocular TEAEs in the study eye is presented in Appendix F.

2.8.1.1.2 Fellow eye

Ocular TEAEs [redacted] and serious ocular TEAEs [redacted] affecting the fellow eye were [redacted] in the ILUVIEN group than the sham group during the 36-month study period. Considering relationship with study treatment, treatment-related ocular TEAEs in the fellow eye were experienced by a [redacted] of patient in the ILUVIEN treatment group [redacted] and the sham injection treatment group [redacted] serious treatment-related TEAEs occurred in [redacted] A summary of TEAEs affecting the fellow eye is shown in Table 17 with more details provided in Appendix F.

Note that all events associated with the fellow eye were reported, irrespective of history of uveitis in the fellow eye. [redacted] fatal ocular AEs, serious study treatment-related TEAEs, TEAEs leading to treatment discontinuation, or TEAEs leading to study discontinuation were reported in the fellow eye.

Table 17. PSV-FAI-001 study (Safety population): Overall Summary of Ocular Treatment-Emergent Adverse Events for the Fellow Eye Through Month 36 Visit

Number of patients with:	ILUVIEN (N=87) n (%)	Sham (N=42) n (%)	Total (N=129) n (%)
Any TEAE	[redacted]	[redacted]	[redacted]
Any serious TEAE	[redacted]	[redacted]	[redacted]
Any study treatment- related TEAE	[redacted]	[redacted]	[redacted]
Any study treatment- related serious TEAE	[redacted]	[redacted]	[redacted]
Any TEAE leading to treatment discontinuation	[redacted]	[redacted]	[redacted]
Any TEAE leading to study discontinuation	[redacted]	[redacted]	[redacted]
Any AE leading to death	[redacted]	[redacted]	[redacted]

AE: adverse event; TEAE: treatment-emergent adverse event.

2.8.2 Non-ocular Treatment-Emergent Adverse Events

Of the total safety population, [redacted] patients experienced at least one non-ocular TEAE, with [redacted] in the ILUVIEN and sham arms affected [redacted] of patients experienced a serious TEAE, [redacted] Treatment-related non-ocular TEAEs were experienced by [redacted] patients in the ILUVIEN treatment group and [redacted] in the sham injection treatment group. [redacted] in this study experienced a serious treatment-related TEAE or a non-ocular TEAE leading to treatment discontinuation or study discontinuation. [redacted] died during the study due to a non-ocular AE that was deemed unrelated to study treatment by the investigator. Non-ocular TEAEs are summarised in Table 18.

Table 18. PSV-FAI-001 study (Safety population): Overall Summary of Non-Ocular Treatment-Emergent Adverse Events Through Month 36 Visit

Number of patients with	ILUVIEN (N=87) n (%)	Sham (N=42) n (%)	Total (N=129) n (%)
Any TEAE	[redacted]	[redacted]	[redacted]
Any serious TEAE	[redacted]	[redacted]	[redacted]
Any study treatment- related TEAE	[redacted]	[redacted]	[redacted]
Any study treatment- related serious TEAE	[redacted]	[redacted]	[redacted]
Any TEAE leading to treatment discontinuation	[redacted]	[redacted]	[redacted]
Any TEAE leading to study discontinuation	[redacted]	[redacted]	[redacted]
Any AE leading to death	[redacted]	[redacted]	[redacted]

AE: adverse event; TEAE: treatment-emergent adverse event.

Overall, the most frequently reported non-ocular TEAE was [redacted] in the ILUVIEN and sham injection treatment groups, respectively) [redacted] was considered treatment-related. [redacted] of non-ocular TEAEs and treatment-related non-ocular TEAEs were mild or moderate; details are provided in Appendix F.

2.8.3 Intraocular pressure

The proportion of patients who experienced increased IOP in the study eye was [redacted] in the ILUVIEN and sham groups [redacted] However,

[redacted]in the ILUVIEN group experienced treatment-related increased IOP in the study eye compared with the sham group [redacted]In both treatment groups, [redacted]of non-treatment-related and treatment-related increases in IOP were mild or moderate, [redacted]of severely increased IOP in [redacted](Table 19).

Table 19. PSV-FAI-001 (Safety population): Increase in IOP in the study eye over 36 months of follow-up

	Treatment-emergent IOP increased			Treatment-related treatment-emergent IOP increased		
	ILUVIEN (N=87) n (%)	Sham (N=42) n (%)	Total (N=129) n (%)	ILUVIEN (N=87) n (%)	Sham (N=42) n (%)	Total (N=129) n (%)
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

IOP: intraocular pressure

Over the 36-month follow-up period, [redacted]of patients in the ILUVIEN than sham arm required at least one IOP-lowering medication in the study eye [redacted]subjects in the ILUVIEN arm required 3 or more IOP-lowering medications compared to the sham arm [redacted]In terms of surgical interventions to control IOP in the study eye, [redacted]in the ILUVIEN arm required at least one surgical intervention; all of this involved incisional surgery. In the sham group, [redacted]patients required at least one surgical intervention to control IOP. [redacted]and the nature of the interventions was as follows [redacted]

2.8.4 Cataract

The proportion of patients who developed a cataract in the study eye was [redacted] in the ILUVIEN arm than the sham arm ([redacted] Cataracts considered related to study treatment were [redacted]in the ILUVIEN arm than the sham arm [redacted]of non-treatment-related and treatment-related cataracts were mild or moderate in both treatment groups.

[redacted] of patients in the ILUVIEN and sham treatment groups [redacted] developed a cataract in the study eye that was reported as a severe TEAE. [redacted] cases of severe treatment-related cataract in the study eye were reported in the sham group, while [redacted] in the ILUVIEN group [redacted] developed a treatment-related severe cataract. A summary of cataract events in the study eye is provided in Table 20.

Table 20. PSV-FAI-001 (Safety population): Cataract in the study eye over 36 months of follow-up

	Treatment-emergent cataract			Treatment-related treatment-emergent cataract		
	ILUVIEN (N=87) n (%)	Sham (N=42) n (%)	Total (N=129) n (%)	ILUVIEN (N=87) n (%)	Sham (N=42) n (%)	Total (N=129) n (%)
Cataract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cataract subcapsular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mild	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Moderate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

2.9 *Ongoing studies*

PSV-FAI-005 is an ongoing phase 3, multicentre, randomised, masked (outcomes assessors), controlled study to evaluate the safety and efficacy of either ILUVIEN or sham injection in patients with chronic [redacted]

The ILUVIEN contains 0.19 mg FAc and releases FAc at a nominal rate of approximately 0.2µg/day over the course of 36 months. ILUVIEN was administered post-screening on Day 1 to the study eye by injection through the pars plana using a preloaded applicator with a 27-gauge needle.

The sham applicator contained a blunt-end 14-gauge needle and was empty; it was used to press against the eye without penetrating any ocular tissue.

The primary efficacy and safety analyses at Months 6 and 12 are available and additional efficacy and safety analyses will be conducted at Month 36 (April 2020).

The primary efficacy endpoint was defined as the proportion of subjects who had a recurrence of uveitis in the study eye within 6 months after receiving study treatment. The updated analysis of uveitis recurrence at 12 months is presented in Table 21 (proportion of patients experiencing a recurrence in the study eye) and Table 22 (the number of uveitis recurrences in the study and fellow eye).

Table 21. PSV-FAI-005 (ITT and PP populations): Proportion of patients with recurrence of uveitis in the study eye within 12 months

	Study Eye		Fellow Eye	
Outcome, n (%)	**ILUVIEN**	**Sham injection**	**ILUVIEN**	**Sham injection**
ITT (n)	**101**	**52**	**66**	**31**
Recurrence within 12 months, n (%)				
Protocol-defined recurrence				
Imputed recurrence				
Missing data				
Prohibited medication or rescue medication				
Systemic steroid or immunosuppressant				
Intra/peri-ocular steroid				
Topical steroid				
No recurrence within 12 months, n (%)				
Difference from sham injection[a]				
Odds ratio				
95% confidence interval				
P value				
PP (n)				
Recurrence within 12 months, n (%)				
Protocol-defined recurrence				
Imputed recurrence				
No recurrence within 12 months, n (%)				
Difference from sham injection[a]				
Odds ratio				
95% confidence interval				
P value				

ITT: intention-to-treat

Table 22. PSV-FAI-005 (ITT population): Number of recurrences of uveitis in the study and fellow eyes through Month 12

Outcome	**Study eye**		**Fellow eye**	
	ILUVIEN	**Sham injection**	**ILUVIEN**	**Sham injection**
ITT (N)				
Total number of recurrences				

Number of patients with at least 1 recurrence in 12 months	[redacted]	[redacted]	[redacted]	[redacted]
Number of recurrences per patient				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Number of recurrences per patient, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
>5	[redacted]	[redacted]	[redacted]	[redacted]

ITT, intention-to-treat; SD, standard deviation.

2.10 *Innovation*

ILUVIEN is an innovative implant, providing a sustained and continuous release of FAc for up to three years with a single intravitreal injection. It is the only long-lasting (up to 36 months) ocular implant that has been designed to deliver a sustained, continuous low dose (0.2 µg/day) of FAc to the posterior segment of the eye. This means, ILUVIEN requires fewer injections compared to alternative treatments, which brings significant benefits to patients with [redacted], including a reduced risk of injection-associated AEs, lower treatment burden due to fewer injections and visits, less anxiety associated with intravitreal injections, improved treatment adherence and decreased fluctuation in disease control at an individual patient level compared to shorter-acting treatment options.

[redacted] As described in Section 2.6, ILUVIEN showed significant clinical effectiveness by lower numbers of recurrences of uveitis in the ILUVIEN treatment group compared to the sham injection treatment group; an effect that continued through to month 36. The safety profile of ILUVIEN showed no new or unexpected safety risks.

In summary, the key benefits of ILUVIEN, which may not be fully captured in the economic model by the utility and QALY assessment, and include the following:

- A single injection lasting for up to 36 months, therefore reducing the risks associated with frequent intravitreal injections

- Improved treatment adherence
- Decreased fluctuation in disease control
- Reduction of treatment burden
- Acceptable safety profile

2.11 *Interpretation of clinical effectiveness and safety evidence*

The primary source of clinical evidence was PSV-FAI-001 – a Phase III, multi-national, multi-centre, randomized, masked, controlled safety and efficacy study of ILUVIEN in subjects with chronic [redacted] ILUVIEN significantly reduced the proportion of patients experiencing recurrences of uveitis in the study eye. When recurrences occurred, they were less frequent in ILUVIEN-treated than active sham-treated patients who were receiving treatments representative of UK standard practice. Time to first uveitis recurrence was also significantly longer in the ILUVIEN arm than in the sham arm. The effects of the implant persisted up to 36 months. A similar efficacy pattern is emerging from the PSV-FAI-005 trial at 12-months follow-up and available evidence suggests that ILUVIEN provides superior uveitis control compared with standard practice alone. Importantly, this improved uveitis control appears to translate into visual acuity improvements, with more than double the number of patients gaining ≥15 letters in the ILUVIEN arm compared with the sham arm of the PSV-FAI-001 study.

In the PSV-FAI-001 trial, fewer patients treated with ILUVIEN than sham required additional treatments to control inflammation, i.e. systemic steroids or immunosuppressants, and intra/ peri-ocular and topical steroids administered to the study eye. Where such treatments were required, patients in the ILUVIEN arm received fewer of them compared with the sham arm. Thus, addition of ILUVIEN to routine uveitis management may reduce both patient exposure to systemic corticosteroids and the number of relatively invasive (intra/peri-ocular) treatments that patients receive.

Recurrence rate in the fellow eye of ILUVIEN-treated patients was slightly higher than that observed in the sham arm, potentially due to the lower use of systemic

steroids in ILUVIEN-treated patients. Indeed, fellow eye recurrence data suggests that in patients who have both eyes affected by uveitis, ILUVIEN should be used bilaterally, as it has clear clinical benefits in terms of lower recurrence rate, improved visual acuity and prompt reduction of macular oedema.

In terms of safety, there were no new or unexpected AEs associated with ILUVIEN administration. The AE profile was similar to that observed in the patients with DMO and treated with ILUVIEN. Indeed, cataracts and increases in IOP were the most common ocular TEAEs, each affecting approximately a third of patients.

The outcomes assessed and patient population enrolled in the PSV-FAI-001 trial can be considered highly relevant to the uveitis population in England as the study included UK patients. At the time of enrolment, there was an equal split of patients with active and quiescent disease; however, acute uveitis events can usually be well-controlled with various steroid-based strategies. The more serious problem is achieving long-term disease control and prevention of recurrences as they have a higher negative impact on maintenance of good visual function. It is primarily in this area where there is still a substantial unmet need and also where the benefits of ILUVIEN will be the most important. Nonetheless, inclusion of patients with more severe active uveitis at baseline could have provided a fuller picture of the effect of treatment with ILUVIEN on visual acuity. Baseline visual acuity was relatively high across both treatment arms and somewhat better in the ILUVIEN than the sham arm (mean of 66.9 vs 64.9 letters), so that there was relatively little improvement to be obtained with treatment in many of the patients, particularly in the ILUVIEN arm. Despite this, ILUVIEN still showed an increase in visual acuity through to Month 36, compared with the sham arm.

Further limitations of the available evidence include the fact that patients in PSV-FAI-001 were not stratified according to the anatomical location and/or aetiology of their [redacted]. Therefore, conclusions on ILUVIEN efficacy in specific subgroups according to the SUN classification of uveitis cannot be readily drawn. A further limitation is a lack of HRQoL assessment. Hence, data directly demonstrating the impact of treatment with ILUVIEN on HRQoL of patients with [redacted] is not available.

Although a quantitative comparison of ILUVIEN and the dexamethasone implant was not possible, real world experience with both implants suggests that ILUVIEN may offer significantly longer-term, sustained disease control with less fluctuation in ocular parameters over time[32]. Although difficult to quantify, the use of ILUVIEN is likely to have further benefits over available therapies (see Section 2.10). A single implant lasts for up to 36 months, which reduces the risks associated with frequent intravitreal injections and may improve treatment adherence and reduce treatment burden experienced by patients with [redacted].

End-of-life criteria are not applicable to ILUVIEN.

3 Cost effectiveness

Summary of the Cost-Effectiveness Analysis

- The model developed for this submission is based upon a previous model developed by the Evidence Review Group for TA460[16], with some minor adaptations.
- The model starts with patients On Treatment with either ILUVIEN implant or (Limited) Current Practice ((L)CP). Patients can then move to Remission or Subsequent Therapy. Once on Subsequent Therapy, they may move to Permanent Blindness.
- Changes in rates of recurrence of uveitis were based on Kaplan-Meier (KM) data reporting time to first recurrence in the pivotal PSV-FAI-001 trial [35].
- Health-related quality of life was not measured within the pivotal trial and therefore was estimated from mapped Visual Function Questionnaire (VFQ)-25 values reported in the Multicenter Uveitis Steroid Treatment trial[40].
- Cost and healthcare resource use (HCRU) were estimated from the UK perspective, and include the patient access scheme (PAS) price for ILUVIEN, supplemental therapy costs, AE costs, subsequent therapy costs and monitoring costs.

Base case analysis

- Deterministic analysis demonstrated that ILUVIEN is cost-effective versus (L)CP at a willingness-to-pay (WTP) threshold of £20,000/QALY under base case assumptions.
- The deterministic ICER was £7,183 with a net monetary benefit (NMB) of £3,479

Sensitivity analysis

- Probabilistic analysis resulted in a mean ICER of £7,702, with 79% of 1,000 iterations demonstrating ILUVIEN as cost-effective at the £20,000/QALY WTP threshold.
- One-way sensitivity analysis (OWSA) revealed that the model is sensitive to health state occupancy, particularly with reference to the utility applied to each health state. ILUVIEN remained cost-effective when varying 9 out of 10 most influential parameters using their upper and lower bounded values.
- In all scenarios explored, except for that with a one-year time horizon, ILUVIEN could be considered cost-effective at the £20,000/QALY WTP threshold.
- In summary, the cost-effectiveness analysis presents a robust methodology, closely aligned to that used by the Assessment Group (AG) in TA460[16]. We identified consistent findings supporting the cost-effectiveness of ILUVIEN.

3.1 *Published cost-effectiveness studies*

3.1.1 Systematic Literature Review of cost-effectiveness studies

In line with the NICE guide to the methods of technology appraisal, an SLR was conducted in September 2018 to identify any literature describing cost-effectiveness models relevant to the decision problem, [redacted]. The search strategies for this SLR are described in detail in Appendix G, along with detailed results. Included studies reported model structure and economic outcomes as part of a full economic evaluation; the full inclusion and exclusion criteria are provided in Table 23.

Table 23: Inclusion and Exclusion criteria for economic modelling studies

	Inclusion criteria	Exclusion criteria
Population	o [redacted] Eligible populations were considered for inclusion regardless of the type of [redacted] (i.e. active or inactive uveitis; unilateral or bilateral uveitis; presence or absence of uveitis-related systemic disease or previous treatments for uveitis).	• Paediatric patients • Infectious uveitis • Uveitis as part of masquerade syndrome • Non-human studies
Interventions	• Interventions and comparators aimed at treating [redacted]	• Interventions and

	Inclusion criteria	Exclusion criteria
and comparators		comparators not aimed at treating [redacted]
Outcomes	• Model structure and any health economic outcome, including (but not restricted to) QALYs, ICERs, LYG or resource use/ costs	• Outcomes of interest not reported
Study design	• Economic evaluation, pharmacoeconomic evaluation, cost-effectiveness study, cost-utility study, cost-benefit study or cost minimisation study	• Randomised clinical trial, non-randomised clinical trial, prospective study, longitudinal study, retrospective study, guideline, cohort study, case reports, letter, editorial, review, retracted
Language restrictions	• English language only	• Studies published in languages other than English

ICER: incremental cost-effectiveness ratio; LYG: life-year gained; [redacted] QALY: quality-adjusted life-year

The review included searches of the following electronic databases:

- MEDLINE (including MEDLINE® In-Process)
- Excerpta Medica Database (EMBASE®)
- The Cochrane Library
- The Cochrane Database of Systematic Reviews (CDSR)
- The Cochrane Central Register of Controlled Trials (CENTRAL)

- Cochrane Clinical Answers (CCAs)

  As of Q3 2018, HTA, NHS-EED, and DARE have been removed from the Cochrane database and are no longer publicly available, and instead were largely replaced with Cochrane Clinical Answers.

- EconLit

In addition to the database search, reference lists from relevant studies were visually scanned to identify further studies that may meet eligibility criteria and a search of the grey literature was conducted including a search of relevant conference programs and a review of HTA websites (e.g. NICE, Scottish Medicines Consortium [SMC] and All Wales Medicines Strategy Group [AWMSG]).

Proceedings from the following conference websites (January 2016 to August 2018) were also searched:

- The Royal College of Ophthalmologists Annual Congress
- European Society of Ophthalmic Plastic and Reconstructive Surgery
- American Academy of Ophthalmology
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Annual European and International Meetings
- European Society of Retina Specialists
- The Association for Research in Vision and Ophthalmology
- International Ocular Inflammation Society

NICE and SMC websites were searched for technical assessment reports or manufacturer submissions related to uveitis. Finally, the reference lists of recent (2016 to 2018) and relevant SLRs identified through the literature searches were reviewed in order to identify any additional publications of interest not otherwise captured through the literature review.

Once studies were identified, they were reviewed and assessed for their eligibility and full texts were retrieved for articles that were considered relevant. Data were extracted by a single reviewer and then checked by a second reviewer.

A total of 528 studies was identified from database studies, and 42 studies were identified from additional sources. After removing duplicates, 516 studies were screened, of which 505 studies were excluded. Of the 11 studies remaining, full-text articles were retrieved and seven studies were excluded based on the eligibility criteria. The number of studies remaining for data extraction was four. The PRISMA flow diagram can be seen in Figure 9.

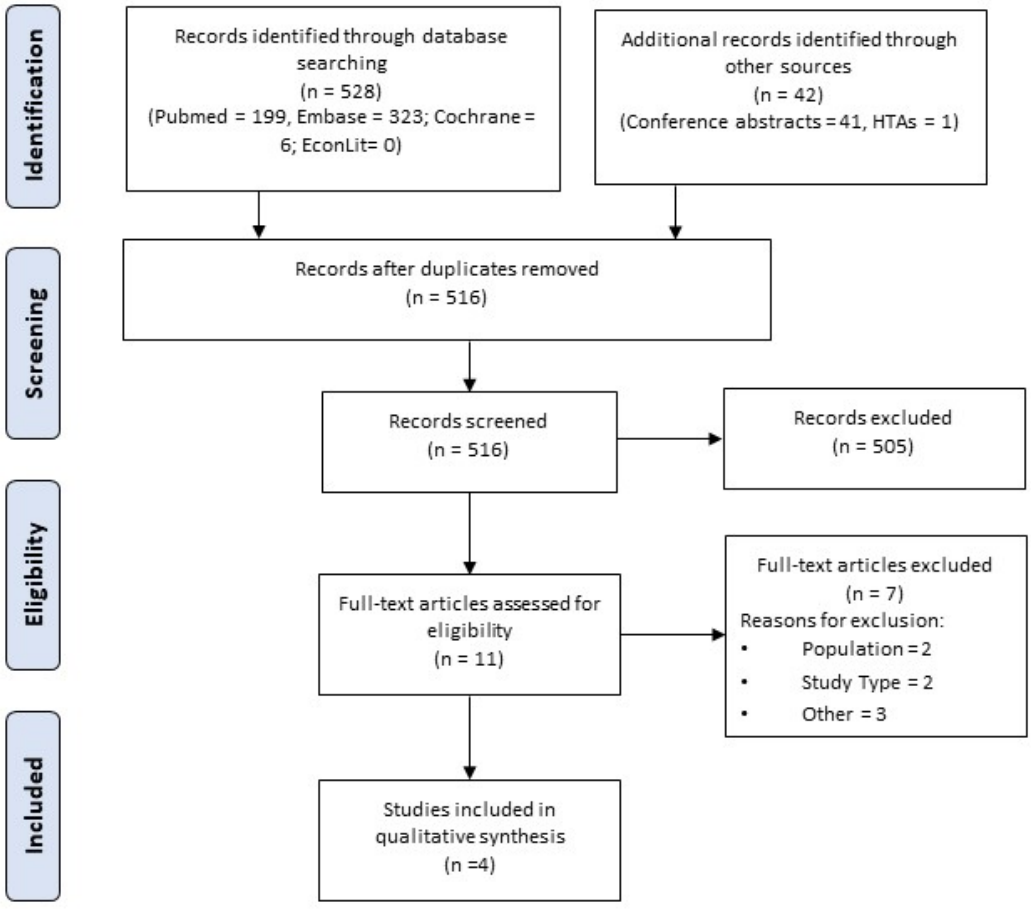


Figure 9: PRISMA flow diagram for model-based cost-effectiveness studies

The SLR identified two articles and two published abstracts which are described in Table 24. One of the full text studies evaluated the cost-effectiveness of a 0.59 mg FAc implant (Retisert™). The other article was a systematic review and evaluation of adalimumab and dexamethasone that was presented as part of TA460[16]. Both

studies evaluated treatments in non-infectious posterior uveitis and so may be considered directly relevant to the decision problem presented in this document.

3.1.2 Applicability of studies identified in SLR to economic model

The papers identified in the SLR are summarised in Table 24 and described fully in Appendix G. Of the four papers identified in the cost-effectiveness SLR, two did not provide enough detail about methods to be informative as they were only available as an abstract[41,42]. Sugar et al[43]. evaluated the cost-effectiveness of Retisert and used available data from the Multicenter Uveitis Steroid Treatment (MUST) trial directly to assign costs and utility, therefore no explicit health states were used or required. This study used a within-trial analysis and so a modelling framework was not required given that there was no extrapolation of outcomes.

Squires et al.[44] conducted an SLR and economic evaluation of adalimumab and dexamethasone which was presented as part of TA460[16]. This paper provided insight into the model design and a similar model structure was replicated for the cost-effectiveness analysis undertaken in this submission. Key components of the model presented by Squires et al.[44] are summarised in Table 26. Other aspects of the model by Squires et al. (settings and assumptions) were also deemed appropriate for the decision problem presented in this document and, where relevant, are described throughout.

TA460 presented separate analyses for the evaluation of adalimumab and dexamethasone versus their respective standards of care, as their position in the treatment pathway was not considered to be the same. This decision was taken after clinical advice about the current use of adalimumab and dexamethasone. Although there is some overlap in the respective licenses, currently, adalimumab is most often used at a later stage of disease than dexamethasone and FAc implants (the intervention considered here). Therefore, adalimumab is not considered a relevant comparator for this submission.

Table 24: Summary of modelling papers identified in the SLR

Study	Year	Summary of model	Patient population	QALYs	Costs	ICER (per QALY gained)
Cost-Effectiveness of Fluocinolone Acetonide Implant Versus Systemic Therapy for Non-infectious Intermediate, Posterior and Panuveitis[43] (Available as journal article)	2014	Cost-utility evaluation of MUST trial data with a 1-year extension (3-year total time horizon). Costs and utilities were calculated or directly applied to available data. Analysis conducted in US dollars, taking a payer's perspective for costs and patient's perspective for outcomes	Patients aged ≥13 years with non-infectious intermediate uveitis, posterior uveitis or panuveitis in one or both eyes (active within ≤ 60 days) for which systemic corticosteroids were indicated. Average age not reported.	Only difference in change in QALYs between arms reported as Implant – Systemic. For bilateral disease, incremental QALYs, 0.057. For unilateral disease, incremental QALYs, 0.130	For bilateral disease, the three-year cumulative cost (in US Dollars) was approximately $69,300 in the implant group and $52,500 in the systemic therapy group For individuals with unilateral disease, the mean costs through three years was approximately $38,800 in the implant group and $33,400 in the systemic group	For bilateral disease at 3 years, $2,800. For unilateral disease at 3 years, $41,200.
A systematic review and economic evaluation of adalimumab and dexamethasone for treating non-infectious intermediate uveitis, posterior uveitis or	2017	Cost utility evaluation of VISUAL I and II and HURON trial data. Markov model with a lifetime time horizon and 2-week cycle. Analysis conducted in GBP from an	All patients had non-infections intermediate, posterior or panuveitis with either active disease (supported by VISUAL I), or in active disease (VISUAL II) for			For dexamethasone vs LCP £19,509 For adalimumab vs LCP £94,523 and £317,547 for active and inactive uveitis respectively.

panuveitis in adults.[44]		NHS perspective in the UK	adalimumab or active disease (HURON) for dexamethasone comparison			
A Cost-effectiveness analysis off off-label biologics to treat sarcoid posterior uveitis vs standard of care: Comparing infliximab to methotrexate and systemic steroids.[41]	2011	Cost-utility evaluation conducted in US dollars taking a societal perspective. The model was semi-Markov and followed patients for a lifetime time horizon.	Patients with sarcoid posterior uveitis	Systemic steroids resulted in 14.58 QALYs Methotrexate, 15.92 Infliximab, 15.04	Systemic steroids $26,871 Methotrexate, $40,351 Infliximab, $46,547	Methotrexate was cost-effective compared to steroids, ICER $10,053/QALY. Methotrexate dominated infliximab.
Comparing Prednisone and Methotrexate to Off-label Infliximab for the Management of Posterior Uveitis and Panuveitis: A Cost-Effectiveness Analysis[42]	2017	Cost-utility evaluation conducted in US dollars taking a societal perspective. Markov model following patients for a life time horizon.	Patients with posterior and panuveitis	Prednisone, 15.80 QALYs Methotrexate, 16.21 QALYs Infliximab, 15.04 QALYs	Prednisone, $306.95 Methotrexate, $36,232.24 Infliximab, $74,762.63	ICER of methotrexate vs prednisone = $86,901.16/QALY Prednisone and methotrexate dominated infliximab.

ICER: incremental cost-effectiveness ratio; LCP: limited current practice; QALYs: quality-adjusted life years

3.2 *Economic analysis*

The economic case presented in this submission is based on conventional cost-utility analysis, assessing use of ILUVIEN in comparison with (L)CP for the [redacted], taking into account [redacted] for ILUVIEN. This analysis uses a similar approach to that used by the Assessment Group (AG) in a previous submission to NICE for a similar indication (TA460)[16]. Although some patients may have bilateral uveitis, the model considers only the study eye data in PSV-FAI-001.

Five exclusive health states were used and are described in Section 3.2.2 in line with a scenario presented in TA460[16]. Time to first recurrence was informed by extrapolation of data from PSV-FAI-001[35] and is described in Section 3.3.1. The rate at which patients experience permanent blindness was informed by the rate used in TA460[16] which is based on literature. The transition to death was estimated with general population mortality estimates.

Costs are sourced from the Personal Social Services Research Unit (PSSRU)[45], Monthly Index of Medical Specialities (MIMS)[46] and NHS reference costs for the most part, and the most recent publications were used. Where costs were not available, those used in TA460[16] were inflated to current costs; a full description of cost and resource use is provided in Section 3.5.

Utilities assigned to the health states were as reported in TA460[16] for permanent blindness[16], mapped from VFQ-25 values collected in the MUST trial[40] for On Treatment and Subsequent Therapy and for Remission, general population values were used[47]. The methods and rationale are described in Section 3.4. The rate at which AEs are expected to occur was derived from reported AEs in PSV-FAI-001[35] for the ILUVIEN and (L)CP arms (described in Section 3.3.6). The resource use and the costs of AEs were validated by a clinical expert and costed with the most recent NHS reference costs, PSSRU[45] or MIMS costs[46] which are detailed in Section 3.5.

Dexamethasone was compared to (L)CP in the HURON trial[31] and ILUVIEN was compared to (L)CP in PSV-FAI-001[35]. However, the two trials differed in relation to the availability of supplemental therapy during the treatment period. Most notably, in

the HURON trial[31] patients were permitted the use of topical corticosteroids, systemic corticosteroids and systemic immunosuppressants if the investigator deemed it appropriate[16]. Conversely, PSV-FAI-001[35] prohibited the use of any steroidal treatment or immunosuppressant; if patients were receiving such therapies at baseline, they were required to taper off such treatment within three months. Patients in the PSV-FAI-001[35] trial were allowed to use periocular corticosteroid treatment only if they experienced recurrence. Due to the ambiguity surrounding the treatment pathway, it is not clear that (L)CP described in the HURON trial[31] is representative of (L)CP in the UK for non-infectious uveitis. After considering this, and the differences in trial design, it was deemed inappropriate to compare ILUVIEN to either the dexamethasone arm or the (L)CP arm of the HURON trial[31].

The most notable difference between the HURON trial and PSV-FAI-001[35] was the difference in primary and secondary outcomes. PSV-FAI-001[35] was powered to detect the recurrence of uveitis in the study eye at six months and three years (primary and secondary outcomes, respectively). HURON[31] 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).

As discussed, 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.

The sham injection arm of PSV-FAI-001[35] is considered largely representative of current practice in the UK for the treatment of uveitic flares and recurrence. Patients in this arm followed the same practice as the ILUVIEN arm, where systemic treatments were initially tapered off over 3 months (see Section 2.3.3.3) and, subsequently, if a patient experienced recurrence they were treated first with

periocular steroids or intravitreal corticosteroids and then systemic treatments, such as systemic corticosteroids and systemic immunosuppressants, in accordance with the clinical study protocol (CSP)[48]. In the context of ILUVIEN being a preventative treatment for the recurrence of uveitis, treating with periocular steroids before systemic treatments means that the sham injection arm represents (L)CP in the UK; the assumption that this is representative has been validated (clinical experts, personal communication) and is in line with the model diagram and supported by literature[49]. Therefore, the comparison of ILUVIEN to the active sham arm of the PSV-FAI-001 trial[35] (described herein a (L)CP) forms the economic analysis in this submission. This submission therefore presents an economic evaluation of the PSV-FAI-001 trial[35] utilising methodology similar to that reported in TA460[16].

3.2.1 Patient population

This economic evaluation was predominantly informed by the PSV-FAI-001 trial[35] which enrolled patients with [redacted] ILUVIEN. Patients in PSV-FAI-001[35] were required to have displayed a history of [redacted] and during the previous 12 months have received either systemic therapy for 3 months or at least 2 intra or peri ocular administrations of corticosteroids as dictated in the CSP[48] (see Section 2.3 for details of trial methodology).

Parameters for the patient population presented in the economic evaluation are aligned to the proposed indication and are derived from PSV-FAI-001[35] as summarised in Table 25 below.

Table 25. Baseline patient parameters

Parameter	Input	SE	Source
Base case analysis			
Baseline age (years)	48.3	4.83 (assumed)	Population from 001 (CSR)[35]
Proportion of cohort male	38%	3.8% (assumed)	
Study participants (ITT)	129		

CSR: clinical study report; SE: standard error

3.2.2 Model structure

The model used to evaluate the cost-effectiveness of ILUVIEN is a 5 state Markov model; the schematic can be seen in Figure 10. The model was developed in Microsoft Excel® 2016 and has 5 distinct and exclusive health states:

- On treatment with ILUVIEN/(L)CP
- Subsequent therapy/end of first line treatment effect
- Remission (therapy has alleviated symptoms of disease for >2 years)
- Permanent blindness
- Death

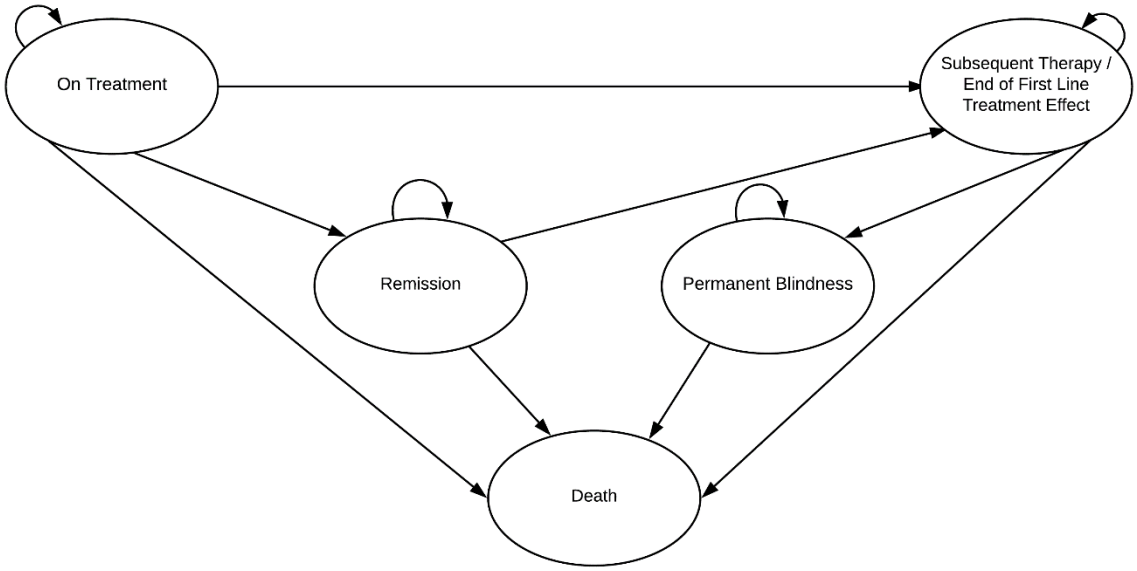


Figure 10: Economic model schematic.

This model structure was proposed by the AG for TA460[16]; however, was not used in TA460[16] base case analyses due to the uncertainty surrounding the remission health state. The remission health state was discussed in relation to the adalimumab evaluations as after 2 years, patients who had “stable disease” were considered to be in Remission. This means that they could accrue the same HRQoL as they did on treatment without incurring further costs, as they would no longer require systemic treatment.

Such uncertainty in the Remission proportion was due to the underlying studies informing the analysis having mean follow-up time less than that required to inform confirmation of remission (no recurrence after 2 years). Therefore, in the case of TA460[16], remission would need to be informed by extrapolated outcomes, rather than those observed in the trial. Instead, the model structure described above informed a scenario analysis with the remission health state incorporated. The base case analysis in TA460[16] assumed no transition to the remission health state. In contrast, PSV-FAI-001[35] observed 36 months of follow-up and so it is possible to model patients whose disease remained stable for greater than two years. It is therefore appropriate to consider the Remission health state in this model though patients in this model are considered in Remission from ocular disease if there has not been recurrence for more than 2 years. This is in contrast to the definition used in TA460[16] where patients were considered to be in remission from systemic disease. This clarification is important because the model presented here models the main outcomes from PSV-FAI-001[35] which were related to ocular disease in the study eye and not systemic disease. In PSV-FAI-001[35], systemic treatments were prohibited, and this model does not consider a patient to be in remission from systemic disease but rather from ocular disease. Anyone with no uveitis recurrence after two years in this trial would qualify for Remission as validated by clinical experts (personal communication) and supported by literature[49]. Therefore, it is considered appropriate to model the Remission health state in this submission as it has important HRQoL implications for patients whose disease responds in this way.

Aside from the Remission health state, the model in this submission considers 4 other states; On Treatment, End of Treatment Effect/Subsequent Therapy, Permanent Blindness and Death. Patients progress through health states in line with trial-based and published efficacy and disease progression data[16,35,47]. The On Treatment and Remission health states represent outcomes for patients who respond positively to treatment for any given length of time. If a patient is responding to treatment for under 2 years, direct costs and HRQoL are captured within the On Treatment health state. If a patient continues to respond after 2 years, their HRQoL outcomes are considered akin to the general population (Remission health state) and they will incur utility at an age-matched rate. The End of Treatment

Effect/Subsequent Therapy and Permanent Blindness health states represent the potential downstream consequences for patients whose treatment with ILUVIEN or (L)CP is not successful.

Patients are initiated within the model in the On Treatment health state, receiving either ILUVIEN (intervention arm) or (L)CP (comparator arm) and may subsequently move to the state of Remission, End of Treatment Effect/Subsequent Therapy or Death in line with time-dependent estimates of response. While patients are responding to treatment (On Treatment or Remission) they cannot move directly to blindness. Consistent with TA460[16], this assumption was made in line with expert advice and assumes that a patient's treatment must be failing before their condition can escalate to blindness. Further supporting this assumption are the trial-reported outcomes in which no incidence of permanent blindness in the ILUVIEN arm was observed over the 36-month follow-up period. Patients who experience treatment failure will move to End of Treatment Effect/Subsequent Therapy and can move directly to the state of Blindness from here. If a patient is in the Remission health state and their treatment effect ceases, they move to the End of Treatment Effect/Subsequent Therapy health state. The probability of recurrence of uveitis over time for those treated with ILUVIEN or (L)CP is estimated directly from PSV-FAI-001[35], where this was described by primary and secondary outcomes (See Section 2.3.4).

As uveitis is a chronic condition, the model considers a lifetime horizon which in the base case is 51 years (assuming a maximum age of 100). Patients enter the model at 48.3 years of age (the average age reported in PSV-FAI-001[35]); mortality from uveitis is assumed to be no different to that of the general population, as such general population mortality estimates are utilized to estimate transitions to death. The modelling approach is consistent with that undertaken in TA460[16]; an overview of key model settings is provided in Table 26 with a comparison to TA460[16] methodology were relevant.

Table 26: Features of the current economic model for evaluation

	Previous Appraisal	Current Appraisal	
Factor	**TA460[16]**	**Chosen values**	**Justification**
Time horizon	Lifetime - 55 years	Lifetime – 51 years	As per NICE reference case[50]
Source of utilities	Dexamethasone utilities estimated from VFQ-25 data captured at 3 time points in the HURON trial and mapped to EQ-5D	Estimated from VFQ-25 data mapped to EQ-5D from the MUST trial	Methodology as per previous TA. Values taken from comparable population.
Source of costs	Drug costs were sourced from the latest drug tariffs. Resource use and AE costs were sourced from PSSRU, NHS reference costs or literature.	Drug costs are sourced from MIMS. Resource use and AE costs are sourced from the most recent PSSRU, NHS reference costs or literature.	As per NICE reference case[50]
Perspective	NHS/PSS	NHS/PSS	As per NICE reference case[50]
Model cycle length	2 weeks	2 weeks (14 days)	As per previous TA[16]
Discount for costs and utilities	3.5%	3.5%	As per NICE reference case[50]

AE: adverse event; MINS: Monthly Index of Medical Specialities; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; TA: technology appraisal; VFQ: Visual Function Questionnaire

3.2.3 Intervention technology and comparators

The intervention considered is ILUVIEN, a long-lasting (36 months) implant proposed for the treatment of [redacted], in line with the decision problem form. See Section 1.2 for more details on ILUVIEN.

It is proposed for use for patients who have [redacted] and is administered only once every 36 months, as dictated in PSV-FAI-001[35]. This is in line with the trial population from PSV-FAI-001[35] and also the proposed indication. There is considerable ambiguity in the treatment pathway for non-infectious uveitis, an issue debated in TA460[16]. The two pathways considered in TA460[16]; describing systemic and local treatment are presented in Figure 2.

First line treatment for non-infectious uveitis is likely to be systemic or local steroid treatment and PSV-FAI-001[35] stipulated that for inclusion, patients must have received systemic corticosteroids, other therapies or at least 2 corticosteroid injections within the previous 12 months. Therefore, this evidence is directly supportive for an alternative to (L)CP in recurrent disease. Hereafter, first-line treatment refers to the position of ILUVIEN and the comparator as represented in this model.

The comparator treatment in PSV-FAI-001[35] was sham injection. In cases of recurrence, all patients could take supplemental therapies regardless of which active treatment they received. Therefore, the comparator (L)CP refers to the supplemental therapies described below.

3.2.3.1 Supplemental medications

It is assumed that patients taking either intervention or comparator will also be receiving supplemental therapies. The rates at which these are taken are informed by PSV-FAI-001[35] with only those given to more than 3% taken into consideration, as this represents treatments that are likely to be disease-related. The treatments and the rates at which patients take these drugs are displayed in Table 27. The CSP for PSV-FAI-001[35] states that systemic immunosuppressants and any steroidal treatment are prohibited for study patients. However, if patients presented at the study initiation taking these treatments they will be tapered off in the first three months. Therefore, the treatments shown in Table 27 are only applied for the first three months. These treatments are all medications listed as supplemental therapies in PSV-FAI-001[35] and constitute systemic and local therapies used by patients in the observed period. These treatments are likely to have been used in the first three months only, if otherwise prohibited (as dictated by the CSP).

Patients who experienced recurrence in PSV-FAI-001[35] would be first treated with periocular steroids or intravitreal corticosteroids and, if there is no response, systemic treatment. At this time, they would be considered in subsequent therapy, as described in Section 3.2.4. The periocular treatments would be accounted for in

supplemental therapy, while the systemic treatments are accounted for in Subsequent Therapy costs. Some systemic treatments are shown in the Table 27 as supplemental therapies; these are present because some patients presented at trial initiation taking these treatments and so would taper off in the first three months.

Table 27: Supplemental medications

Supplemental medication	ILUVIEN	(L)CP
Mycophenolate mofetil	[redacted]	[redacted]
Methotrexate	[redacted]	[redacted]
Cyclosporine	[redacted]	[redacted]
Azathioprine	[redacted]	[redacted]
Prednisolone	[redacted]	[redacted]
Tacrolimus	[redacted]	[redacted]
Beta-interferon	[redacted]	[redacted]
Abatacept	[redacted]	[redacted]
Golimumab	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]
aetazolamide	[redacted]	[redacted]
apraclonidine	[redacted]	[redacted]
anti-inflammatory agents and anti-infectives	[redacted]	[redacted]
artificial tears	[redacted]	[redacted]
Atropine	[redacted]	[redacted]
besifloxacin hydrochloride	[redacted]	[redacted]
Bevacizumab	[redacted]	[redacted]
bimatoprost	[redacted]	[redacted]
Brimonidine tartate	[redacted]	[redacted]
Bromfenac	[redacted]	[redacted]
Budesonide w formoterol fumarate	[redacted]	[redacted]
carmellose	[redacted]	[redacted]
carmellose sodium	[redacted]	[redacted]
Carbomer	[redacted]	[redacted]
chloramphenicol	[redacted]	[redacted]
ciprofloxacin	[redacted]	[redacted]
corticosteroids and anti-infectives in combination	[redacted]	[redacted]
combigan	[redacted]	[redacted]

Cosopt	[redacted]	[redacted]
Cyclopentolate hydrochloride	[redacted]	[redacted]
Difluprednate	[redacted]	[redacted]
Fluticasone propionate	[redacted]	[redacted]
Fluoracine oph soln	[redacted]	[redacted]
Flurbiprofen	[redacted]	[redacted]
Fluress	[redacted]	[redacted]
Gatifloxacin	[redacted]	[redacted]
Gentamicin	[redacted]	[redacted]
Homatropine hydrobromide	[redacted]	[redacted]
Hyaluronate sodium	[redacted]	[redacted]
Iodine	[redacted]	[redacted]
Ketorolac/ Ketorolac tromethamine	[redacted]	[redacted]
Latanoprost	[redacted]	[redacted]
Lidocaine	[redacted]	[redacted]
Loteprednol	[redacted]	[redacted]
Maxitrol	[redacted]	[redacted]
Moxifloxacin	[redacted]	[redacted]
Moxifloxacin hydrochloride	[redacted]	[redacted]
Methylprednisolone/Methylprednisolone sodium succinate	[redacted]	[redacted]
Nepafenac	[redacted]	[redacted]
Ofloxacin	[redacted]	[redacted]
Other opthalmologicals	[redacted]	[redacted]
Oxybuprocaine	[redacted]	[redacted]
Oxybuprocaine hydrochloride	[redacted]	[redacted]
Paremyd	[redacted]	[redacted]
Phenylephrine	[redacted]	[redacted]
Phenylephrine hydrochloride	[redacted]	[redacted]
Phenylephrine w tropicamide	[redacted]	[redacted]
Povidone-Iodine	[redacted]	[redacted]
Proxymetacaine	[redacted]	[redacted]
Simbrinza	[redacted]	[redacted]
Systane lubricant	[redacted]	[redacted]
Tears plus	[redacted]	[redacted]
Tetracaine hydrochloride	[redacted]	[redacted]

Timolol	[redacted]	[redacted]
Timolol maleate	[redacted]	[redacted]
Tobradex	[redacted]	[redacted]
Triamcinolone acetonide	[redacted]	[redacted]
Systemic corticosteroids	[redacted]	[redacted]
Prednisone	[redacted]	[redacted]
Azarga	[redacted]	[redacted]
Brinzolamide	[redacted]	[redacted]
Fluocinolone Acetonide	[redacted]	[redacted]
Hypromellose	[redacted]	[redacted]
Idoxuridine	[redacted]	[redacted]
Polytrim	[redacted]	[redacted]
Tropicamide	[redacted]	[redacted]
Viscoat	[redacted]	[redacted]
Vancomycin	[redacted]	[redacted]
Seretide	[redacted]	[redacted]
Ceftazidime	[redacted]	[redacted]

(L)CP: (limited) current practice

3.2.4 Subsequent therapy

Upon first recurrence of uveitis in the model, patients from both arms will move to Subsequent Treatment; this is as described in the CSP as treatment upon recurrence of uveitis[48]. Subsequent Therapy is described in TA460[16] as a range of immunosuppressants and assumed to be the same as the supplemental therapy for dexamethasone. This is in line with the proposed treatment pathway and TA460. The CSR for PSV-FAI-001[35] provides a list of treatments that were given to patients upon recurrence of uveitis which is shown in Table 28. The cost of the treatments was applied once as patients moved to Subsequent Treatment (upon transition). These costs were not used for the duration of a patient's time in the Subsequent Treatment health state because they do not contain any immunosuppressants and are therefore considered unlikely to represent true Subsequent Treatment. Subsequent Treatment for the duration of time in the Subsequent Treatment health state was assumed to be as described in TA460[35]; a weighted cost of immunosuppressant therapies as

described in the HURON trial and systemic prednisolone. The proportions taking these can be seen in and resulting costs can be seen in Table 44.

Table 28: Treatments used upon transition to subsequent therapies

Recurrence medications	ILUVIEN	(L)CP
Bromfenac sodium	[redacted]	[redacted]
Dexamethasone	[redacted]	[redacted]
Nepfenac	[redacted]	[redacted]
Prednisolone acetate	[redacted]	[redacted]
Difluprednate	[redacted]	[redacted]
Triamcinolone acetonide	[redacted]	[redacted]
Corticosteroids	[redacted]	[redacted]
Cyclopentolate Hydrochloride	[redacted]	[redacted]
Lidocaine	[redacted]	[redacted]
Povidone-Iodine	[redacted]	[redacted]
Triamcinolone	[redacted]	[redacted]

3.3 *Clinical parameters and variables*

3.3.1 Time to First Recurrence

3.3.1.1 ILUVIEN

The pivotal study informing the comparative efficacy of ILUVIEN vs (L)CP was PSV-FAI-001[35]. The primary outcome for PSV-FAI-001 was the proportion of recurrence of uveitis in the study eye at six months and the secondary outcome was the recurrence at three years [35]. The time to first uveitis recurrence is shown as KM data in Figure 5. The trial data would allow for the expected proportion of patients in remission to be calculated for only one year (between 24 and 36 months of observed data) but would not allow for any further potential time in this health state to be evaluated. Also, as demonstrated by the shape of the KM curve in Figure 5, there is reason to believe that the probability of experiencing recurrence of disease (transition probability from On Treatment to Off Treatment) would change over time and so a single point estimate of transition probability would not be appropriate. Therefore, for use over a lifetime horizon, it was necessary to extrapolate the data to consider a longer time than 36 months. This was important because there are

substantial cost and HRQoL differences expected between the proportion in remission and on subsequent therapies. As described in following paragraphs, there is uncertainty as to the time for which patients with an ILUVIEN implant may not experience recurrence. Figure 5 shows some events occurring after the defined trial end period (1,080 days) and after this time confidence intervals (CIs) are wide. Additionally, the CSP details that there may be reasons other than recurrence for which recurrence is imputed[48]. Therefore, curves are fit to the proportion experiencing recurrence and extrapolated past the observed period.

The KM data shown in Figure 5 was digitized using DigitizeIt™ and this information then read into R, version 3.5.1. No numbers at risk were available for this population and so patient-level data (PLD) were reconstructed using the YoungAlgorithmn function which is an adapted version of the Guyot algorithm as part of the SurvivalDigitisation package, version 0.1.0[51]. To use this function, it was necessary for the KM data to start at 1 and so the curve shown in Figure 5 were inverted before use.

Standard parametric curves were fit to the observed data; however, none provided a good visual fit; these can be seen in Figure 11. All curves show overestimation across [redacted] and considerable underestimation at latter stages. Most models also fall outside the CI estimates between approximately 840 and 1120 days. The CIs also seem to be quite narrow at the late stages of observed data, which does not seem reasonable given the relatively small number of patients included (n=87).

[redacted] The 36 month CSR for PSV-FAI-001[35] defines a month as 30 days and details follow up appointments as happening initially every month and after three months at intervals of three months. The large drop may therefore be due to clinicians prioritising safety for borderline patients and recording events. For this reason, it is inappropriate to fit a continuous model for the entire observed time period.

Figure 11: Parametric curve fits to all observed data of the primary outcome of PSV-FAI-001: Not used due to poor fit

PLD was edited under the assumption that all patients missing data experienced recurrence in line with the number of events listed in the 36-month [redacted] event numbers were verified against those recorded in the CSR. Parametric curves were fit and evaluated from 30 day time points and while up to and including 90 days has to be excluded as it is still in the middle of the discontinuity period, post 120 days there is no good reason to reject a parametric model as can be seen in the cumulative hazard plot from 120 days onwards in Figure 12.

Figure 12: Cumulative hazard plot for time to recurrence: ILUVIEN

Therefore, parametric models were fit from 120 days onward and showed a better visual fit. These can be seen in Figure 13; this image shows the KM data starting at 1 as when models are fit it is assumed that survival is 1 initially. These values were then rescaled to be used from 120 days onwards. While these do not fit the three tail events particularly well, as there are very large confidence intervals (CIs) with the edited PLD at this time point, this is to be expected. It is feasible that these events are due to late assessments, [redacted]. It was considered appropriate to extrapolate through this period due to the wide CIs and the very limited patient numbers on which to base analysis in this time (3 patients). Additionally, recurrence in PSV-FAI-001[35] was imputed for patients who were unable to attend follow up or who took systemic treatments for other reasons[48]. Therefore, the tail events are not considered entirely representative and the wide CIs reflect the uncertainty surrounding them.

Figure 13: Parametric curves fit to PSV-FAI-001 observed data for the primary outcome from 3 months onward for ILUVIEN

Of these, the Exponential curve showed the best fit as assessed visually and by the fit statistics (as suggested in the NICE Decision Support Unit Technical Support

Document 14[52]). All models estimate median time to first recurrence as being between 621 and 673 days (640 for the exponential curve)

[redacted]

The fit statistics can be seen in Table 29. Time to recurrence estimated by these curves was then scaled such that time to recurrence after 3 months is dependent on no recurrence up to that point. After three months, the parametric model informs the estimate of the probability of first recurrence used in the cost-effectiveness model and prior to this time point, the model reads directly from the observed data.

Table 29: Fit statistics for parametric models fit to observed data in PSV-FAI-001for ILUVIEN from 120 days onwards

Distribution	AIC	BIC	Median time to recurrence
Exponential	**573.63**	**575.81**	**640.05**
Weibull	574.74	579.09	673.45
Log-Logistic	575.35	579.70	650.72
Log-Normal	576.99	581.34	621.17
Generalised Gamma	576.89	583.42	657.11
Gompertz	574.73	579.08	688.73
Gamma	574.77	579.11	668.28
Generalised F	579.14	587.84	654.84

AIC, Akaike information criterion; BIC, Bayesian information criterion

These values provided the estimation for the patients who are on first-line treatment throughout the considered time horizon. The model considers the proportion of patients who are alive and on treatment as those who are on first-line treatment (with ILUVIEN or (L)CP) before 2 years. Any patient still estimated to be in this condition at 2 years is considered in remission as described in Section 3.2.2.

At any time, those who are not on first-line treatment or in remission can move to subsequent therapy; defined as the proportion still alive minus those who are responding to treatment. Once in subsequent therapy, patients will remain there unless they die or move to permanent blindness. At any time, patients may go blind as a result of their condition but can only move to this state from a state of non-response (subsequent therapy). This follows this assumption that while a patient is not experiencing recurrence, i.e. responding to treatment, they will not experience

permanent blindness due to their disease and is in line with the reported outcomes from PSV-FAI-001[35].

3.3.1.2 (L)CP

As described in Section 3.3.1.1, the informing trial for time to first recurrence in the (L)CP arm was PSV-FAI-001[35]. The same methodology was used for (L)CP as for ILUVIEN with regards to digitizing and fitting parametric models to the KM data shown in Figure 5.

The cumulative hazard plot for time to first recurrence with (L)CP can be seen in Figure 14 and shows no reason to disregard a parametric model for the observed period. As can be seen in Figure 14, the log-logistic model follows the cumulative hazard the most closely. Parametric models were fit to the KM data and can be seen in Figure 15 with accompanying fit statistics shown in Table 30. Of these models, the best visual fit and model with lowest fit statistics was the Log-Logistic model. This model was chosen as the base case and estimates median time to first recurrence on (L)CP as 70 days which

[redacted] The other models estimated median time to first recurrence as being between 62.39 and 82.20 days demonstrating little variation between model estimates. [redacted]

Figure 14: Cumulative hazard plot of time to first recurrence: (L)CP

[redacted]

Figure 15: Parametric curves fit to PSV-FAI-001 observed data for the primary outcome for (L)CP

Table 30: Fit statistics for parametric models fit to observed data in PSV-FAI-001for (L)CP

Distribution	AIC	BIC
Exponential	471.91	473.65
Weibull	473.83	477.30
Log-Logistic	**458.83**	**462.31**
Log-Normal	461.60	465.07
Generalised Gamma	463.59	468.81
Gompertz	466.85	470.33

Gamma	473.34	476.82
Generalised F	467.92	474.87

AIC, Akaike information criterion; BIC, Bayesian information criterion

3.3.2 Subsequent therapy

When patients experience recurrence, they will move to subsequent therapy which is comprised of a range of immunosuppressants and systemic steroids in line with the treatment pathway shown in Figure 2. For patients who have ILUVIEN and (L)CP, the proportion moving to subsequent treatment is dictated by the proportion who have stopped responding to treatment, have not gone blind as a result of their disease and have not died. This proportion can be seen as the area above the fitted curves shown in Figure 13 and Figure 15 for ILUVIEN and (L)CP, respectively.

3.3.3 Remission

Patients enter the Remission health state after they have been responding to first-line treatment for over 2 years, specifically they have not experienced recurrence of their ocular disease. This assumption was used in the TA460[16] model in a scenario and was based on clinical evidence presented to the AG. The use of this state in this model is described in Section 3.2.2. For patients who have ILUVIEN or (L)CP, membership of this state is dictated in the same way as for response to first-line treatment, conditional on no recurrence at two years (shown in Figure 13 and Figure 15). Therefore, transition out of this state to Subsequent Treatment is dictated by the proportion who are not estimated to be on treatment post two years.

3.3.4 Permanent blindness

In the most severe cases of uveitis, patients may go blind as a consequence of uveitis that does not respond to treatment. The assumption was made that patients who are On Treatment or in Remission will not go blind. This follows the assumption that patients whose disease is in remission will not suffer the worst consequence of progressing disease. Additionally, the CSR for PSV-FAI-001[35] reports [redacted]. This assumption is therefore conservative, favouring (L)CP. Therefore, for a patient to transition to permanent blindness, they must first experience treatment failure (recurrence of symptoms) and move to subsequent therapy. Once there, the model will allow

transition to permanent blindness at the rate described in TA460 (6.6% over 10 years)[53].

The rate of blindness was sourced from Dick et al[53] and indicates the estimated rate of blindness for [redacted] and was therefore considered the most relevant source of evidence found. TA460 also identified two other estimates for the rate of blindness but deemed them to be either over or underestimating due to mixed populations being considered in the calculation; detailed in Table 31.

When patients enter subsequent therapy in this model, this rate of blindness applies and there is no anticipated avoidance from the previous therapy. Alternative rates can be seen in Table 31 which were described in TA460 and are used in scenario analysis. Results can be seen in Section 3.8.3.

Table 31: Rates of blindness from literature

Source	Annual rate	Comments
Dick et al 2016[53] (TA460)	0.0066	Population was exclusively comprised of patients with [redacted]
Tomkins-Netzer et al.[54]	0.0038	Estimate was considered an underestimate by clinical advisor to the AG
Durrani et al.[10]	0.0374	Population comprised patients who were already suffering sever and often bilateral uveitis. Authors warned caution when applying this rate to the general population.

3.3.5 Death

It is assumed that uveitis does not directly affect mortality and so the probability of death is informed by the most recent national life tables (2015–2017)[47].

3.3.6 Adverse Events

PSV-FAI-001[35] recorded TEAEs that were related to treatment (TRAEs). Any TRAE that occurred in over 5% of the treatment arm was recorded and included in the model. The rates at which these occurred in the observed time period (1,080 days in PSV-FAI-001) were converted to a cycle probability of experiencing the event. Every cycle, the proportion of patients estimated to experience this adverse event would incur the cost associated with it. The proportions are presented in Table 32 and

show that the most common AEs recorded were cataract, raised intraocular pressure and serious infection. The proportion experiencing the AE in the trial period was transformed to a cyclical probability of experiencing the AE based on the observed time period (36 months).

Table 32: Adverse Events recorded in PSV-FAI-001 for ILUVIEN

Adverse Event	%	ILUVIEN Cycle probability	%	(L)CP Cycle probability	Source
Cataract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Raised IOP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctival haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Iridocyclitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Macular oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Foreign body sensations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular discomfort	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ocular hyperaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eyelid ptosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Macular fibrosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Photopsia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Posterior capsule opacification	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VA reduced	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Visual impairment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous floaters	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyperthyroidism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anterior chamber flare	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vision blurred	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous opacities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctivitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Viral infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.3.7 Summary of Clinical Parameters used in the model

Table 33 details the clinical parameters that are included in the economic model. Time to recurrence informs the On Treatment health state where time is less than 2 years and the Remission heath state where time is greater than 2 years.

Table 33: Clinical parameters used in economic model

Parameter	Method Used	Model applied	Parameter values	Transition probability	Comments
Time to First	Parametric model fitted from	Exponential	Rate = [redacted]	n/a	Fit from 120 days onwards, KM data

Recurrence: ILUVIEN	120 days onwards				used prior to 120 days
Time to First Recurrence: (L)CP	Parametric model	LogLogistic	[redacted]		
Transition to subsequent therapy	Transition dictated by time to first recurrence in respective arm				Proportion calculated as those who have experienced recurrence since previous cycle
Permanent Blindness	Transition probability			0.0006 annually	As per TA460[53]
Mortality	Transition probability			Age-dependent	Calculated from life tables[47]

KM: Kaplan-Meier; (L)CP: (limited) current practice

3.4 *Measurement and valuation of health effects*

3.4.1 Health-related quality-of-life data from clinical trials

PSV-FAI-001[35] did not record any HRQoL measures[35] which is a substantial limitation in the assessment of patient outcomes. Therefore, data to inform HRQoL was sourced from the SLR described in Section 3.4.2. Additionally, key authors were contacted to ask if there was additional literature or data that could be used or had not yet been published. Some authors replied to these requests although no additional data or literature was available. The detailed methods used to identify literature related to HRQoL can be seen in detail in Appendix H and are summarised in Section 3.4.2.1.

The information sourced was mapped to EQ-5D using the methodology outlined in TA460[16] and then applied to the health states in the submission model. This is described in the following sections.

3.4.2 Health-related quality-of-life studies

3.4.2.1 Identification of utility studies

The search was performed to identify any studies that contained HRQoL information pertaining to the decision problem. The search strategy considered adult patients with [redacted] and no restrictions were made on interventions. Specifically, the searches were for utility or disutility values; the inclusion and exclusion criteria can be seen in Appendix H. The following electronic databases were searched:

- MEDLINE (including MEDLINE® In-Process)
- Excerpta Medica Database (EMBASE®)
- Cochrane Library

Additional sources of HRQoL studies were obtained from visually scanning reference lists from relevant studies to identify further studies that may meet eligibility criteria. A free text internet search was also conducted to identify any further studies that may meet eligibility criteria.

3.4.2.2 Identified studies

In total, 870 studies were identified from the database searches and one additional study from additional sources. Once duplicates were removed, 711 studies were screened and 650 were excluded. Of the 61 studies remaining, full-text articles were retrieved, and 36 studies were excluded based on the eligibility criteria. The number of studies remaining for data extraction was 25. The PRISMA diagram for this search can be seen in Figure 16.

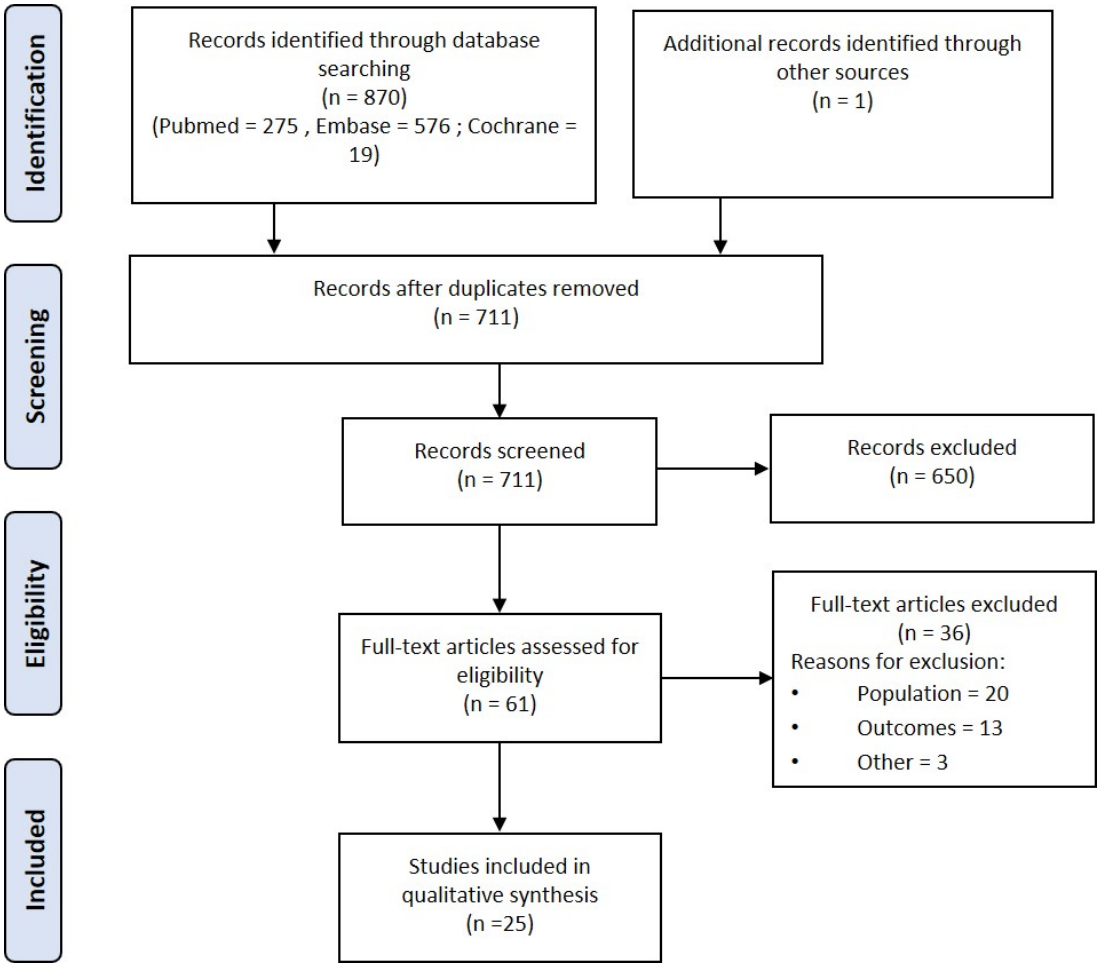


Figure 16: PRISMA diagram for HRQoL studies

3.4.2.3 Study Results

Full study results are shown in Appendix H. Studies that reported EQ-5D or EQ-VAS values can be seen below in Table 34. Two studies were found that provided utility values for a 0.59 mg FAc implant (Retisert); the MUST trial reported EQ-5D values across time for Retisert and systemic treatment arm although this used a US validation set. The European Medicines Agency application for a marketing authorisation for Retisert was withdrawn on 16th July 2017 and therefore it is not a considered comparator[55]. The Frick (2012) study is also a publication from the MUST trial and so these values are also US-validated[56].

Table 34: HRQoL outcomes from studies that reported EQ-5D or EQ-VAS

Author (year)	Treatment	EQ-5D index	EQ-VAS
Multicenter Uveitis Steroid Treatment Trial Research Group (2015)[40]	Retisert	Mean (SE): Enrolment (n=254) = 0.81 (0.02) 12 months (n=235) = 0.83 (0.02) 24 months (n=232) = 0.83 (0.02) 36 months (n=216) = 0.83 (0.02) 48 months (n=207) = 0.84 (0.02) 54 months (n=198) = 0.82 (0.02)	Mean (SE): Enrolment (n=253) = 72.87 (1.96) 12 months (n=234) = 77.61 (1.88) 24 months (n=232) = 78.21 (1.87) 36 months (n=212) = 77.37 (2.15) 48 months (n=204) =75.73 (2.17) 54 months (n=195) = 76.49 (2.17)
	Systemic therapy - oral corticosteroids supplemented by immunosuppressive therapy	Mean (SE): Enrolment (n=254) = 0.83 (0.02) 12 months (n=235) = 0.80 (0.02) 24 months (n=232) = 0.81 (0.02) 36 months (n=216) = 0.81 (0.02) 48 months (n=207) = 0.81 (0.02) 54 months (n=198) = 0.82 (0.02)	Mean (SE): Enrolment (n=253) = 74.48 (2.03) 12 months (n=234) = 71.42 (2.15) 24 months (n=232) = 73.60 (1.91) 36 months (n=212) = 77.68 (1.81) 48 months (n=204) =75.87 (1.80) 54 months (n=195) = 74.33 (2.08)
Frick (2012)[56]	Retisert vs Systemic corticosteroid therapy supplemented with immunosuppression	Median (IQR) at Baseline: All patients (n=255) = 0.8 (0.8-1.0) Intermediate (n=97) = 0.8 (0.8-1.0) Panuveitis (n=158) = 0.8 (0.8-1.0)	Median (IQR) at Baseline: All patients (n=255) = 80 (67-90) Intermediate (n=97) = 75 (60-87) Panuveitis (n=158) = 80 (70-90)
Haasnoot (2017)[57]	NR	Median (range) = 0.8 (0.1-1.0) Mean = 0.8	Median (range) = 74.9 (30.5-100.0) Mean = 72.4
Naik (2013)[58]	Dexamethasone intravitreal implant	Mean (SD) at Baseline= 0.84 (0.13)	NA
Sakai (2013)[59]	Infliximab	Composite scores for baseline / month 6 / month 12 (SD): 0.66 (0.17) / 0.97 (0.08) / 0.96 (0.07)	NA
Squires (2017)[44]	Adalimumab; Dexamethasone	VISUAL I/II, adalimumab, mean (SD): Baseline = 0.83 (0.15) / 0.86 (0.160)	NR

		Best value prior to week 6 = 0.89 (0.128) / NA Final or early termination = 0.86 (0.153) / 0.85 (0.165)	

EQ-5D: EuroQol-five dimensions; EQ-VAS: EuroQol-visual analogue scale; IQR: interquartile range; NA: not applicable; NR: not reported; SD: standard deviation; SE: standard error

Two studies did not report the treatment arms[57,60], one was for dexamethasone and provided only the baseline utility[58] and the other was the SLR and economic evaluation presented as part of TA460[44].

In the MUST trial, the baseline utility with US validation was estimated to be 0.81 for the Retisert arm and 0.83 for the systemic treatment[40]. In TA460, EQ-5D values were available for the adalimumab evaluations but the HURON trial did not collect this information for dexamethasone. For the dexamethasone evaluation, EQ-5D values were available at baseline and VFQ-25 values were available for baseline and follow up times. A regression analysis was performed to examine the relationship between EQ-5D and VFQ-25 in the HURON population. This formula was then used to estimate EQ-5D values for patients across the time of the evaluation of dexamethasone.

The SLR performed for this economic analysis also extracted any VFQ-25 values in case these could be used to inform utility in this submission. The full list can be seen in Appendix H. Only two studies recorded VFQ-25 values for Retisert: Frick 2012 and the MUST trial paper[40]. The data extracted from these two studies can be seen in Table 35.

Table 35: HRQoL outcomes from studies that reported VFQ-25

Author (year)	Treatment	VFQ-25	VFQ-39
Multicenter Uveitis Steroid Treatment Trial Research Group (2015)[40]	Retisert	Mean (SE) Overall composite only Enrolment (n=255) = 61.17 (2.41) 12 months (n=235) = 73.39 (2.45) 24 months (n=232) = 72.61 (2.43) 36 months (n=218) = 73.08 (2.40) 48 months (n=208) = 70.51 (2.43) 54 months (n=197) = 69.96 (2.54)	NA
	Systemic therapy - oral corticosteroids supplemented by immunosuppressive therapy	Mean (SE) Overall composite only Enrolment (n=255) = 65.45 (2.47) 12 months (n=235) = 70.32 (2.48) 24 months (n=232) = 72.19 (2.58) 36 months (n=218) = 74.43 (2.49) 48 months (n=208) = 73.87 (2.62) 54 months (n=197) = 75.28 (2.61)	NA
Frick (2012)[56]	Retisert vs Systemic corticosteroid therapy supplemented with immunosuppression	Median (IQR) at Baseline: All patients (n=255) General health = 65 (55-78) General vision= 55 (40-65) Ocular pain= 75 (50-88) Near activities= 58 (35-75) Distance activities= 58 (38-79) Vision-specific social functioning= 75 (58-92) Vision-specific mental health = 45 (25-65) Vision-specific role difficulties= 56 (38-75) Vision-specific dependency= 69 (38-94) Driving = 50 (0-75) Colour= 100 (75-100) Peripheral vision= 75 (50-75) Overall composite= 62 (44-78)	NA

		Intermediate (n=97) General health = 60 (52-78) General vision= 55 (40-65) Ocular pain= 75 (50-88) Near activities= 62 (42-79) Distance activities= 67 (42-83) Vision-specific social functioning= 83 (67-100) Vision-specific mental health = 45 (20-65) Vision-specific role difficulties= 56 (38-75) Vision-specific dependency= 75 (44-94) Driving = 58 (0-75) Colour= 100 (75-100) Peripheral vision= 75 (50-75) Overall composite= 66 (47-81) Panuveitis (n=158) General health = 65 (55-78) General vision= 55 (40-65) Ocular pain= 75 (50-88) Near activities= 58 (33-75) Distance activities= 55 (38-75) Vision-specific social functioning= 75 (50-92) Vision-specific mental health = 45 (25-65) Vision-specific role difficulties= 56 (38-75) Vision-specific dependency= 69 (38-94) Driving = 42 (0-75) Colour= 100 (75-100) Peripheral vision= 50 (25-75) Overall composite= 60 (44-7)	

IQR: interquartile range; NA: not applicable; SE: standard error; VFQ: visual function questionnaire

3.4.3 Applicability of studies identified in SLR to economic model

3.4.3.1 On Treatment and Off Treatment Utility

The MUST trial has several differences to PSV-FAI-001[35] and so while this information can be used to inform, it should not be considered to be completely representative. The FAc implant used in the MUST trial (Retisert) was a higher strength than in PSV-FAI-001[35] (0.59 mg compared to 0.19 mg in the PSV-FAI-001 trial) and so was associated with different AE incidence and has a slightly different release profile. Another important difference was that the MUST trial did not show significant improvements in vision (the primary outcome described in an earlier paper; Kempen 2011[61]) for patients receiving Retisert, which is contrary to the results from PSV-FAI-001 (described in Section 2.6.3 and shown in Figure 7).

. Some of the patients in the MUST trial Retisert arm also received systemic therapy (20%) which was prohibited in the PSV-FAI-001 trial[35]. Bilateral disease was reported and treated in 67% of patients in the MUST trial whereas only the study eye was treated in PSV-FAI-001[48,61]. Macular oedema was present in 41% of patients at enrolment in the MUST trial[61] [redacted] This indicates that the baseline population was slightly different between the two trials.

However, Kempen 2011[61] reports that at 24 months, only 6% of patients have active uveitis which is indicative of a response to treatment with an implant[61]. At enrolment 78% of patients in the implant arm had active uveitis and so this value is considered representative of being off treatment. When patients enrolled in the MUST trial they were accepted if they displayed recurrence and were permitted to be taking systemic treatments. This matches the criteria for patients in subsequent therapy in this economic model.

As no generic measures using a UK validation were sourced from the SLR, mapping the VFQ-25 to EQ-5D from the MUST trial was considered the most appropriate approach for On Treatment and Off Treatment health states. While the populations are not identical, they are using a similar technology and are in the same indication, so this was considered the most conservative approach. This is the method that was

used for the dexamethasone comparison in TA460[35] where the same problem arose. Mapping is described in Section 3.4.4.

3.4.3.2 Blindness Utility

In the base case, the utility value for blindness is the same as was used in TA460[16] and was sourced from this document. This value was reported in Czoski-Murray et al.[62] as 0.38. This value was based on public valuations of utility but the AG note that it does not provide values for the worst states of blindness and therefore could result in an underestimation of the overall utility. An additional value was identified in TA460[16] as being potentially applicable and this is tested in scenario analysis described in Section 3.8.3 and is shown in Table 36.

Table 36: Blindness utility values

Source	Reported utility	Comments
Czoski-Murray et al[62] (TA460)	0.38	Used contact lenses to simulate blindness associated with macular degeneration
Brown et al[63] (TA460)	0.57	Valuations made by patients with a range of conditions associated with blindness

3.4.3.3 Remission Utility

When patients enter the Remission, they are not expected to experience any HRQoL detriment because of uveitis and therefore accrue utility as the general population would (clinical experts, personal communication). These values assigned to the remission population are age-matched EQ-5D values and can be seen in Table 37. The utility values were sourced from Janssen and Szende 2013[64] and are country specific TTO EQ-5D values in line with the preference listed in the NICE Methods Guide 2013[50].

Table 37: Age matched utility values used for Remission health state

Age group (years)	Utility Value	Source
18-24	0.929	Janssen and Szende (2013)[64]
25-34	0.919	
35-44	0.893	
45-54	0.855	
55-64	0.810	
65-74	0.773	

75+	0.703	

3.4.4 Mapping

As no generic measures using a UK validation were sourced from the SLR, mapping the VFQ-25 to EQ-5D from the MUST trial was considered the most appropriate approach initially. TA460 used a regression analysis to estimate the relationship between VFQ-25 and EQ-5D values for use in the evaluation for dexamethasone[16]. This strategy was employed because the HURON trial recorded EQ-5D data at baseline but not at any other time point, but VFQ-25 data was reported for follow up times. The regression equation used was as follows:

EQ-5D utility = 0.4454059 + VFQ-25 score * 0.0051322

It was acknowledged that this model is not bounded and is likely to have poor performance with extreme utility values however no extreme values are used in this equation. The model also assumes that the relationship between VFQ-25 and EQ-5D is independent of treatment.

Results from the MUST trial for VFQ-25[40] can be seen in Table 38. These show that the implant group reported slightly worse vision related outcomes than the systemic group. This data as reported does not provide insight as to whether the patients in the group from which the mean is estimated are responding to treatment. Specifically, in the case of the implant group whether these patients have experienced recurrence and are therefore receiving systemic treatment. When the mean change in EQ-5D or VFQ-25 are plot (shown in Figure 17 this becomes more apparent because the reported outcome and EQ-5D in the implant arm shows a decrease over time. Conversely the systemic arm shows increasing utility and outcomes over time which is contrary to the clinical profile described and validated by expert clinicians (personal communication).

Table 38: Reported VFQ-25 values from the MUST trial and calculated EQ-5D values

		Reported VFQ-25[40]		**Calculated EQ-5D**	
		Implant	**Systemic**	**Implant**	**Systemic**
Visit	**N**	**Estimated mean**	**Estimated mean**	**Estimated mean**	**Estimated mean**

Enrolment	255	61.17	65.45	0.759	0.781
12 months	235	73.39	70.32	0.822	0.806
24 months	232	72.61	72.19	0.818	0.8159
36 months	218	73.08	74.43	0.820	0.827
48 months	208	70.51	73.87	0.807	0.825
54 months	197	69.96	75.28	0.804	0.832

Figure 17: Change in EQ-5D as predicted from MUST trial VFQ-25 values

Importantly, the MUST trial reports that from 12 to 24 months there is no significant difference in the primary outcome (visual acuity – letters read) between arms[61]. This outcome data was not found for 24 months onwards so no judgement can be made for this time. This is not representative of the data from PSV-FAI-001 which indicates improving vision in the ILUVIEN arm; a mean change from baseline

. The MUST trial reports a mean change 3.19-3.90 for the implant arm (better eye) compared to 1.43-1.92 for the systemic treatment arm.

Butt et al. 2016[65] report a positive correlation between better reading acuity and EQ-5D scores and so it is possible that the utility of patients in the ILUVIEN arm of PSV-FAI-001 would have a different utility profile over time than that shown in the MUST trial[65]. The assumption that better visual acuity is related to better HRQoL outcomes is also investigated and supported by Brazier et al 2017[66]. This is also true when considering the differing AE profile associated with the implant considered in the MUST trial and ILUVIEN.

3.4.4.1 Use of mapped values in the economic model

Given the differences described in Section 3.4.4 regarding the population differences between the MUST and PSV-FAI-001 patients and the pattern of utility shown in

Figure 17 it was not considered appropriate to use these values for the base case analysis.

Instead, the baseline estimated EQ-5D value (0.759) from the Retisert arm was chosen to represent “off treatment/subsequent therapy” in the base case. At enrolment, 87% of the implant arm had active uveitis and which is in line with the inclusion criteria for PSV-FAI-001. Given that at baseline, [redacted] and the differing supplemental therapy profile, this is a conservative estimate.

At 24 months, the MUST trial reports that only 6% of patients still have active uveitis[61]. The calculated EQ-5D value was therefore chosen to represent “on treatment/responding to treatment” (0.818). At this time, 22% of patients in the MUST trial had macular oedema. [redacted] so this is also considered a conservative estimate[35].

These values are therefore appropriate for both ILUVIEN and (L)CP as they take into account the ocular diseases response to therapy as opposed to the treatment specifically. These also will account for common adverse events experienced by patients who are either experiencing no recurrence of disease or have experienced recurrence and are now taking systemic therapies.

3.4.5 Adverse reactions

As the values used for on and off treatment were estimated from patients using (L)CP and mapped to UK validated EQ-5D values (from the MUST trial) it was not considered appropriate to also include disutilities for AEs as this would constitute double counting.

3.4.6 Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of the utilities applied to each health state as discussed in this section can be seen in Table 39.

Table 39: Summary of utility values used in cost-effectiveness analysis

Health state	Utility (mean)	Lower Bound	Upper Bound	Justification	Reference in submission
On treatment	0.818	0.654	0.982	MUST trial mapped value at 24 months	
Subsequent therapy	0.759	0.607	0.911	MUST trial mapped value at baseline	
Permanent blindness	0.38	0.304	0.456	As per TA460 – sourced from Czoski-Murray et al[62]	
Remission: Ages 45-54	0.855	0.684	1.000	Clinical opinion – Age matched utilities [64]	
Remission: Ages 55-64	0.81	0.648	0.972		
Remission: Ages 65-74	0.773	0.618	0.928		
Remission: Ages 75+	0.703	0.562	0.844		
Disutilities	Not applied as health state values taken from patients who are taking either implant or subsequent therapy. This should be captured.				

3.5 *Cost and healthcare resource use identification, measurement and valuation*

A comprehensive search was undertaken to systematically identify costs and recourse use for [redacted]

Databases were searched from database inception to 25th September 2018. The literature searches included the following electronic databases:

- MEDLINE (including MEDLINE® In-Process)
- Excerpta Medica Database (EMBASE®)

- Cochrane Library
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Methodology Register (CMR)
- Database of Abstracts of Reviews of Effects (DARE)
- Health Technology Assessment Database (HTA)
- NHS Economic Evaluation Database (EED)
- EconLit

Figure 18 presents an overview of study flow. A total of 1,568 studies was identified from database studies, together with seven studies from additional sources. After removing duplicates, 1,313 studies were screened, of which 1,278 studies were excluded. Of the 35 studies remaining, full-text articles were retrieved, and 30 studies were excluded based on the eligibility criteria. The number of studies remaining for data extraction was five, of which two publications reported the same study (Adan-Civera (2016)[67] and Blanco (2013)[68]).

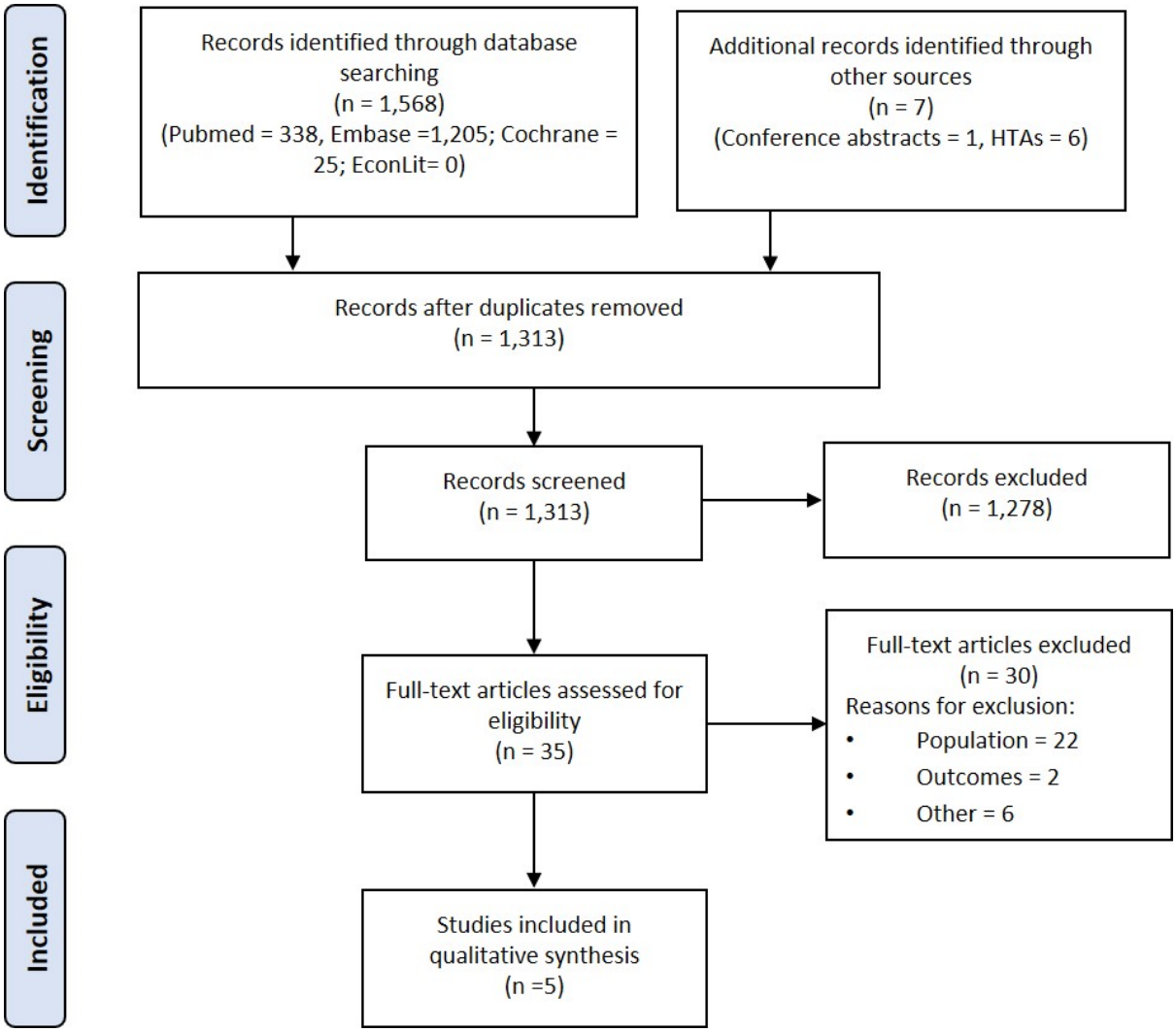


Figure 18: PRISMA diagram for Cost and Resource Use Studies

The main outcomes of this literature review are provided in Table 40, from a total of five included studies.

Table 40: Outcomes reported in key papers sourced in Cost and Resource SLR

Author (year)	Country	Patient population	Intervention/ comparator	Year costs reported	Costs	Resource use
Adan-Civera (2016)[67] Blanco (2013)[68]	Spain	Non-infectious posterior uveitis	Including: Mydriatic and cycloplegic agents, topical and systemic corticosteroids, sulfasalazine, antimetabolites, and T-cell and anti-TNF inhibitors.	2011	Total costs (costs per patient), Euro: Initial drug therapy = 16,561,092 (11,747.96) Drug therapy for flares = 978,178 (693.89) Overall annual cost (Euro) = 22,283,330.50 Cost per patient per year (Euro) = 15,919.52	Total costs (costs per patient), Euro: Referral = 330,613 (149.57) Diagnostic visits = 1,386,383 (983.46) Diagnostic tests = 557,618 (395.56) Follow-up visits = 830,087 (588.84) Follow-up tests = 1,493,577 (1059.50) Treatment of complications = 145,778 (300.75)
Gavaghan (2013)[69]	USA	Patients with non-infectious posterior uveitis	corticosteroids, corticosteroid injections, immunomodulators, and biologics	NR	Average cost per patient (USD): Prior to diagnosis (n=5775) = $185.43 24 months post-diagnosis (n=11570) = $249.01	Prior to diagnosis: 58.0% topical/systemic corticosteroids, 22.7% corticosteroid injections, 15.7% immunomodulators, 3.7% biologics 24 months post-diagnosis: 45.7% topical/systemic corticosteroids, 37.4% corticosteroid injections,16.4% immunomodulators, 3.2% biologics

Padula (2011)[41]	USA	Patients with sarcoid posterior uveitis	Infliximab versus Methotrexate and systemic steroids	2010	Costs (USD): systemic steroids = $26871 Methotrexate = $40351 Infliximab = $46547	Not reported
Squires (2017)[44]	UK	Adult patients for non-infectious uveitis (intermediate uveitis, posterior uveitis or panuveitis)	Adalimumab and Dexamethasone versus Immunosuppressants and corticosteroids	2015	6-monthly cost (£): Adalimumab = £4578 Dexamethasone = £870 Mycophenolate mofetil =£136 Methotrexate = £16 Ciclosporin = £985 Azathioprine = £27 Systemic prednisolone = £12	Administration costs: Adalimumab = £44 Dexamethasone = £113.42 Monitoring costs = £96.11 Costs of adverse events (resource use): Cataract (cataract surgery) = £852.40 (one-off) Raised IOP (treatment) = £23.42 (one-off) Glaucoma (surgery) = £581.25 (one-off) Serious infection (hospitalisation) = £5940.50 (one-off) Hypertension (antihypertensive prescription) = £7.04 (one-off) Permanent blindness (blind registration, low-vision aids, rehabilitation, depression, hip replacement, community care, residential care) = £237

						(transition) or £7659 (annual) Fracture (hospitalisations, A&E visits, referrals, prescriptions, GP contacts) = £2116.17-6022.62 (one off) Diabetes (treatment and hospitalisation for complications) = £1521.46 (annual)

3.5.1 Applicability of studies identified in SLR to economic model

Of the identified studies, one contained costs and resource use sourced in the UK; this was the SLR that informed TA460 (Squires et al[44]). Other studies reported costs that were applicable to healthcare systems in Europe[67,68] and the US (other 2)[41,69]. Adan-Civera[67] and Blanco[68] report total costs and the total patients requiring the use of resources but unit costs were not reported. Similarly, Gavaghan[69] and Padula[41] report average costs in USD, Gavaghan also reports the proportion requiring topical/systemic corticosteroids, corticosteroid injections, immunomodulators and biologics prior to therapy and 24 months after diagnosis. Of these four studies, none contained a treatment arm where the treatment was implant treatment similar to ILUVIEN. Therefore, generalisation of these costs to the current economic analysis is not appropriate.

Squires et al 2017 reports unit costs that were applicable to patients with a dexamethasone implant[44]. This technology is similar to ILUVIEN in that it is a local treatment and therefore was considered the most appropriate source to inform the economic analysis. Consequently, costs are applied in this model in line with those reported in Squires et al 2017 and used in TA460.

3.5.2 Intervention and comparators' costs and resource use

3.5.2.1 ILUVIEN and (L)CP treatment costs

ILUVIEN is administered only once at the beginning of the treatment. One ILUVIEN implant is priced at [redacted] and an administration cost of £99.58 is added to this in the first cycle to represent fitting. The administration cost is assumed to be an outpatient appointment, based on the NHS Reference Cost listed for a minor vitreous procedure for patients aged 19 years and above (code BZ87A). This is in line with the assumption made about administration in TA460.

Treatment with (L)CP would not incur an acquisition cost as cost would be incurred as supplemental therapies.

The one-off costs associated with treatment for ILUVIEN are shown in Table 41.

Table 41: One-off treatment costs for ILUVIEN (L)CP

First Line treatment	Total Cost	Cost components
ILUVIEN	[redacted]	[redacted]
(L)CP	£0	No acquisition cost or administration cost

3.5.2.2 Patient Access Scheme

A Patient Access Scheme (PAS) has been applied, comprising a discount of [redacted] from the ILUVIEN list price. In order to best replicate the true economic impact of a positive recommendation for ILUVIEN, the economic evaluation presented in this submission applies the PAS in the base case analysis. The list cost for ILUVIEN is £5,500. With the agreed discount, the cost of ILUVIEN used in this model is [redacted]

	ILUVIEN Cost
No PAS	£5,500
[redacted]	[redacted]

3.5.2.3 Supplemental therapy costs

While patients are taking either ILUVIEN or (L)CP it is assumed that they are taking supplemental therapy. This assumption is in line with the assumption reported in TA460 and are as reported in PSV-FAI-001. The proportion taking the supplemental therapies in the ILUVIEN arm is as reported in the 36-month CSR. The CSR reports those taking immunosuppressants and systemic steroids is prohibited during the trial period. However, it is also reported that patients who present at trial onset taking these therapies will be tapered off during the first three months. As such, the cost of supplemental therapies is only applied for the first three months. After that time they do not receive any supplemental therapies.

These proportions can be seen in Table 27 and the cost of each treatment can be seen in Table 42. Administrative costs are not considered as it is assumed that treatment would be prescribed or administered in the monitoring appointments; this is in line with the approach taken in TA460. This results in a cost of £96.49 and £122.02 per model cycle for ILUVIEN and (L)CP respectively for supplemental therapies. Two treatments, Flubriprofen and Fluress are not available in the UK and are therefore cost at £0 as these costs would not be applicable in the UK setting.

The cyclical cost of the supplemental therapies for ILUVIEN and CP are only applied for the first three months in line with the CSP for PSV-FAI-001. The costs shown in Table 42 are also applied to the proportion who take medication upon recurrence shown in Table 28 and are applied only once when a patient transitions to subsequent therapy.

One patient in the ILUVIEN arm and three patients in the (L)CP arm received Fluocinolone acetonide in PSV-FAI-001. These were not costed as it is assumed that these were for recurrence and a patient would not have two implants in the study eye at once while responding to treatment.

Table 42: Medication costs for supplemental and subsequent therapies

Medication	Unit Cost (Sourced from MIMS[46])	Availability and dosage	Cyclical Cost
Mycophenolate mofetil	£6.53	500mg tab, 50 1g twice daily	£3.67
Methotrexate	£47.50	10mg tab, 100 15mg weekly	£1.43
Cyclosporine	£102.30	100mg/ml, 50ml 2mg per kg twice daily	£88.64
Azathioprine	£2.25	50mg tab 56 1mg per kg daily	£0.87
Systemic prednisolone	£0.70	5mg tab, 28 7.5mg daily	£0.53
Tacrolimus	£205.74	5mg capsule, 50 0.2 mg/kg daily	£159.17
Beta-interferon	£596.63	250ug/ml, 15 sachets 250ug every other day	£18.63
Abatacept	£1,209.60	4 x 125mg prefilled pen One dose weekly	£606.88
Golimumab	£762.97	1 pen, 50mg Assumed as rheumatoid arthritis, 50mg once a month	£352.14
Dexamethasone	£8.78	0.1% single use drops, 20x0.4ml 1 drop 4 times when inflamed	£2.20
aetazolamide	£16.07	250mg tab, 112 250mg daily	£2.02

apraclonidine	£10.88	0.5% eye drops, 5ml (assumed 100drops) 3 drops daily	£4.59
Anti-inflammatory agents and anti-infectives	£0.00	TBC	£0.00
artificial tears	£4.80	assumed as carmellose	£0.34
Atropine	£15.10	20 single use drops Assume use for whole cycle	£1.51
besifloxacin hydrochloride	£4.70	assumed as ciprofloxacin	£2.64
Bevacizumab	£924.40	400mg/16ml, 1 vial Assumed as RCC as no supplemental medications. 10mg/kg once every 2 weeks	£1,781.78
Bimatoprost	£10.30	300microgram/ml, 1 x 3ml (assumes 20 drops each, 60 drops total) 1 drop daily	£2.41
Brimonidine tartate	£1.35	5ml assumes 100 drops 2 drops daily	£0.38
Bromfenac	£8.50	5ml assumes 100 drops 2 drops daily	£2.39
Budesonide w formoterol fumarate	£21.50	60 inhalations 2 inhalations daily	£10.07
Carmellose	£4.80	10ml assumes 200 drops 1 drop daily	£0.34
carmellose sodium	£4.80	assumed as carmellose	£0.34
Carbomer	£1.59	Assume 10mg is equal to 0.01ml, 10g =10000mg = 10ml = 200 drops 4 drops daily	£0.45
Chloramphenicol	£1.38	10ml assumes 200 drops 6 drops daily	£0.58
Ciprofloxacin	£4.70	0.3% eye drops, 5ml (assumes 100 drops) Assumed as conjunctivitis as chronic condition, Conjunctivitis: 1 or 2 drops into affected eye(s) four	£2.64

		times daily. (therefore assumed 4 drops daily)	
Corticosteroids and anti-infectives in combination	£0.00	TBC	£0.00
Combigan	£27.00	3x5ml assumes 300 drops 2 drops daily	£2.53
Cosopt	£10.05	5ml assumes 100 drops 2 drops daily	£2.82
Cyclopentolate hydrochloride	£11.41	20 single use drops 1 daily	£8.01
Difluprednate	£8.78	corticosteroid drops assumed as dexamethasone	£2.20
Fluticasone propionate	£4.00	60 inhalations (50micrograms per inhalation) 100 micrograms per day (2 inhalations)	£0.27
Fluoracine oph soln	£0.00	TBC	£0.00
Flurbiprofen	£0.00	NSAID – costed at £0 as not available in the UK NSAID	£0.00
Fluress	£0.00		£0.00
Gatifloxacin	£2.47	Assumed as gentamicin	£0.69
Gentamicin	£2.47	10ml assumes 200 drops 4 drops daily	£0.69
Homatropine hydrobromide	£0.00		£0.00
Hyaluronate sodium	£4.80	assumed as Carmellose	£0.34
Iodine	£0.00	diagnostic so seems odd?	£0.00
Ketorolac/ Ketorolac tromethamine	£3.00	5ml assumes 100 drops 3 drops daily	£1.26
Latanoprost	£1.85	2.5ml assumes 50 drops 1 drop daily	£0.07
Lidocaine	£0.00	TBC	£0.00
Loteprednol	£5.50	5ml assumes 100 drops 4 drops daily for 2 weeks	£3.09
Maxitrol	£1.68	5ml assumes 100 drops 6 drops daily	£1.42

Moxifloxacin	£2.47	assumed as gentamicin	£0.69
Moxifloxacin hydrochloride	£2.47	assumed as gentamicin	£0.69
Methylprednisolone/ Methylprednisolone sodium succinate	£17.17	16mg tablets - 30 12-40 (assumed 16 for ease) mg per day for ophthalmologic disorders https://www.medicines.org.uk/emc/medicine/1534	£1.14
Nepafenac	£14.92	3mg/ml 3ml assumes 60 drops once daily	£3.49
Ofloxacin	£2.17	3mg/ml 3ml assumes 60 drops 4 drops daily for	£2.03
Other ophthalmologicals	£0.00		£0.00
Oxybuprocaine	£10.56	20 single use eye drops Once daily	£7.42
Oxybuprocaine hydrochloride	£10.56	assumed as oxybuprocaine	£7.42
Paremyd	£0.00	TBC	£0.00
Phenylephrine	£11.87	Single use eye drops 20 one as required	£0.59
Phenylephrine hydrochloride	£16.00	Single use eye drops 20 2 as required	£1.60
Phenylephrine w tropicamide	£16.00	assumed as phenylephrine hydrochloride	£1.60
Povidone-Iodine	£16.00	20 drops 2 drops only	£1.60
Proxymetacaine	£12.12	20 drops 2 drops only	£1.21
Simbrinza	£9.23	5ml assumes 100 drops 2 drops daily	£2.59
Systane lubricant	£4.66	28x single use 1 as required	£0.17
Tears plus	£4.80	assumed as Carmellose	£0.34
Tetracaine hydrochloride	£10.57	20 single use eye drops 1 as required	£0.53
Timolol	£1.01	5ml assumes 100 drops 2 drops daily	£0.28
Timolol maleate	£1.01	assumed as timolol	£0.28

Tobradex	£5.37	5ml assumes 100 drops 4 drops daily	£0.43
Triamcinolone acetonide	£8.78	Assumed as Dexamethasone	£2.20
Systemic corticosteroids	£0.00		£0.00
Prednisone	£12.25	20 single use drops 1 as required	£0.61
Lidocaine	£0.00	TBC	£0.00
Bromfenac	£8.50	5ml assumes 100 drops 2 drops daily	£2.39

3.5.3 Health-state unit costs and resource use

3.5.3.1 Monitoring Costs

While patients are taking subsequent treatment, it is assumed that they will receive monitoring every 6 weeks. This is comprised of outpatient visits to assess visual functioning and monitor potential AEs and have blood tests. This assumption is in line with that made about monitoring costs and resource use presented in TA460. A cost of £110.48, representing the monitoring every 6 weeks is applied in the model as a cyclical cost of £36.83, this can be seen in Table 43. This cost is sourced from the NHS Reference costs, listed as an outpatient attendance visit, outpatient, face to face visit (WF01A)[70].

When a patient has an implant treatment and no systemic treatments, clinical advice confirms that there is no need for them to have such frequent monitoring (clinical experts, personal communication). It is recommended that these patients come in for observation every 12 weeks. The model applies the cost of an outpatient visit once every 12 weeks for patients on first line treatment after 3 months (when they have tapered off systemic treatment) and for those in remission.

Table 43: Monitoring costs applied to patients On Treatment

		Monitoring frequency assumed	
		Every 6 weeks	Every 12 weeks
Unit cost	£110.48[70]		
Model cycle cost		£36.83	£18.41

3.5.3.2 Subsequent Therapy

Subsequent therapy is assumed to be treatment with immunosuppressants and systematic steroids. The costs were sourced from MIMS[46] and are shown in Table 42. Where multiple costs were available for the same drug, the least costly was used in the model. These costs are multiplied by the proportion receiving the therapy as shown in Table 44 and are then applied cyclically to patients in subsequent therapy.

The proportion taking the immunosuppressants and systemic prednisolone in subsequent therapy is assumed to be as reported for TA460. This then forms a weighted immunosuppressant cost. The proportion who receive systemic steroids and immunosuppressants in subsequent therapy is assumed to be as it was at enrolment of PSV-FAI-001, i.e. the patient has returned to the untreated state[35]. These values and calculations can be seen in Table 44.

Table 44: Cost of subsequent therapies

	Reported proportion (TA460)[16]	**Weighted proportion**	**Cost**
Mycophenolate mofetil	*21%*	*33%*	£1.22
Methotrexate	*31%*	*50%*	£0.71
Cyclosporine	*7%*	*11%*	£9.85
Azathioprine	*3%*	*5%*	£0.05
Proportion taking immunosuppressants[35]	*19%*		
Proportion taking corticosteroids[35]	*31%*		
Total cost of immunosuppressants	£2.29		
Total cost of corticosteroids	£0.16		
Total cyclical cost of subsequent therapy	**£2.45**		

3.5.3.3 Permanent Blindness

In the base case, the cost and resource use related to blindness were sourced from TA460. These estimates were based on a search that was limited between 2006 and 2016. The costs quoted in TA460 were inflated to 2015 costs and for this submission they were inflated to 2017 values using the Hospital and Community health services index from PSSRU 2017[45]. The values reported in TA460 were presented in a HTA for age-related macular degeneration but were considered the best source of

evidence available. These are shown in Table 45. Registration, low vision aids and low vision rehabilitation are one-off costs and so applied on transition. This cost of £4,592.36 is applied when a patient moves to the permanent blindness health state. Depression, hip replacement, community care and residential care are provided as annual costs. The annual cost for these components is £1,206.07 and is applied cyclically in the model for the length of time a patient resides in this state. It is estimated that 30% of patients pay for their own residential care, which is the assumption reported in TA460 and therefore this proportion is not incorporated into the model.

Table 45: Cost associated with permanent blindness

Cost Element	% receiving service	Resource use SE+/-	Cost	Cost SE+/-	Cost Source	Resource use source
Registration	95%	**9.5%**	£150.580[c]	£15.06	TA460 - inflated	TA460[16]
Low vision aids	33%	**3.3%**	£197.00[c]	£19.70	TA460 - inflated	
Low vision rehabilitation	11%	**1.1%**	£339.33[c]	£33.93	TA460 - inflated	
Depression	39%	**3.9%**	£2,452.64[a]	£245.26	TA460 - inflated	
Hip replacement	5%	**0.5%**	£4,642.93[a]	£424.29	NHS reference costs – intermediate hip procedures for non-trauma	
Community Care	6%	**0.6%**	£289.82[a]	£28.98	TA460 - inflated	
Residential Care	30%	**3%**	£22,414.44[a,b]	£2,241.41	TA460 - inflated	

a: Annual cost. b: 30% of patients pay for this themselves. c: One off cost

3.5.4 Adverse reaction unit costs and resource use

The AEs reported in Section 3.3.6 may incur costs associated with treatment. The resource for any other AEs was indicated by a clinician (clinical experts, personal communication) and costed from NHS reference costs[70], PSSRU 2016[45] and MIMS[46] for drug treatments.. These costs and resource use can be seen in Table 46. These

costs are multiplied by the cyclical probabilities shown in Table 32 according to the proportion who experienced these in PSV-FAI-001 to provide the cost of treating AEs with ILUVIEN and (L)CP. Costs are assumed to occur only once as these are applied cyclically and there is no information available to indicate how many patients experienced these events more than once.

Table 46: Cost and resource use of treating Adverse Events

Adverse Event	Resource Use	Resource use source	Cost	Frequency	Cost Source
Cataract	Cataract Surgery	TA460[16]	£919.05	Once	NHS reference costs (BZ33Z)[70]
Raised IOP	Treatment with 2 doses of bimatoprost	TA460[16]	£2.40	Once	Cost - Table 27
Hypertension	Anti-hypertensive prescription	TA460[16]	£7.26	Once	TA460[16]
Iridocyclitis	Uveitis - considered recurrence	CS/ clinical expert advice	£0.00	Once	n/a
Conjunctival hyperaemia	General Practitioner appointment	CS/ clinical expert advice	£38.00	Once	PSSRU 2017 Table 10.3b incl direct staff costs, with qualification[45]
Macular oedema	Avastin, Eylea, and Lucentis injection into eye (outpatient appointment and drug treatment)	CS/ clinical expert advice	£119.78	Once	Assume treatment with Lucentis (cheapest option) - 10mg/ml, 0.23ml vial = 2.3mg per vial = 2300 micrograms. 500micrograms for an administration = 4.6 administrations per vial. Cost of £551

					divided by 4.6
Dry eye	Artificial tears	CS/ clinical expert advice	£0.34	Once	Cost - Table 27
Eye pain	Cyclosporine	CS/ clinical expert advice	£88.34	Once	Cost - Table 27
Foreign body sensations	No treatment	Assumption	£0.00	Once	n/a
Ocular discomfort	As eye pain	CS/ clinical expert advice	£88.34	Once	Cost - Table 27
Ocular hyperaemia	As conjunctival hyperaemia	Assumption	£0.00	Once	n/a
Gastrointestinal disorders	No treatment	Assumption	£0.00	Once	n/a
Eyelid ptosis	Surgery	CS/ clinical expert advice	£1,689.32	Once	NHS reference costs (BZ45A) [70]
Macular fibrosis	No treatment	CS/ clinical expert advice	£0.00	Once	n/a
Photopsia	As myodesopsia	CS/ clinical expert advice	£0.00	Once	n/a
Posterior capsule opacification	Laser surgery	CS/ clinical expert advice	£148.38	Once	NHS reference costs (BZ86B) [70]
VA reduced	Assumed recurrence	Assumption	£0.00	Once	n/a
Visual impairment	Assumed recurrence	Assumption	£0.00	Once	n/a
Vitreous floaters	As myodesopsia	Assumption	£0.00	Once	n/a
Nasopharyngitis	Over the counter medications - No cost	CS/ clinical expert advice	£0.00	Once	n/a
Headache	NSAIDs	Assumption	£0.00	Once	n/a
Depression	General Practitioner appointment	CS/ clinical expert advice	£38.00	Once	PSSRU 2017 Table 10.3b incl direct staff costs, with

					qualification[4 5]
Hyperthyroidism	carbimazole or propylthiouracil prescription	CS/ clinical expert advice	£143.45	Once	Assume 20mg per day. Treat until patient is euthyroid (assume whole packet for ease) 100 tablets
Anterior chamber flare	Uveitis - considered recurrence	Assumption	£0.00	Once	n/a
Vision blurred	General Practitioner appointment	CS/ clinical expert advice	£38.00	Once	PSSRU 2017 Table 10.3b incl direct staff costs, with qualification[4 5]
Vitreous opacities	As myodesopsia	CS/ clinical expert advice	£0.00	Once	n/a
Conjunctivitis	No treatment	CS/ clinical expert advice	£0.00	Once	n/a
Pain	NSAIDs – over the counter medications	Assumption	£0.00	Once	n/a
Viral infection	Drs appointment	CS/ clinical expert advice	£38.00	Once	PSSRU 2017 Table 10.3b incl direct staff costs, with qualification[4 5]
Nausea	Over the counter medications - No cost	CS/ clinical expert advice	£0.00	Once	n/a
Fatigue	No treatment	Assumption	£0.00	Once	n/a
Cough	No treatment	Assumption	£0.00	Once	n/a

Multiplying the presented costs with the proportion reported to be experiencing an AE in PSV-FAI-001 results in a cyclical cost of £8.98 and £5.07 being added for ILUVIEN and (L)CP respectively.

3.5.5 Miscellaneous unit costs and resource use

No additional costs are were applied to patients receiving treatment in this economic analysis. All costs applied are reported in Sections 3.5.2 to 3.5.4.

3.6 *Summary of base-case analysis inputs and assumptions*

3.6.1 Summary of base-case analysis inputs

All inputs for the economic analysis can be seen in Table 47. The base case value is shown with the distribution applied in sensitivity analysis, lower and upper bound values used and cross referenced to the section where information about this parameter is described.

Table 47: Summary of variables included in the economic model

Parameter	Base case value	Distribution applied	Lower Bound	Upper Bound	Reference in Submission
Monitoring Health state costs	£110.48	Gamma	£88.38	£132.58	Section 3.5.3.1
Blindness proportion using resource					
Registration resource use: Blindness	95.00%	Beta	76.00%	100.00%	Section 3.5.3.3
Low vision aids resource use: Blindness	33.00%	Beta	26.40%	39.60%	
Low vision rehabilitation resource use: Blindness	11.00%	Beta	8.80%	13.20%	
Depression resource use: Blindness	39.00%	Beta	31.20%	46.80%	
Hip replacement resource use: Blindness	5.00%	Beta	4.00%	6.00%	
Community Care resource use: Blindness	6.00%	Beta	4.80%	7.20%	
Residential Care resource use: Blindness	30.00%	Beta	24.00%	36.00%	
Blindness costs					
Registration cost: Blindness	£150.58	Gamma	£120.47	£180.70	Section 3.5.3.3
Low vision aids cost: Blindness	£197.00	Gamma	£157.60	£236.39	
Low vision rehabilitation cost: Blindness	£339.33	Gamma	£271.46	£407.19	
Depression cost: Blindness	£2,452.64	Gamma	£1,962.11	£2,943.17	
Hip replacement cost: Blindness	£4,642.93	Gamma	£3,714.34	£5,571.51	
Community Care cost: Blindness	£289.82	Gamma	£231.86	£347.78	
Residential Care cost: Blindness	£22,414.14	Gamma	£17,931.31	£26,896.96	
Supplemental therapy costs					
Mycophenolate mofetil Cost	£6.53	Not varied			

Methotrexate Cost	£47.50	Not varied			Section 3.5.2.3
Cyclosporine Cost	£102.30	Not varied			
Azathioprine Cost	£2.25	Not varied			
Systemic prednisolone Cost	£0.70	Not varied			
Tacrolimus Cost	£205.74	Not varied			
Beta-interferon Cost	£596.63	Not varied			
Abatacept Cost	£1,209.60	Not varied			
Golimumab Cost	£762.97	Not varied			
Dexamethasone Cost	£8.78	Not varied			
aetazolamide Cost	£16.07	Not varied			
apraclonidine Cost	£10.88	Not varied			
artificial tears Cost	£4.80	Not varied			
besifloxacin hydrochloride Cost	£4.70	Not varied			
bimatoprost Cost	£10.30	Not varied			
carmellose Cost	£4.80	Not varied			
carmellose sodium Cost	£4.80	Not varied			
chloramphenicol Cost	£1.38	Not varied			
ciprofloxacin Cost	£4.70	Not varied			
corticosteroids and anti-infectives in combination Cost	£0.00	Not varied			
combigan Cost	£27.00	Not varied			
Cosopt Cost	£10.05	Not varied			
Difluprednate Cost	£8.78	Not varied			
Fluoracine oph soln Cost	£0.00	Not varied			
Flurbiprofen Cost	£0.00	Not varied			

Fluress Cost	£0.00	Not varied			
Gatifloxacin Cost	£2.47	Not varied			
Gentamicin Cost	£2.47	Not varied			
Homatropine hydrobromide Cost	£0.00	Not varied			
Hyaluronate sodium Cost	£4.80	Not varied			
Iodine Cost	£0.00	Not varied			
Lidocaine Cost	£0.00	Not varied			
Loteprednol Cost	£5.50	Not varied			
Maxitrol Cost	£1.68	Not varied			
Moxifloxacin Cost	£2.47	Not varied			
Moxifloxacin hydrochloride Cost	£2.47	Not varied			
Nepafenac Cost	£14.92	Not varied			
Ofloxacin Cost	£2.17	Not varied			
Oxybuprocaine Cost	£10.56	Not varied			
Oxybuprocaine hydrochloride Cost	£10.56	Not varied			
Paremyd Cost	£0.00	Not varied			
Phenylephrine Cost	£11.87	Not varied			
Phenylephrine hydrochloride Cost	£16.00	Not varied			
Phenylephrine w tropicamide Cost	£16.00	Not varied			
Povidone-Iodine Cost	£16.00	Not varied			
Simbrinza Cost	£9.23	Not varied			
Systane lubricant Cost	£4.66	Not varied			
Tetracaine hydrochloride Cost	£10.57	Not varied			
Timolol Cost	£1.01	Not varied			

Timolol maleate Cost	£1.01	Not varied			
Triamcinolone acetonide Cost	£8.78	Not varied			
Systemic corticosteroids Cost	£0.00	Not varied			
Prednisone Cost	£12.25	Not varied			
Lidocaine Cost	£0.00	Not varied			
Bromfenac Cost	£8.50	Not varied			
anti-inflammatory agents and anti-infectives Cost	£0.00	Not varied			
Atropine Cost	£15.10	Not varied			
Bevacizumab Cost	£924.40	Not varied			
Brimonidine tartate Cost	£1.35	Not varied			
Bromfenac Cost	£8.50	Not varied			
Budesonide w formoterol fumarate Cost	£21.50	Not varied			
Carbomer Cost	£1.59	Not varied			
Cyclopentolate hydrochloride Cost	£11.41	Not varied			
Fluticasone propionate Cost	£4.00	Not varied			
Ketorolac/ Ketorolac tromethamine Cost	£3.00	Not varied			
Latanoprost Cost	£1.85	Not varied			
Methylprednisolone/Methylprednisolone sodium succinate Cost	£17.17	Not varied			
Other ophthalmologicals Cost	£0.00	Not varied			
Proxymetacaine Cost	£12.12	Not varied			
Tears plus Cost	£4.80	Not varied			
Tobradex Cost	£5.37	Not varied			
Azarga Cost	£11.05	Not varied			
Brinzolamide Cost	£2.52	Not varied			

Fluocinolone Acetonide Cost	£5,500.00	Not varied			
Hypromellose Cost	£1.31	Not varied			
Idoxuridine Cost	£0.00	Not varied			
Polytrim Cost	£0.00	Not varied			
Tropicamide Cost	£11.18	Not varied			
Viscoat Cost	£4.80	Not varied			
Vancomycin Cost	£88.31	Not varied			
Seretide Cost	£18.00	Not varied			
Ceftazidime Cost	£0.00	Not varied			
Supplemental therapy ILUVIEN					
Mycophenolate mofetil resource proportion: ILUVIEN	[redacted]	Beta	0.92%	1.38%	Section 3.2.3.1
Methotrexate resource proportion: ILUVIEN	[redacted]	Beta	0.92%	1.38%	
Cyclosporine resource proportion: ILUVIEN	[redacted]	Not varied	0.00%	0.00%	
Azathioprine resource proportion: ILUVIEN	[redacted]	Beta	0.92%	1.38%	
Prednisolone resource proportion: ILUVIEN	[redacted]	Beta	22.99%	34.48%	
Tacrolimus resource proportion: ILUVIEN	[redacted]	Not varied	0.00%	0.00%	
Beta-interferon resource proportion: ILUVIEN	[redacted]	Not varied	0.00%	0.00%	
Abatacept resource proportion: ILUVIEN	[redacted]	Not varied	0.00%	0.00%	
Golimumab resource proportion: ILUVIEN	[redacted]	Not varied	0.00%	0.00%	
Dexamethasone resource proportion: ILUVIEN	[redacted]	Beta	19.31%	28.97%	
aetazolamide resource proportion: ILUVIEN	[redacted]	Beta	4.60%	6.90%	
apraclonidine resource proportion: ILUVIEN	[redacted]	Beta	3.68%	5.52%	
artificial tears resource proportion: ILUVIEN	[redacted]	Beta	7.36%	11.03%	
besifloxacin hydrochloride resource proportion: ILUVIEN	[redacted]	Beta	14.71%	22.07%	

bimatoprost resource proportion: ILUVIEN	[redacted]	Beta	5.52%	8.28%	
carmellose resource proportion: ILUVIEN	[redacted]	Beta	4.60%	6.90%	
carmellose sodium resource proportion: ILUVIEN	[redacted]	Beta	7.36%	11.03%	
chloramphenicol resource proportion: ILUVIEN	[redacted]	Beta	6.44%	9.66%	
ciprofloxacin resource proportion: ILUVIEN	[redacted]	Beta	6.44%	9.66%	
corticosteroids and anti-infectives in combination resource proportion: ILUVIEN	[redacted]	Beta	6.44%	9.66%	
combigan resource proportion: ILUVIEN	[redacted]	Beta	7.36%	11.03%	
Cosopt resource proportion: ILUVIEN	[redacted]	Beta	10.11%	15.17%	
Difluprednate resource proportion: ILUVIEN	[redacted]	Beta	8.28%	12.41%	
Fluoracine oph soln resource proportion: ILUVIEN	[redacted]	Beta	7.36%	11.03%	
Flurbiprofen resource proportion: ILUVIEN	[redacted]	Beta	2.76%	4.14%	
Fluress resource proportion: ILUVIEN	[redacted]	Beta	7.36%	11.03%	
Gatifloxacin resource proportion: ILUVIEN	[redacted]	Beta	12.87%	19.31%	
Gentamicin resource proportion: ILUVIEN	[redacted]	Beta	6.44%	9.66%	
Homatropine hydrobromide resource proportion: ILUVIEN	[redacted]	Beta	6.44%	9.66%	
Hyaluronate sodium resource proportion: ILUVIEN	[redacted]	Beta	6.44%	9.66%	
Iodine resource proportion: ILUVIEN	[redacted]	Beta	7.36%	11.03%	
Lidocaine resource proportion: ILUVIEN	[redacted]	Beta	26.67%	40.00%	
Loteprednol resource proportion: ILUVIEN	[redacted]	Beta	5.52%	8.28%	
Maxitrol resource proportion: ILUVIEN	[redacted]	Beta	4.60%	6.90%	
Moxifloxacin resource proportion: ILUVIEN	[redacted]	Beta	11.03%	16.55%	
Moxifloxacin hydrochloride resource proportion: ILUVIEN	[redacted]	Beta	7.36%	11.03%	
Nepafenac resource proportion: ILUVIEN	[redacted]	Beta	13.79%	20.69%	

Ofloxacin resource proportion: ILUVIEN	[redacted]	Beta	16.55%	24.83%	
Oxybuprocaine resource proportion: ILUVIEN	[redacted]	Beta	3.68%	5.52%	
Oxybuprocaine hydrochloride resource proportion: ILUVIEN	[redacted]	Beta	6.44%	9.66%	
Paremyd resource proportion: ILUVIEN	[redacted]	Beta	9.20%	13.79%	
Phenylephrine resource proportion: ILUVIEN	[redacted]	Beta	16.55%	24.83%	
Phenylephrine hydrochloride resource proportion: ILUVIEN	[redacted]	Beta	7.36%	11.03%	
Phenylephrine w tropicamide resource proportion: ILUVIEN	[redacted]	Beta	6.44%	9.66%	
Povidone-Iodine resource proportion: ILUVIEN	[redacted]	Beta	47.82%	71.72%	
Simbrinza resource proportion: ILUVIEN	[redacted]	Beta	4.60%	6.90%	
Systane lubricant resource proportion: ILUVIEN	[redacted]	Beta	6.44%	9.66%	
Tetracaine hydrochloride resource proportion: ILUVIEN	[redacted]	Beta	11.03%	16.55%	
Timolol resource proportion: ILUVIEN	[redacted]	Beta	10.11%	15.17%	
Timolol maleate resource proportion: ILUVIEN	[redacted]	Beta	3.68%	5.52%	
Triamcinolone acetonide resource proportion: ILUVIEN	[redacted]	Beta	10.11%	15.17%	
Systemic corticosteroids resource proportion: ILUVIEN	[redacted]	Beta	24.83%	37.24%	
Prednisone resource proportion: ILUVIEN	[redacted]	Beta	11.03%	16.55%	
anti-inflammatory agents and anti-infectives resource proportion: ILUVIEN	[redacted]	Beta	2.76%	4.14%	
Budesonide w formoterol fumarate resource proportion: ILUVIEN	[redacted]	Beta	3.68%	5.52%	
Atropine resource proportion: ILUVIEN	[redacted]	Beta	5.52%	8.28%	
Bevacizumab resource proportion: ILUVIEN	[redacted]	Beta	3.68%	5.52%	
Brimonidine tartate resource proportion: ILUVIEN	[redacted]	Beta	4.60%	6.90%	
Bromfenac resource proportion: ILUVIEN	[redacted]	Beta	12.87%	19.31%	
Carbomer resource proportion: ILUVIEN	[redacted]	Beta	3.68%	5.52%	

Cyclopentolate hydrochloride resource proportion: ILUVIEN	[redacted]	Beta	2.76%	4.14%	
Fluticasone propionate resource proportion: ILUVIEN	[redacted]	Beta	3.68%	5.52%	
Ketorolac/ Ketorolac tromethamine resource proportion: ILUVIEN	[redacted]	Beta	10.11%	15.17%	
Latanoprost resource proportion: ILUVIEN	[redacted]	Beta	2.76%	4.14%	
Methylprednisolone/Methylprednisolone sodium succinate resource proportion: ILUVIEN	[redacted]	Beta	5.52%	8.28%	
Other ophthalmologicals resource proportion: ILUVIEN	[redacted]	Beta	2.76%	4.14%	
Proxymetacaine resource proportion: ILUVIEN	[redacted]	Beta	45.98%	68.97%	
Tears plus resource proportion: ILUVIEN	[redacted]	Beta	2.76%	4.14%	
Tobradex resource proportion: ILUVIEN	[redacted]	Beta	2.76%	4.14%	
Azarga resource proportion: ILUVIEN	[redacted]	Not varied			
Brinzolamide resource proportion: ILUVIEN	[redacted]	Not varied			
Fluocinolone Acetonide resource proportion: ILUVIEN	[redacted]	Not varied			
Hypromellose resource proportion: ILUVIEN	[redacted]	Not varied			
Idoxuridine resource proportion: ILUVIEN	[redacted]	Not varied			
Polytrim resource proportion: ILUVIEN	[redacted]	Not varied			
Tropicamide resource proportion: ILUVIEN	[redacted]	Beta	31.26%	46.90%	
Viscoat resource proportion: ILUVIEN	[redacted]	Beta	2.76%	4.14%	
Vancomycin resource proportion: ILUVIEN	[redacted]	Beta	0.92%	1.38%	
Seretide resource proportion: ILUVIEN	[redacted]	Not varied			
Ceftazidime resource proportion: ILUVIEN	[redacted]	Beta	1.90%	2.86%	
Supplemental therapy (L)CP					
Mycophenolate mofetil resource proportion: (L)CP	[redacted]	Not varied			Section 3.2.3.1
Methotrexate resource proportion: (L)CP	[redacted]	Not varied			

Cyclosporine resource proportion: (L)CP	[redacted]	Beta	5.71%	8.57%	
Azathioprine resource proportion: (L)CP	[redacted]	Beta	3.81%	5.71%	
Prednisolone resource proportion: (L)CP	[redacted]	Beta	41.90%	62.86%	
Tacrolimus resource proportion: (L)CP	[redacted]	Not varied			
Beta-interferon resource proportion: (L)CP	[redacted]	Not varied			
Abatacept resource proportion: (L)CP	[redacted]	Not varied			
Golimumab resource proportion: (L)CP	[redacted]	Not varied			
Dexamethasone resource proportion: (L)CP	[redacted]	Beta	36.19%	54.29%	
aetazolamide resource proportion: (L)CP	[redacted]	Beta	1.90%	2.86%	
apraclonidine resource proportion: (L)CP	[redacted]	Not varied			
anti-inflammatory agents and anti-infectives resource proportion: (L)CP	[redacted]	Not varied			
artificial tears resource proportion: (L)CP	[redacted]	Beta	9.52%	14.29%	
Atropine resource proportion: (L)CP	[redacted]	Beta	7.62%	11.43%	
besifloxacin hydrochloride resource proportion: (L)CP	[redacted]	Beta	7.62%	11.43%	
Bevacizumab resource proportion: (L)CP	[redacted]	Beta	3.81%	5.71%	
bimatoprost resource proportion: (L)CP	[redacted]	Beta	1.90%	2.86%	
Brimonidine tartate resource proportion: (L)CP	[redacted]	Beta	5.71%	8.57%	
Bromfenac resource proportion: (L)CP	[redacted]	Beta	17.14%	25.71%	
Budesonide w formoterol fumarate resource proportion: (L)CP	[redacted]	Beta	0.92%	1.38%	
carmellose resource proportion: (L)CP	[redacted]	Beta	9.52%	14.29%	
carmellose sodium resource proportion: (L)CP	[redacted]	Beta	7.62%	11.43%	
Carbomer resource proportion: (L)CP	[redacted]	Not varied			
chloramphenicol resource proportion: (L)CP	[redacted]	Beta	3.81%	5.71%	

ciprofloxacin resource proportion: (L)CP	[redacted]	Beta	9.52%	14.29%	
corticosteroids and anti-infectives in combination resource proportion: (L)CP	[redacted]	Beta	7.62%	11.43%	
combigan resource proportion: (L)CP	[redacted]	Beta	1.90%	2.86%	
Cosopt resource proportion: (L)CP	[redacted]	Beta	3.81%	5.71%	
Cyclopentolate hydrochloride resource proportion: (L)CP	[redacted]	Beta	11.43%	17.14%	
Difluprednate resource proportion: (L)CP	[redacted]	Beta	13.33%	20.00%	
Fluticasone propionate resource proportion: (L)CP	[redacted]	Beta	1.90%	2.86%	
Fluoracine oph soln resource proportion: (L)CP	[redacted]	Beta	1.90%	2.86%	
Flurbiprofen resource proportion: (L)CP	[redacted]	Beta	1.90%	2.86%	
Fluress resource proportion: (L)CP	[redacted]	Beta	9.52%	14.29%	
Gatifloxacin resource proportion: (L)CP	[redacted]	Beta	9.52%	14.29%	
Gentamicin resource proportion: (L)CP	[redacted]	Beta	9.52%	14.29%	
Homatropine hydrobromide resource proportion: (L)CP	[redacted]	Beta	11.43%	17.14%	
Hyaluronate sodium resource proportion: (L)CP	[redacted]	Beta	5.71%	8.57%	
Iodine resource proportion: (L)CP	[redacted]	Beta	5.71%	8.57%	
Ketorolac/ Ketorolac tromethamine resource proportion: (L)CP	[redacted]	Beta	13.33%	20.00%	
Latanoprost resource proportion: (L)CP	[redacted]	Beta	5.71%	8.57%	
Lidocaine resource proportion: (L)CP	[redacted]	Beta	41.90%	62.86%	
Loteprednol resource proportion: (L)CP	[redacted]	Beta	15.24%	22.86%	
Maxitrol resource proportion: (L)CP	[redacted]	Beta	3.81%	5.71%	
Moxifloxacin resource proportion: (L)CP	[redacted]	Beta	20.95%	31.43%	
Moxifloxacin hydrochloride resource proportion: (L)CP	[redacted]	Beta	17.14%	25.71%	
Methylprednisolone/Methylprednisolone sodium succinate resource proportion: (L)CP	[redacted]	Beta	1.90%	2.86%	

Nepafenac resource proportion: (L)CP	[redacted]	Beta	11.43%	17.14%	
Ofloxacin resource proportion: (L)CP	[redacted]	Beta	20.95%	31.43%	
Other ophthalmologicals resource proportion: (L)CP	[redacted]	Not varied			
Oxybuprocaine resource proportion: (L)CP	[redacted]	Beta	3.81%	5.71%	
Oxybuprocaine hydrochloride resource proportion: (L)CP	[redacted]	Beta	7.62%	11.43%	
Paremyd resource proportion: (L)CP	[redacted]	Beta	5.71%	8.57%	
Phenylephrine resource proportion: (L)CP	[redacted]	Beta	19.05%	28.57%	
Phenylephrine hydrochloride resource proportion: (L)CP	[redacted]	Beta	11.43%	17.14%	
Phenylephrine w tropicamide resource proportion: (L)CP	[redacted]	Beta	7.62%	11.43%	
Povidone-Iodine resource proportion: (L)CP	[redacted]	Beta	57.14%	85.71%	
Proxymetacaine resource proportion: (L)CP	[redacted]	Beta	45.71%	68.57%	
Simbrinza resource proportion: (L)CP	[redacted]	Beta	45.71%	68.57%	
Systane lubricant resource proportion: (L)CP	[redacted]	Beta	3.81%	5.71%	
Tears plus resource proportion: (L)CP	[redacted]	Not varied			
Tetracaine hydrochloride resource proportion: (L)CP	[redacted]	Beta	15.24%	22.86%	
Timolol resource proportion: (L)CP	[redacted]	Beta	9.52%	14.29%	
Timolol maleate resource proportion: (L)CP	[redacted]	Beta	5.71%	8.57%	
Tobradex resource proportion: (L)CP	[redacted]	Not varied			
Triamcinolone acetonide resource proportion: (L)CP	[redacted]	Beta	34.29%	51.43%	
Systemic corticosteroids resource proportion: (L)CP	[redacted]	Beta	24.76%	37.14%	
Prednisone resource proportion: (L)CP	[redacted]	Beta	9.52%	14.29%	
Azarga resource proportion: (L)CP	[redacted]	Beta	3.81%	5.71%	
Brinzolamide resource proportion: (L)CP	[redacted]	Beta	5.71%	8.57%	
Fluocinolone Acetonide resource proportion: (L)CP	[redacted]	Beta	5.71%	8.57%	

Hypromellose resource proportion: (L)CP	[redacted]	Beta	3.81%	5.71%	
Idoxuridine resource proportion: (L)CP	[redacted]	Beta	3.81%	5.71%	
Polytrim resource proportion: (L)CP	[redacted]	Beta	3.81%	5.71%	
Tropicamide resource proportion: (L)CP	[redacted]	Beta	36.19%	54.29%	
Viscoat resource proportion: (L)CP	[redacted]	Beta	1.90%	2.86%	
Vancomycin resource proportion: (L)CP	[redacted]	Beta	5.71%	8.57%	
Seretide resource proportion: (L)CP	[redacted]	Beta	3.81%	5.71%	
Ceftazidime resource proportion: (L)CP	[redacted]	Beta	3.81%	5.71%	
ILUVIEN subsequent therapy proportions					
Bromfenac sodium subsequent therapy proportion after ILUVIEN	[redacted]	Beta	2.76%	4.14%	Section 3.5.3.2
Dexamethasone subsequent therapy proportion after ILUVIEN	[redacted]	Beta	6.44%	9.66%	
Nepfenac subsequent therapy proportion after ILUVIEN	[redacted]	Beta	5.52%	8.28%	
Prednisolone acetate subsequent therapy proportion after ILUVIEN	[redacted]	Beta	11.03%	16.55%	
Difluprednate subsequent therapy proportion after ILUVIEN	[redacted]	Beta	2.76%	4.14%	
Triamcinolone acetonide subsequent therapy proportion after ILUVIEN	[redacted]	Beta	2.76%	4.14%	
Corticosteroids subsequent therapy proportion after ILUVIEN	[redacted]	Beta	3.68%	5.52%	
Cyclopentolate Hydrochloride subsequent therapy proportion after ILUVIEN	[redacted]	Not varied			
Lidocaine subsequent therapy proportion after ILUVIEN	[redacted]	Beta	0.92%	1.38%	
Povidine-Iodine subsequent therapy proportion after ILUVIEN	[redacted]	Beta	0.92%	1.38%	
Triamcinolone subsequent therapy proportion after ILUVIEN	[redacted]	Beta	0.92%	1.38%	
(L)CP subsequent therapy proportions					
Bromfenac sodium subsequent therapy proportion after (L)CP	[redacted]	Beta	1.90%	2.86%	Section 3.5.3.2
Dexamethasone subsequent therapy proportion after (L)CP	[redacted]	Beta	15.24%	22.86%	

Nepfenac subsequent therapy proportion after (L)CP	[redacted]	Not varied			
Prednisolone acetate subsequent therapy proportion after (L)CP	[redacted]	Beta	20.95%	31.43%	
Difluprednate subsequent therapy proportion after (L)CP	[redacted]	Beta	7.62%	11.43%	
Triamcinolone acetonide subsequent therapy proportion after (L)CP	[redacted]	Beta	7.62%	11.43%	
Corticosteroids subsequent therapy proportion after (L)CP	[redacted]	Beta	5.71%	8.57%	
Cyclopentolate Hydrochloride subsequent therapy proportion after (L)CP	[redacted]	Beta	3.81%	5.71%	
Lidocaine subsequent therapy proportion after (L)CP	[redacted]	Beta	3.81%	5.71%	
Povidine-Iodine subsequent therapy proportion after (L)CP	[redacted]	Beta	3.81%	5.71%	
Triamcinolone subsequent therapy proportion after (L)CP	[redacted]	Beta	9.52%	14.29%	
Acquisition Costs					
ILUVIEN Acquisition Cost	[redacted]	[redacted]	[redacted]	[redacted]	Section 3.5.2.1
(L)CP Acquisition Cost	£0.00	Not varied	£0.00	£0.00	
Administration Costs					
ILUVIEN administration	£99.58	Gamma	£79.66	£119.49	Section 3.5.2.1
(L)CP administration	£0.00	Not varied	£0.00	£0.00	
Adverse Event Costs					
Cataract cost	£919.05	Gamma	£735.24	£1,102.86	Section 3.5.4
Raised IOP cost	£2.40	Gamma	£1.92	£2.88	
Serious infection cost	£5,513.05	Gamma	£4,410.44	£6,615.66	
Hypertension cost	£7.26	Gamma	£5.81	£8.71	
Retinal detachment cost	£2,003.92	Gamma	£1,603.13	£2,404.70	
Conjunctival haemorrhage cost	£0.00	Not varied	£0.00	£0.00	
Iridocyclitis cost	£0.00	Not varied	£0.00	£0.00	

Ocular hypertension cost	£2.40	Gamma	£1.92	£2.88	
Myodesopsia cost	£0.00	Not varied	£0.00	£0.00	
Conjunctival hyperaemia cost	£38.00	Gamma	£30.40	£45.60	
Macular oedema cost	£119.78	Gamma	£95.83	£143.74	
Dry eye cost	£0.34	Gamma	£0.27	£0.40	
Eye pain cost	£88.34	Gamma	£70.67	£106.01	
Foreign body sensations cost	£0.00	Not varied	£0.00	£0.00	
Ocular discomfort cost	£88.34	Gamma	£70.67	£106.01	
Ocular hyperaemia cost	£0.00	Not varied	£0.00	£0.00	
Gastrointestinal disorders cost	£0.00	Not varied	£0.00	£0.00	
Eyelid ptosis cost	£1,689.32	Gamma	£1,351.45	£2,027.18	
Macular fibrosis cost	£0.00	Not varied	£0.00	£0.00	
Photopsia cost	£0.00	Not varied	£0.00	£0.00	
Posterior capsule opacification cost	£148.38	Gamma	£118.70	£178.05	
VA reduced cost	£0.00	Not varied	£0.00	£0.00	
Visual impairment cost	£0.00	Not varied	£0.00	£0.00	
Vitreous floaters cost	£0.00	Not varied	£0.00	£0.00	
Nasopharyngitis cost	£0.00	Not varied	£0.00	£0.00	
Headache cost	£0.00	Not varied	£0.00	£0.00	
Depression cost	£38.00	Gamma	£30.40	£45.60	
Hyperthyroidism cost	£143.45	Gamma	£114.76	£172.14	
Anterior chamber flare cost	£0.00	Not varied	£0.00	£0.00	
Vision blurred cost	£38.00	Gamma	£30.40	£45.60	
Vitreous opacities cost	£0.00	Not varied	£0.00	£0.00	

Conjunctivitis cost	£0.00	Not varied	£0.00	£0.00	
Pain cost	£0.00	Not varied	£0.00	£0.00	
Viral infection cost	£38.00	Gamma	£30.40	£45.60	
Nausea cost	£0.00	Not varied	£0.00	£0.00	
Fatigue cost	£0.00	Not varied	£0.00	£0.00	
Cough cost	£0.00	Not varied	£0.00	£0.00	
Itching cost	£0.00	Not varied	£0.00	£0.00	
Swelling cost	£0.00	Not varied	£0.00	£0.00	
Adverse Event Rates ILUVIEN					
Cataract AE rates: ILUVIEN	[redacted]	Beta	35.86%	53.79%	Section 3.3.6
Raised IOP AE rates: ILUVIEN	[redacted]	Beta	25.75%	38.62%	
Serious infection AE rates: ILUVIEN	[redacted]	Not varied			
Hypertension AE rates: ILUVIEN	[redacted]	Beta	5.52%	8.28%	
Retinal detachment AE rates: ILUVIEN	[redacted]	Not varied			
Conjunctival haemorrhage AE rates: ILUVIEN	[redacted]	Beta	11.95%	17.93%	
Iridocyclitis AE rates: ILUVIEN	[redacted]	Beta	0.92%	1.38%	
Ocular hypertension AE rates: ILUVIEN	[redacted]	Not varied			
Myodesopsia AE rates: ILUVIEN	[redacted]	Not varied			
Conjunctival hyperaemia AE rates: ILUVIEN	[redacted]	Not varied			
Macular oedema AE rates: ILUVIEN	[redacted]	Beta	5.52%	8.28%	
Dry eye AE rates: ILUVIEN	[redacted]	Beta	13.79%	20.69%	
Eye pain AE rates: ILUVIEN	[redacted]	Beta	10.11%	15.17%	
Foreign body sensations AE rates: ILUVIEN	[redacted]	Beta	7.36%	11.03%	
Ocular discomfort AE rates: ILUVIEN	[redacted]	Beta	4.60%	6.90%	

Ocular hyperaemia AE rates: ILUVIEN	[redacted]	Beta	6.44%	9.66%	
Gastrointestinal disorders AE rates: ILUVIEN	[redacted]	Beta	14.71%	22.07%	
Eyelid ptosis AE rates: ILUVIEN	[redacted]	Beta	4.60%	6.90%	
Macular fibrosis AE rates: ILUVIEN	[redacted]	Beta	4.60%	6.90%	
Photopsia AE rates: ILUVIEN	[redacted]	Beta	4.60%	6.90%	
Posterior capsule opacification AE rates: ILUVIEN	[redacted]	Beta	4.60%	6.90%	
VA reduced AE rates: ILUVIEN	[redacted]	Beta	14.71%	22.07%	
Visual impairment AE rates: ILUVIEN	[redacted]	Beta	7.36%	11.03%	
Vitreous floaters AE rates: ILUVIEN	[redacted]	Beta	7.36%	11.03%	
Nasopharyngitis AE rates: ILUVIEN	[redacted]	Beta	11.03%	16.55%	
Headache AE rates: ILUVIEN	[redacted]	Beta	5.52%	8.28%	
Depression AE rates: ILUVIEN	[redacted]	Beta	4.60%	6.90%	
Hyperthyroidism AE rates: ILUVIEN	[redacted]	Beta	4.60%	6.90%	
Anterior chamber flare AE rates: ILUVIEN	[redacted]	Not varied			
Vision blurred AE rates: ILUVIEN	[redacted]	Beta	1.84%	2.76%	
Vitreous opacities AE rates: ILUVIEN	[redacted]	Beta	1.84%	2.76%	
Conjunctivitis AE rates: ILUVIEN	[redacted]	Beta	11.95%	17.93%	
Pain AE rates: ILUVIEN	[redacted]	Beta	1.84%	2.76%	
Viral infection AE rates: ILUVIEN	[redacted]	Beta	1.84%	2.76%	
Nausea AE rates: ILUVIEN	[redacted]	Beta	2.76%	4.14%	
Fatigue AE rates: ILUVIEN	[redacted]	Not varied			
Cough AE rates: ILUVIEN	[redacted]	Beta	0.92%	1.38%	
Itching AE rates: ILUVIEN	[redacted]	Not varied			
Swelling AE rates: ILUVIEN	[redacted]	Not varied			
Adverse Event Rates (L)CP					

Cataract AE rates: (L)CP	[redacted]	Beta	19.05%	28.57%	Section 3.3.6
Raised IOP AE rates: (L)CP	[redacted]	Beta	24.76%	37.14%	
Serious infection AE rates: (L)CP	[redacted]	Not varied			
Hypertension AE rates: (L)CP	[redacted]	Beta	7.62%	11.43%	
Retinal detachment AE rates: (L)CP	[redacted]	Not varied			
Conjunctival haemorrhage AE rates: (L)CP	[redacted]	Beta	9.52%	14.29%	
Iridocyclitis AE rates: (L)CP	[redacted]	Beta	11.43%	17.14%	
Ocular hypertension AE rates: (L)CP	[redacted]	Not varied			
Myodesopsia AE rates: (L)CP	[redacted]	Not varied			
Conjunctival hyperaemia AE rates: (L)CP	[redacted]	Not varied			
Macular oedema AE rates: (L)CP	[redacted]	Beta	30.48%	45.71%	
Dry eye AE rates: (L)CP	[redacted]	Beta	9.52%	14.29%	
Eye pain AE rates: (L)CP	[redacted]	Beta	17.14%	25.71%	
Foreign body sensations AE rates: (L)CP	[redacted]	Beta	3.81%	5.71%	
Ocular discomfort AE rates: (L)CP	[redacted]	Not varied			
Ocular hyperaemia AE rates: (L)CP	[redacted]	Beta	9.52%	14.29%	
Gastrointestinal disorders AE rates: (L)CP	[redacted]	Beta	7.62%	11.43%	
Eyelid ptosis AE rates: (L)CP	[redacted]	Beta	1.90%	2.86%	
Macular fibrosis AE rates: (L)CP	[redacted]	Beta	9.52%	14.29%	
Photopsia AE rates: (L)CP	[redacted]	Beta	5.71%	8.57%	
Posterior capsule opacification AE rates: (L)CP	[redacted]	Beta	5.71%	8.57%	
VA reduced AE rates: (L)CP	[redacted]	Beta	9.52%	14.29%	
Visual impairment AE rates: (L)CP	[redacted]	Beta	5.71%	8.57%	
Vitreous floaters AE rates: (L)CP	[redacted]	Beta	9.52%	14.29%	
Nasopharyngitis AE rates: (L)CP	[redacted]	Beta	9.52%	14.29%	
Headache AE rates: (L)CP	[redacted]	Beta	5.71%	8.57%	
Depression AE rates: (L)CP	[redacted]	Beta	1.90%	2.86%	

Hyperthyroidism AE rates: (L)CP	[redacted]	Beta	1.90%	2.86%	
Anterior chamber flare AE rates: (L)CP	[redacted]	Beta	5.71%	8.57%	
Vision blurred AE rates: (L)CP	[redacted]	Beta	5.71%	8.57%	
Vitreous opacities AE rates: (L)CP	[redacted]	Beta	7.62%	11.43%	
Conjunctivitis AE rates: (L)CP	[redacted]	Beta	5.71%	8.57%	
Pain AE rates: (L)CP	[redacted]	Beta	5.71%	8.57%	
Viral infection AE rates: (L)CP	[redacted]	Beta	5.71%	8.57%	
Nausea AE rates: (L)CP	[redacted]	Beta	7.62%	11.43%	
Fatigue AE rates: (L)CP	[redacted]	Beta	5.71%	8.57%	
Cough AE rates: (L)CP	[redacted]	Beta	7.62%	11.43%	
Itching AE rates: (L)CP	[redacted]	Not varied			
Swelling AE rates: (L)CP	[redacted]	Not varied			
Utilities					
On treatment utility	0.818	Beta	0.654	0.982	Section 3.4.6
Blindness utility	0.380	Beta	0.304	0.456	
Off treatment utility	0.759	Beta	0.607	0.911	
18-24 years age matched utilities	0.929	Beta	0.743	1.000	
25-34 years age matched utilities	0.919	Beta	0.735	1.000	
35-44 years age matched utilities	0.893	Beta	0.714	1.000	
45-54 years age matched utilities	0.855	Beta	0.684	1.000	
55-64 years age matched utilities	0.810	Beta	0.648	0.972	
65-74 years age matched utilities	0.773	Beta	0.618	0.928	
75+ years age matched utilities	0.703	Beta	0.562	0.844	
Settings					
Start Age	48.300	Not varied			Section 3.2
Rate of blindness (over 10 years)	6.6%	Beta	0.053	0.079	
Proportion Male	38.3%	Not varied			

Average patient weight	77.100	Normal	61.680	1.000	
Subsequent corticosteroid %	31.0%	Beta	0.248	0.372	
Subsequent immunosuppressant %	19.4%	Beta	0.155	0.233	
Survival values					
ILUVIEN time to recurrence	See Section 3.3.1.1				Section 3.3.1
CP time to recurrence	See Section 3.8.2				

3.6.2 Assumptions

In the course of modelling, it was necessary to make a number of assumptions. Where possible, these were corroborated by an expert clinician and can be seen in Table 48. This table also shows the rationale for the assumption and section where this is discussed in detail.

Table 48: Assumptions used in base case analysis

Assumption	Rationale	Section
Patient population of PSV-FAI-001 assumed to be representative of UK patients	There is no evidence to suggest that disease progression would be different in any other countries. Additionally, the supplemental therapy in PSV-FAI-001 is as would be used in the UK and therefore the clinical outcomes are assumed applicable to this perspective.	
Clinical efficacy is assumed to be best represented by the time to first recurrence recorded in PSV-FAI-001 for both ILUVIEN and (L)CP	The economic analysis reflects the trial and the clinical evidence from this trial is therefore the most appropriate source of evidence to inform. The protocol for treating patients is in line with (L)CP in the UK and so is directly supportive of an analysis for the UK health care system.	
Patients who respond to treatment for a period of greater than two years are considered in remission	Clinical input suggests that if patients have stable disease for over 2 years the disease would be considered in remission from ocular disease (clinical experts, personal communication). This health state was used in a scenario in TA460.	
Patients who are responding to treatment cannot experience permanent blindness from this state. They must first experience treatment failure/lack of effect.	Patients who are responding to treatment and not experiencing recurrence (i.e. disease is not progressing) are not expected to suffer the most severe consequence of disease. This assumption was used for the evaluations of adalimumab in TA460 but not for dexamethasone.	
Mortality is the same as the general population	There is no evidence to suggest that uveitis directly affects mortality. Ocular disease is the study eye is modelled rather than the systemic disease.	
Patients who move to the remission health state will	Patients in remission as informed by PSV-FAI-001 are not taking systemic treatments and have not experienced	

experience HRQoL akin to that of the general population	recurrence for over 2 years. This assumption has been validated by clinical advice as the only potential impact to HRQoL is quarterly monitoring visits to hospital. This assumption was not used in TA460, instead patients would continue to receive On Treatment utility.	
Utility values calculated from the MUST trial are reflective of the health states in this model	Patients in the MUST trial, for the majority, had inactive uveitis at 24 months meaning there was no inflammation/recurrence. This value is therefore representative of “on treatment” in the context of the definition of the health states in this model. At enrolment of the MUST trial, the majority of patients had active uveitis and so were not responding to treatment. Therefore, this value was chosen to represent “end of treatment effect”.	
Patients who are responding to treatment will require monitoring every 12 weeks rather than every 6 weeks	Clinical advice indicated that one of the most important benefits of treatments that negate the need for systemic treatments was the reduction in necessary monitoring for patients and clinicians. When patients have controlled uveitis and are not taking systemic therapies it was indicated by clinical experts that these patients would only be required to be seen once every three months. This assumption was not use in TA460.	
Subsequent therapy is expected to be as reported in TA460; a weighted cost of immunosuppressants and corticosteroids	It is assumed that patients who experience recurrence with (L)CP or ILUVIEN would experience the same treatment to those who experienced recurrence with a dexamethasone implant. This assumption was used in TA460 to define subsequent therapy.	
The proportions receiving immunosuppressants and corticosteroids in subsequent therapy are expected to be as patients reported at baseline of PSV-FAI-001	The baseline characteristics of patients from PSV-FAI-001 are representative of patients who have recurrent disease, and some were using systemic treatments to control this. These patients are considered representative of patients who are experiencing the “end of treatment effect”.	

3.7 *Base-case results*

All results are produced under the assumption that the willingness-to-pay (WTP) is £20,000 per QALY.

3.7.1 Base-case incremental cost-effectiveness analysis results

The results of the base case analysis are summarised in Table 49 (including PAS).

Total discounted costs associated with ILUVIEN (with PAS), accrued over the modelled time horizon, were predicted to be [redacted]. By comparison, total discounted costs associated with (L)CP were lower, with the majority of costs coming from health state costs. Incremental discounted costs were expected to be [redacted], under base case assumptions. The resultant incremental cost-effectiveness ratio (ICER) for ILUVIEN versus (L)CP was £7,183. Therefore, the base case ICER is below a £20,000 per QALY WTP threshold when the current PAS discount is applied.

Table 49: Summary of base case results for deterministic analysis

Outcome	ILUVIEN	(L)CP	Δ	ICER	INMB
Total Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time on first line treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£7,182.79	[redacted]

In summary, ILUVIEN is estimated to be associated with incremental clinical benefit when compared to (L)CP. This results in additional QALYs being accrued over a patient's lifetime and an ICER of £7,183 when the current PAS discount is applied. This is below the £20,000/QALY threshold and so would be considered cost-effective under these assumptions.

3.8 *Sensitivity analyses*

In order to assess the impact of parameters on the model outcomes, deterministic sensitivity analyses have been used to vary the data inputs by a set amount. Uncertainty around the input data has been assessed using probabilistic analyses, while alternative assumptions have been examined in scenario analyses.

3.8.1 Probabilistic sensitivity analysis

Sampling utilises information on the mean and standard error of parameters to derive an estimated value using an appropriate distribution (costs: gamma; age and survival parameters: normal; proportions and percentages: beta). These analyses are used to estimate the overall uncertainty that exists in the model results due to uncertainty in the chosen input parameters.

Survival estimates for ILUVIEN were generated from a bootstrap method and all curves are varied between the upper and lower 95% CI values assuming semi-normality with a log transformation. This was necessary because the initial 120 days of the efficacy was not varied and informed from KM data directly.

The mean results from 1,000 samples can be seen in Table 50. These results are similar to the deterministic results under base case assumptions demonstrating limited uncertainty in the base case results. The mean results also demonstrate an ICER that is below the £20,000/QALY threshold. Disaggregated results can be seen in Table 51 to Table 54 for mean (95% CI) for costs and utilities respectively.

Costs are varied with a gamma distribution (where appropriate) and so show lower bound CI values closer to the mean than the upper bound as expected. However, the upper bound total costs for both ILUVIEN and (L)CP are in both cases approximately [redacted].

Table 50: Summary of mean results for probabilistic analysis

Outcome	ILUVIEN	(L)CP	Δ	ICER	NMB
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£7,701.71	[redacted]

Table 51: Disaggregated costs from PSA: ILUVIEN

Cost breakdown: ILUVIEN	Mean	Lower 95%	Upper 95%
Acquisition Costs (1L)	[redacted]	[redacted]	[redacted]
Supplemental therapy costs (1L)	[redacted]	[redacted]	[redacted]
Health state costs (1L)	[redacted]	[redacted]	[redacted]
Subsequent therapy acquisition costs	[redacted]	[redacted]	[redacted]
Health state costs (subsequent therapy)	[redacted]	[redacted]	[redacted]
Health state costs (blindness)	[redacted]	[redacted]	[redacted]
Adverse Event costs	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Table 52: Disaggregated costs from PSA: (L)CP

Cost breakdown: (L)CP	Mean	Lower 95%	Upper 95%
Acquisition Costs (1L)	[redacted]	[redacted]	[redacted]
Supplemental therapy costs (1L)	[redacted]	[redacted]	[redacted]
Health state costs (1L)	[redacted]	[redacted]	[redacted]
Subsequent therapy acquisition costs	[redacted]	[redacted]	[redacted]
Health state costs (subsequent therapy)	[redacted]	[redacted]	[redacted]
Health state costs (blindness)	[redacted]	[redacted]	[redacted]
Adverse Event costs	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Table 53: Disaggregated utilities from PSA: ILUVIEN

Utility breakdown: ILUVIEN	Mean	Lower 95%	Upper 95%
On treatment (1L)	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]
Blindness	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Table 54: Disaggregated utilities from PSA: (L)CP

Utility breakdown: (L)CP	Mean	Lower 95%	Upper 95%
On treatment (1L)	[redacted]	[redacted]	[redacted]
Subsequent therapy	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]
Blindness	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]

Utilities are varied with a beta distribution and so show mean values that are central to the upper and lower bound. Noticeably, the upper bound utilities accrued on

treatment for (L)CP are lower than the lower bound utilities accrued on treatment with ILUVIEN.

Figure 19 shows the ICER scatterplot for ILUVIEN vs (L)CP; results from 1,000 simulations; 91% of these iterations appear in the North West Quadrant (NWQ) indicating incrementally higher patient outcomes and costs. Figure 19 shows that there is a spread of incremental efficacy as would be expected with extrapolation but that this is largely favourable. Incremental costs show some variation but are bound between £1,500 and £2,500 for the majority of iterations.

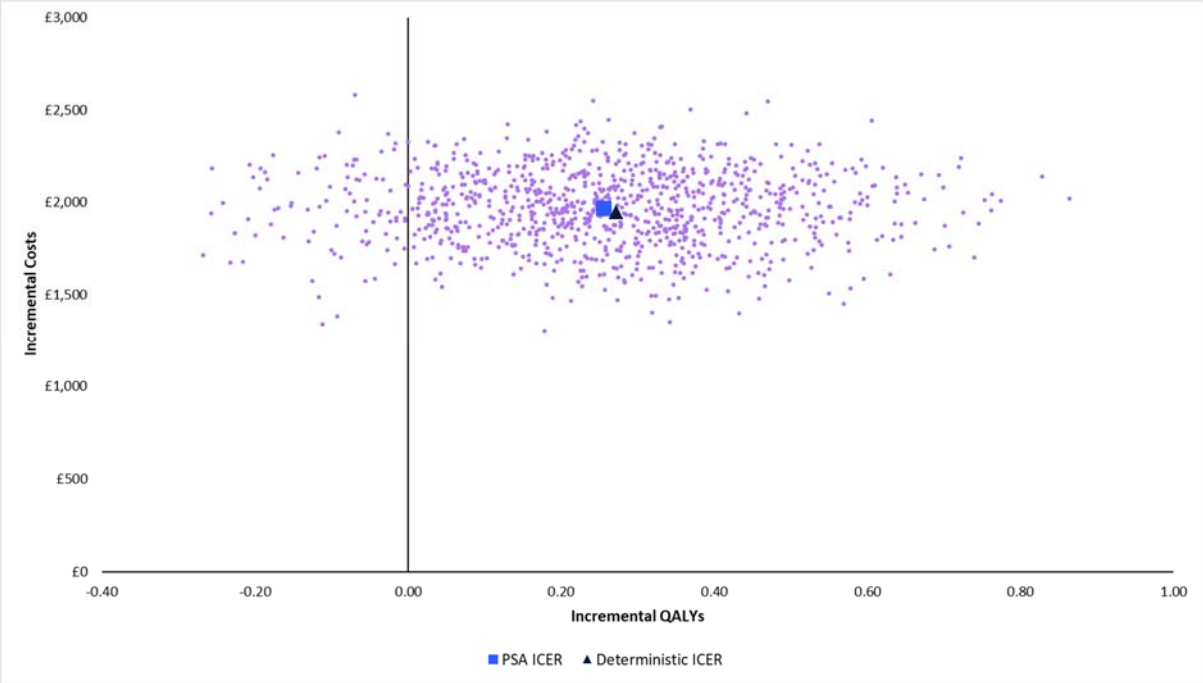


Figure 19. ICER scatterplot: ILUVIEN vs (L)CP

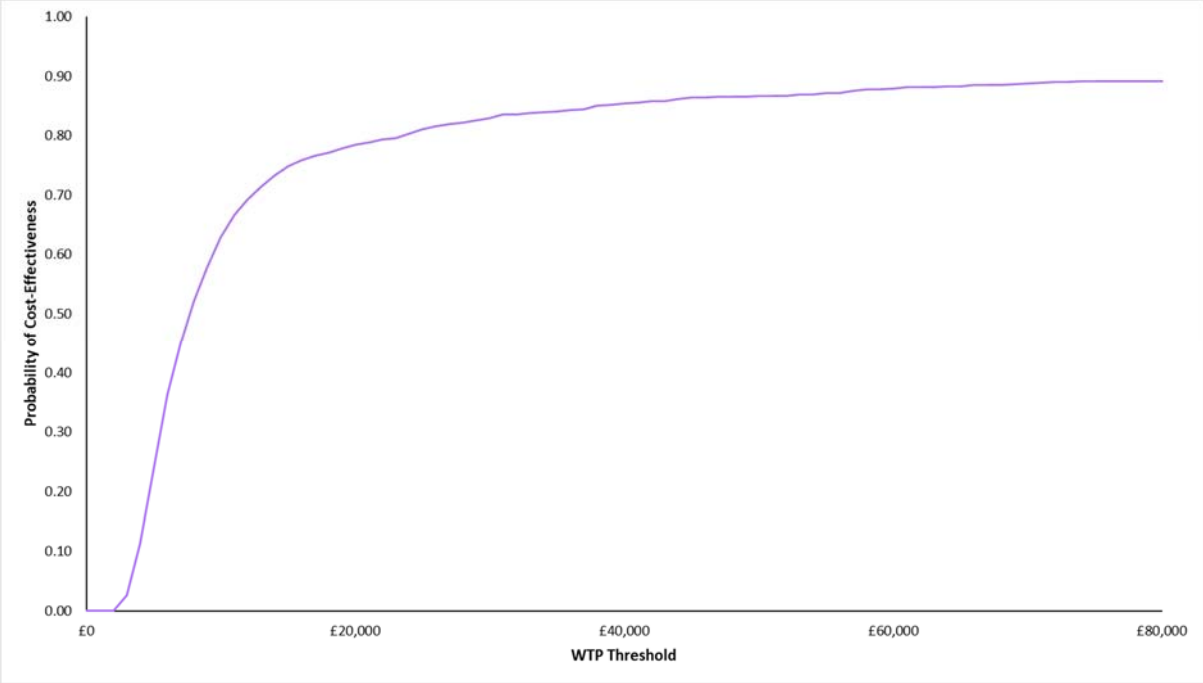


Figure 20: Cost-effectiveness acceptability curve: ILUVIEN vs(L) CP

Figure 20 shows the cost-effectiveness acceptability curve (CEAC) for a range of willingness to pay (WTP) thresholds. At a WTP threshold of £20,000, the probability of cost-effectiveness is 79%.

3.8.2 Deterministic sensitivity analysis

A range of one-way sensitivity analyses have been conducted, regarding the following assumptions:

- Health state health state utility: On Treatment (± 20%)
- Health state health state utility: Permanent Blindness (± 20%)
- Health state health state utility: Remission/General population estimates (± 20%)
- Health state health state utility: End of Treatment Effect (± 20%)
- Rates of discounting: costs (0% and 6%)
- Rates of discounting: QALYs (0% and 6%)

- Adverse event rates (± 20%)
- Adverse event costs (± 20%)
- Rate at which patients experience permanent blindness (± 20%)
- Average patient weight (± 20%) – affecting supplemental therapy costs
- Proportions receiving immunosuppressants and corticosteroids in subsequent therapy (± 20%)
- Proportions receiving systemic therapies in subsequent therapy (± 20%)
- Proportions receiving supplemental therapies (± 20%)
- Costs associated with permanent blindness (± 20%)
- Monitoring costs (± 20%)

Note: Where (± 20%) is specified, the mean value is multiplied by 1.2 or 0.8 so as to assess the impact of a 20% change in value.

Parameters were available for the parametric models used to inform time to recurrence for (L)CP. These were sampled probabilistically 1,000 times and the upper and lower bounds of this set of values was used to inform the upper and lower bounds used in univariate analysis.

Tornado plots showing results of the univariate sensitivity analyses are presented in Figure 21 and **Figure 22 for impact on the ICER and Incremental Net Monetary Benefit (INMB) respectively. Table 55 and Table 56 detail the impact of specific parameters on the ICER and INMB shown in the tornado plots.

Table 55 shows that the utility value assigned to the Off Treatment health state results in a negative ICER when the upper bound value is used. This is because in this situation, a higher number of QALYs are obtained by patients in taking CP. The higher bound value for this parameter is 0.911 which is higher than any other value assigned to a health state used in the model. When this value is assigned to the Off Treatment health state, given more patients are expected in this health state on CP

there is nowhere else in the model where utility will be accrued at a higher rate. In this situation, costs remain unchanged from the base case and results in a negative ICER. For this reason and completeness, the most influential parameters on INMB are also shown (Table 56 and **Figure 22).

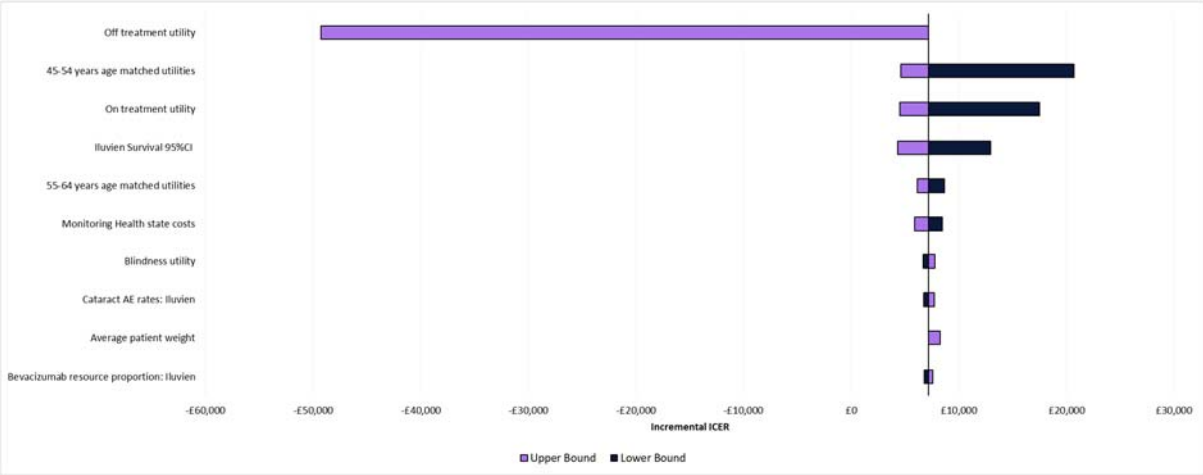


Figure 21: Tornado plot showing most influential parameters on ICER

Table 55: Most influential parameters on ICER

	Parameter	Lower Bound ICER	Upper Bound ICER	Difference
1	Off treatment utility	£3,347.36	-£49,261.51	£52,608.88
2	45-54 years age matched utilities	£20,723.39	£4,621.99	£16,101.40
3	On treatment utility	£17,476.72	£4,520.31	£12,956.41
4	ILUVIEN Survival 95%CI	£12,948.48	£4,304.86	£8,643.62
5	55-64 years age matched utilities	£8,664.79	£6,133.72	£2,531.07
6	Monitoring Health state costs	£8,448.09	£5,917.51	£2,530.58
7	Blindness utility	£6,688.16	£7,756.45	£1,068.28
8	Cataract AE rates: ILUVIEN	£6,733.18	£7,711.23	£978.05
9	Average patient weight	£7,400.19	£8,255.61	£855.43
10	Bevacizumab resource proportion: ILUVIEN	£6,784.07	£7,581.54	£797.47

Of the ten most influential parameters on the ICER, five of them are utility values and one (ILUVIEN efficacy) is directly related to efficacy and therefore dictate state occupancy. Indirectly these parameters indicate that the model is very sensitive to health state occupancy, i.e. efficacy of the intervention in all scenarios bar one, the ICER is under the £20,000/QALY WTP threshold.

The rate of cataracts is influential on the ICER because this is a costly procedure and a large proportion of patients in PSV-FAI-001 were recorded as needing this [redacted]. Any variation in this proportion can have a large impact on costs as the CP arm experiences a lesser proportion needing cataract surgery [redacted]. Similarly, the proportion requiring bevacizumab as an supplemental therapy appears as influential because of the high list price of one unit for bevacizumab. As bevacizumab is administered by weight, the average patient weight also influences the model. The proportion receiving bevacizumab in the (L)CP arm is the 16th most influential parameter on the ICER.

[redacted]Figure 22: Tornado plot showing most influential parameters on INMB

Table 56: Most influential parameters on INMB

	Parameter	Lower Bound NMB	Upper Bound NMB	Difference
1	Off treatment utility	[redacted]	[redacted]	[redacted]
2	45-54 years age matched utilities	[redacted]	[redacted]	[redacted]
3	On treatment utility	[redacted]	[redacted]	[redacted]
4	Iluvien Survival 95%CI	[redacted]	[redacted]	[redacted]
5	55-64 years age matched utilities	[redacted]	[redacted]	[redacted]
6	Blindness utility	[redacted]	[redacted]	[redacted]
7	Monitoring Health state costs	[redacted]	[redacted]	[redacted]
8	Cataract AE rates: Iluvien	[redacted]	[redacted]	[redacted]
9	(L)CP Survival 95%CI	[redacted]	[redacted]	[redacted]
10	Average patient weight	[redacted]	[redacted]	[redacted]

**Figure 22 and Table 56 show the most influential parameters on INMB. These are for the majority, the same parameters as are influential on ICER however as some of the analyses result in negative ICERs it is appropriate to show INMB. When the Off Treatment utility value takes the upper bound value, there is a negative INMB.

3.8.3 Scenario analysis

In order to populate a model, a number of structural assumptions are required. Here the impact of these decisions is assessed. Scenarios alternative to the base case are explored and results displayed in Table 57.

3.8.3.1 Base case Settings

A lifetime horizon was considered most appropriate for examining the clinical benefit and costs for ILUVIEN versus (L)CP. Similarly, discount rates are standard although both of these assumptions could be subject to change and so it is appropriate to examine the impact of any change to these assumptions. Varying the time horizon shows results stabilise after approximately 5 years. This is expected as the initial costs and efficacy are experienced in the first 3 years. Altering the discount rate up and down results in an increased and decreased ICER as would be expected.

3.8.3.2 Efficacy estimates for ILUVIEN and (L)CP

As the best fitting efficacy curves are open to interpretation, it is important to assess the impact of the base case choice. The ICER varies from £3,852 to £10,299.07 dependent on the distribution chosen to best represent time to recurrence for ILUVIEN. Importantly, none of these choices render ILUVIEN not cost-effective. The same is true for the choice of parameterization chosen to best represent time to recurrence for (L)CP with resultant ICERs ranging from £7,159 to £8,329.

Table 57: Scenario analysis results

Scenario	**Incremental Costs**	**Incremental QALYs**	**ICER**	**INMB**
Base case	[redacted]	[redacted]	£7,182.79	[redacted]
Time Horizon (years)				
1	[redacted]	[redacted]	£117,696.27	[redacted]
5	[redacted]	[redacted]	£17,906.12	[redacted]
10	[redacted]	[redacted]	£11,641.20	[redacted]
20	[redacted]	[redacted]	£9,075.83	[redacted]
30	[redacted]	[redacted]	£7,881.57	[redacted]
40	[redacted]	[redacted]	£7,298.18	[redacted]
Discount (costs and utilities)				
0%	[redacted]	[redacted]	£5,391.60	[redacted]
6%	[redacted]	[redacted]	£9,256.04	[redacted]
Efficacy Curve Fits: ILUVIEN, parametric fits from 120 days onwards				
LogNormal	[redacted]	[redacted]	£8,568.11	[redacted]
LogLogistic	[redacted]	[redacted]	£4,606.17	[redacted]
Gompertz	[redacted]	[redacted]	£10,299.26	[redacted]
Gamma	[redacted]	[redacted]	£8,167.22	[redacted]

Generalised Gamma	[redacted]	[redacted]	£7,306.82	[redacted]
Weibull	[redacted]	[redacted]	£3,854.44	[redacted]
Efficacy Curve Fits: (L)CP parametric curve fits				
LogNormal	[redacted]	[redacted]	£7,160.20	[redacted]
Gompertz	[redacted]	[redacted]	£8,327.45	[redacted]
Gamma	[redacted]	[redacted]	£8,027.44	[redacted]
Generalised Gamma	[redacted]	[redacted]	£7,328.74	[redacted]
Weibull	[redacted]	[redacted]	£7,240.56	[redacted]
Exponential	[redacted]	[redacted]	£7,211.66	[redacted]
Include AEs				
No	[redacted]	[redacted]	£5,071.60	[redacted]
Blindness Rate				
0.0038 (annual)	[redacted]	[redacted]	£8,218.57	[redacted]
0.0374 (annual)	[redacted]	[redacted]	£4,144.58	[redacted]
Blindness Utilities				
0.57	[redacted]	[redacted]	£8,812.07	[redacted]
Remission Health State				
No	[redacted]	[redacted]	£10,971.74	[redacted]

3.8.3.3 Utility associated with permanent blindness

An assumption is made that the utility reported for permanent blindness and used in the base case is the most appropriate and accurate value to represent this patient population and outcome. This assumption is however, open to interpretation. In the base case [redacted] QALYs per year are accrued by patients in this health state. An alternative value was sourced in TA460 (0.57 from Brown 1999[63]) and when applied in this model the ICER is higher than in the base case due to slightly reduced incremental utilities though still would be considered at the WTP.

3.8.3.4 Rate of blindness

The assumptions made with regard to permanent blindness were also assessed. The rate at which patients go blind is debated in the literature and two values were sourced as used in TA460. One rate was higher than the base case; Durrani et al[10] reported 0.0374 annually and one was lower, Tomkins-Netzer[54] et al reported 0.0038 annually. These result in lower and higher ICERs respectively than the base case. As the model assumes patients will not transition to permanent blindness from a position where ocular inflammation is controlled, this is indirectly driven by health

state occupancy. As the same proportion are estimated to go blind in this scenario as with the base case, less or more patients will experience worse outcomes with a higher or lower rate of assumed blindness respectively.

3.8.3.5 Remission health state

The remission health state was not used in the base case for TA460 however for the base case of this analysis it was considered appropriate. The impact of this structural assumption was tested and when this health state is not included, ILUVIEN is still cost-effective when compared to (L)CP. In this scenario, there are reduced incremental utilities and increased costs resulting in an ICER of £10,972 which would still be cost-effective at a WTP threshold of £20,000/QALY.

3.8.3.6 Inclusion of AEs

In the base case analysis, it was considered appropriate to include the cost of AEs as this is a consequence of treatment. Results are presented where these have not been included as all listed AEs may not apply to all patients. This was done because the list of AEs is extensive and incidence of individual AEs often low leading to uncertainty in the method of treatment. Exclusion of AEs results in a lower ICER than in the base case as more costly AEs are expected to occur without active treatment.

3.8.4 Summary of sensitivity analyses results

Sensitivity analysis has shown that the base case result that ILUVIEN is cost-effective at the WTP threshold of £20,000/QALY is robust. The probabilistic analysis demonstrates that this is true in 79% of the 1,000 iterations. Importantly, the upper bound utilities accrued on first line treatment with (L)CP is considerably less than the lower bound utilities accrued with ILUVIEN demonstrating additional HRQoL outcomes for patients. The probabilistic average ICER is £7,702 which is very similar to the base case ICER indicating stability in this estimate.

The OWSA reveals that the model is sensitive to health state occupancy with the survival estimates and utility applied to each health state exerting influence over results. Large additional costs such as the cost of bevacizumab, cataract treatment and the monitoring cost also influence results.

The structural uncertainty was explored with scenario analysis and none of these scenarios rendered ILUVIEN not cost-effective when compared to (L)CP aside from a time horizon of one year. As the largest cost of treatment with ILUVIEN is accrued in the first cycle, this is to be expected. The results from scenario analysis demonstrate that the structural assumptions are not changing the outcome of cost-effectiveness for ILUVIEN.

3.9 *Subgroup analysis*

In line with the decision problem form, no subgroup analyses were performed.

3.10 *Validation*

3.10.1 Validation of cost-effectiveness analysis

As [redacted] has a relatively low prevalence there is a paucity of data informing this subject. As such, there is limited evidence to describe the current treatment pathways resource use and associated costs and progress of disease. In general, where no evidence has been identified, pragmatic assumptions have been made based on independent sources, such as published literature, clinical advice or previous NICE appraisals. These assumptions were then assessed for clinical plausibility; uncertainty has been characterised through the use of sensitivity analyses. Extensive sensitivity analyses were then undertaken, and the majority of ICERs remain below the £20,000/QALY threshold.

The model predicts that [redacted] will be spent on first line treatment, i.e. not experiencing recurrence, when patients are treated with ILUVIEN compared to (L)CP. The KM curves for ILUVIEN and (L)CP and the fitted curves are described in Section 3.3.1 and shown in Appendix J.

[redacted]

The model predicts that at 10 years 4.4% and 6% have experienced permanent blindness in the ILUVIEN and (L)CP arms respectively. After accounting for mortality these estimates are expected given that the difference between arms is driven by the

proportion who initially do not experience recurrence. This indicates that ILUVIEN is associated with incremental clinical benefit.

A technical review of the cost-effectiveness model was conducted, and the relevance of the model structure and assumptions was validated at a clinical advisory board held in October 2018 (clinical experts, personal communication). This allowed the model approach to be validated and permitted areas of disagreement to be resolved prior to generation of model results. In addition, quality control was undertaken, whereby a cell-by-cell verification process was conducted to allow checking of all input calculation, formulae and visual basic code.

3.10.2 Validation of Outcomes

Primary evidence on the clinical efficacy of ILUVIEN versus (L)CP for the current submission has been derived from PSV-FAI-001, as the study is an active sham comparison trial comparing ILUVIEN with (L)CP. However, calculations were validated by using data presented in TA460 for dexamethasone vs (L)CP. These were used to calculate LYs and QALYs and compare these to reported results which were considered to be in line. Total LYs accrued on both arms were reported to be 20.529 in TA460 and estimated to be 20.357 in this economic model. Time on Treatment was presented in Squires et al.[44] as combined (dexamethasone and subsequent therapy) and reported as being 18.703 LYs which is similar to the estimated 18.490 LYs by this economic model.

QALYs accrued on treatment (considering the intervention and subsequent therapy) were reported in Squires et al.[44] as being 13.904 and 13.946 for the (L)CP and dexamethasone arms respectively. This model estimated these to be 13.982 and 14.077 (L)CP and dexamethasone arms respectively. This demonstrates that calculations and assumptions are in line with those used in the model used in TA460.

It was not possible to replicate costs in the dexamethasone analysis in the model presented in this economic analysis due to some perceived ambiguity surrounding the reporting of costs. Supplemental therapy for dexamethasone was reported as being sourced from a publication however these values were not available in the

listed publication[31]. It was not considered completely clear how these costs were applied in subsequent therapy either.

Additionally, outcomes from the model were compared to reported outcomes from PSV-FAI-001; clinical outcomes are described in Section 3.7. The modelled outcomes for time to first recurrence are consistent with the reported measures.

3.10.3 Validation of clinical parameters

The utilities chosen to represent Remission were validated by a clinical expert as it was indicated that patients in remission from ocular disease may be considered to have HRQoL akin to the general population.

Due to the paucity of data, it is challenging to validate the utilities that are assigned to the On Treatment and Subsequent Treatment health states. However, efforts have been made to examine the uncertainty and influence of these parameters.

3.11 *Interpretation and conclusions of economic evidence*

As previously noted, this analysis has been designed to be comparable with previous HTAs in uveitis, facilitating review and transparency. Further, the approach has been chosen to reflect the most important treatment outcomes for most uveitis patients: time to first recurrence, side effects and quality of life.

The clinical evidence for ILUVIEN highlights its superiority to (L)CP in a number of definitions for recurrence: Time to recurrence, number of recurrences and the proportion of patients who would expect a recurrence in 6 and 36 months. This economic analysis uses the time to first recurrence as the primary clinical input as delaying the first recurrence can prolong the time to which a patient experiences more serious consequences of the disease.

In the base case analysis, it was estimated that ILUVIEN would result in an additional [redacted] spent without recurrence when compared to (L)CP. This in turn would result in an additional [redacted] QALYs under base case assumption (i.e. no retreatment). Discounted incremental costs are expected to be £1,949 when compared to (L)CP. The result is an ICER of £7,183 which is considered cost-effective at a WTP of £20,000/QALY.

A range of sensitivity analyses were conducted and the ICER was under the WTP of £20,000/QALY in the large majority of cases. Additionally, structural uncertainty was explored in the scenario analysis and in all scenarios except a one year time horizon, ILUVIEN would be considered cost-effective. As the largest cost difference is accrued in the first year, this result is to be expected.

The additional years spent on treatment where disease is not recurring means slower progression of disease, offering improved quality of life to patients with uveitis. This additional time will also reduce the burden to the health care system in this time and reduce the onset of the most serious consequences of disease for patients. As a treatment with such extended efficacy is not currently available for patients in the UK, introduction of ILUVIEN will meet a significant unmet need for patients with this disease.

3.11.1 Limitations

The main limitations of these estimates are that AEs, subsequent therapy (discontinuation) and the costs associated with blindness are not taken into account in the calculations. However, while AEs are estimated to be more costly in the ILUVIEN arm than the (L)CP arm, discontinuation is considerably higher in the (L)CP arm and so use of subsequent therapies will be higher and the estimated proportion of patients experiencing permanent blindness is lower in the ILUVIEN arm.

AEs for the ILUVIEN arm are estimated to be £8.98 per two weeks compared to £5.07 per two weeks for the (L)CP arm (described in Section 3.5.4); £233.54 and £131.91 annually. However, as detailed in Section 3.10, median time to recurrence and the switch to subsequent therapy in the (L)CP arm, happens approximately [redacted] weeks prior to the median time to recurrence in the ILUVIEN arm. For those [redacted] weeks, the subsequent therapy cost of £2.45 is applied every two weeks for patients on the (L)CP arm which would not be incurred by patients in the ILUVIEN arm.

The cost associated with permanent blindness are estimated to be an initial £4,952 and an annual cost of £1,206. The model estimates that 1.6% of patients taking (L)CP will experience permanent blindness than those taking ILUVIEN and therefore incur these costs more frequently. Therefore, the base case analysis presented is considered to be conservative despite these limitations.

Another key limitation of the analysis is that there is uncertainty surrounding the variety and proportions of supplemental therapies that will be used. The supplemental therapies and proportions used are taken directly from PSV-FAI-001 and this relies on the assumption that this patient group is completely reflective of patients in England and Wales. The patient group and protocol for treatment is considered to be reflective of current practice and so this limitation is not considered to be unrealistic.

3.11.2 Summary

The implications for NHS resources should ILUVIEN be approved for use are estimated to be approximately [redacted] in the next six years.

The total costs will allow for treatment of an estimated [redacted] patients in the first year, rising to [redacted] in the sixth year under base case assumptions.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Clarification questions

January 2019

File name	Version	Contains confidential information	Date
ID1039 fluocinolone clarification letter 20190110.docx	**20190110**	**Yes**	**10/01/2019**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Literature Searches – All sections

A1. The search appendices for clinical effectiveness, cost effectiveness and health-related quality of life (HRQoL) all report additional searches of resources such as HTA agencies, clinical trials registries, conferences proceedings and websites. Please provide full search strategies and details of dates searched for each of these resources, in the table below:

	Required for		
Resource name	**Clinical Effectiveness**	**Cost Effectiveness**	**HRQoL**
NICE	**Date of search** September 2018 **Search terms** uveitis	**Date of search** September 2018 **Search terms** uveitis	
SMC	**Date of search** September 2018 **Search terms** uveitis	**Date of search** September 2018 **Search terms** uveitis	
AWMSG	**Date of search** September 2018 **Search terms** uveitis	**Date of search** September 2018 **Search terms** uveitis	
Conference proceedings for:			
The Royal College of Ophthalmologists Annual Congress	**Date of search** September 2018 **Search terms** Iluvien fluocinolone acetonide Fluocinolone Dexamethasone Ozurdex Adalimumab Humira uveitis	**Date of search** September 2018 **Search terms** Uveitis+ costs	
European Society of Ophthalmic Plastic and Reconstructive Surgery	**Date of search** September 2018 **Search terms** Iluvien fluocinolone acetonide Fluocinolone Dexamethasone Ozurdex Adalimumab Humira uveitis	**Date of search** September 2018 **Search terms** Uveitis+ costs	
American Academy of Ophthalmology	**Date of search** September 2018 **Search terms** uveitis Iluvien + uveitis fluocinolone acetonide + uveitis Fluocinolone + uveitis Dexamethasone + uveitis Ozurdex + uveitis Adalimumab + uveitis Humira + uveitis	**Date of search** September 2018 **Search terms** Uveitis+ costs	

European Society of Retina Specialists	**Date of search** November 2018 **Search terms** uveitis Iluvien + uveitis fluocinolone acetonide + uveitis Fluocinolone + uveitis Dexamethasone + uveitis Ozurdex + uveitis Adalimumab + uveitis Humira + uveitis	**Date of search** November 2018 **Search terms** Uveitis+ costs	
The Association for Research in Vision and Ophthalmology	**Date of search** November 2018 **Search terms** uveitis Iluvien + uveitis fluocinolone acetonide + uveitis Fluocinolone + uveitis Dexamethasone + uveitis Ozurdex + uveitis Adalimumab + uveitis Humira + uveitis	**Date of search** November 2018 **Search terms** Uveitis+ costs	
International Ocular Inflammation Society	**Date of search** November 2018 **Search terms** uveitis Iluvien + uveitis fluocinolone acetonide + uveitis Fluocinolone + uveitis Dexamethasone + uveitis Ozurdex + uveitis Adalimumab + uveitis Humira + uveitis	**Date of search** November 2018 **Search terms** Uveitis+ costs	
ISPOR annual European and International meetings		**Date of search** September 2018 **Search terms** Uveitis+ costs	
Clinical Trials registries			
ClinicalTrials.gov	**Date of search** September 2018 **Search terms** Condition of disease: uveitis, posterior Other terms: fluocinolone acetonide OR fluocinolone OR iluvien OR dexamethasone OR ozurdex OR adalimumab OR humira		

International Clinical Trials Registry Platform	**Date of search** September 2018 **Search terms** fluocinolone acetonide OR Fluocinolone OR Iluvien OR Dexamethasone OR Ozurdex OR Adalimumab OR Humira		
European Union's Clinical Trials Register	**Date of search** September 2018 **Search terms** Uveitis AND (fluocinolone acetonide OR Fluocinolone OR Iluvien OR Dexamethasone OR Ozurdex OR Adalimumab OR Humira)		
Free text internet search			**Date of search** September 2018 **Search terms** Uveitis with posterior or fluocinolone acetonide or Fluocinolone or Iluvien or Dexamethasone or Ozurdex or Adalimumab or Humira

A2. Appendix I: 'Cost and healthcare resource use identification' states that "…a search of the grey literature will be conducted including a search of relevant conference programs and a review of HTA websites (e.g. NICE, SMC and AWMSG)" Please confirm if these additional searches took place and provide a full list of resources searched including both the date of the search and a full search strategy.

The searches of the HTA websites for NICE, SMC and AWMSG have been conducted in September 2018. The websites were each searched for any uveitis related technology assessments using uveitis as the search term.

A3. For all search appendices (for example appendix D, D1.1) the company submission states that Pubmed was searched for both Medline and Medline in Process; please confirm that this is the case. However, the Embase searches (see

example Appendix D, Table 2) state that these searches also cover both Embase and Medline. Please clarify if these Embase strategies report a single search conducted simultaneously over both the Embase and Medline individual databases (creating a duplicate set of results) or a single search of Embase conducted on the understanding that it now contains all records from Medline.

The provided search strategies were applied for each interface: Medline via Pubmed and Embase via Elsevier. Duplicates were removed during the screening process. Therefore, a duplicate set of results was not created.

A4. All searches had a reported search date of September 2018, please confirm if these are update searches or the only searches undertaken for this for this submission? If they are update searches, please provide details of any original searches.

All searches were conducted in September 2018. These represent the original searches. However, three additional conference websites were searched in November 2018. Please see the table in A1 for further details on these additional conference websites.

Literature Searches – Clinical Effectiveness

A5. Please could you confirm if the searches were also intended to inform the following: Indirect & Mixed Treatment Comparisons, Non-RCT evidence and Adverse Events.

Yes, the searches were intended to inform indirect and mixed treatment comparisons as well as to identify non-RCT evidence and adverse events. However, the search results of the SLR couldn't inform an indirect/mixed treatment comparison nor was any relevant non-RCT evidence identified. The adverse events reported in the pivotal study, PSV-FAI-001, were the only identified source for adverse events data

A6. For all searches in Appendix D: All strategies contain searches for only 3 comparators; adalimumab, dexamethasone and “best supportive care”. Whilst this is in the line with the comparators listed in the exclusion table (Appendix D table 4), this is not in line with the NICE final scope (See also Question A11). Please explain what effect this may have had on the overall recall of results.

This search strategy was adopted in order to be in line with the search strategy applied in TA460. All relevant results were captured through this approach.

Literature Searches – Cost Effectiveness

A7. The Embase search strategy appears to contain an error in the costs filter combined in line #22. Lines #2 and #3 appear to have been missed in this combination. Please can you confirm whether this is a reporting error (if so please provide the original strategy) or if this is a search error and if so what effect this may have had on the overall recall of results.

Please see below for the Embase original search strategy applied in the cost-effectiveness modelling SLR. Line #2 and #3 were included in the search string in line #22. Therefore, the missing lines #2 and #3 in the submission represent a reporting error which had no effect on the overall recall of results.

```
ï»¿Embase
Session Results
.....................................................
No.  Query Results                                        Results
Date
#26. #1 AND #22 NOT #25                                      323  11
Sep 2018
#25. #23 OR #24                                          10,384,246  11
Sep 2018
#24. 'case report' OR 'case study' OR letter OR           6,380,086  11
Sep 2018
     editorial OR 'case reports':it OR letter:it OR
     editorial:it OR review:it
#23. 'controlled clinical trial' OR 'clinical study'      4,479,355  11
Sep 2018
     OR 'clinical trial' OR 'observational study'
#22. #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR      1,822,477  11
Sep 2018
     #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR
     #17 OR #18 OR #19 OR #20 OR #21
#21. unit NEAR/1 cost*                                       4,014  11
Sep 2018
```

```
#20. cost NEAR/1 variable*                                          515  11
Sep 2018
#19. cost NEAR/1 estimate*                                        6,126  11
Sep 2018
#18. fiscal:ti,ab OR financial:ti,ab OR finance:ti,ab           160,632  11
Sep 2018
     OR funding:ti,ab
#17. 'hospital cost'/exp                                         34,329  11
Sep 2018
#16. 'health economics'/exp                                     781,672  11
Sep 2018
#15. 'health care financing'/exp                                 12,757  11
Sep 2018
#14. 'health care cost'/exp                                     265,385  11
Sep 2018
#13. 'financial management'/exp                                 389,307  11
Sep 2018
#12. 'economic aspect'/exp                                    1,524,074  11
Sep 2018
#11. 'cost controls'                                                164  11
Sep 2018
#10. 'cost of illness'/exp                                       17,564  11
Sep 2018
#9.  'socioeconomics'/exp                                       344,558  11
Sep 2018
#8.  budget*:ti,ab                                               33,608  11
Sep 2018
#7.  economic*:ti,ab OR pharmacoeconomic*:ti,ab                 292,443  11
Sep 2018
#6.  'cost minimization analysis'/exp OR 'cost                    3,914  11
Sep 2018
     minimi*':ti,ab
#5.  'cost utility analysis'/exp OR 'cost                         9,817  11
Sep 2018
     utilit*':ti,ab
#4.  'cost effectiveness'/exp OR 'cost effectiveness'           245,829  11
Sep 2018
     OR 'cost-effectiveness':ti,ab OR 'cost
     effective*':ti,ab OR cea:ti,ab
#3.  'cost consequence':ti,ab                                       332  11
Sep 2018
#2.  'cost-benefit analysis'/exp OR 'cost-benefit                 79,199  11
Sep 2018
     analysis':ti,ab
#1.  'uveitis'/exp OR uveitis:ti,ab                               56,005  11
Sep 2018
.....................................................
```

A8. The Cochrane Library strategy for both the clinical effectiveness and HRQoL searches reports using the Wiley host interface. The strategies for both cost

effectiveness and resource use identification appear to contain a different search syntax i.e.

#1 uveitis[MeSH descriptor] **Should display as “MeSH descriptor: [Uveitis] explode all trees”

#3 (‘cost consequence’ OR ‘cost-benefit analysis’):ti.ab,kw **This line generates an error regarding the use of commas

Please confirm the host interface used for both the cost effectiveness and resource use searches.

Please find below the original CEM SLR search strategy applied in the Cochrane Library database. Line #1 and #3 were reported in error which had no effect on the overall recall of results.

Cochrane Library

Advanced Search

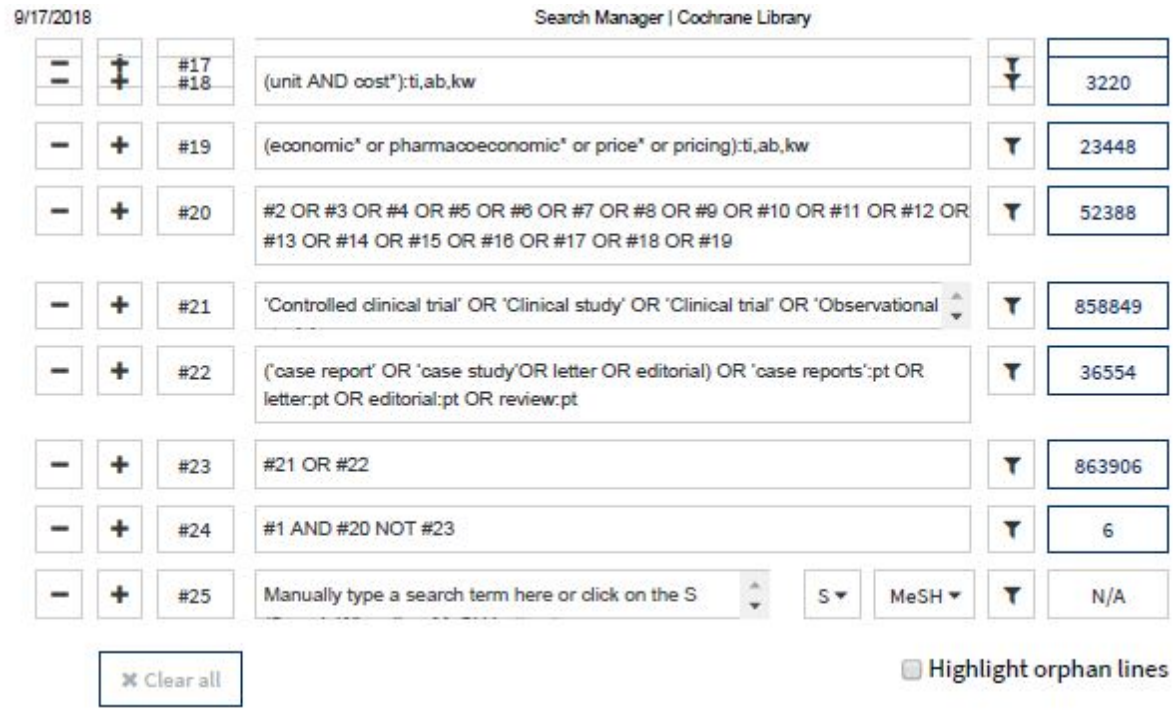
Please note that the Advanced Search is optimised for English search terms. Certain features, such as search operators and MeSH terms, are only available in English.

Search manager

Save this search | View saved searches | ? Search help

View fewer lines | Print

−	+	#1	MeSH descriptor: [Uveitis] explode all trees	MeSH	537
−	+	#2	MeSH descriptor: [Cost-Benefit Analysis] explode all trees	MeSH	6179
−	+	#3	('cost consequence' OR 'cost-benefit analysis'):ti,ab,kw		1441
−	+	#4	MeSH descriptor: [Costs and Cost Analysis] explode all trees	MeSH	9518
−	+	#5	('cost effectiveness' OR 'cost-effectiveness' OR 'cost effective*' OR CEA):ti,ab,kw		26440
−	+	#6	'cost utilit*':ti,ab,kw		1773
−	+	#7	'cost minimi*':ti,ab,kw		1406
−	+	#8	(economic* OR pharmacoeconomic*):ti,ab,kw		22619
−	+	#9	Budget*:ti,ab,kw		706
−	+	#10	MeSH descriptor: [Cost of Illness] explode all trees	MeSH	772
−	+	#11	MeSH descriptor: [Cost Control] explode all trees	MeSH	557
−	+	#12	MeSH descriptor: [Financial Management] explode all trees	MeSH	244
−	+	#13	MeSH descriptor: [Health Care Costs] explode all trees	MeSH	3208
−	+	#14	MeSH descriptor: [Hospital Costs] explode all trees	MeSH	579
−	+	#15	(fiscal or financial or finance or funding):ti,ab,kw		10370
−	+	#16	(cost AND estimate*):ti,ab,kw		6053
			(cost AND variable):ti,ab,kw		



Please find below the original resource use SLR search strategy applied in the Cochrane Library database. Line #1 and #3 were reported in error which had no effect on the overall recall of results.

Cochrane Library

Advanced Search

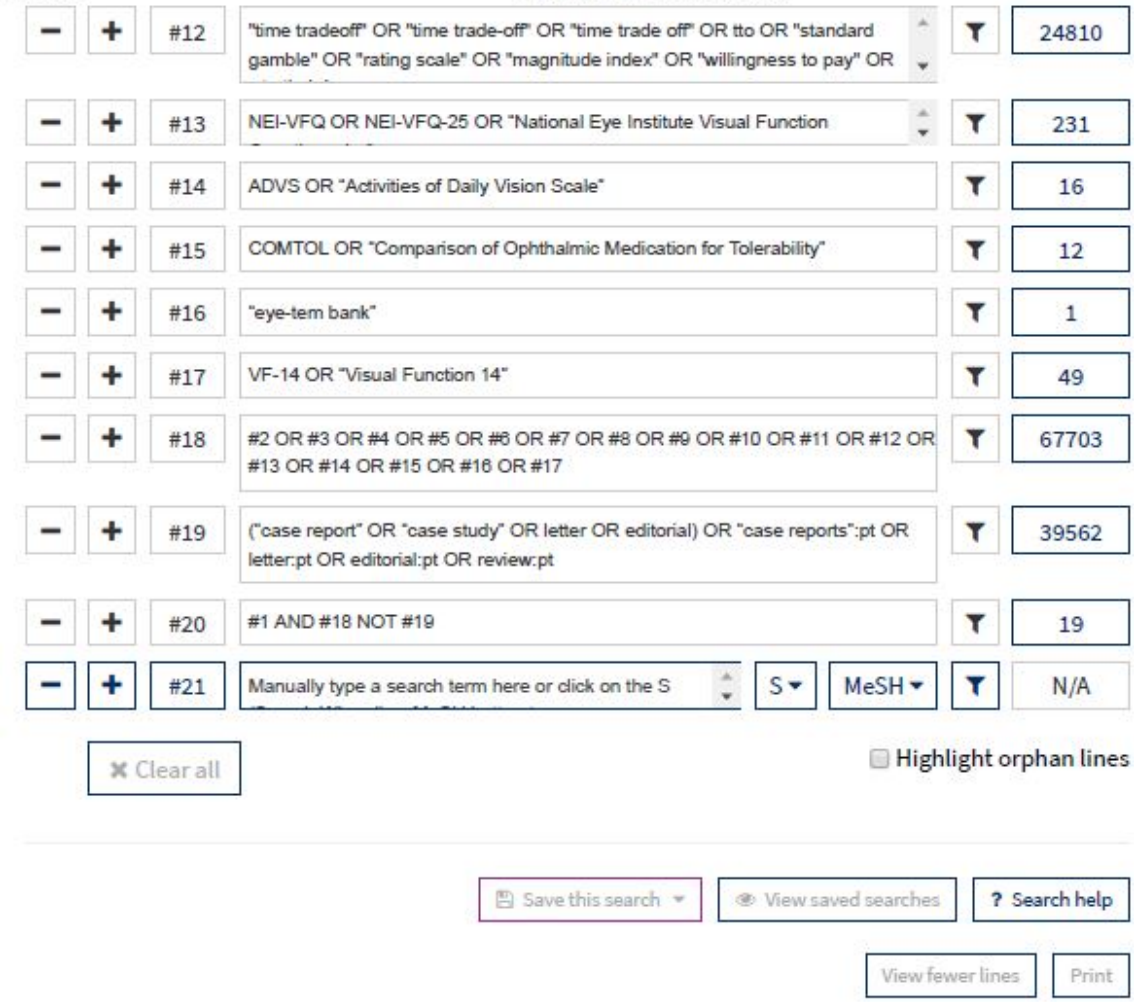
Please note that the Advanced Search is optimised for English search terms. Certain features, such as search operators and MeSH terms, are only available in English.

Search manager

Save this search | View saved searches | ? Search help

View fewer lines | Print

−	+	#1	MeSH descriptor: [Uveitis] explode all trees	MeSH	537
−	+	#2	MeSH descriptor: [Quality of Life] explode all trees	MeSH	20385
−	+	#3	MeSH descriptor: [Quality-Adjusted Life Years] explode all trees	MeSH	1029
−	+	#4	QALY* OR QALD* OR QALE*		2414
−	+	#5	"health related quality of life" OR HRQoL OR "health related qol" OR HRQL		12117
−	+	#6	"disability adjusted life" OR DALY		1179
−	+	#7	utility OR utilities OR 'health utility' OR 'health utilities' OR disutili*		12048
−	+	#8	hsuv OR hsuvs		9
−	+	#9	hui OR hui1 OR hui2 OR hui3		1552
−	+	#10	"EQ 5D" OR "EQ 5" OR EQ5D OR euroqol		4610
−	+	#11	sf6 OR "sf 6" OR sf6d OR "sf 6d" OR "sf six" OR sfsix OR sf8 OR "sf 8" OR "sf eight" OR sfeight OR sf12 OR "sf 12" OR "sf twelve" OR sftwelve OR sf16 OR "sf 16" OR "sf sixteen" OR sfsixteen OR sf20 OR "sf 20" OR "sf twenty" OR		1882


#12
"time tradeoff" OR "time trade-off" OR "time trade off" OR tto OR "standard gamble" OR "rating scale" OR "magnitude index" OR "willingness to pay" OR
24810
#13
NEI-VFQ OR NEI-VFQ-25 OR "National Eye Institute Visual Function
231
#14
ADVS OR "Activities of Daily Vision Scale"
16
#15
COMTOL OR "Comparison of Ophthalmic Medication for Tolerability"
12
#16
"eye-tem bank"
1
#17
VF-14 OR "Visual Function 14"
49
#18
#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
67703
#19
("case report" OR "case study" OR letter OR editorial) OR "case reports":pt OR letter:pt OR editorial:pt OR review:pt
39562
#20
#1 AND #18 NOT #19
19
#21
Manually type a search term here or click on the S
S
MeSH
N/A
Clear all
Highlight orphan lines
Save this search
View saved searches
Search help
View fewer lines
Print

Treatment Pathway

A9. In table 1 of the company submission (page 10) the population is described as "[redacted]". While the scope describes the population as "adults with recurrent non-infectious uveitis".

A. Please explain the difference between "recurrent or persistent" and "recurrent".
B. Please explain whether this difference in meaning influences treatment choice.

The company has submitted to the MHRA a marketing authorisation for the proposed indication of:

[redacted]. The proposed indication is still confidential.

An expert perspective from members of the Standardisation of Uveitis Nomenclature (SUN) project aiming to describe an integrated clinical approach to diagnosing uveitis (Jabs and Busingye 2013) provided the following disease description:

'The course of the disease is determined by its onset (sudden or insidious) and duration (limited or persistent). Sudden-onset disease of limited duration is considered acute disease, whereas chronic disease typically is insidious in onset but with a persistent duration. Acute disease may be monophasic with a single, limited-in-duration episode (for research purposes defined as less than 3 months), or recurrent. The key feature of recurrent acute disease is the presence of episodes of active inflammation separated by periods of no inflammation when not on therapy. Conversely, chronic disease relapses promptly when therapy is discontinued. If these terms are used precisely, the often seen term "chronic/recurrent uveitis" has no meaning. Furthermore, precise characterization will guide therapy. Recurrent acute disease may need only treatment of acute attacks, whereas chronic disease is likely to need chronic suppressive therapy'

Therefore, the proposed indication for the FAc implant provides clinicians to potentially prescribe this technology to patients who:

1. Have repeated acute attacks of [redacted] that require repeated treatments – i.e. have recurrent uveitis that resolves upon treatment, but then re-occurs. The use of the FAc implant in these patients will reduce both recurrence of inflammation and the use of systemic treatments with associated side effects, consequently lowering treatment burden.

2. Have more persistent (chronic) uveitis that is always present unless the patient receives continued therapy with systemic corticosteroids/immunosuppressants to control the inflammation. The use of the FAc implant in this patient group will provide long-term treatment that prevents uveitis recurrence when systemic therapy is stopped, allowing patients to discontinue burdensome systemic treatments.

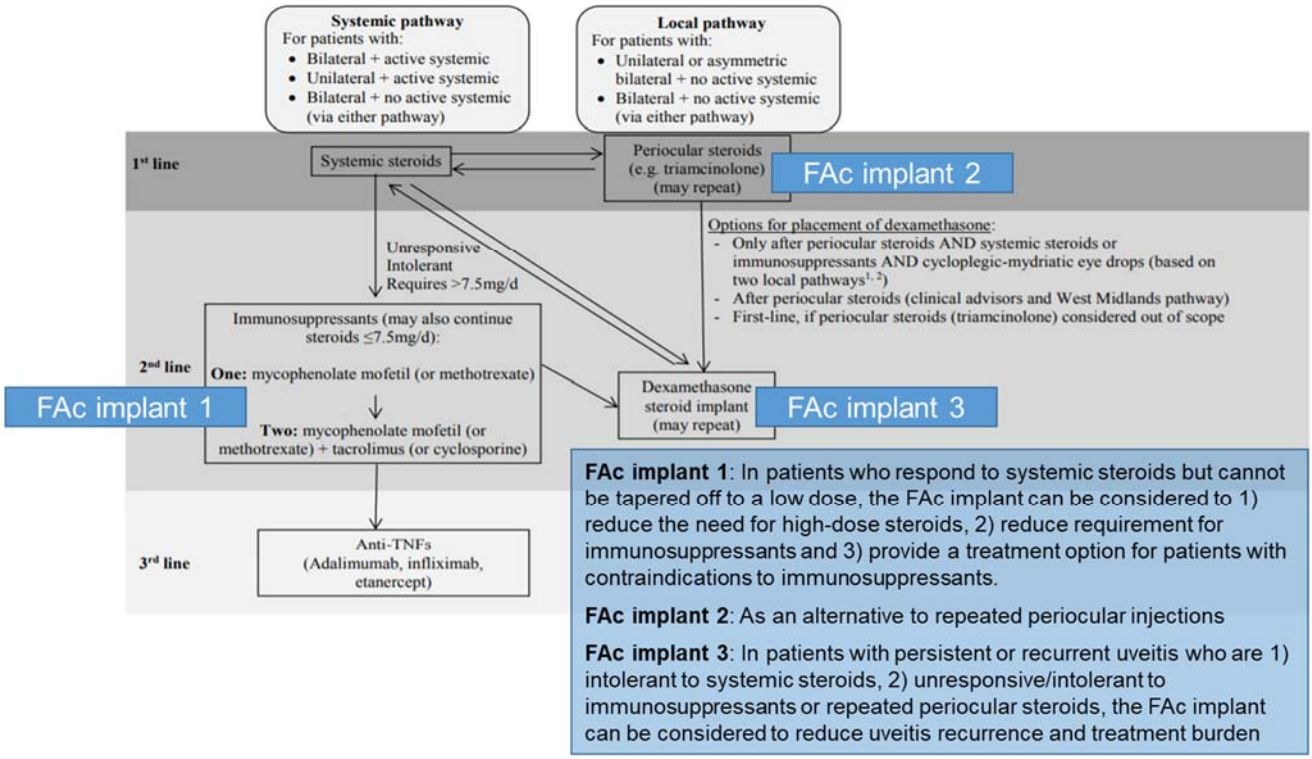
The unique nature of the FAc implant provides release of FAc for three years and can both reduce the recurrence of uveitis in patients whose disease is active at the time of treatment and prevent recurrence in patients with quiescent disease at the time of treatment. The PSV-FAI-001 study included patients who had:

- History of [redacted] which duration was ≥1 year
- Evidence of recurrence within 12 months preceding enrolment:
    - the study eye has either received treatment with systemic corticosteroid or other systemic therapies for at least 3 months, and/or at least 2 intra- or peri-ocular injections of corticosteroid for the management of uveitis
    - or the study eye has experienced recurrence (at least 2 separate recurrences of uveitis requiring systemic, intra- or peri-ocular injection of corticosteroid)
- At time of enrolment (day 1), study eye has vitreous haze ≤ grade 2 and <10 anterior chamber cells per high-powered field

Approximately 50% of the FAc implant-treated arm were on systemic corticosteroids at baseline that was tapered off over the following 12 weeks. Hence, these patients did have some "active " [redacted] at baseline, although this was being treated with systemic corticosteroids. It is worth noting at this point that tapering is commonly utilised when discontinuing corticosteroid therapy, to avoid the adverse effects associated with stopping the drug abruptly; hence the inclusion of the tapering-off period in the PSV-FAI-001 study was in line with best clinical practice.

A10. Priority question: Please indicate where in figure 2 (company submission, page 23) fluocinolone should be placed. If necessary, use multiple locations.

The FAc implant represents a unique treatment modality, since a single treatment lasts up to 3 years and can significantly reduce the disease recurrence with the associated treatment burden of intra- or peri-ocular steroids, systemic corticosteroids and immunosuppressants in patients who have recurrent or persistent [redacted]. The availability of the FAc implant for the treatment of [redacted] on the NHS could therefore change the treatment pathway and alter clinical decision-making. Some suggestions where the FAc implant could be considered are shown in following diagram.



Systematic Review

A11. According to the inclusion criteria for the systematic review (company submission, appendix D, table 4), only two comparators were included (adalimumab and dexamethasone). Please explain why none of the other comparators listed in the scope were included: periocular or intravitreal corticosteroid injections, intravitreal corticosteroid implants other than dexamethasone, systemic corticosteroids, systemic immunosuppressive therapies, and TNF-alpha inhibitors other than adalimumab.

As mentioned in A6, the decision to not specifically search for periocular or intravitreal corticosteroid injections, intravitreal corticosteroid implants other than dexamethasone, systemic corticosteroids, systemic immunosuppressive therapies, and TNF-alpha inhibitors other than adalimumab, was due to search strategy applied in TA460. Therefore, the search strategy for this submission was designed to only capture evidence for potentially relevant comparators. However, the reasons for eventually not performing indirect comparisons with dexamethasone or adalimumab are outlined in A 37.

A12. According to the systematic review described in appendix D (section D.2.1, figure 1), seven studies were included. According to the main submission (page 26) four publications were identified in the systematic literature review (SLR), and eventually only one trial is used in the submission. Please clarify which four publications were identified (is there overlap with the 7 mentioned in appendix D?), and clarify why each of the 7 from appendix D and the 4 from the submission were not used.

The statement on page 26 that four publications were identified in the SLR represents an error. The SLR identified publications.

Erckens (2012) reported on adalimumab in sarcoidosis patients with refractory chronic non-infectious. Since adalimumab is not considered a comparator anymore this study has not been included the submission.

Jaffe (2008) reported on reimplantation of a FAc implant in chronic non-infectious uveitis patients, which made it eligible for inclusion in the SLR according to the inclusion criteria but not relevant for the submission.

Similar to this, Taban (2008) reported on reimplantation of Retisert for chronic non-infectious posterior uveitis and was not relevant for the submission for the same reason.

Jaffe (2017), Pavesio (2018), Nguyen (2018) and Suhler (2018) represent conference abstracts of the pivotal study PSV-FAI-001, which is presented in the submission.

PSV-FAI-001 trial - Population

A13. Priority question: Please describe the population in each arm of the PSV-FAI-001 trial in terms of number of patients with intermediate, posterior, panuveitis and anterior uveitis (where the posterior segment of the eye is also affected) and in terms of unilateral, bilateral or symmetrical uveitis.

Data on anatomical location of uveitis (intermediate, posterior or panuveitis) was not recorded in the PSV-FAI-001 study and is therefore not available. However, all patients enrolled in PSV-FAI-001 had ≥1 year history of recurrent uveitis affecting the posterior segment of the eye, as per the eligibility criteria. We wish to emphasise that the intention of the study was to evaluate the impact of the FAc 190 µg intravitreal implant on the treatment of [redacted], regardless of the presence or absence of uveitis in other parts of the eye.

Regarding further details of anatomical location, the trial only allowed to distinguish whether a subject had anterior uveitis at baseline or not and, assuming that all study eyes had posterior uveitis, three categories based on anatomical uveitis could be identified:

- Active anterior uveitis: defined as a baseline anterior chamber cell grading of 1+ or worse. Given the concomitant posterior segment involvement in all patients, this could be considered panuveitis.

- Inactive anterior uveitis: defined as a baseline anterior chamber cell grading <1+ but with the eye receiving topical steroids on the day of randomisation for uveitis or recurrence of uveitis. This could also be considered panuveitis.

- No anterior uveitis: defined as a baseline anterior chamber cell grading of <1+ and no topical steroids being administered on the day of randomisation. These patients could be considered as having posterior and/or intermediate uveitis.

The number of patients that could be assigned into each of the three aforementioned groups at baseline is presented in Table 1 below. The majority of patients did not have anterior uveitis at baseline.

Table 1. PSV-FAI-001: Sample size by anterior uveitis category at baseline (ITT population)

Anterior uveitis category	FAc implant, n	Sham, n
Active anterior uveitis	10	9
Inactive anterior uveitis	20	3
No anterior uveitis	56	30

A recent 2013 epidemiological review which included North and South America, Europe, Australia, Asia and Africa found similar patterns of uveitis across regions, with respect to distribution of anatomic location of uveitis and diagnosis of posterior uveitis(Miserocchi et al. 2013). Given these findings and the fact that PSV-FAI-001 was a large, international multi-center, randomised clinical trial; it would seem reasonable to assume that the distribution of the type of uveitis and diagnosis of uveitis is similar to other large, multi-center clinical trials assessing the efficacy of therapies for uveitis .

Fifty-nine (67.8%) patients in the FAc implant arm and 31 (73.8%) patients in the sham arm had bilateral disease at baseline, while the remaining patients had unilateral disease affecting the study eye only. As per the trial protocol, for patients with unilateral uveitis, the study eye was the affected eye; for patients with bilateral

uveitis, the study eye was the more severely affected eye meeting the inclusion/exclusion criteria; and for patients with symmetrical uveitis, the study eye was the right eye.

A14. Priority question: Please provide underlying cause of uveitis for the population included in the trial by treatment arm.

The PSV-FAI-001 trial enrolled patients with an ≥1-year history of [redacted]; however, the underlying cause of uveitis was not captured in the clinical trial reporting forms. In a 2009 review of the literature related to the epidemiology and prevalence of uveitis across 12 countries including India, France and the United States, the distribution of uveitis aetiologies was broadly similar between the reviewed studies, with idiopathic uveitis (i.e. uveitis of unknown aetiology) accounting for 35–45% of causes in the majority of the studies, although two studies reported notably lower rate of idiopathic uveitis (Chams et al. 2009). Given these geographic similarities and the fact PSV-FAI-001 was an international multi-centre trial, there is no good reason to believe that the distribution of underlying causes of uveitis is different in PSV-FAI-001 than in other large multicentre trials in uveitis.

Alimera have also discussed this question in unstructured interviews with one of the Principal Investigators of the PSV-FAI-001 trial, Mr Carlos Pavesio (M.D. Consultant Ophthalmic Surgeon, Moorfields Eye Hospital, London). Mr Pavesio explained that due to the multiple potential aetiologies of [redacted] (17 or more types) and the fact many cases are idiopathic, the likely small number of patients with any one uveitis cause in the treatment arm (including a total of 87 patients) would make relevant subgroup analysis difficult and potentially misleading. Mr Pavesio also mentioned that a similar issue of small patient subgroups samples was encountered in HURON and VISUAL trials and only emergence of real-world data with wider patient exposure can allow clinicians to gauge effectiveness in different patient subgroups.

A15. Please explain how active and inactive uveitis would be treated differently (according to the definitions of active and inactive uveitis in TA460). How many patients in each arm of the PSV-FAI-001 trial had active or inactive disease?

In TA460, both adalimumab and dexamethasone intravitreal implant were recommended as an option for treating [redacted] if there was active disease, that is current inflammation in the eye (National Institute for Health and Care Excellence 26 July 2017). Definitions of active and inactive disease were aligned with the trials for the assessed technologies:

- Active disease:
    - the VISUAL I trial of adalimumab enrolled patients with active non-infectious intermediate, posterior, or panuveitis characterized by at least one active inflammatory chorioretinal or retinal vascular lesion, anterior chamber cell grade ≥2+ or higher or vitreous haze grade ≥2+ despite the use of prednisone (10 to 60 mg per day) or an equivalent glucocorticoid for 2 or more weeks before screening (Jaffe et al. 2016),
    - the HURON trial of dexamethasone implant included patients with non-infectious intermediate or posterior uveitis who had a vitreous haze score of ≥+1.5 and a best-corrected visual acuity of 10 to 75 letters (Lowder et al. 2011)
- Inactive disease: the VISUAL II trial of adalimumab enrolled patients with inactive non-infectious intermediate, posterior, or panuveitis ≥28 days prior to the baseline visit, defined as no active inflammatory chorioretinal and/or retinal vascular lesions, anterior chamber cell grade ≤0·5+ and/or vitreous haze grade ≤0·5+ while on daily oral prednisone ≥10 to ≤35mg to maintain inactive uveitis (Nguyen et al. 2016).

Therefore, based on the definitions used in TA460, inactive disease can be seen as no active inflammatory chorioretinal and/or retinal vascular lesions and both vitreous haze and anterior chamber cell grade ≤0·5+ while on systemic anti-inflammatory treatment. Active disease can be defined as active inflammatory chorioretinal or

retinal vascular lesion, or anterior chamber cell grade ≥2, or vitreous haze grade ≥2 while on systemic anti-inflammatory treatment.

In the PSV-FAI-001 trial approximately 50.6% of FAc implant-treated patients and 50.0% of sham-treated patients were receiving systemic corticosteroids or immunosuppressants to control uveitis at baseline, which were then tapered over the following 12 weeks. In addition, at baseline:

- 40 out of 86 evaluable patients in the FAc implant arm (46.5%) and 23 of 42 patients in the sham arm (54.8%) had macular oedema present,
- 39 (44.8%) patients in the FAc implant arm and 21 (50%) in the sham arm had vitreous haze ≥grade 1+,
- 10 (11.5%) patients in the FAc implant arm and 9 (21.4%) patients in the sham arm had anterior chamber cells ≥grade 1+.

Few patients had completely quiescent uveitis, defined as a vitreous haze and anterior chamber cells scores of 0, or these two criteria combined with a central subfield thickness below 300 µm (Table 2).

Table 2. PSV-FAI-001: Patients with ocular characteristics of quiescent uveitis in the study eye at baseline (ITT population)

	FAI Insert (N=87)	Sham injection (N=42)	Total (N=129)
VH=0, AND AC cells=0, AND Severity of edema: CSFT<300microns	11 (12.6%)	2 (4.8%)	13 (10.0%)
Other	76 (87.4%)	40 (95/2%)	116 (89.9%)
VH=0 AND AC cells=0	16 (18.4%)	3 (7.1%)	19 (14.7%)
Other	71 (81.6%)	39 (92.9%)	110 (85.3%)

AC: anterior chamber; FAI: fluocinolone acetonide intravitreal; VH: vitreous haze

These characteristics indicate that a number of patients had some degree of “active uveitis”, although perhaps inflammation was not as severe as in the adalimumab or dexamethasone implant trials, since the PSV-FAI-001 trial enrolled patients with vitreous haze and anterior chamber cell grade ≤2. This is, however, understandable as the primary endpoint of the trial was based on disease recurrence rather than resolution of pre-existing uveitis. Nonetheless, in this mixed population of patients with active and inactive disease, the FAc 190 µg intravitreal implant significantly reduced the amount of recurrence over 3 years and delayed recurrence of uveitis

compared to patients receiving current standard treatment in case of uveitis recurrences.

A16. Please explain why, in the subgroup analysis, Europe, the Middle East, and Africa were grouped together, particularly as there were no patients enrolled in Africa.

Table 15 from the submission has been pasted below (Table 3). In this table, EMEA is defined as "Europe, the Middle East, and Africa" which is a correct definition of the EMEA, but unfortunately this created confusion for the reviewer. The company apologizes for this confusion.

Table 3. PSV-FAI-001 study (ITT population): Proportion of subjects with recurrence of uveitis in the study eye at 6 months by region and randomisation strata(pSivida Corp 2017)

Subgroup	FAc 190 µg intravitreal implant arm	Sham arm
US	[redacted]	[redacted]
EMEA	[redacted]	[redacted]
India	[redacted]	[redacted]
Not receiving systemic treatment	[redacted]	[redacted]
Receiving systemic corticosteroid therapy	[redacted]	[redacted]
Receiving systemic immunosuppressive therapy	[redacted]	[redacted]

EMEA: Europe, the Middle East, and Africa; ITT, intention-to-treat, US: United States
Data are presented as the number patients with recurrence within 6 months / the number of all patients in the subgroup (%)

For the PSV-FAI-001 clinical trial, the countries involved were Germany, Great Britain, Hungary, Israel, India and the USA. Therefore, for the subgroup analyses, EMEA includes Germany, Great Britain, Hungary and Israel. It DOES NOT include the Middle East or Africa.

Again, the Sponsor apologizes for the confusion.

A17. Priority question: The submission states that the PSV-FAI-001 trial includes patients from 49 centres within 6 countries (page 31). Please provide a breakdown of the number of patients per country for each study arm.

A breakdown of the number of patients per country for each study arm can be found in Table 4 below:

Table 4. Country breakdown of PSV-FAI-001

Country N (%)	FAc 190 µg intravitreal implant arm (N=87)	Sham Injection (N=42)	Total (N=129)
Germany	8 (9.2)	3 (7.1)	11 (8.5)
Great Britain	16 (18.4)	4 (9.5)	20 (15.5)
Hungary	0 (0.0)	1 (2.4)	1 (0.8)
India	20 (23.0)	11 (26/2)	31 (24.0)
Israel	6 (6.9)	4 (9.5)	10 (7.8)
USA	37 (42.5)	19 (45.2)	56 (43.4)

PSV-FAI-001 trial - Treatments

A18. Priority question: The submission states that patients in the control group of the PSV-FAI-001 trial received sham injection followed by standard practice during the trial (page 31). Please describe which treatments were used for 'standard practice' and how many patients received each treatment for how many days.

The PSV-FAI-001 protocol states that: 'In the event of a uveitis recurrence in either eye (defined as an "Endpoint"), peri-ocular or intraocular corticosteroid injections, or topical medications should be administered as first line local therapy, in accordance with the protocol. Investigators should consider treatment with topical steroids as first line therapy for a recurrence that involves only an increase in anterior chamber cells with no increase in vitreous opacity. Systemic immunosuppressants or systemic steroids should be used only if local therapy fails. Subjects who experience a recurrence of uveitis will continue participation in the study. Once the subject's recurrence is controlled, the treatment regimen (local or systemic therapy) will be ended in a manner that follows the standard of care for ending the specific treatment regimen.'

Available summary data on additional treatments for uveitis administered during the study was provided in the company submission (Table 12 page 56), also reproduced below (Table 5). Note that the number of days for which each specific treatment was administered was not recorded in the PSV-FAI-001 study. Despite less frequent use of supplemental therapies in the FAc implant arm, median time to first recurrence of uveitis was 657.0 days (95% CI: 395.0, 1051.0 days) or 21.6 months in the FAc implant group compared with 70.5 days (95% CI: 57.0, 91.0 days) or 2.3 months in the sham group.

Table 5. PSV-FAI-001 study (ITT population): Number of supplemental treatments within 36 months by type of treatment

Outcome	Study eye	
	FAc 190 µg intravitreal implant arm (n=87)	Sham arm (n=42)
Systemic steroid or immunosuppressant		
Total no. of supplemental treatments	[redacted]	[redacted]
No. of patients with ≥1 supplemental treatment	[redacted]	[redacted]
No. of supplemental treatments per patient		
0, n (%)	[redacted]	[redacted]
1, n (%)	[redacted]	[redacted]
2, n (%)	[redacted]	[redacted]
3, n (%)	[redacted]	[redacted]
4, n (%)	[redacted]	[redacted]
5, n (%)	[redacted]	[redacted]
>5, n (%)	[redacted]	[redacted]
Intra/peri-ocular steroid (study eye)		
Total no. of supplemental treatments	[redacted]	[redacted]
No. of patients with ≥1 supplemental treatment	[redacted]	[redacted]
No. of supplemental treatments per patient		
0, n (%)	[redacted]	[redacted]
1, n (%)	[redacted]	[redacted]
2, n (%)	[redacted]	[redacted]
3, n (%)	[redacted]	[redacted]
4, n (%)	[redacted]	[redacted]
5, n (%)	[redacted]	[redacted]
>5, n (%)	[redacted]	[redacted]
Topical steroid (study eye)		
Total no. of supplemental treatments	[redacted]	[redacted]
No. of patients with ≥1 supplemental treatment	[redacted]	[redacted]
No. of supplemental treatments per patient		
0, n (%)	[redacted]	[redacted]
1, n (%)	[redacted]	[redacted]
2, n (%)	[redacted]	[redacted]
3, n (%)	[redacted]	[redacted]
4, n (%)	[redacted]	[redacted]
5, n (%)	[redacted]	[redacted]
>5, n (%)	[redacted]	[redacted]

CI: confidence interval; ITT: intention-to-treat

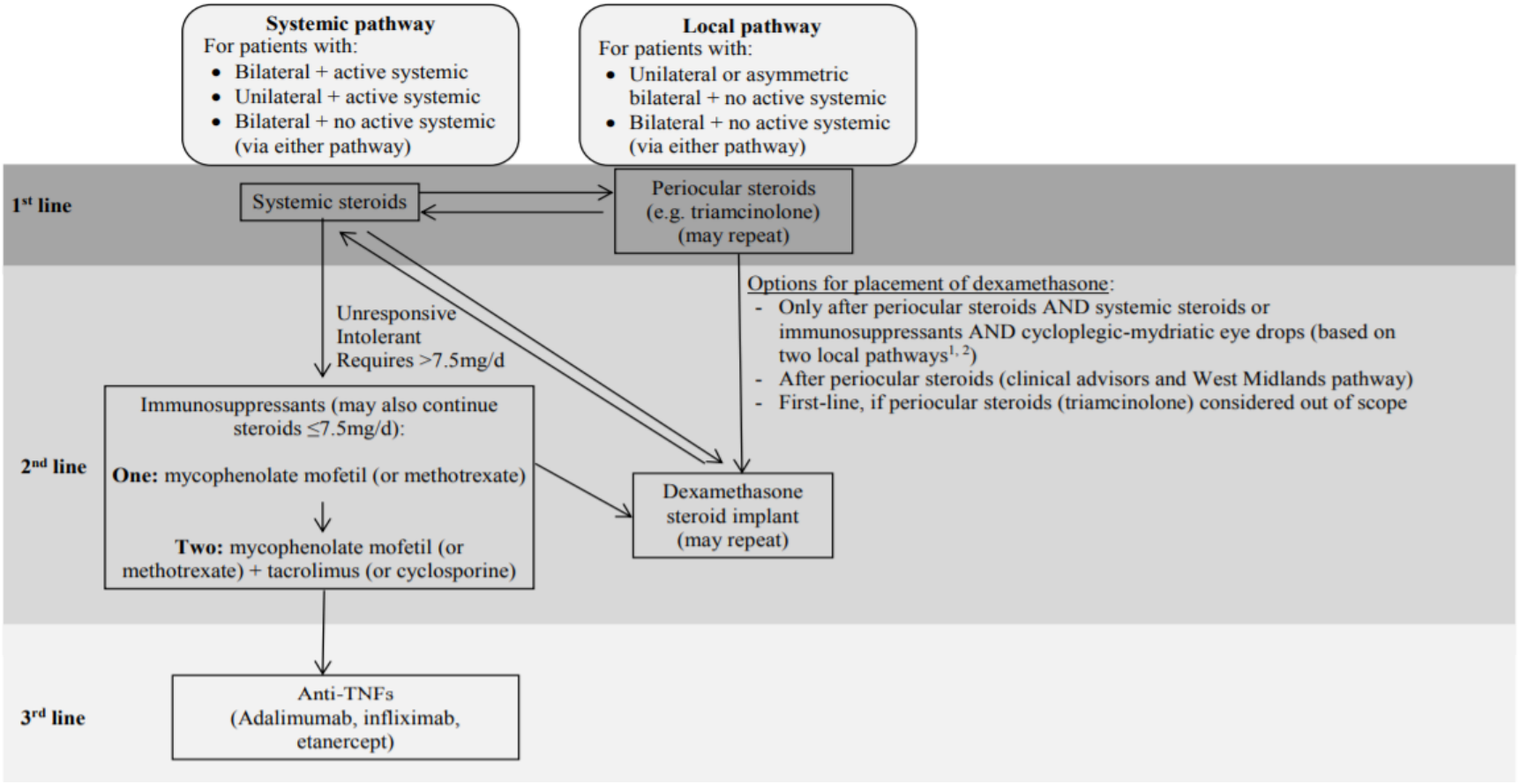
The treatment of uveitis recurrences described in the PSV-FAI-001 trial protocol does reflect standard clinical practice in the UK for the treatment of active [redacted]; this has been confirmed by recent discussions during unstructured interviews between Alimera and clinical experts (Mr Fahd Quhill, M.D. Consultant Ophthalmic Surgeon, Royal Hallamshire Hospital, Sheffield , UK and Mr Carlos Pavesio, M.D. Consultant

Ophthalmic Surgeon, Moorfields Eye Hospital, London). Furthermore, the PSV-FAI-001 trial did include UK patients.

A19. Priority question: Please explain how representative limited current practice ((L)CP) in the control group (i.e. sham injection) of the PSV-FAI-001 trial is of current practice in the UK for non-infectious uveitis. Especially as oral, systemic, injectable, or topical steroids, and systemic immunosuppressants were not allowed other than during the initial tapering-off or in case of uveitis recurrence.

Although there is no nationally agreed treatment pathway for non-infectious uveitis, (L)CP as defined in the PSV-FAI-001 trial is well-aligned with the treatment pathway presented in TA460 (Figure 2 from the submission, reproduced below). Consequently, the Sponsor believes (L)CP does represent standard UK practice, allowing patients to be treated for uveitis recurrences with local steroids or, if these fail, with systemic steroids or immunosuppressants. Applicability of the treatment received by patients in the sham control arm of PSV-FAI-001 to UK clinical practice for treating active [redacted] has been confirmed by clinical experts in unstructured interviews with clinical experts (Mr Fahd Quhill, M.D. Consultant Ophthalmic Surgeon, Royal Hallamshire Hospital, Sheffield , UK and Mr Carlos Pavesio, M.D. Consultant Ophthalmic Surgeon, Moorfields Eye Hospital, London).

Figure 1. Treatment of non-infectious uveitis in England(National Institute for Health and Care Excellence 26 July 2017)



TNF: tumour necrosis factor

Systemic pathway: Treatment pathway proposed for patients with uveitis in one or both eyes in the presence of an active systemic disease or those with severe bilateral uveitis with or without an underlying active systemic condition. Local pathway: Treatment pathway proposed for patients with unilateral uveitis or asymmetrically 'severe' bilateral uveitis with no active systemic condition. Unilateral uveitis may be a first episode or a re-activation of a previous inflammation (flare).

A20. Priority question: Please describe how many patients in each study group of the PSV-FAI-001 trial received corticosteroids or immunosuppressants or both during the trial.

In the PSV-FAI-001 trial, [redacted] patients in the FAc implant arm and [redacted] patients in the sham arm received systemic treatment (steroid or immunosuppressant), as shown in the table below (Table 6).

Table 6.PSV-FAI-001 study (ITT population): Number of supplemental systemic treatments within 36 months

Outcome	Study eye	
	FAc 190 µg intravitreal implant arm (n=87)	Sham arm (n=42)
Systemic steroid or immunosuppressant		
Total no. of supplemental treatments	[redacted]	[redacted]
No. of patients with ≥1 supplemental treatment	[redacted]	[redacted]
No. of supplemental treatments per patient		
0, n (%)	[redacted]	[redacted]
1, n (%)	[redacted]	[redacted]
2, n (%)	[redacted]	[redacted]
3, n (%)	[redacted]	[redacted]
4, n (%)	[redacted]	[redacted]
5, n (%)	[redacted]	[redacted]
>5, n (%)	[redacted]	[redacted]

Breakdown by type of therapy received (steroid, immunosuppressant or both) during the trial is not available.

A21. Priority question: Please explain the reasons for treatments received at baseline. Was treatment given for uveitis only, or could it also have been for underlying (auto)immune conditions (at the time of enrolment but also ongoing, since uveitis is modelled as an isolated disease in the current assessment)?

As described in the response to question A14, the underlying cause of uveitis was not captured in the clinical trial reporting forms and it is therefore unclear how many enrolled patients had underlying autoimmune conditions. Due to the multiple potential aetiologies of [redacted] (17 or more types) and the fact many cases are

idiopathic, it would be extremely difficult to model uveitis in conjunction with underlying conditions. Furthermore, since the FAc implant is a local ocular treatment, such modelling would be of limited relevance to the technology being appraised.

Regarding treatment of uveitis at baseline, PSV-FAI-001 trial protocol permitted treatment of patients prior to enrolment to meet eligibility criteria (for example, reduce vitreous haze to ≤grade 2), with the objective to control over uveitis prior to enrolment. Since the primary endpoint of the study could be considered a measure of 'worsening' of uveitis, this approach facilitated adequate capturing of any increase in inflammation. If a subject was receiving systemic corticosteroids or immunosuppressants, or topical steroids to control uveitis prior to study enrolment, they had such treatment ended within three months from Day 1, in a manner that followed standard practice for ending the treatment (i.e. some systemic treatment regimens may be ended immediately, while others require a period of gradual dose reduction [tapering]).

Since no details on the underlying uveitis cause were collected in PSV-FAI-001, some patients may have received systemic corticosteroids or immunosuppressants for the treatment of systemic auto-immune diseases during the course of the study. Therefore, some recurrences may have been imputed in both arms of the trial due to systemic treatment for auto-immune disease. However, since the FAc 190 µg intravitreal implant is a local treatment not expected to affect systemic disease in any way, the effect of underlying systemic conditions on recurrence imputation should be balanced across treatment arms and thus not lead to bias in the trial.

A22. Please explain how many patients needed to have their treatment tapered in each arm. Please also list for each arm which treatments were tapered and for what duration of time. Please also explain whether the uveitis had been adequately treated before the treatments were tapered, or whether there might still have been residual disease activity. The protocol allowed investigators to treat subjects prior to entry to meet study inclusion criteria. The objective of prior treatment was to obtain a relatively quiet eye prior to enrolment. At baseline, 43 patients (49.4%) in the FAc implant arm and 21 patients (50%) in the sham arm were receiving systemic

treatment to control uveitis. Specifically, 27 (31%) and 13 (31%) patients in the FAc implant and sham arms, respectively, received systemic corticosteroids and 17 (19.5%) and 8 (19%), respectively, received immunosuppressive therapy. As per the trial protocol, such systemic treatments had to be ended within the first 3 months from Day 1 in a manner that followed the standard of care for ending the specific treatment (immediately or through gradual dose taper). Systemic medications or topical steroids administered as part of gradual dose reduction were not considered prohibited medications.

Despite treatment, patients could have had some residual disease at enrolment, as the protocol allowed for some vitreous haze (≤grade 2) or anterior chamber cells (<10 per high power field) to be present. Indeed, at baseline 39 (44.8%) patients in the FAc implant arm and 21 (50%) in the sham arm had vitreous haze ≥grade 1+, while anterior chamber cells ≥grade 1+ were observed in 10 (11.5%) patients in the FAc implant arm and 9 (21.4%) patients in the sham arm (Table 7). Furthermore, 39.5% of patients across both arms had severe macular oedema at baseline (central subfield thickness [CSFT] ≥300 µm); this was slightly more common in the sham arm than the FAc implant than (64.3% vs 55.2%).

Table 7. PSV-FAI-001: Vitreous haze and anterior chamber cell scores at baseline in the study eye (ITT population)

	FAI Insert (N=87)	Sham injection (N=42)	Total (N=129)
Vitreous haze			
Absent (0)	22 (25.3%)	8 (19.0%)	30 (23.3%)
Trace (0.5)	26 (29.9%)	13 (31.0%)	39 (30.2%)
1+	29 (33.3%)	19 (45.2%)	48 (37.2%)
2+	10 (11.5)	2 (4.8%)	12 (9.3)
3+	0	0	0
4+	0	0	0
Anterior chamber cells			
0	54 (62.1%)	20 (47.6%	74 (57.4%)
0.5+	23 (26.4%)	13 (31.0%)	36 (27.9%)
1+	10 (11.5%)	8 (19.0%)	18 (14.0%)
2+	0	1 (2.4%)	1 (0.8%)
3+	0	0	0
4+	0	0	0
Severity of edema			
CSFT < 300 microns	37 (42.5)	14 (33.3)	51 (39.5)
CSFT≥ 300 microns	48 (55.2)	27 (64.3)	75 (58.1)
[1] Fort partial uveitis onset dates, a missing month is imputed as January and a missing day is imputed as the first of the month.			

[2] Only assessed for eyes with a lens status of phakic. Percentages are based on the number of phakic eyes.
[3] Incisional surgery history was collected following approval of protocol version 5.0 and was not collected for subjects that enrolled in the study prior to the amendment's approval.
[4] Percentage is based on the number of patients with incisional surgery history collected.
[5] Fellow eyes without occurrence of uveitis are excluded in the summary for fellow eye.

Since all patients enrolled in PSV-FAI-001 had to have at least 1-year history of chronic uveitis or recurrent uveitis, based on the number of patients receiving systemic treatment at baseline, approximately 50% of patients in both arms of the trial could be considered as having active disease, while the remaining patients as having quiescent disease at study entry. The trial's eligibility criteria did not require complete absence of disease activity, but excluded patients with overt disease, since the primary endpoint was based on uveitis recurrence rather than resolution of pre-existing uveitis.

The fact that PSV-FAI-001 permitted systemic corticosteroid or immunosuppressant treatment at baseline is not unusual in uveitis trials. In fact, the VISUAL 1 trial in patients with active non-infectious uveitis all patients received a 60 mg/day prednisone burst at trial entry, followed by a taper leading to discontinuation of oral prednisone by week 15 (Jaffe et al. 2016). In contrast to VISUAL 1, in the PSV-FAI-001 trial treatment with oral corticosteroids or immunosuppressants at baseline was not mandatory, but could be administered at the discretion of the treating physician had to be tapered within 3 months of receiving study treatment.

A23. Priority question: Table 21 of the submission (page 69) states that at 12 months, [redacted] of patients in the ILUVIEN group and [redacted] in the control group took prohibited medications or rescue medications. Please explain why so many patients took prohibited medications; and please explain why there were instances of taking prohibited medications without it being recorded as a recurrence.

Please note that Table 21 pertains to the ongoing **PSV-FAI-005** trial and not to the PSV-FAI-001 trial primarily supporting the submission. In PSV-FAI-005 recurrence was defined similarly to the PSV-FAI-001 study, could be observed based on examination of the study eye (in case of ≥2-step increase in the number of anterior

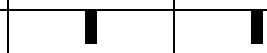
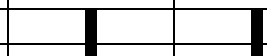
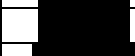
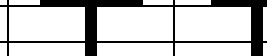
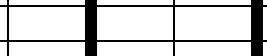
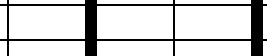
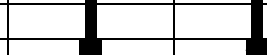
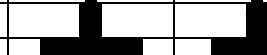
chamber cells or vitreous haze, or and ≥15 letter decrease in visual acuity relative to baseline or any visit prior to Month 6) or imputed in patients who had a missing eye examination or took a prohibited medication outside of the 3-month post-enrolment tapering period. Please note that 'prohibited medication' can be considered a misnomer and should be interpreted as rescue medication for the treatment of uveitis, since the trial protocol permitted the use of local or systemic steroids or immunosuppressants to treat uveitis recurrences in both treatment arms.

Imputation of recurrence in patients who received prohibited medication ensured that uveitis recurrence was duly recorded even if the physician decided to administer treatment before the study eye met the criteria for observed recurrence (e.g. the increase in vitreous haze was less than 2 steps). However, it also meant that recurrence was likely overestimated, since some patients could have received systemic corticosteroids or immunosuppressants to treat conditions other than uveitis.

Recurrence at 12 months was one of the exploratory endpoints of the PSV0-FAI-005 study and was defined analogously to recurrence at 6 months. Consequently, Table 21 in the Company Submission (reproduced as Table 8 below) provides information on the number of patients experiencing any recurrence within 12 months with a breakdown of how many of these recurrences were protocol-defined (observed) and how many were imputed. For the imputed recurrences, the reason for imputation (missing data or use of prohibited/rescue medication) was provided. For instance, in the ITT population, of the 37 patients in the FAc implant arm experiencing a recurrence within 12 months, [redacted] had imputed recurrences, primarily due to use of rescue medication ([redacted] patients) rather than missing data ([redacted] patients).

Table 8. PSV-FAI-005 (ITT and PP populations): Proportion of patients with recurrence of uveitis in the study eye within 12 months

	Study Eye		Fellow Eye	
Outcome, n (%)	**ILUVIEN**	**Sham injection**	**ILUVIEN**	**Sham injection**
ITT (n)	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence within 12 months, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Protocol-defined recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Imputed recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Missing data	[redacted]	[redacted]	[redacted]	[redacted]

Prohibited medication or rescue medication				
Systemic steroid or immunosuppressant				
Intra/peri-ocular steroid				
Topical steroid				
No recurrence within 12 months, n (%)				
Difference from sham injection[a]				
Odds ratio				
95% confidence interval				
P value				
PP (n)				
Recurrence within 12 months, n (%)				
Protocol-defined recurrence				
Imputed recurrence				
No recurrence within 12 months, n (%)				
Difference from sham injection[a]				
Odds ratio				
95% confidence interval				
P value				

ITT: intention-to-treat

A24. The submission states that in the case of bilateral uveitis, fluocinolone acetonide should be used in both eyes (company submission, page 72). If both eyes are treated with fluocinolone acetonide, is the required dose different to when 1 eye is treated?

The citation on page 72 of the Company Submission is the following: 'Recurrence rate in the fellow eye of ILUVIEN-treated patients was slightly higher than that observed in the sham arm, potentially due to the lower use of systemic steroids in ILUVIEN-treated patients. Indeed, fellow eye recurrence data suggests that in patients who have both eyes affected by uveitis, ILUVIEN should be used bilaterally, as it has clear clinical benefits in terms of lower recurrence rate, improved visual acuity and prompt reduction of macular oedema.'

Indeed, the company believes that the superior clinical outcomes observed with the FAc implant compared with the sham arm representing standard practice warrant bilateral use of the implant in patients with both eyes qualifying for treatment. Furthermore, relatively poor outcomes were observed in the fellow eye of patients in the FAc 190 µg intravitreal implant arm of PSV-FAI-001, likely due to reduced exposure to systemic corticosteroids and immunosuppressants compared with sham-treated patients. Thus, the Sponsor believes treatment of both eyes is likely to be beneficial in patients with bilateral disease. However, in keeping with trial design

for the purposes of obtaining a Marketing Authorisation, bilateral treatment was not investigated in the PSV-FAI-001 trial and the current Summary of Product Characteristics for the FAc 190 µg intravitreal implant does not recommend concurrent administration of the implant in both eyes, until the patient's systemic and ocular response to the first implant is known (Alimera Sciences Limited 13 October 2015). Hence, the Sponsor recommends that clinician initially treats one eye and assesses the patient's response before considering FAc 190 µg intravitreal implant for the fellow eye.

Due to the technology of the FAc implant, is it not possible to administer a different dose to the two eyes, as long as a single implant is administered in each eye. Each implant contains 190 µg of fluocinolone acetonide that is released for up to 36 months (Alimera Sciences Limited 13 October 2015). The implant is loaded into a sterile applicator and the injection should be performed in aseptic conditions as outlined in the Summary of Product Characteristics (Alimera Sciences Limited 13 October 2015). Therefore, dose modification is not possible, and it would not be considered necessary: as fluocinolone acetonide is undetectable in systemic circulation after local, intraocular treatment, systemic exposure to fluocinolone acetonide from the implant is expected to be very low (Alimera Sciences Limited 13 October 2015) and both eyes should be considered independent of each other for the purpose of treatment with the FAc implant.

PSV-FAI-001 trial – In/exclusion criteria

A25. Priority question: One of the trial inclusion criteria (submission, page 34) was that 'visual acuity of study eye was at least 15 letters on the early treatment diabetic retinopathy study (ETDRS) chart'. Please explain what proportion of the population within the anticipated marketing authorisation this applies to. Similarly, patients with a 'history of posterior uveitis only, that was not accompanied by vitritis or macular oedema' were excluded (submission, page 35). Please explain what proportion of the population within the anticipated marketing authorisation this applies to.

As stated in the response to question A28, patients with a visual acuity <15 letters on the ETDRS chart can be considered severely sight impaired. Inclusion of patients

with such poor vision in a trial that considers change in visual acuity as an endpoint would undermine the clinical significance of trial results, since little improvement in visual acuity can be expected in these patients regardless of treatment they may receive for uveitis. However, in unstructured discussions with the Sponsor, one of the Principal Investigators of the PSV-FAI-001 trial, Mr Carlos Pavesio (Moorfields Eye Hospital, London) highlighted that visual acuity is only one of the visual parameters and, outside of the clinical trial setting, clinicians may elect to treat patients with <15 EDTRS letters on a case by case basis, aiming to preserve any remaining visual function. Although these patients may have poor visual acuity resulting from impaired central foveal vision, they may have better peripheral fields and less damage to other areas of the macula that require protection from inflammation and oedema caused by recurrence of [redacted]. The aim of clinical care in uveitis is to stop the inflammation and preserve any vision (and not just visual acuity). Mr Pavesio also suggested that the number of patients with <15 ETDRS letter would likely be small, constituting less than 10% of the overall patient population eligible for treatment with the FAc implant.

As for patients with posterior uveitis not accompanied by vitritis or macular oedema, there is no objective, validated method to define recurrence in these patients. Some cases may show only subretinal disease, which may be clinically detectable but not gradable in a meaningful way. In an unstructured interview, Mr Pavesio stated these patients represent a minority of patients they see and are less likely to be offered an intravitreal implant for their treatment.

Overall, the Company believes that the exclusion of these patient groups from the pivotal trial may have only a marginal, if any, effect on clinical and cost-effectiveness or prescribing of the FAc implant in UK clinical practice. There is no reason to believe that, in the real-world setting, the FAc implant would be any less effective in the treatment of [redacted] in patients with poor visual acuity or those in whom recurrence may be difficult to define (although quantifying some of the treatment effects may present a challenge). In patients with poor visual acuity, clinicians may want to consider treatment with the FAc implant to reduce inflammation and its associated risks to sight and preserve remaining vision for as long as possible.

A26. According to the trial exclusion criteria (company submission, page 36) 'prior intravitreal treatment of study eye with Triesence or Trivaris within 3 months prior to Day 1' was not allowed. Please clarify whether a three month wash-out period for these treatments is sufficient.

The FDA approval package for Triesence (triamcinolone acetonide) injectable suspension was supported by a publication by Beer et al. investigating ocular exposure to triamcinolone acetonide following intravitreal administration in elderly patients with macular oedema (US Food and Drug Administration 24 May 2007; Beer et al. 2003). The same publication was also cited in the FDA labelling package for Tivaris (US Food and Drug Administration 15 August 2007). After a single intravitreal injection of 4 mg triamcinolone acetonide, elimination half-life was estimated to be 18.6 days in the vitreous of non-vitrectomised eyes and much shorter (3.2 days) in a patient who had undergone a vitrectomy prior to study inclusion (Beer et al. 2003). The plots of intravitreal concentration of triamcinolone over time from this publication are shown below. Based on the assumption that approximately 97% of the drug is cleared from the vitreous in 5 half-lives, triamcinolone acetonide concentrations should be detectable in the vitreous for approximately 93 days (3 months) (US Food and Drug Administration 24 May 2007, 15 August 2007).

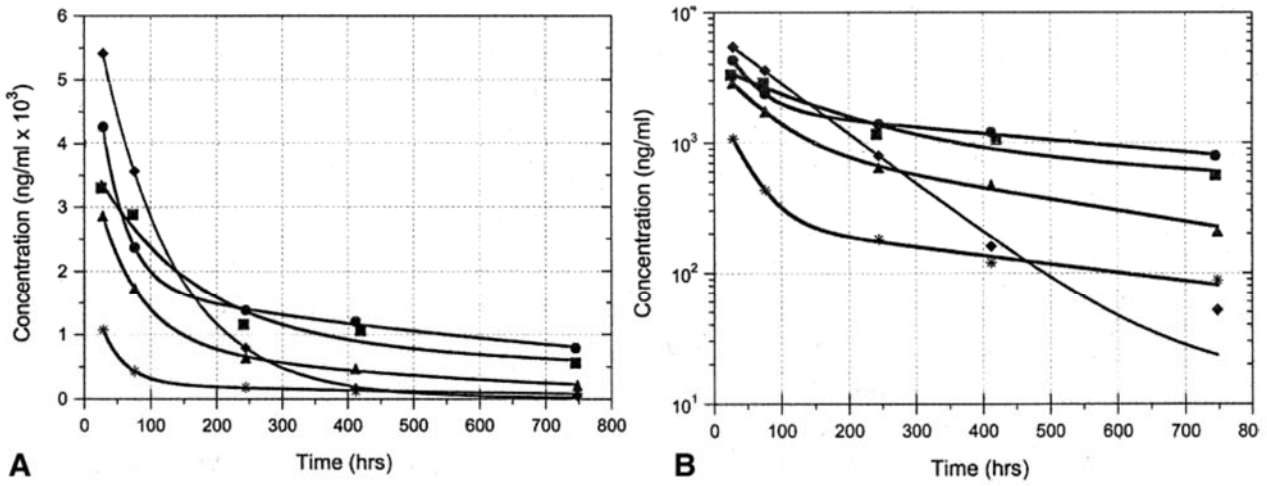


Figure 1. Intravitreal triamcinolone concentrations after a single intravitreal triamcinolone acetonide injection plotted arithmetically (A) and semilogarithmically (B). Concentration-time data for each vitreous sample for all patients are shown along with two-compartment model-derived pharmacokinetic curves. patient 1, ▲; patient 2 = ◆; patient 3 = ● patient 4 = ■; patient 5 = *.

Figure 2. Triamcinolone intravitreal concentration following a single intravitreal injection (Beer et al. 2003)

In terms of re-treatment with triamcinolone acetonide in clinical trials, the recently published, 24-week POINT trial in uveitic macular oedema permitted retreatment

with intravitreal triamcinolone acetonide at 8 weeks (Thorne et al. 2018). On the other hand, the 3-year DRCR.net protocol B study permitted retreatments with intravitreal triamcinolone acetonide at slightly longer, approximately 4-monthly, intervals (no less than 3.5 months) (Diabetic Retinopathy Clinical Research 2008).

Overall, the 3-month wash-out period is well-aligned with the clinical pharmacology profile of triamcinolone acetonide and the Sponsor believes it should be considered sufficient.

A27. The submission states that patients were excluded from the PSV-FAI-001 trial if they had "any other systemic or ocular condition which, in the judgment of the investigator, could have made the patient inappropriate for entry into this study" (submission, page 36). Please provide specific conditions that were excluded from the trial, with the number of patients for each by treatment arm.

The exclusion criteria of the PSV-FAI-001 protocol included various ocular and systemic conditions, with affected patients ineligible for the clinical trial. The particular exclusion criterion referred to in this question was to play a precautionary role in the event that some ocular or systemic condition, which was not specifically listed in the exclusion criteria, was encountered, prompting the investigator to consider the affected patient as inappropriate for inclusion in the study. However, such instances of patient exclusion were not captured in the study records, just as there is no record of the number of patients who failed to meet any other inclusion/exclusion criteria.

A28. Please provide a justification for excluding patients in whom visual acuity in the study eye was less than 15 letters on the early treatment diabetic retinopathy study (ETDRS) chart.

Visual acuity of <15 letters on the ETDRS chart translates to less than 3/60 on the Snellen chart according to a published conversion table (Table 9) and may be able to read even more letters in practice (Chen et al. 2014). Therefore, patients with a

visual acuity <15 letters would very likely be certified as severely sight impaired per UK standards (Royal National Institute of Blind People).

Table 9.Letter sizes in Snellen chart and theoretical equivalent logMAR and letter score on ETDRS chart (Available as supplementary material to (Chen et al. 2014))

Line	Snellen Chart				Theoretical Equivalents to Snellen Faction			
	Optotypes	Optotypes height (mm)	Distance from Chart (mm)	Optotype height (min arc)	LogMAR	ETDRS Letter score	ETDRS chart equivalent line at 1 meter	ETDRS chart equivalent line at 4 meter
1/60	A	85	1000	292	1.78	-4		
2/60	A	85	2000	146	1.48	11		
3/60	A	85	3000	97	1.30	20	4	
4/60	A	85	4000	74	1.18	26		
5/60	A	85	5000	58	1.08	31		
6/60	A	85	6000	49	1.00	35	7	1
6/36	OE	57	6000	33	0.78	46		
6/24	HLA	35	6000	20	0.60	55	11	5
6/18	NTCO	27	6000	15	0.48	61		
6/12	HLAOT	18	6000	10	0.30	70	14	8
6/9	HTOLAE	13.5	6000	7.7	0.18	76		
6/6	LNETHOA	9	6000	5.2	0.00	85		11
6/5	OTLHENAC	7	6000	4.0	-0.08	89		
6/4	LHTOCNEA	6	6000	3.4	-0.18	94		

Grey boxes: similar letter sizes between Snellen and ETDRS charts

In the real-world clinical practice setting physicians may want to consider treatment with the FAc implant in patients whose visual acuity is <15 ETDRS letters to reduce inflammation and preserve remaining vision for as long as possible. However, inclusion of patients with such poor visual acuity (and likely very little hope for sight recovery) in the PSV-FAI-001 trial, which measured change from baseline visual acuity as an exploratory endpoint, would jeopardise the end result of the trial and reduce its clinical significance. It is also worth noting that a higher best corrected visual acuity cut-off (<20 ETDRS letters in at least one eye) was used in the VISUAL

I (Jaffe et al. 2016) and VISUAL II studies (Clinicaltrials.gov 11 August 2016), although the HURON trial used a slightly lower cut off than PSV-FAI-001, enrolling patients with a best corrected visual acuity of 10 to 75 letters (Lowder et al. 2011).

PSV-FAI-001 trial - Blinding

A29. Trial PSV-FAI-001 is described as a sham-controlled, double-blind study (submission, page 31). Please clarify whether the treating physician was also blinded. Please also explain whether any attempt was made to estimate the success of blinding among patients, physicians and outcome assessors.

The following measures were taken to minimise bias, as per the PSV-FAI-001 study protocol:

'To minimize bias, two investigators will be used at each study site. One investigator will serve as the unmasked treating investigator (Investigator 1) and the other investigator will serve as the masked assessing investigator (Investigator 2). On study Day 1, Investigator 1 will inject the FAI insert or perform a sham injection, and will perform all study Day 1 assessments. All other study assessments will be performed by Investigator 2. Only Investigator 1 will know the assigned treatment. Study personnel will use every reasonable effort to maintain the study mask.'

Therefore, the physician administering the implant was not blinded, but the physician providing subsequent study assessments was. Although the success of blinding among patients, physicians and outcome assessors was not estimated in PSV-FAI-001, the same approach to blinding was used in the trials of the FAc implant in diabetic macular oedema (DMO), proving successful.

Specifically, one way to assess the effectiveness of the masking in the uveitis clinical trial is to examine the retreatment rates in the Diabetic Macular Oedema (DMO) phase 3 clinical trials. Unlike in PSV-FAI-001, in the DMO clinical studies, retreatment with the study drug was allowed after 12 months if oedema increased by 50 microns or more or visual acuity declined by 5 letters or more. If the assessing investigator recommending retreatment knew that a patient was randomised to sham

treatment, that investigator would not have recommended retreatment with the study drug in the event of a worsening of the patient's condition warranting some therapeutic intervention. Table 10 below presents the percentage of patients in each arm of the DMO studies receiving one or more treatments with the study drug. During the course of the trials, retreatment with masked study drug occurred in 28.6% of sham patients, 25.6% of patients receiving the 0.2 µg/day FAI insert, and 29.3% of patients receiving the 0.5 µg/day FAI insert. As these data demonstrate, the percent of patients undergoing retreatment and the mean number of treatments are very similar. This is a very strong indication of how effective the masking was for the DMO clinical trials. Since the insert in the DMO trials has the same dimensions and is inserted the same way in the uveitis clinical studies, we can conclude that the decision to use a prohibited medication in the uveitis clinical trials was not influenced by knowledge of treatment assignment.

Table 10. Exposure to study treatment in the FAME trials (safety population)

	Sham (N=185)	0.2 µg/day FAI (N=375)	0.5µg/day FAI
Number of Treatments completed			
Number of treatments	252	488	534
Number of subjects receiving at least on treatment	185	375	393
Mean (SD)	1.4 (0.7)_	1.3 (0.6)	1.4 (0.6)
1 treatment	132 (71.4%)	279 (74.4%)	278 (70.7%)
2 treatments	44 (23.8%)	81 (21.6%)	91 (23.2%)
3 treatments	6 (3.2%)	13 93.5%)	22 (5.6%)
4 treatments	2 (1.1%)	2 (0.5%)	2 (0.5%)
>4 treatments	1 (0.5%)	0 (0.0%)	0 (0.0%)

PSV-FAI-001 trial - Results

A30. Priority question: The imputation rates for the primary endpoint, recurrence of uveitis in the study eye (company submission, table 10, pages 52-53) are high. Please provide details of the reasons for imputed data for each outcome and each

treatment group at each time point. Please also provide the results of the two sensitivity analyses as described in section 2.4.1.3.2 (submission, page 46).

Disallowing the use of any and all systemic steroids or immunosuppressant and/or local steroids during a 3-year study involving subjects with recurrent uveitis and other significant co-morbidities would not be possible or likely permitted by those IRBs and ethic committees overseeing the trial, due to the potential for irreparable harm to the subject's health. Yet, the potential confounding of these concomitant therapies had to be addressed. The Sponsor felt the following approach presented in the statistical analysis plan for the PSV-FAI-001 trial would provide the most conservative estimate of treatment effect:

'Data for the primary outcome only (recurrence of uveitis) will be imputed using a straightforward method:

- A subject who has not previously experienced a recurrence and does not have the required eye examination data for assessing recurrence at Month 6 (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) for any reason will be considered as having a recurrence. If one or more of the required eye examinations, including BCVA, vitreous haze, and anterior chamber cells, is not completed at Month 6 (or Month 12 or Month 36), the subject will be considered as having a recurrence. Reasons for missing recurrence data at Month 6 (or 12 or 36) include, but are not limited to: discontinuation from the study prior to visit, visit occurred outside of the visit window, and missed visit.

- A subject who has not previously experienced a recurrence and takes a prohibited systemic concomitant medication as defined in Section 9.10.2 of the protocol any time during the study prior to Month 6 (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) will be considered as having a recurrence.

- A subject who has not previously experienced a recurrence and takes a prohibited local concomitant medication in the study eye as defined in Section 9.10.2 of the protocol any time during the study prior to Month 6 (or Month 12

or Month 36 for the Month 12 or 36 analyses, respectively) will be considered as having a recurrence.

Systemic medications and topical steroids administered as part of a gradual dose reduction (tapering) will not be considered prohibited medications. Additionally, topical steroids administered as part of short-term standard treatment following an ocular surgical procedure will not be considered prohibited medications.

The prohibited medication data (based on preferred terms and/or ATC codes) will be reviewed and medications will be categorized as either having a potential impact on the efficacy assessments or no impact on the efficacy assessments. Only prohibited medications determined to have a potential impact on efficacy assessments will be taken into consideration for data imputation.'

Imputation of recurrence in the aforementioned cases:

1) ensured that uveitis recurrence was duly recorded even if the physician decided to administer treatment before the study eye met the criteria for observed recurrence (e.g. the increase in vitreous haze was less than 2 steps), which were approved with US and EU health authorities and represent a significant worsening of the disease.

2) was conservative, in that patients with missing data were assumed to experience a recurrence.

However, it also meant that recurrence was likely overestimated, since some patients could have received systemic corticosteroids or immunosuppressants to treat conditions other than uveitis and patients with missing data may have, in reality, not experience a recurrence of uveitis.

The purpose of this method of imputation was to avoid the possibility of an additive effect of unknown degree. If it can be assumed that the process of randomisation produced two groups of subjects with relatively similar health states requiring similar use of prohibited medications for treating any underlying co-morbidities, then the only differential in the rate of imputation due to prohibited medications would be because of the fact that the sham injection group need more rescue therapy for

recurrence of uveitis, i.e. any reduction in imputed recurrence in the FAc implant vs the sham arm could be attributed to the action of the implant.

Table 11 provides details of observed (protocol-defined) and imputed recurrences in the ITT and PP populations of PSV-FAI-001.

Table 11.Proportion of patients with recurrence of uveitis in the study eye within 6, 12 and 36 months

6 months, ITT population	**FAc implant (N=87)**	**Sham (N=42)**
Recurrence within 6 months, n (%)		
Protocol-defined recurrence		
Imputed recurrence		
Missing data[a]		
Prohibited medication		
Systemic steroid or immunosuppressant		
Intra/peri-ocular steroid		
Topical steroid		
No recurrence within 6 months, n (%)		
Difference from sham injection[b]		
Odds ratio		
95% confidence interval		
P value		

12 months, ITT population	**FAc implant (N=87)**	**Sham (N=42)**
Recurrence within 12 months, n (%)	33 (37.9)	41 (97.6)
Protocol-defined recurrence	3 (3.4)	12 (28.6)
Imputed recurrence	30 (34.5)	29 (69.0)
Missing data	1 (1.1)	0
Prohibited medication	29 (33.3)	29 (69.0)
Systemic steroid or immunosuppressant	14 (16.1)	5 (11.9)
Intra/peri-ocular steroid	3 (3.4)	16 (38.1)
Topical steroid	12 (13.8)	8 (19.0)
No recurrence within 12 months, n (%)	54 (62.1)	1 (2.4)
Difference from sham injection[b]		
Odds ratio	67.09	–
95% confidence interval	(8.81, 511.06)	–
P value	<0.001	–

36 months, ITT population	**FAc implant (N=87)**	**Sham (N=42)**
Recurrence within 36 months, n (%)		

Protocol-defined recurrence		
Imputed recurrence		
Missing data		
Prohibited medication		
Systemic steroid or immunosuppressant		
Intra/peri-ocular steroid		
Topical steroid		
No recurrence within 36 months, n (%)		
Difference from sham injection[b]		
Odds ratio		
95% confidence interval		
P value		
6 months, PP population	**FAc implant (N=60)**	**Sham (N=16)**
Recurrence within 6 months, n (%)		
Protocol-defined recurrence		
Imputed recurrence		
No recurrence within 6 months, n (%)		
Difference from Sham injection[b]		
Odds ratio		
95% confidence interval		
P value		
12 months, PP population	**FAc implant (N=53)**	**Sham (N=13)**
Recurrence within 12 months, n (%)	3 (5.7)	12 (92.3)
Protocol-defined recurrence	3 (5.7)	12 (92.3)
Imputed recurrence	0	0
No recurrence within 12 months, n (%)	50 (94.3)	1 (7.7)
Difference from sham injection[b]		
Odds ratio	200.00	–
95% confidence interval	(19.09, 2095.51)	–
P value	<0.001	–
36 months, PP population	**FAc implant (N=33)**	**Sham (N=13)**
Recurrence within 36 months, n (%)		
Protocol-defined recurrence		
Imputed recurrence		
No recurrence within 36 months, n (%)		
Difference from sham injection[b]		
Odds ratio		
95% confidence interval		
P value		

ITT, intent-to-treat; PP, per protocol

a One study eye in the sham injection group was missing a recurrence assessment (BCVA) at Month 6, but was not imputed for recurrence at Month 6, because the study eye had prior imputed recurrences, due to treatment with prohibited medications.
b The odds ratio (FAI insert/sham) and 95% confidence interval for no recurrence within 6/12/36 months were based on Mantel-Haenszel. P value was from a continuity corrected Chi-square test comparing the number of subjects with and without recurrence at 6/12/36 Months between treatment conditions.

Sensitivity analyses

Sensitivity analyses were performed for recurrence of uveitis and are presented below for the primary endpoint (recurrence at 6 months) and the entire 36-month study duration. Note that there were no patients with missing recurrence data (i.e. all patients had required eye examinations) at Month 6, so that the results of the sensitivity analyses are very similar to the results of the primary analysis. At 36 months, sensitivity analyses suggested that missing data have little effect on the relative efficacy of the FAc implant vs sham.

At 6 months

1) **Patients with missing data considered as having no recurrence** (Table 12): Rather than being considered as having a recurrence, subjects with no recurrence prior to Month 6 who did not have recurrence assessed at Month 6 (for any reason) were counted as having no recurrence of uveitis. Subjects with no recurrence prior to Month 6 who took a prohibited systemic or local concomitant medication prior to Month 6 were counted as having a recurrence.

Table 12. Recurrence rate sensitivity analysis (patients with missing data considered as not having a recurrence, 6-month time point)

36 months, ITT population	FAc implant (N=87)	Sham (N=42)
Recurrence within 6 months, n (%)	[redacted]	[redacted]
Protocol-defined recurrence, n (%)	[redacted]	[redacted]
Imputed recurrence, n (%)	[redacted]	[redacted]
No recurrence within 6 months, n (%)	[redacted]	[redacted]
Difference from sham injection[a]		
Odds ratio	[redacted]	[redacted]
95% confidence interval	[redacted]	[redacted]
P value	[redacted]	[redacted]

a The odds ratio (FAc implant/sham) and 95% confidence interval for no recurrence within 6 months are based on Mantel-Haenszel. P-value is from a continuity corrected Chi-square test comparing the number of subjects with and without recurrence at 6 Months between treatment conditions

2) **Tipping point method** (Table 13): Subjects with no recurrence prior to Month 6 who took a prohibited systemic or local concomitant medication prior to Month 6 were counted as having a recurrence of uveitis. In the initial analysis, subjects with no recurrence prior to Month 6 and a missing recurrence assessment at Month 6 (for any reason) were imputed as follows:

   - FAc implant subjects were counted as having a recurrence and Sham subjects as having no recurrence
   - For each subsequent analysis, one imputed FAI insert subject was counted as having no recurrence

Table 13. Recurrence rate sensitivity analysis (tipping point method, 6-month time point)

6 months, ITT population	FAc implant (N=87)	Sham (N=42)
Recurrence within 6 months, n (%)		
No recurrence within 6 months, n (%)		
Number (%) of imputed values at month 6 due to missing data		
Difference from sham injection[a]		
Odds ratio		
95% confidence interval		
P value		

a The odds ratio (FAc implant/sham) and 95% confidence interval for no recurrence within 6 months are based on Mantel-Haenszel. P-value is from a continuity corrected Chi-square test comparing the number of subjects with and without recurrence at 6 Months between treatment conditions

3) **Multiple imputation method** (Table 14): Subjects with no recurrence prior to Month 6 who took a prohibited systemic or local concomitant medication prior to Month 6 were counted as having a recurrence. Subjects with missing recurrence data for any reason were imputed using multiple imputation with 5 imputations performed. The percentage of recurrence-free patients was calculated for each imputation and the average across the 5 imputations is presented in the table below.

Table 14. Recurrence rate sensitivity analysis (multiple imputation method, 6-month time point)

6 months, ITT population	FAc implant (N=87)	Sham (N=42)
Average percentage of patients with no recurrence within 6 months		
Difference from sham injection[a]		
Odds ratio		
95% confidence interval		
P value		

a The 5 imputations were analysed using a logistic regression model with a term for treatment. The results from the 5 imputations were combined to produce the p-value, odds ratio (FAc implant/sham) and 95% confidence interval. 95% confidence interval and p-value were not calculated as there were no missing recurrence values in the study eye at Month 6.

At 36 months

Sensitivity analyses conducted at 36 months

1) **Patients with missing data considered as having no recurrence** (Table 15): Analysis was conducted as for the 6-month time point.

Table 15. Recurrence rate sensitivity analysis (patients with missing data considered as not having a recurrence, 36-month time point)

36 months, ITT population	FAc implant (N=87)	Sham (N=42)
Recurrence within 36 months, n (%)		
Protocol-defined recurrence, n (%)		
Imputed recurrence, n (%)		
No recurrence within 36 months, n (%)		
Difference from sham injection[a]		
Odds ratio		
95% confidence interval		
P value		

a The odds ratio (FAc implant/sham) and 95% confidence interval for no recurrence within 36 months are based on Mantel-Haenszel. P-value is from a continuity corrected Chi-square test comparing the number of subjects with and without recurrence at 36 Months between treatment conditions

2) **Tipping point method** (Table 16): Analysis was conducted as for the 6-month time point

Table 16. Recurrence rate sensitivity analysis (tipping point method, 36-month time point)

36 months, ITT population	FAc implant (N=87)	Sham (N=42)
Recurrence within 36 months, n (%)	[redacted]	[redacted]
No recurrence within 36 months, n (%)	[redacted]	[redacted]
Number (%) of imputed values at month 36 due to missing data	[redacted]	[redacted]
Difference from sham injection[a]		
Odds ratio	[redacted]	[redacted]
95% confidence interval	[redacted]	[redacted]
P value	[redacted]	[redacted]
Number of FAc implant subjects with imputed recurrence switched to no recurrence within 36 months	[redacted]	
Difference from sham injection[a]		
Odds ratio	[redacted]	
95% confidence interval	[redacted]	
P value	[redacted]	
Number of FAc implant subjects with imputed recurrence switched to no recurrence within 36 months	[redacted]	
Difference from sham injection[a]		
Odds ratio	[redacted]	
95% confidence interval	[redacted]	
P value	[redacted]	
Number of FAc implant subjects with imputed recurrence switched to no recurrence within 36 months	[redacted]	
Difference from sham injection[a]		
Odds ratio	[redacted]	
95% confidence interval	[redacted]	
P value	[redacted]	
Number of FAc implant subjects with imputed recurrence switched to no recurrence within 36 months	[redacted]	
Difference from sham injection[a]		
Odds ratio	[redacted]	
95% confidence interval	[redacted]	
P value	[redacted]	

a The odds ratio (FAc implant/sham) and 95% confidence interval for no recurrence within 36 months are based on Mantel-Haenszel. P-value is from a continuity corrected Chi-square test comparing the number of subjects with and without recurrence at 36 Months between treatment conditions

3) **Multiple imputation method** (Table 17): Analysis was conducted as for the 6-month time point

Table 17. Recurrence rate sensitivity analysis (multiple imputation method, 36-month time point)

36 months, ITT population	FAc implant (N=87)	Sham (N=42)
Average percentage of patients with no recurrence within 36 months		
Difference from sham injection[a]		
Odds ratio		
95% confidence interval		
P value		

a The 5 imputations were analysed using a logistic regression model with a term for treatment. The results from the 5 imputations were combined to produce the p-value, odds ratio (FAc implant/sham) and 95% confidence interval. 95% confidence interval and p-value were not calculated as there were no missing recurrence values in the study eye at Month 6.

A31. Priority question: Please complete the equivalent of table 10 (submission, page 52-53) for the per protocol (PP) population. Some of this information is in the text, but not all the denominators are there, nor is it clear if any of these data were imputed.

This is provided in the response to the previous question (A30). The PP population was defined as follows (from the clinical protocol for the PSV-FAI-001 clinical study):

'The per protocol (PP) population will be defined separately for the month 6, month 12 and month 36 analyses and will exclude all subjects in the ITT population who meet any of the following criteria:

- Received systemic treatment for recurrence of uveitis in fellow eye
- Received an imputed endpoint at the 6 month (or the 12 month or the 36 month) endpoint of the study
- Failed screening, without exemption, but received FAI insert
- Had a major protocol deviation (Protocol deviations, both major and minor, will be defined prior to database lock)'

A32. The clinical effectiveness data presented in the submission appear to indicate that the vast majority of reoccurrences were imputed due to the use of prohibited

medication. This is a deviation from the trial protocol. Please explain on what basis prohibited medications were provided to patients by the clinicians that were not in line with the protocol.

Please note that the use of the term “prohibited medication” is a misnomer and should actually be interpreted primarily as “rescue medication”, although the former language was used in the study reports. As specified in the company submission (Section 2.3.3.3.2, page 38), the use of oral, systemic, injectable, or topical steroids or systemic immunosuppressants was prohibited during the study other than during the initial tapering-off or in case of uveitis recurrence. Additionally, topical steroids administered as short-term standard treatment following an ocular surgical procedure were not considered prohibited medications.

The PSV-FAI-001 trial protocol specified the following for treatment of uveitis recurrences:

‘In the event of a uveitis recurrence in either eye (defined as an “Endpoint”), peri-ocular or intraocular corticosteroid injections, or topical medications should be administered as first line local therapy, in accordance with the protocol. Investigators should consider treatment with topical steroids as first line therapy for a recurrence that involves only an increase in anterior chamber cells with no increase in vitreous opacity. Systemic immunosuppressants or systemic steroids should be used only if local therapy fails.

Subjects who experience a recurrence of uveitis will continue participation in the study. Once the subject’s recurrence is controlled, the treatment regimen (local or systemic therapy) will be ended in a manner that follows the standard of care for ending the specific treatment regimen.’

However, subjects with an imputed recurrence in the study eye, or those who received systemic treatment for uveitis recurrence in the fellow eye were excluded from the per-protocol population. Specifically, the study populations were defined as follows in the PSV-FAI-001 trial protocol (also described in Section 2.4.2, page 48 of the company submission):

- ‘The ITT population will include all subjects randomized into the study; analysed as randomized.’
- ‘The safety population will include all subjects randomized into the study; analysed as treated.’
- ‘The per protocol (PP) population will be defined separately for the month 6, month 12 and month 36 analyses and will exclude all subjects in the ITT population who meet any of the following criteria:
    - Received systemic treatment for recurrence of uveitis in fellow eye
    - Received an imputed endpoint at the 6-month (or the 12 month or the 36 month) endpoint of the study
    - Failed screening, without exemption, but received FAI insert
    - Had a major protocol deviation (Protocol deviations, both major and minor, will be defined prior to database lock)’

A33. The submission states that health-related quality of life measures are not available from the PSV-FAI-001 trial, and that therefore they are not included in the clinical effectiveness section of the submission. However, health-related quality of life is included in the cost-effectiveness section using estimations from “mapped Visual Function Questionnaire (VFQ-25) values reported in the Multicenter Uveitis Steroid Treatment trial” (page 74) The affiliated reference for this information states the focus of the study was patients with intermediate uveitis, posterior uveitis, or panuveitis. As the submission focuses solely on [redacted], is the health-related quality of life information used based only on the available data for posterior uveitis? If not, please describe how this may differ from the health-related quality of life for [redacted] and whether any attempts were made to adjust the results for the difference.

The HRQoL information used was for the overall population of the MUST trial. Please note, however, that that uveitis affecting the posterior segment of the eye is not solely posterior uveitis. As stated in the company submission (page 17), ‘[redacted]; however, some cases of anterior uveitis, where the posterior segment of the eye is also affected (e.g. if macular

oedema is present), can also be considered a form of [redacted]. Given that PSV-FAI-001 included patients in whom the anterior segment was involved (who can be considered as having panuveitis, see response to question A33), in the absence of QoL data in PSV-FAI-001, patients enrolled in the Multicenter Uveitis Steroid Treatment (MUST) trial were considered a reasonable approximation the PSV-FAI-001 trial population.

A34. Please provide the number at risk for each group in figures 5, 11 and 15 of the company submission.

The numbers at risk can be seen in for ILUVIEN and (L)CP. The numbers at risk are shown for the follow up times specified in the clinical study protocol Table 18. Where a value for that day were not available exactly, the closest time is listed.

Table 18. Numbers at risk in PSV-FAI-001

		Number at risk	
	Time	**ILUVIEN**	**(L)CP**
Days	0	87	42
	1	87	42
	7	87	42
	28	85	37
Month	2	82	27
	3	79	18
	6	64	5
	9	62	3
	12	59	2
	18	48	2
	24	42	2
	30	37	2
	36	21	1

Adverse Events

A35. The submission states that there were no new or unexpected adverse events or further safety concerns associated with fluocinolone acetonide. However, the submission does not describe the process of removing the device (or implanting a

subsequent device) upon completion of the 36-month treatment. Could this become a safety concern?

The FAc implant is non-bioerodable and releases FAc for up to 3 years. It is designed to stay in the eye and after 36 months a second implant may be injected. The implant is made of polyimide and essentially similar to an intraocular lens haptic; its small size (3.5 mm x 0.37 mm) means there is very small risk of intra-ocular issues (floaters or implant dislocation).

If complications arise, the ILUVIEN implant can be removed by vitrectomy. During the FAME trials in diabetic macular oedema (DMO), three patients had to have the study implant removed – two due to increased intraocular pressure and one due to a visual disturbance caused by the implant. All three patients were in the 0.5µg/day treatment group. In patients with increased intraocular pressure, removal of the implant resulted in prompt decrease in IOP.

Re-implant Experience

The US Prescribing Information states that over the three-year follow-up period of the DMO trials, approximately 75% of the FAc implant-treated subjects received only one implant. In these trials, subjects were eligible for retreatment no earlier than 12 months after study entry (Alimera Sciences September 2014). Table 19 shows the number of study treatments that were given during the FAME trials. During the study, retreatments were allowed after Month 12 but no later than Month 33 if evidence of progression of oedema had occurred as per the assessing (masked) investigator based on:

- a decrease in visual acuity of ≥5 letters in ETDRS or
- OCT measurement of macular oedema showing thickening of at least 50 µm at the centre of the fovea.

It is important to note that at the time of the FAME trials, the pharmacokinetic study had not been completed, and it was not confirmed at the time that the FAc implant would release the drug for up to 36 months (Campochiaro et al. 2012).

Table 19. Patient exposure to study treatment in the FAME trials

	Treatment group		
	Control	**0.2 µg/d FAc implant**	**0.5 µg/d FAc implant**
Study treatments, n (%)	N = 185	N = 375[1]	N = 393[1]
1	132 (71.4%)	279 (74.4%)	278 (70.7%)
2	44 (23.8%)	81 (21.6%)	91 (23.2%)
≥3	9 (4.8%)	15 (4.0%)	24 (6.1%)

[1] Three randomized patients did not receive study treatment, one in the 0.2 µg/d FAc implant group and two in the 0.5 µg/d FAc implant group.

Pharmacokinetics with multiple implants – FAMOUS Phase II Study

The US Prescribing information provides the following information: 'In a human pharmacokinetic study of ILUVIEN, fluocinolone acetonide concentrations in plasma were below the lower limit of quantitation of the assay (100 pg/mL) at all post-administration time points from Day 7 through Month 36 following intravitreal administration of a 0.2 mcg/day or 0.5 mcg/day fluocinolone acetonide insert' (Alimera Sciences September 2014).

In the Phase 2, randomized clinical trial (NCT00490815) FAMOUS study, the aqueous levels of fluocinolone acetonide (FAc) were further characterized including the approved 0.2 µg/day dose and the 0.5 µg/day (high dose) group (Campochiaro et al. 2013). Of the 37 subjects in the DMO FAMOUS Study, 14 were treated more than once with the FAc implant during the 3-year study which allowed for assessment of pharmacokinetics and safety in patients that received a single treatment and those that received retreatment with the 0.2 µg/day and 0.5 µg/day FAc. The pharmacokinetic study also included a comparison with Retisert (0.59 mg FAc implant) administered to patients with chronic non-infectious posterior uveitis who were scheduled to receive it as part of standard care.
The concentration of FAc in aqueous specimens was measured by liquid chromatography-mass spectroscopy method with lower limit of quantification set as 100 pg/ml. In subjects receiving a single 0.2 µg/day insert, FAc levels were stable with steady-state aqueous FAc levels in the range of 0.5 to 1 ng/ml and were maintained at least through 36 months after insertion. Steady-state levels were

achieved between 6 and 9 months. In subjects who were retreated with FAc implant, mean FAc levels were somewhat higher compared with those patients who received only one treatment. Only 2 of 14 subjects who were re-treated had aqueous levels <0.5 ng/ml, whereas 7 of 14 subjects had levels >1 ng/ml. Among the subjects who were re-treated, 6 of 14 experienced an IOP increase of >3 mm Hg compared with their highest value before re-treatment. None of the subjects in the FAMOUS Phase II study who were re-treated with the FAc implant required IOP lowering surgery. Study results showed that low and high dose FAc implants both provided stable long-term release of FAc with comparable peak levels in the aqueous.

A36. In table 19 of the submission (page 67), increases in intraocular pressure (IOP) are subdivided into mild, moderate, and severe. Please provide definitions for these mild, moderate, and severe classifications?

The PSV-FAI-001 protocol defined adverse events severity according to the following criteria:

'AE severity is defined as a qualitative assessment of the degree of intensity of an AE as determined by the investigator or reported to him/her by the subject. The assessment of severity is made irrespective of test article relationship or seriousness of the event and should be evaluated according of the following scale:

- Mild: Awareness of event but easily tolerated. Usually transient, requiring no special treatment, and does not interfere with the subject's daily activities.
- Moderate: Discomfort enough to cause some interference with usual activity. Traditionally introduces a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually relieved by simple therapeutic measures.
- Severe: Causes an interruption of the subject's usual daily activity and traditionally requires systemic drug therapy or other treatment.'

In the case report form (CRF) completion guidelines, the following guidance was provided to study investigators with respect to grading the intensity of an adverse event:

'Intensity: Mark the intensity from the options below:

- Mild: The subject has awareness of the event but it is easily tolerated. Usually transient, requiring no special treatment, and does not interfere with the subject's daily activities.
- Moderate: The subject has enough discomfort to cause some interference with usual activity. The AE introduces a low level of inconvenience or concern to the subject and may interfere with daily activities, but it is usually relieved by simple therapeutic measures.
- Severe: The AE causes an interruption of the subject's usual daily activity and requires systemic drug therapy or other treatment.'

While this provides a very useful comparison of the IOP signal across the treatment arms, the 36-month CSR provides a more quantitative comparison in the following table:

Table 20. Treatment-emergent protocol-defined ocular adverse events through month 36 visit by protocol-defined criteria (Safety Population, Study eye)

	FAc implant (N=87), n (%)	Sham (N=42), n (%)	Total (N=129), n (%)
Increase in IOP of ≥ 10 mmHg at 2 visits at least 1 week apart or an increase in IOP to ≥ 25 mmHg	[redacted]	[redacted]	[redacted]
Total number of TEAEs			
Number of subjects with at least 1 TEAE	[redacted]	[redacted]	[redacted]
Investigations			
IOP increased	[redacted]	[redacted]	[redacted]

IOP: intraocular pressure, FAc: fluocinolone acetonide; TEAE: treatment-emergent adverse event

This more quantitative measure of IOP increase corroborates the adverse event reports and further supports that the risk of elevated IOP associated with the FAc implant is not significantly different than with the standard of care, which is what the sham injection patients received. However, the FAc implant provides continuous treatment over 36 months and, as the results of the clinical trial demonstrate, this continuous treatment results in continuous protection from recurrences of uveitis.

Indirect Comparisons

A37. Priority question: Please provide indirect comparisons of fluocinolone versus dexamethasone intravitreal implant using the PSV-FAI-001 and HURON trials, and versus systemic immunosuppressive therapies and periocular or intravitreal

corticosteroid injections separately. Please also perform indirect comparisons of fluocinolone versus systemic corticosteroids and TNF-alpha inhibitors.

A meta-analysis comparing the FAI insert with dexamethasone insert was not performed, as it was not considered appropriate due to the very different patient populations enrolled in the HURON trial compared with PSV-FAI-001 and the fact that the HURON trial did not specifically report the outcomes of patients in whom the posterior segment of the eye was affected. The latter was, in fact, the reason for exclusion of the HURON trial from our systematic review and subsequently from the submission. A comparison of key differences in study population and design between PSV-FAI-001 and HURON trials is presented in Table 21 with key differences highlighted in bold. All information on the HURON trial and the results thereof presented in this section are based on the 2011 publication by Lowder et al (Lowder et al. 2011).

Table 21. Key differences in study design between PSV-FAI-001 and HURON trials

	PSV-FAI-001(pSivida Corp 2017)	HURON(Lowder et al. 2011)
Population	Included patients with one or both eyes having a [redacted] (with or without anterior uveitis) Excluded patients with a history of posterior uveitis only, that was not accompanied by vitritis or macular oedema	Included patients with a diagnosis of non-infectious **intermediate or posterior** uveitis
	Included patients who, at the time of enrolment (Day 1), had < 10 anterior chamber cells /high power field and a vitreous haze grade ≤2 in the study eye	Included patients with a vitreous haze score ≥1.5+
	Included patients whose visual acuity in study eye was at least 15 letters on the ETDRS chart	Included patients with BCVA of 10–75 letters Excluded patients with BCVA <34 letters in the fellow eye
Study design	36-month follow-up	6-month follow-up (26 weeks)
	Primary endpoint: the proportion of subjects who had a recurrence of uveitis in the study eye within 6 months following treatment Other efficacy endpoints: • Proportion of subjects who have a recurrence of uveitis in	**Primary endpoint:** proportion of patients with a vitreous haze score of 0 at week 8 Other efficacy endpoints: • Time to a vitreous haze score of 0

	the study eye within 12 months or 36 months • Proportion of subjects who have a recurrence of uveitis in the fellow eye (within 6 months, 12 months and 36 months) • Mean change from baseline in BCVA letter score in the study eye (at 6 months, 12 months and 36 months) • Number of recurrences of uveitis (within 6 months, 12 months and 36 months) • Time to recurrence of uveitis (within 6 months, 12 months and 36 months) • Number of adjunctive treatments required to treat recurrences of uveitis (within 6 months, 12 months and 36 months) • Resolution of macular oedema, as measured by OCT imaging (at 6 months, 12 months and 36 months)	• The proportion of patients achieving at least 2 units of improvement in vitreous haze score • Mean change from baseline in vitreous haze scores through week 26 • BCVA measured using a standardized ETDRS protocol • central macular thickness measured by optical coherence tomography (at selected sites)

BVCA: best corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; [redacted]: non-infectious uveitis affecting the posterior segment of the eye; OCT: optical coherence tomography

The HURON trial enrolled 229 patients from 18 countries, who were randomised to receive the 0.7 mg (n=77) or 0.35 mg (n=76) dexamethasone insert, or sham (n=76). Mean age of included patients was 45 years; over 60% of patients were female, and more than 60% of patients were white. The majority (81%) had intermediate uveitis. In comparison, the PSV-FAI-001 trial enrolled fewer patients (n=129) whose mean age (48.3 years) was similar to that in the HURON trial, as was the proportion of females (61.2%) and white patients (66.7%). Mean baseline visual acuity was 58–63 letter (depending on study group) in the HURON trial and slightly higher (66.3) in the PSV-FAI-001 trial. Importantly, only 46.5% of patients in the PSV-FAI-001 study had a vitreous haze score of 1+ or 2+ and no patients had a 3+ or 4+ vitreous haze score. In the HURON trial, all patients had a vitreous haze score of at least 1.5+, in line with the inclusion criteria, and 13–21% had a score of 3+ or 4+.

The comparison of vitreous haze between dexamethasone and the FAI insert needs to be interpreted with caution due to the very different baseline vitreous haze scores

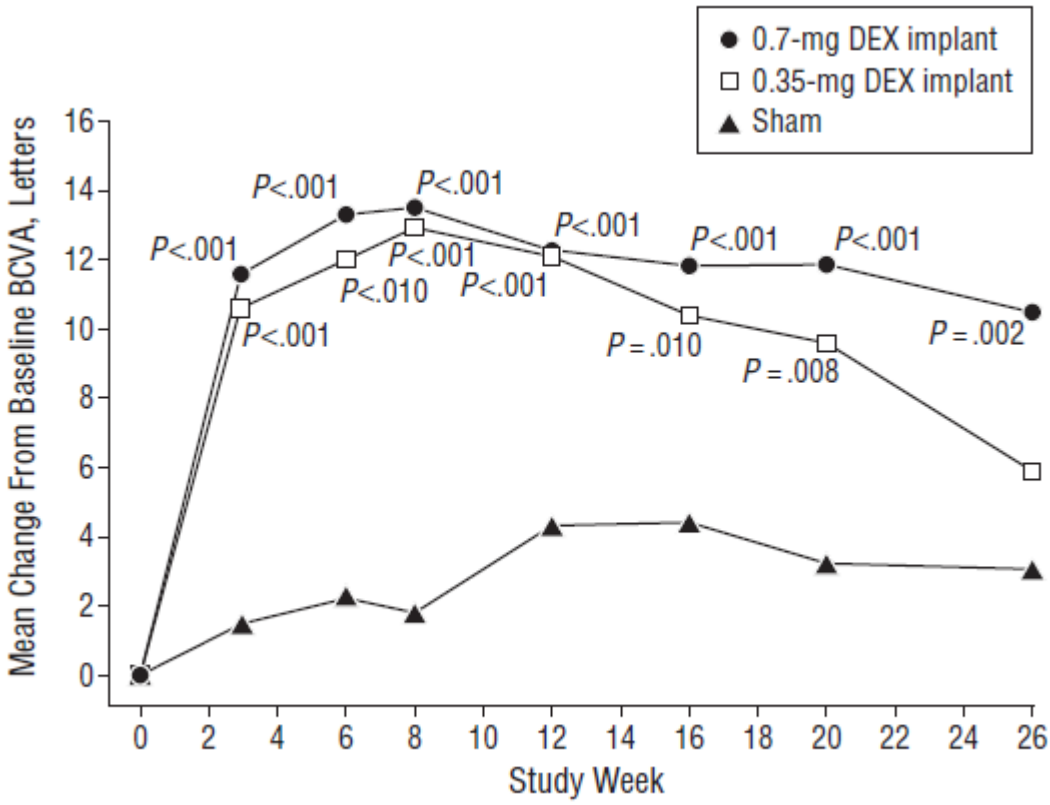
in HURON and PSV-FAI-001. In the FAI insert arm of PSV-FAI-001, the proportion of patients with absent vitreous haze increased from 25.3% at baseline to 63.3% at 2 months and 80.5% at 6 months – an increase by 38% and 55.2%, respectively. In the sham arm, the proportion of patients with absent vitreous haze increased by 25.7% from baseline to Month 2 and by 40.5% to Month 6. In the dexamethasone insert HURON study, there were no patients with absence of vitreous haze at baseline. At 2 months (week 8), 36% of patients in the 0.35 mg group and 47% in the 0.7 mg group had no vitreous haze, compared to 12% in the sham group ($p < 0.001$ for both comparisons); this significant improvement over sham was also observed at 6 months.

The percentage of patients with uveitis recurrences, the number of recurrences of uveitis per patient and time to recurrence were not reported in the HURON trial. The use of systemic immunosuppressive therapy or corticosteroids (systemic, periocular, intravitreal, or topical) by Month 6 was required by 38% of patients in the sham arm, 25% in the 0.35 mg dexamethasone insert arm and 22% in the 0.7 mg dexamethasone insert arm ($p=0.30$ vs sham) in HURON, while in the PSV-FAI-001 trial 14.9% of patients in the FAI insert arm and 38.1% of patients in the sham arm received these medications by Month 6.

At 6 months, mean improvement from baseline BCVA in the HURON study was significantly greater in the dexamethasone insert arms than the sham arm (Figure 3

Figure 3). However, it is worth noting that the effect of dexamethasone on BCVA appeared to start wearing off from week onwards, which is in stark contrast with the long-term, sustained BCVA improvement observed with the FAI insert (see Section **Error! Reference source not found.**).

Figure 3. BCVA improvement from baseline in the HURON trial(Lowder et al. 2011)



BVCA: best corrected visual acuity; DEX: dexamethasone

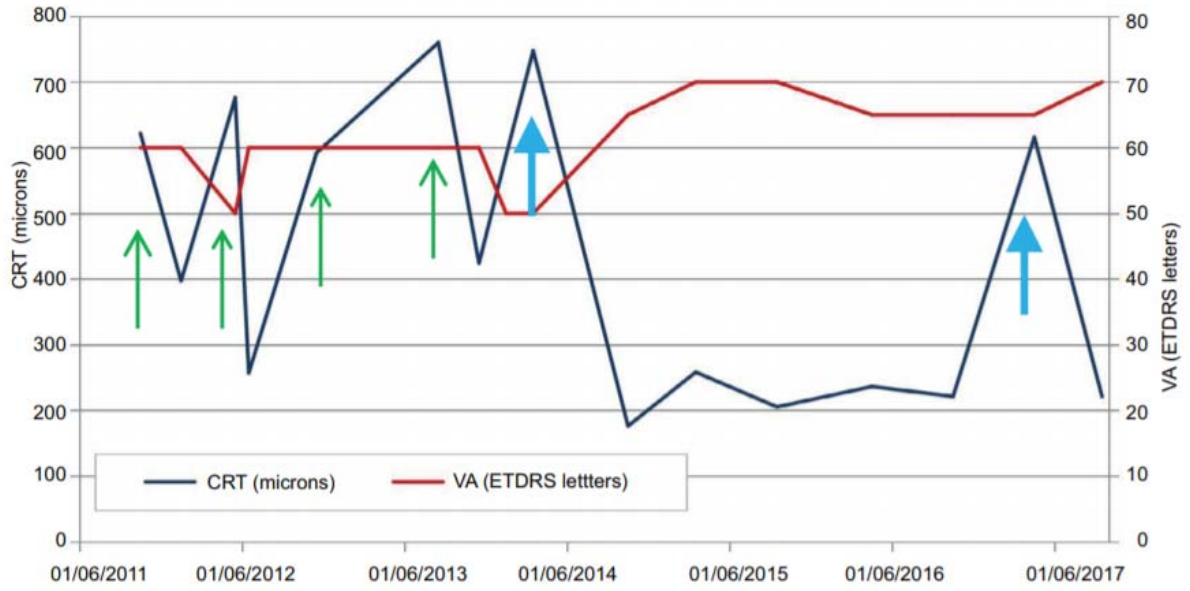
In terms of macular oedema, the HURON trial assessed central macular thickness, while the PSV-FAI-001 trial assessed CFT, so that the actual measurements cannot be readily compared. Central macular thickness decreased by significantly more in the 0.7 mg and 0.35 mg dexamethasone groups compared with the sham group at week 8 (decrease by a mean of 99.4 [SD: 151.8] µm and 91.0 [SD: 132.8] µm vs 12.4 [SD: 123.7] µm, respectively; p ≤0.004), but the difference was no longer significant at 6 months (decrease by a mean of 50.2 [SD: 102.9] µm and 68.1 [SD: 138.8] µm vs 35.5 [SD: 134.9] µm, respectively; p ≥0.227). In the PSV-FAI-001 trial, CFT decreased by a mean of 94.8 (SD: 154.05) µm with the FAI insert, compared to 43.8 (SD: 177.62) µm with sham and this effect was sustained up to Month 36 (see **Error! Reference source not found.**).

In terms of safety outcomes, the percentage of eyes in the 0.7 mg dexamethasone insert group requiring at least one IOP-lowering medication was ≤23% throughout the 6-month HURON study period, while the corresponding figure for the study eye in the FAI insert PSV-FAI-001 trial was 18.4%. In the HURON trial, cataracts were

reported as AEs in 15%, 12% and 7% of phakic eyes in the 0.7 mg dexamethasone, 0.35 mg dexamethasone and sham groups, respectively. Over the first 6 months of the PSV-FAI-001 trial, cataracts affecting the study eye were reported in 14.9% of subjects in the FAI insert arm, compared with 4.8% in the sham arm.

The differences in study design (duration and endpoints) and enrolled patient populations preclude a more quantitative comparison between dexamethasone and FAI inserts. We believe that the crucial differentiator of the FAI insert from the dexamethasone insert is its long-term sustained action, from which patients with chronic or recurrent uveitis are likely to benefit. The difference in the effects of the two inserts at individual patient level are striking, as illustrated by a case study in DME where the patient received four dexamethasone inserts followed by the FAI insert(Singh et al. 2018) (Figure 4). While the dexamethasone insert generally appeared effective at reducing CRT and maintaining or improving visual acuity, its effects wore off promptly resulting in large fluctuations in CFT. There was little positive effect on visual acuity. In comparison, the FAI insert produced prolonged control of macular oedema, with CFT remaining stable for approximately 2 years and the patients visual acuity improved following treatment with the FAI insert; this improvement was sustained for over 2 years. Although this case report pertains to DME and not uveitis, similar temporal patterns may reasonably be expected in uveitis, due to the different duration of action of dexamethasone and FAI inserts. In trials, fluctuations in ocular parameters observed at an individual level may become less clear due to regression to the mean; however, in clinical practice they are likely to substantially affect treatment decisions.

Figure 4. CRT and visual acuity in a patient with DME treated with four dexamethasone inserts followed by the FAI insert(Singh et al. 2018)



Intravitreal injections of dexamethasone and FAI inserts are shown in green and blue, respectively. The patient was re-treated with a second FAI insert in April 2017.
CRT: central retinal thickness; DEX, dexamethasone; ETDRS, Early Treatment Diabetic Retinopathy Study; FAI, fluocinolone acetonide intravitreal; VA, visual acuity

Section B: Clarification on cost-effectiveness data

During the course of responding to questions it was necessary to make changes to the cost-effectiveness model resulting in a new base case ICER. Table 22 details the changes made to the cost-effectiveness model and if applicable, the question that this change relates to. Each change is reported cumulatively until the revised base case is reached.

Table 22: Revised base case

Submitted Model – Company Submission					
Outcome	*ILUVIEN*	*(L)CP*	*Δ*	*ICER*	*NMB*
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£7,182.79	[redacted]
Change 1: Transition cost for subsequent therapy applied to (L)CP (Response to question B18)					
Outcome	*ILUVIEN*	*(L)CP*	*Δ*	*ICER*	*NMB*
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]

Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£7,178.93	[redacted]
Change 2: The cost of residential care is applied every year (Response to question B21)					
Changes 1 and 2					
Outcome	*ILUVIEN*	*(L)CP*	*Δ*	*ICER*	*NMB*
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£1,238.29	[redacted]
Change 3: Formula in column BR referring to an empty cell (Response to question B26)					
Changes 1 to 3					
Outcome	*ILUVIEN*	*(L)CP*	*Δ*	*ICER*	*NMB*
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£1,156.48	[redacted]
Change 4: ILUVIEN costs for subsequent therapy referring to the discounted LYs					
Changes 1 to 4					
Outcome	*ILUVIEN*	*(L)CP*	*Δ*	*ICER*	*NMB*
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£2,510.07	[redacted]
Change 5: Cost of (L)CP was multiplied by proportion eligible for treatment in that arm					
Changes 1 to 5					
Outcome	*ILUVIEN*	*(L)CP*	*Δ*	*ICER*	*NMB*
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£2,510.07	[redacted]
Change 6: Efficacy for (L)CP and Iluvien base case changed to be estimated from patient level data (Response to question B6) – Revised base case					

Changes 1 to 6					
Outcome	*ILUVIEN*	*(L)CP*	*Δ*	*ICER*	*NMB*
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£1,071.91	[redacted]

Model Structure

B1. Priority question: The health states included in the company cost-effectiveness model are defined in terms of the treatment pathway of patients (e.g. on treatment, subsequent therapy), except for the 'blindness' health state. However, these definitions do not provide an indication of the health status of the patients in the different health states in terms of visual acuity and other symptoms of the disease. For example, patients may suffer from bilateral disease which would impair their quality of life. Please justify why the health states in the model are homogeneous in terms of visual acuity (in both eyes) and other symptoms related to uveitis (and thus in terms of quality of life and costs).

Due to paucity in available literature, the cost-effectiveness model and the health states used aimed to reflect the available data from the key trial (PSV-FAI-001). The trial clearly details those who are "on treatment" or who experience recurrence and so move to a Subsequent Treatment. For completeness the model incorporates other relevant events that may occur as a result of disease and that were recorded in the trial; remission (of the ocular disease in the study eye) and permanent blindness. Although no difference between arms was estimated, death was also modelled.

The health states are homogenous in terms of symptoms related to uveitis as these are related to the type of treatment that the patient is taking; on treatment/in remission with an implant and no systemic therapy, in subsequent treatment with immunosuppressant therapy or experiencing permanent blindness and so not requiring treatment for ocular disease in the modelled study eye any longer. Whilst visual acuity was not explicitly modelled, assumptions surrounding this endpoint have been made in order to characterise the health states. Patients in the "On treatment" health state will not have experienced a reduction of more than 2 stages

in a visual acuity measure or else they would have moved to the “Subsequent Therapy” health state as dictated by the CSP. Similarly, patients in the remission health state have maintained this health status for more than two years. Patients who have moved to “Subsequent Therapy” have experienced a decrease in their visual acuity. While the exact score is not modelled, it is unlikely to change the course of treatment as only a substantial decrease would result in a new line of treatment.

Additionally, it is acknowledged that patients may have bilateral disease, however, it was deemed not appropriate to model bilateral disease with the available data. The trial design focused on the initiation of treatment within one eye only, therefore, the impact of treatment within two eyes for bilateral disease was not evaluated. Further, the informing trial was powered to evaluate primary endpoints related to the study eye only. Although evidence was collected for the fellow eye also; the trial was not powered to detect differences between such endpoints and therefore it would not be appropriate to potentially drive results with this data. The model is designed to reflect ocular disease in the study eye only and the health states reflect the costs and benefits incurred by the defined health states as were collected in the informing trial.

B2. Several transitions between health states are not incorporated in the cost-effectiveness model:

a. Patients cannot transition from the ‘subsequent therapy/end of first-line treatment effect' health state to the ‘remission’ health state, which implies that patients will not experience a (long-term) response to second-line treatment.

   i. Please justify this assumption.

   ii. Please provide a scenario analysis in which patients may enter the ‘remission’ health state as a consequence of response to second-line treatment.

We were unable to identify data that could support estimating the rate at which patients would enter remission from the subsequent therapy health state. The model currently assumes that patients only leave this health state if they experience permanent blindness or death which are sourced from published literature. The only assumptions that could be made about transition to the remission health state would

be arbitrary and would require an additional remission health state to be included so as to incorporate a different definition of remission; remission from systemic disease as opposed to the ocular disease currently included. Please note that remission from systemic disease was also not incorporated in the model for TA460.

Additionally, were a rate available for movement into the health state, there is no data to support an estimation of the rate at which patients would move out of this health state.

It is acknowledged that this is a limitation of the modelling approach. However, without information to support assumptions, it does not seem appropriate to implement this. This assumption follows that made in TA460.

b. Patients cannot transition from the 'on treatment' health state to the 'blindness' health state. However, blindness could occur as a consequence of adverse events, such as cataract and glaucoma.

    i. Please provide a scenario analysis in which patient may transition from the 'on treatment' health state to the 'blindness' health state in both treatment arms. Please inform this transition probability by the probability that is used to inform the transition from 'subsequent treatment' to 'blindness', as performed in the dexamethasone analyses of TA460.

It is acknowledged that a patient may experience an adverse event that may result in blindness. However, in the trial that informs efficacy in the model recurrence is defined as:

- A > 2 step increase in the number of cells in the anterior chamber per high powered field (1.6 X using a 1-mm beam) (Hogan 1959), compared to baseline or any visit time point prior to Month 6

OR

- An increase in the vitreous haze of > 2 steps compared to baseline or any visit time point prior to Month 6

OR

- A deterioration in visual acuity of at least 15 letters BCVA, compared to baseline or any visit time point prior to Month 6

Therefore, if a patient had an AE that was causing substantial decrease in visual acuity they would be recorded as a recurrence and this would be reflected in the model as a move to subsequent therapy prior to the move to permanent blindness. It is also probable that patients with worsening vision or inflammation due to an AE such as glaucoma or cataract would use a prohibited treatment that would also result in imputed recurrence and as such be reflected in the efficacy curves used in the model. Therefore, it does not seem appropriate to introduce a scenario where patients could move from a position of no visual acuity decrease from baseline to permanent blindness where this is already accounted for in their movement from "On Treatment" to "Subsequent Therapy" as informed by observed data.

ii. Please provide scenario analyses in which it is assumed that fluocinolone acetonide decreases the probability to transition from 'on treatment' to 'blindness' (implemented in B2.b.i.) by 0%, 25%, 50%, or 75%, as was performed in TA460.

This scenario was not implemented as explained in response to B2.b.i

B3. In the model, it is assumed that after a period of 2 years, all patients who are still on treatment and did not experience a recurrence, enter the 'remission' health state.

a. Please justify why the 2-year cut-off value was selected and provide evidence to support this assumption.

The assumption that remission occurred at 2 years was taken initially from TA460 and corroborated with clinical advice. If there have been no incidences of recurrence for over 2 years, the patient would be considered to be in remission from ocular disease in the eye concerned.

b. Please provide scenario analyses in which the proportion of patients (0%, 10%, 25%, 50%, 75%) and the cut-off value (3, 5, 10, 20 years) for entering the 'remission' health state are varied.

The proportion of patients who enter the remission health state is estimated from the observed data as this occurs during the observed trial period. Therefore, it is not considered appropriate to vary this value against observed evidence. The time at which a patient achieves remission was not based on observed data; it was informed by clinical opinion so this could be varied. The results are presented below for 3, 5, 10 and 20 year cut offs as requested.

3 years

Table 23: Scenario - remission considered after 3 years

Outcome	Iluvien	(L)CP	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£1,777.78	[redacted]

5 years

Table 24: Scenario - remission considered after 5 years

Outcome	Iluvien	(L)CP	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£2,829.68	[redacted]

10 years

Table 25: Scenario - remission considered after 10 years

Outcome	Iluvien	(L)CP	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]

QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£3,849.62	[redacted]

20 years

Table 26: Scenario - remission considered after 20 years

Outcome	Iluvien	(L)CP	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£4,096.06	[redacted]

Intervention and Comparator

B4. Priority question: The model assumes that patients in the intervention group will only receive a single fluocinolone acetonide implant at the start of the cost effectiveness model.

a. Please clarify what would be the course of action when the insert is 'empty', i.e. after 3 years.

i. Would the implant be removed?

The implant is designed to remain in the eye; please see the response to question A35.

ii. If yes,

1. In which proportion of patients would removal of the insert take place?

Not applicable

2. What are the risks and costs associated with the removal of an implant?

Not applicable

iii. Would patients be eligible for a new implant? If so, when (e.g. upon the next recurrence) and how many implants in total would patients be allowed to have?

Although retreatment was not incorporated in the 3-year PSV-FAI-001 trial, in clinical practice patients who have no contraindications and are likely to benefit from retreatment would most probably be retreated after 36 months, when the effectiveness of the initial implant begins to decline (see Figure 5 from the submission, reproduced below as Figure 5). Indeed, emerging real-world data suggest retreatment is utilised in the treatment of diabetic macular oedema (Singh et al. 2018), and the Sponsor believes this is likely to be similar in the uveitis indication. However, retreatment with the FAc 190 µg intravitreal implant cannot reasonably be modelled because sufficient data to support efficacy evaluation is not available.

FAI: fluocinolone acetonide intravitreal; ITT: intention-to-treat

Figure 5.

iv. Based on the responses to the previous questions, please provide a scenario analysis in which a proportion of patients undergo implant removal and/or subsequent implantation.

As it is mostly not necessary to remove the implant, any scenario where this is incorporated would not be representative of routine practice. Additionally, since there is a lack of data to inform the efficacy of retreatment, any such scenario would be based on a series of assumptions that cannot be validated with current data.

b. In case of bilateral uveitis, would an implant in both eyes be considered?

The Sponsor believes that bilateral treatment would be beneficial in patients whose both eyes are affected by ; however, concurrent treatment is not recommended, and the other eye should be treated only once the patient's ocular and systemic response to the first implant is known. Please see response to question A24 for a detailed discussion on this topic. It is also worth noting that in real world clinical practice the FAc 190 µg intravitreal implant has been used bilaterally off label in , and also used bilaterally in chronic diabetic macular oedema.

i. If yes, please provide a scenario analysis in which the possible treatment of bilateral disease with two implants is considered.

Although bilateral treatment is likely to be applied in eligible patients in the real-world setting, the PSV-FAI-001 trial, which provided clinical data to support the model, did not investigate bilateral treatment. Since the FAc 190 µg intravitreal implant is not yet approved for the treatment of [redacted], there are also no large real-world reports that could describe bilateral treatment. This would make identifying data that could adequately support a bilateral treatment scenario extremely difficult and any such scenario would have to be based on assumptions that cannot be readily validated.

Effectiveness

B5. Priority question: Based on the results of the indirect treatment comparisons requested in question A37, please incorporate all comparators considered in the indirect treatment comparisons in the cost-effectiveness model.

a. Please describe the assumptions made for each comparator.

b. Please provide cost-effectiveness results for each comparator, as well as a fully incremental analysis.

It was not considered appropriate to perform an indirect treatment comparison and therefore this analysis is not available. This decision is reported thoroughly in the response to question A37.

B6. Priority question: Please use the original individual patient data to estimate time to recurrence for both treatment arms (in all requested analyses) instead of the digitised (i.e. reconstructed) Kaplan-Meier curves.

Parameters for curve fits were recalculated from patient level data for both the FAc 190 µg intravitreal implant and (L)CP. Upon investigation of the curves, the same decision was made with regard to fitting from day 120 in the FAc 190 µg intravitreal implant arm. This decision is discussed in more detail in response to questions B8 and B9. Parameters and plots can be seen below for FAc 190 µg intravitreal implant and (L)CP. Base case results can be seen in Table 27.

FAc 190 µg intravitreal implant

The parameters for the curves fit from day 120 of the observed period for ILUVIEN can be seen in Table 27 along with the AIC and BIC fit statistics. The curves plot with the KM data can be seen in [redacted]. The fit statistics and the plot were used together to identify the Exponential curve to be the base case.

Table 27. Parameters used for FAc 190 µg intravitreal implant curve fits and fit statistics

Distribution	Parameter	Mean	AIC	BIC
Exponential	rate	[redacted]	[redacted]	[redacted]
Weibull	shape	[redacted]	[redacted]	[redacted]
	scale	[redacted]		
LogLogistic	shape	[redacted]	[redacted]	[redacted]
	scale	[redacted]		
LogNormal	meanlog	[redacted]	[redacted]	[redacted]
	sdlog	[redacted]		
Generalised F	mu	[redacted]	[redacted]	[redacted]
	sigma	[redacted]		
	Q	[redacted]		
	P	[redacted]		
Gamma	shape	[redacted]	[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]
Generalised Gamma	mu	[redacted]	[redacted]	[redacted]
	sigma	[redacted]		
	Q	[redacted]		
Gompertz	shape	[redacted]	[redacted]	[redacted]
	rate	[redacted]		

[redacted]

(L)CP

Table 28 shows the parameters that were derived from curve fits to the (L)CP arm using the patient level data. Figure 6 and Figure 7show the fit statistics, which along with [redacted] led to the Log-logistic distribution being considered the best representative of observed data.

Table 28. Parameters used for (L)CP curve fits

Distribution	Parameter	Mean	L95%	U95%	SE

Exponential	rate	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	shape	[redacted]	[redacted]	[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]
LogLogistic	shape	[redacted]	[redacted]	[redacted]	[redacted]
	scale	[redacted]	[redacted]	[redacted]	[redacted]
LogNormal	meanlog	[redacted]	[redacted]	[redacted]	[redacted]
	sdlog	[redacted]	[redacted]	[redacted]	[redacted]
Generalised F	mu	[redacted]	[redacted]	[redacted]	[redacted]
	sigma	[redacted]	[redacted]	[redacted]	[redacted]
	Q	[redacted]	[redacted]	[redacted]	[redacted]
	P	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	shape	[redacted]	[redacted]	[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]	[redacted]
Generalised Gamma	mu	[redacted]	[redacted]	[redacted]	[redacted]
	sigma	[redacted]	[redacted]	[redacted]	[redacted]
	Q	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	shape	[redacted]	[redacted]	[redacted]	[redacted]
	rate	[redacted]	[redacted]	[redacted]	[redacted]

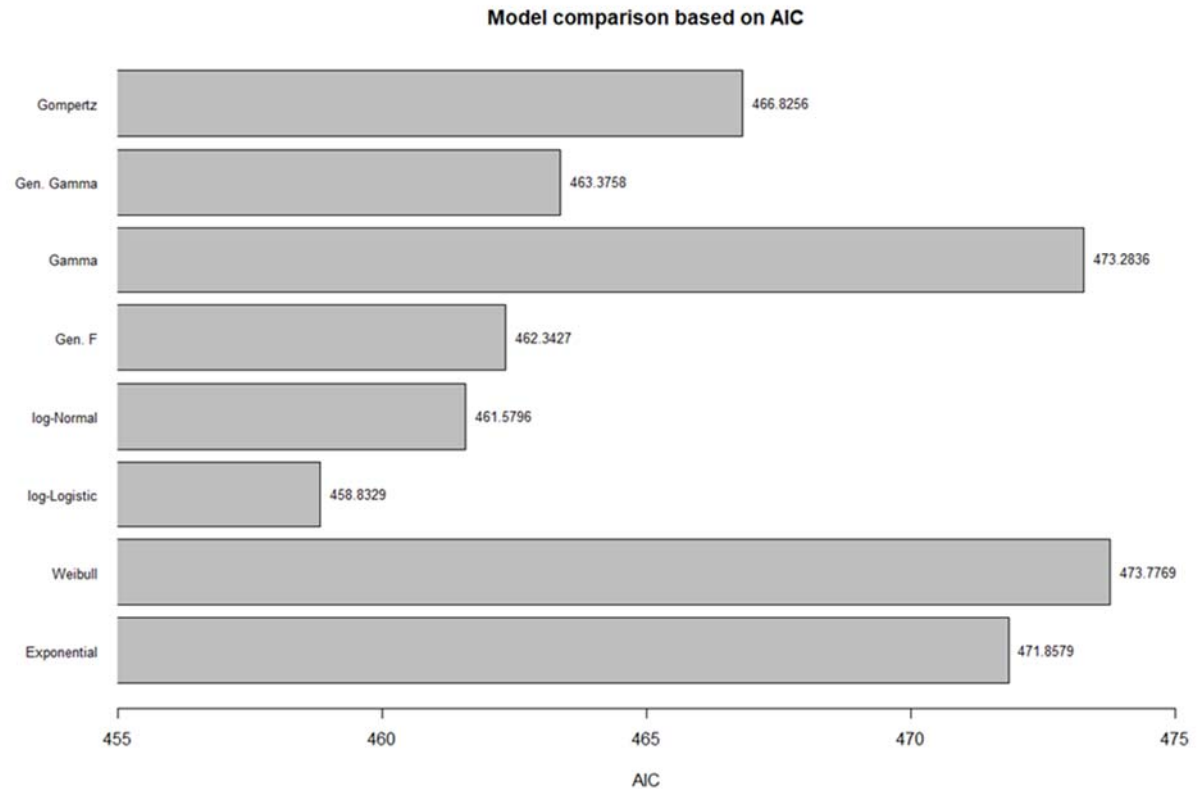


Figure 6. AIC fit statistics for (L)CP arm

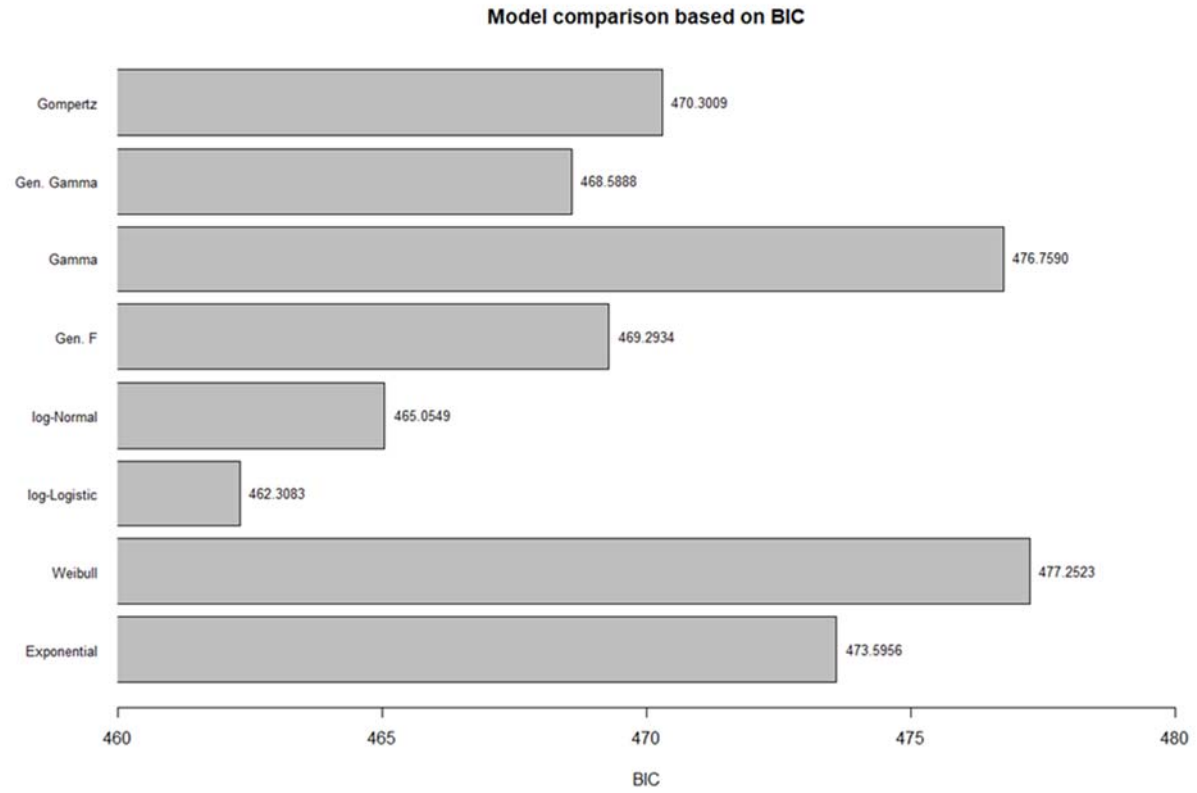


Figure 7. BIC fit statistics for (L)CP arm

[redacted]

Base case results

The base case assumes an Exponential curve fit to the ILUVIEN arm from day 120 of the observed data and a Loglogistic curve fit to the (L)CP arm from the beginning of the observed period. Unless otherwise stated in this document, the assumptions used to generate the results seen in Table 29 are as described in the Company Submission.

Table 29. Base case results using efficacy fit from patient level data

Outcome	ILUVIEN	(L)CP	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£1,071.91	[redacted]

B7. The risk of recurrence of uveitis after 3 years is based on the extrapolation of the PSV-FAI-001 trial results through a time-to-event model. However, the trial follow-up was stopped at 3 years, which implies that there is no observation concerning the effectiveness of the implant after 3 years, when it is 'empty'. Please justify this assumption.

Figure 8 shows the KM curve time to first recurrence in PSV-FAI-001 and shows three events after the defined 36 months (3 years) cut off. Given this, it was considered appropriate to fit curves and extrapolate through the defined end point (1,080 days). As these patients did not experience recurrence inside the defined trial time the evidence shows that while the implant may be "empty", some patients may still not experience a recurrence. As the number of patients that this applies to is low, the fitted model predicts very wide confidence intervals and it is acknowledged that there is an uncertainty present in this period immediately after 36 months. The observed data does show that at the end of the defined trial period of 36 months, a proportion of patients have not experienced the event that the trial is powered to find and so it was not considered appropriate to assume that at 36 months, there was no treatment effect at all.

[redacted]

Figure 8. [redacted]

a. Please provide a scenario analysis in which no treatment effect is assumed after 3 years. Inform this transition probability based on literature or assume that all patients transition to the 'subsequent therapy' health state after 3 years.

Given the uncertainty described above, results are shown below where it is assumed that there is no treatment effect after 3 years. It is not possible to make any other assumption as there is no literature or observed data to support this assumption. Additionally, the observed data shows events after the defined 36-month trial period, indicating that while the implant may not be "active" after 3 years, patients may not experience a recurrence immediately.

A scenario is included where all patients move to subsequent therapy after 3 years and results are shown in Table 30.

Table 30. Scenario: No treatment effect after 3 years in Iluvien implant

Outcome	Iluvien	(L)CP	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£13,136.79	[redacted]

B8. Priority question: The parametric time-to-event models are fitted to the fluocinolone acetonide treatment arm only from 120 days onwards because a sudden 'drop' was identified (between 60 and 120 days of follow-up) in the Kaplan-

Meier curve representing the recurrence-free probability in the fluocinolone acetonide treatment arm.

a. Please justify whether a drop at this time point and of this magnitude would be expected in UK daily clinical practice in patients treated with fluocinolone acetonide inserts.

In the Company Submission, it is speculated that the drop may be due to clinicians erring on the side of caution. The steep drop is around the time at which intervals between visits increase threefold; clinicians may not wish for some patients to wait another three months before being seen if they are concerned that the disease could progress inside that time interval. As such, advice may be given to switch to an alternative therapy, under which patients would be classified as a recurrence. Therefore, such a drop may be attributed to the design of the trial.

b. Please justify why in UK clinical practice such a drop in recurrence-free probability would not be expected in the (L)CP treatment arm.

It is possible that the drop was present in the (L)CP arm but because over [redacted] of patients experience a recurrence before 180 days it was not as pronounced. Between 90 and 120 days the probability of recurrence increases from [redacted] to [redacted] in the (L)CP arm. However, between 30 and 60 days the probability of recurrence increases from [redacted] to [redacted] meaning that this drop would not necessarily be considered a change in the hazard to patients. In contrast, before and after 60 to 120 days the probability of recurrence changes fairly gradually every 30 days. Between 90 and 120 days however, the probability of recurrence increases from [redacted] to [redacted] indicating a substantial change in the hazard. This was the reason it is not appropriate to consider the same types of distribution and statistical methods to represent the time to first recurrence for (L)CP and ILUVIEN.

c. Please provide a clinical rationale for the use of different distributions and approaches (piecewise modelling for the fluocinolone acetonide arm and standard parametric time-to-event model for the (L)CP arm) to estimate the time to recurrence in the fluocinolone acetonide and (L)CP arms.

Bagust and Beale 2014 highlight why it may be appropriate to use different distributions and modelling approaches for arms in the same trial (Bagust and Beale

2014). The paper advises that after examining the hazards in each arm (shown in B9.a), if there is evidence of changing risk profiles over time, fitting a continuous model from the start of the observed time may give trajectories that are not reliable. Instead they recommend focussing on the latter portion of the curves where there is a more linear trend. For the ILUVIEN arm, this is after 120 days and so it is appropriate to fit a continuous estimate from this point. Conversely, the (L)CP arm shows a more consistent hazard across time.

In summary, each of the survival profiles for ILUVIEN and the (L)CP arm observe fundamentally different hazard profiles, justifying the use of different survival distributions.

B9. Priority question: The methods to estimate treatment effectiveness (time to recurrence) in the company cost effectiveness model are not in line with the NICE DSU TSD 14. Please follow the NICE DSU TSD 14 for the selection of the most appropriate parametric time-to-event models, as described in the following points:

a. Investigate whether the proportional hazard assumption holds between the intervention and comparator (e.g. by means of log cumulative hazard plots).

[redacted]Figure 9 shows the log plot for time to first recurrence in both arms in PSV-FAI-001. This shows that the proportional hazards assumption does not hold; the lines are divergent over time. This plot also shows that the hazard changes for the ILUVIEN arm at approximately 90 days. After 120 days it appears to take on another profile and become more stable after this time.

Bagust and Beale describe why the advice detailed in NICE DSU TSD14 may not always be appropriate for robust analysis of data (Bagust and Beale 2014; Latimer 2013). The reasons detailed (and described in response to question B8.c) are why it was considered appropriate to use a piecewise method of modelling for the ILUVIEN arm.

[redacted]Figure 9. [redacted]

b. Based on the response to B9a, please use either stratified or non-stratified models, and provide goodness of fit statistics of each fitted distribution.

The models and approach presented in the company submission are considered appropriate given the response to B9.a. Goodness of fit statistics are shown in Table 27 for ILUVIEN (fit from 120 days) and Figure 10 and Figure 11 for the models considered for ILUVIEN from the start for (L)CP. These were done using the patient level data.

c. Validate the extrapolation of the best fitting curves against external data or expert opinion (please provide the methods and results of the expert opinion elicitation).

It was not possible in the time frame for a clinician to validate the curve fits and external data, as previously stated, is not available.

d. Select the most appropriate distribution based on these assessments. Select the same distribution for both treatment arms.

    i. Or, provide a clinical explanation to justify the use of different distributions in each treatment arm (if necessary).

Bagust and Beale describe that it is generally considered unwise to apply a joint model to a clinical trial with two or more treatment arms where the treatments utilise different mechanisms of action, which is the case with PSV-FAI-001(Bagust and Beale 2014). In trials where this is the case, there will often be different patterns of event hazard over time, which is shown in the response to question B9.a. The paper also advises that the presumption should be against joint modelling unless independent modelling reveals that the functional forms and parameters estimates are closely aligned which they are not. The parameters used in the base case can be seen in Table 27 and Table 28 and demonstrate this.

The fit statistics shown in Table 27 and Figure 6and Figure 7 for ILUVIEN and (L)CP, respectively. These were used in conjunction with visual assessment to judge which were the most appropriate distributions to represent each arm. These were used in the base case analysis.

e. Explore the use of spline models (maximum of 2 knots) to estimate time to recurrence if the standard parametric time-to-event models are not considered to be sufficiently flexible (and justify why this is the case).

The use of a spline model would be inappropriate to estimate the time to first recurrence as these should not be routinely used for extrapolation. Spline models are appropriate for describing internal data but where extrapolation is required, they are not generally considered correct. A piecewise model mechanistically describes the process that forms the extrapolated portion of the curve and is therefore more appropriate where extrapolation is required. Spline models only consider up to and including the last observation value meaning that they are of limited use for predictions beyond the trial period.

B10. Priority question: The parametric time-to-event models are not fitted from the start of the follow-up and a clear clinical rationale for the use of a piecewise model in the fluocinolone acetonide treatment arm is not provided.

a. Please provide scenario analyses in which parametric time-to-event models are fitted from the start of the follow-up for the fluocinolone acetonide treatment arm.

Error! Reference source not found. shows the curves fit to the patient level data for the ILUVIEN arm from the start of the observed period. These models were not considered a good fit to the data with some providing survival estimations outside the confidence intervals. Additionally, when considering the hazard profiles (shown in Figure 9) it is not appropriate to consider a continuous model for the entire observed time. These models were therefore not used in the base case analysis. However, these have been incorporated into the model and results when these are used are shown in Table 32 to Table 39. These analyses assume the base case (L)CP distribution is used (Log logistic). The parameters used are shown in Table 31.

Table 31. Deterministic parameters for models fit to ILUVIEN arm from day 0 (not used in base case)

Deterministic Curve parameters : Iluvien (all ITT population)				
Dist Name	**Lambda/Shape/Mu**	**Scale/Sigma/Rate**	**Q**	**P**
Exponential	[redacted]			

Weibull	[redacted]	[redacted]		
LogLogistic	[redacted]	[redacted]		
LogNormal	[redacted]	[redacted]		
Gamma	[redacted]	[redacted]		
Gompertz	[redacted]	[redacted]		
Generalised Gamma	[redacted]	[redacted]	[redacted]	
Generalised F	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Table 32. Results - Iluvien efficacy fit from day 0, LogNormal

Outcome	Iluvien	(L)CP	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	-£3,629.60	[redacted]

Table 33:Results - Iluvien efficacy fit from day 0, LogLogistic

Outcome	Iluvien	(L)CP	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	-£3,510.87	[redacted]

Table 34: Results - Iluvien efficacy fit from day 0, Gompertz

Outcome	Iluvien	(L)CP	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	-£9,209.43	[redacted]

Table 35: Results - Iluvien efficacy fit from day 0, Gamma

Outcome	Iluvien	(L)CP	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£962.98	[redacted]

Table 36: Results - Iluvien efficacy fit from day 0, Generalised Gamma

Outcome	Iluvien	(L)CP	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	-£4,134.05	[redacted]

Table 37. Results - ILUVIEN efficacy fit from day 0, Weibull

Outcome	Iluvien	(L)CP	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£22.47	[redacted]

Table 38: Results - Iluvien efficacy fit from day 0, Exponential

Outcome	Iluvien	(L)CP	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£3,041.58	[redacted]

Table 39: Results - Iluvien efficacy fit from day 0, Generalised F

Outcome	Iluvien	(L)CP	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	-£4,133.88	[redacted]

b. Please select the most appropriate parametric time-to-event models based on the steps described in the preceding question (B9).

Fitting from day 0 was not considered appropriate because of the change in hazards around day 120 of the observed period as discussed. However, the models were fit and results shown in response to B10.a. Of these, the Log Normal curve was considered to show the best fit. The fit statistics can be seen for AIC and BIC in Figure 10 and Figure 11 respectively. As can be seen in **Error! Reference source not found.**, even this curve does not fit the data especially well, particularly between 60 and 120 days which is where the hazard changes.

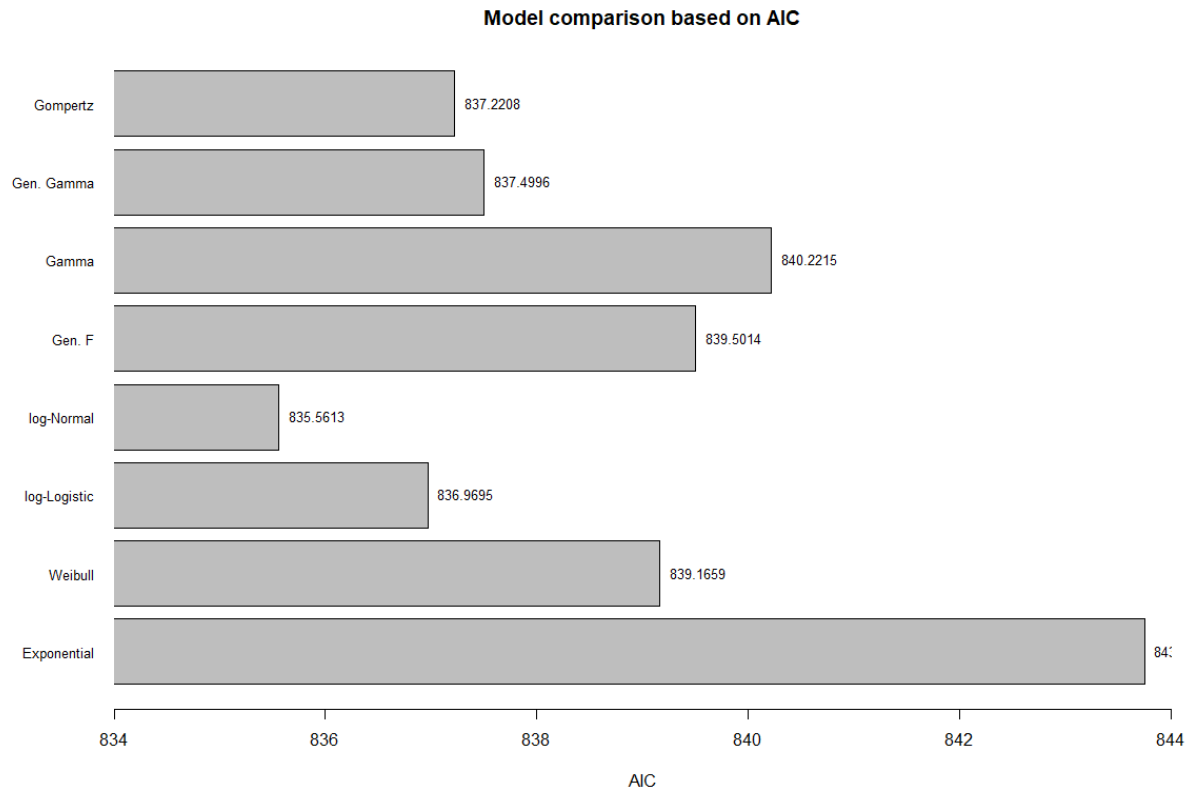


Figure 10: AIC for Iluvein curves fit from day 0 (not used in base case)

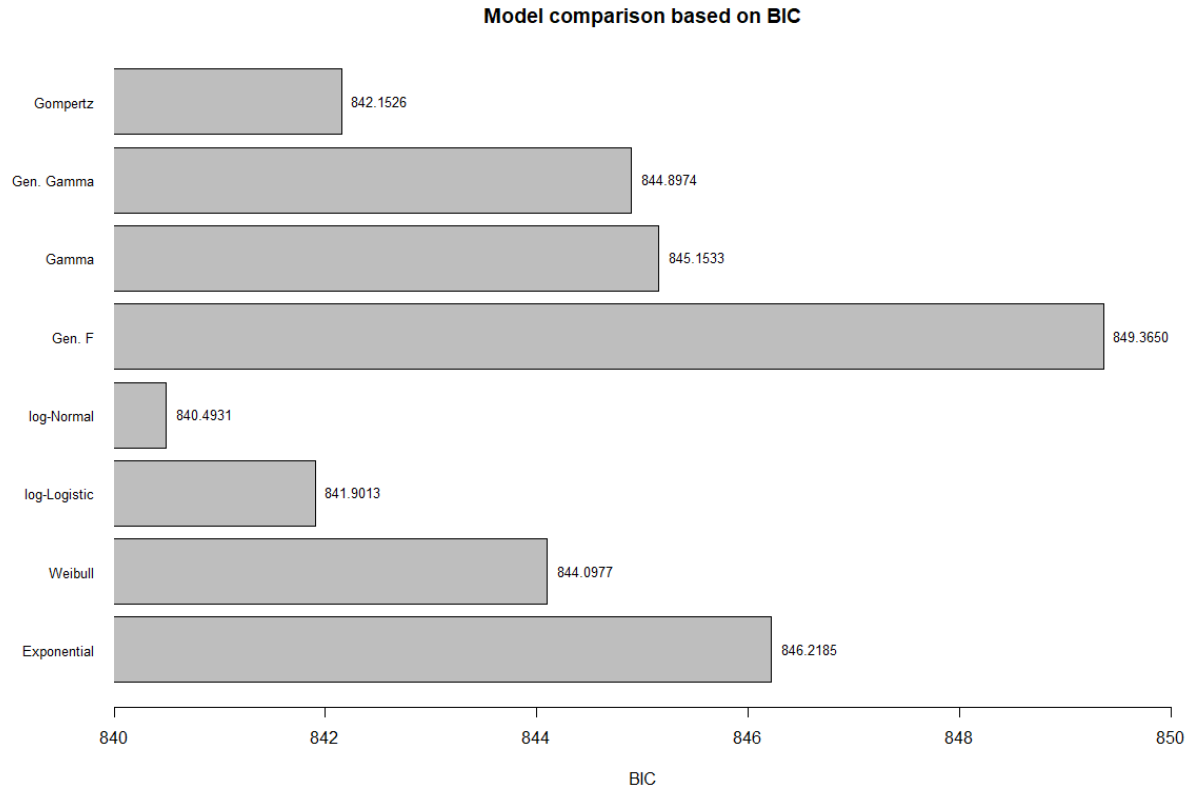


Figure 11: BIC for Iluvein curves fit from day 0 (not used in base case)

Adverse Events

B11. Are there any adverse events that could be caused by the implant device and not by the active substance of the implant?

a. If yes, please include these adverse events in all health states of the model for the duration that patients have an implant.

The FAc "ILUVIEN" implant is a product combining the implant device and drug (fluocinolone acetonide). When adverse events are recorded, these not separated into being caused by the active substance or the delivery vehicle (implant). However, as described in the response to question A35, the implant is designed to remain in the eye after the drug is eluted and its technology means there is only a very small risk of intra-ocular issues.

B12. Adverse events of treatments administered in the 'subsequent therapy' health state are not taken into account.

a. Please provide a scenario analysis in which the costs and quality of life consequences of these treatments are incorporated.

In subsequent therapy, the same costs and disutilities would be expected regardless of first line treatment as treatment is the same for both arms. Therefore, the driving factor for any difference in lifetime cost or utility from this health state is the time it takes a patient to move there from first line therapy. As the model and informing data estimates that the time to subsequent therapy initiation is considerably greater for patients who initiate on ILUVIEN compared to (L)CP, the decision to omit costs and disutilities related to AEs in subsequent therapy is considered to be highly conservative, in favour of (L)CP.

For ILUVIEN to not be considered cost-effective (at a willingness-to-pay threshold of £20,000/QALY) under base case assumptions, patients in the ILUVIEN arm would need to incur an additional [redacted] worth of AEs. Alternatively, the incidence of AEs in the ILUVIEN arm would need to accrue a total per-patient reduction in QALYs of [redacted] before cost-effectiveness is not achieved. As introduction of any costs or disutilities related to AEs in subsequent therapy would only increase the incremental

QALYs and reduce the incremental cost between ILUVIEN and (L)CP, this would not change the decision as to whether ILUVIEN were cost-effective compared to (L)CP.

Quality of Life

B13. The submission states that the impact on quality of life of adverse events is not included in the cost-effectiveness model because it would incur double counting (page 118). However, the cost-effectiveness model does not contain treatment-dependent health state utility values.

a. Please incorporate utility decrements for adverse events in both treatment arms.

Table 12-6 of the 36 months CSR shows the total number of severe TEAEs was [redacted] in the ILUVIEN arm and [redacted] in the (L)CP arm. For moderate TEAEs these numbers are [redacted] and [redacted] respectively. The definitions from the CSP for PSV-FAI-001 are shown below (Section 11.2.2):

- Moderate AEs : “Discomfort enough to cause some interference with usual activity. Traditionally introduces a low level of inconvenience or concern to the subject and may interfere with daily activities but are usually relieved by simple therapeutic measures.”
- Severe AEs: “Causes an interruption of the subject’s usual daily activity and traditionally requires systemic drug therapy or other treatment.”

For ILUVIEN to be not cost-effective under base case assumptions, [redacted] QALYs over the lifetime of a patient in the ILUVIEN arm would be required if costs were assumed the same with no change to the utilities or costs in the (L)CP arm. While there are [redacted] additional incidences of moderate TEAEs in the ILUVIEN arm, these are unlikely to incur any notable disutility by their definition. In contrast, there are [redacted] additional incidences of severe TEAEs in the (L)CP arm which are likely to incur a disutility. Therefore, the omission of these disutilities in the base case is likely to be a conservative estimate and not favour ILUVIEN.

Table 12-6 of the 36-month CSR shows treatment emergent ocular AEs in the study eye by severity, greater than 5% in either treatment group. This table shows that the only severe AEs listed for ILUVIEN is [redacted]

Given the reduction in QALYs that would be required to result in ILUVIEN not being considered cost-effective, incorporating disutilities for severe AEs is not likely to change the decision as to whether ILUVIEN is considered cost-effective compared to (L)CP.

B14. The model assumes that there is an immediate benefit of treatment because it does not include a baseline utility value but an 'on treatment' utility value that is directly applied at model entry.

a. Please justify this assumption.

ILUVIEN is designed to prevent recurrence of non-infectious uveitis of the posterior segment. As this is a preventive medication, rather than a treatment for active disease, it is believed that patients 'on treatment' utility is representative of their baseline utility.

Further, there is no apparent delay in treatment effect, with a relatively constant hazard over the first 90 days of treatment. Until approximately 90 days, the rate at which the probability of experiencing a recurrence changes, does not appear to be different in each of the 30 days intervals prior to this point. Therefore, there is no reason to believe that the time to effect is more than 30 days. As there is no evidence to support an assumption for the time to effect of ILUVIEN there was not perceived to be any benefit in adding a baseline utility value for an initial period within the model.

In addition, little evidence was identified to inform an appropriate baseline utility.

B15. There is uncertainty concerning the representativeness of the health state utility values for the population included in the current assessment.

a. Patients in the ‘remission’ health state are assumed to have the same utility value as the general population. However, patients with uveitis may have bilateral disease, and have an increased risk for auto-immune diseases. In addition, patients may still receive treatment since uveitis is a chronic disease, and they may experience adverse events of the active substance in the implant and/or the implant.

    i. Please provide evidence that patients in the ‘remission’ health state have the same health-related quality of life as the general population (and therefore higher utility values than when on treatment).

It is acknowledged that patients may be experiencing bilateral disease, auto-immune diseases or adverse events. However, the model aims to describe only the ocular disease in the study eye. Additionally, if the bilateral disease, auto-immune disease or any adverse events required treatment with systemic steroids or immunosuppressants, recurrence would be imputed, and the patient would move to subsequent therapy as this is a stipulation of the trial which is represented in the model.

The assumption that a patient in “remission” from ocular disease in the study would be akin to that of the general population was validated by a clinician. The clinician advised that where the ocular disease was in remission, the patient would only be required to see their consultant every 12 weeks with no testing that would cause discomfort, and this was not expected to impact HRQoL substantially for most patients.

b. Please justify the choice of the utility estimate for the ‘blindness’ health state, since this utility value was obtained from a population with age-related macular degeneration.

   i. Please demonstrate that the population in which the utility value has been elicited is representative of the population included in the current assessment.

The value used in the base case analysis to represent the utility associated with permanent blindness was estimated from a population of healthy volunteers (Czoski-Murray et al. 2009). The study reports that “ The majority of participants had excellent vision, as best-corrected VA was measured”. These volunteers were then asked to wear contact lenses that aimed to replicate three severities of blindness which represented (on LogMAR score scale):

- Reading limit (0.6 (20/80))
- Legal Blindness (1.0 (20/200))
- State to which patients with untreated ARMD deteriorate (1.4 (20/500))

In TA460, the AG report that they used a “weighted average based on the number of patients within the studies falling into each category”. They also report that they did this as it follows the assumption that patients with uveitis would have a similar distribution in the different levels of blindness. This assumption is followed in the Company Submission for ILUVIEN also.

It is noted by the AG for TA460 that the study used in the base case did not provide values for what was considered the worst state of blindness. This may result in an underestimate of the overall utility associated with permanent blindness. However, the methods used to elicit values (public valuations with the TTO method) were considered the most appropriate.

B16. Please demonstrate that the mapping algorithm for utility values obtained from the HURON trial is applicable to the population of the MUST trial.

The Assessment Group for TA460 were unable to find a suitable mapping study that was based on a uveitis population. As they had access to patient level data, they

were able to construct a mapping algorithm that described the relationship between visual acuity and HRQoL in a uveitis population (from the HURON trial).

This mapping algorithm is therefore assumed the most appropriate to the population in the MUST trial as while the study populations are not identical, they both describe the same indication. The AG also used the mapping within exploratory analyses comparing the interventions with current practice as provided in the MUST trial.

Costs and Resource Use

B17. The supplemental treatment costs in the 'on treatment' health state are different between the treatment arms.

a. Please justify why these costs are different between the treatment arms.

The model reflects the PSV-FAI-001 trial and therefore costs were assigned as they were incurred in the trial. In the trial, treatments were used in different proportions in each arm and this results in a different cost being applied.

b. Please provide a scenario analysis in which these costs are assumed to be equal across treatment arms.

A scenario was included where the supplemental treatments were the same between arms. The results can be seen below in Table 40. In this scenario, the costs for both arms are assumed as reported for the ILUVIEN arm, £96.49.

Table 40. Scenario: supplemental treatment costs assumed equal between arms

Outcome	ILUVIEN	(L)CP	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£1,500.40	[redacted]

B18. The assumptions underlying the 'subsequent therapy' transition costs are not clearly described in the submission.

a. Please justify why it is necessary to apply transition costs to the transition from 'on treatment' to 'subsequent therapy' health state in the fluocinolone acetonide arm and not in the (L)CP arm.

These were calculated in the model and discussed in the Company Submission however, the omission was a modelling error. This has been rectified and all base case results presented in this document include the transition cost in the (L)CP arm so that the approach is as the Iluvien arm.

b. Please provide the proportion of patients receiving each treatment upon transition to the 'subsequent therapy' health state for each treatment arm, and provide the costs that are applied when patients transition to the 'subsequent therapy' health state for each treatment arm.

The treatments used upon transition to subsequent therapy are shown in table 28 of the Company Submission. The costs applied are shown in table 44 of the Company Submission . These are shown together in Table 41 below. The total cost applied to the proportion making the transition is £0.77 and £1.75 for Iluvien and (L)CP respectively.

Table 41: Treatments given upon transition to the 'subsequent therapy' health state

Iluvien upon reccurrence medications	Iluvien	(L)CP	Iluvien Cost	(L)CP Cost
Bromfenac sodium	[redacted]	[redacted]	£0.08	£0.06
Dexamethasone	[redacted]	[redacted]	£0.18	£0.42
Nepfenac	[redacted]	[redacted]	£0.24	£0.00
Prednisolone acetate	[redacted]	[redacted]	£0.07	£0.14
Difluprednate	[redacted]	[redacted]	£0.08	£0.21
Triamcinolone acetonide	[redacted]	[redacted]	£0.08	£0.21
Corticosteroids	[redacted]	[redacted]	£0.00	£0.00
Cyclopentolate Hydrochloride	[redacted]	[redacted]	£0.00	£0.38
Lidocaine	[redacted]	[redacted]	£0.00	£0.00

Povidine-Iodine	[redacted]	[redacted]	£0.02	£0.08
Triamcinolone	[redacted]	[redacted]	£0.03	£0.26
Total			£0.77	£1.75

B19. The assumptions underlying the 'subsequent therapy' health state costs are not clearly described in the company submission.

a. Please provide the proportion of patients receiving each treatment in the 'subsequent treatment' health state for each treatment arm. Please provide the source on which this proportion is based.

The proportion who are receiving each of the subsequent therapies is shown in table 44 of the Company Submission. The costs assigned for each treatment are shown in table 42 of the Company Submission and these are shown together in Table 42 below. These costs are multiplied by the proportion receiving the therapy as shown in the table below and are then applied cyclically to patients in subsequent therapy.

The proportion taking the immunosuppressants and systemic prednisolone in subsequent therapy is assumed to be as reported for TA460. These proportions are reweighted so that they total 100% and all patients in subsequent therapy are taking some treatment in subsequent therapy which are shown in Table 25. The 36 months CSR for PSV-FAI-001 states the proportion of patients taking corticosteroids and immunosuppressants subsequent to treatment and so these costs are multiplied by 31% and 19% respectively so as to model the trial as closely as feasible.

Table 42: Proportion of patients receiving each treatment in the 'subsequent treatment' health state for each treatment arm

	Reported proportion (TA460)	Weighted proportion	Cyclical cost of drug	Cost
Mycophenolate mofetil	21%	33%	£3.66	£1.22
Methotrexate	31%	50%	£1.43	£0.71
Cyclosporine	7%	11%	£88.34	£9.85
Azathioprine	3%	5%	£0.87	£0.05
Proportion taking immunosuppressants	19%			

Proportion taking corticosteroids	[redacted]			
Total cost of immunosuppressants	£2.29			
Total cost of corticosteroids	[redacted]			
Total cyclical cost of subsequent therapy	£2.45			

B20. The model does not incorporate blood test costs for patients receiving immunosuppressant drugs in the 'subsequent therapy' health state, although these costs were incorporated in TA460.

a. Please justify this assumption.

The health state cost that is applied to the subsequent therapy health state is applied every 6 weeks (as in TA460) and this cost reflects an outpatient appointment where it is assumed that a blood test would be conducted if required although not explicitly costed. This is applied to all patients regardless of which treatment they were taking initially. Patients taking ILUVIEN would be expected to require less treatment from subsequent therapy and therefore would avoid this cost burden more so than those on (L)CP. This assumption has been validated by a clinician. Therefore, the omission is considered not to be favourable to ILUVIEN.

b. Please provide a scenario analysis in which blood test costs are incorporated.

The cost of a blood test was sourced from NHS Reference Costs 2014-2016, DAPS - integrated blood service (DAPS03). This is assumed to be applied when patients go to a monitoring appointment, in the base case every 6 weeks. The results of this scenario are shown in Table 43:

Table 43. Scenario: Blood test costs considered in Subsequent Treatment

Outcome	ILUVIEN	(L)CP	Δ	ICER	NMB
Life Years	[redacted]	[redacted]	[redacted]	-	[redacted]
Time On Treatment	[redacted]	[redacted]	[redacted]	-	[redacted]
QALYs	[redacted]	[redacted]	[redacted]	-	[redacted]
Costs	[redacted]	[redacted]	[redacted]	£967.14	[redacted]

B21. There is uncertainty concerning the representativeness of the cost estimates used in the 'blindness' health state and the implementation of these costs in the cost effectiveness model.

a. Please justify that the costs used in the base-case analysis, based on an age-related macular degeneration population, are representative of the population included in the current assessment.

The costs used were sourced from TA460 where they considered that this best represented the cost of blindness for patients with uveitis. The costs were calculated from an age-related macular degeneration population however these costs are not considered to differ largely where the underlying cause of the blindness is a similar disease and the outcome (permanent blindness) is the same.

b. In the calculation of the costs of blindness, residential care costs are included in the one-off costs applied on the transition to the 'blindness' health state, which is different to TA460. These costs are expected to be recurrent over time and hence incorporated in the health state costs associated with blindness.

i. Please justify the deviation from TA460.

This was an error and it should have been assigned to the recurring cost not the one-off cost. This has been corrected and all references to the base case in this document now include this correction.

ii. Please perform a sensitivity analysis with the costs of blindness modelled as in TA460.

This now forms part of the base case and all base case references in this document include this correction.

Subgroup Analyses

B22. Please provide the following subgroup analyses, as listed in the final scope:

a. Types of uveitis (acute or chronic; single incident or recurrent; posterior segment, posterior, intermediate or pan uveitis)

All patients included in the PSV-FAI-001 trial had [redacted], defined as stated in the company submission, page 34:

- During the 12 months prior to enrolment (Day 1), the study eye had either received treatment:
    - systemic corticosteroid or other systemic therapies given for at least 3 months, and/or
    - at least 2 intra- or peri-ocular injections of corticosteroid for management of uveitis
- OR the study eye had experienced recurrence:
    - at least 2 separate recurrences of uveitis requiring systemic, intra- or peri-ocular injection of corticosteroid

Please see responses to question A9 for discussion on persistent vs recurrent uveitis. As for anatomical location of uveitis, the requested subgroup data was not collected in the PSV-FAI-001 study (please see response to question A13

Further, given the likely small number of patients within each requested subgroup per treatment arm, any relevant subgroup analysis would be difficult and potentially misleading. When interviewed on a related issue (see response to question A14), Mr Carlos Pavesio (M.D. Consultant Ophthalmic Surgeon, Moorfields Eye Hospital, London) mentioned that a similar issue of small patient subgroups samples was encountered in HURON and VISUAL trials and only emergence of real-world data with wider patient exposure can allow clinicians to gauge effectiveness in different patient subgroups. Therefore, the Sponsor feels that providing subgroup analyses would be extremely speculative as they would be difficult to validate.

b. Baseline visual acuity

See response to B22a.

c. Previous treatment history

See response to B22a.

Validation and Transparency

B23. In multiple sections of the submission, the company refers to clinical expert opinion, for instance to justify that patients with an implant require less frequent monitoring visits than patients receiving systemic treatment and to validate the 'remission' health state utility value. Additionally, a clinical advisory board was held in October 2018 to validate the model structure and assumptions.

a. Please provide details on the number of experts interviewed, the questions asked to the experts and their answers for each model input and assumption that were obtained/validated by experts. Please provide this information for both the personal communication with experts and the advisory board

Two clinical experts, Mr Fahd Quhill, M.D. Consultant Ophthalmic Surgeon, Royal Hallamshire Hospital, Sheffield , UK and Mr Carlos Pavesio, M.D. Consultant Ophthalmic Surgeon, Moorfields Eye Hospital, London primarily provided advice supporting the submission. They were interviewed in an unstructured manner at multiple time points in person, on the phone and via email. This communication was held over a considerable time period and was unstructured, so that a complete list of questions and answers would be impossible to provide.

In addition, a European advisory board was held in Vienna in September 2018 and meetings were held to discuss the output of PSV-FAI-001 by the Company.

B24. Please provide a cross validation of the company cost-effectiveness model inputs (assumptions, transition probabilities, and health state utility values and costs) and outputs (life years, quality-adjusted life years and costs) with TA460 and the other cost effectiveness analyses identified in the company's systematic literature review.

Section 3.10 of the Company Submission details the efforts made to validate the cost-effectiveness analysis, outcomes and clinical parameters informing the model. In summary, the clinical inputs can only realistically be validated against the informing trial data as there are no other trials or literature which describe the efficacy of ILUVIEN and (L)CP within [redacted] specifically. Since the PSV-FAI-001 pivotal trial focuses on patients with recurrent or persistent [redacted], this population is

very likely to be reflected in the marketing authorisation for the FAc 190 µg intravitreal implant and, consequently, in the NICE recommendation. Therefore, any other studies would be of limited relevance for validating the model.

The modelled estimates of efficacy inputs match the observed data well. Additionally, the relevance of model structure and assumptions were validated by a clinician and many of the assumptions are in line with those presented in TA460.

The transition probability calculations were validated by using data presented in TA460 for dexamethasone vs (L)CP. These were used to calculate LYs and QALYs and were compared to reported results. The comparisons are presented in section 3.10.2 of the Company Submission in more detail. It was not possible to replicate costs in the dexamethasone analysis in the company model due to some perceived ambiguity in the reporting of costs. Supplemental therapy for dexamethasone was reported as being sourced from a publication; however, these values were not available in the listed publication. It was not considered completely clear how these costs were applied in subsequent therapy either.

Due to limited data, it is challenging to validate the utilities that are assigned to the On Treatment and Subsequent Treatment health states. Additionally, while the initial utilities were reported in Squires et al. (the publication of the SLR and model relating to TA460 (Squires et al. 2017)), the change over time was not as these were driven by changes in VFQ-25 calculated from patient level data which were not shown. Therefore, it is difficult to quantify the difference in utility that occurs with treatment.

The other studies found in the company's systematic literature review reported costs that were not from a UK setting and so it was difficult to compare the cost inputs with either TA460 or the company cost-effectiveness model. Health states were not reported in the papers found other than the Squires et al. publication (Squires et al. 2017) and while Sugar et al. report using utilities from the MUST trial, they do not detail what these are (Sugar et al. 2014).

Model Implementation

B25. Gridlines and headings are masked in the cost-effectiveness model. Please provide a cost effectiveness model in which gridlines and headings are visible.

The model submitted in response to clarification questions has gridlines and headings visible.

B26. In the cost-effectiveness model, the formula in column 'BR' of the 'Outcome Trace'-tab, which aims at calculating the cost of blindness for the (L)CP arm, refers to column 'AR', which is empty. Please amend the cost effectiveness model if necessary.

This was an error and it should have been referring to the cycle (as does the respective formula in the Iluvien arm). This has now been corrected and forms part of the base case. All references to the base case now include this correction.

B27. Priority question: The parameters of all parametric time-to-event models are not provided in the submission or in the cost-effectiveness model. Additionally, the gamma distribution is not implemented for the (L)CP arm.

a. Please provide the deterministic parameters, the covariance matrix and the Cholesky decomposition of the parameters of all fitted parametric time-to-event models included in the cost-effectiveness model and also from the fitted parametric time-to-event models requested in question B10 (i.e. models fitted from the start of follow-up). Please use this information to incorporate all time-to-event models probabilistically in the cost effectiveness model.

In the base case model, all efficacy curves describing time to the event models are available for probabilistic analysis. The parameters for the base case ILUVIEN and (L)CP curves used in the base case can be seen in Table 27 and Table 28. respectively. Additionally, the parameters used in response to question B10 are shown in Table 31.

In the base case, the time to event estimates for ILUVIEN were generated from a bootstrap method and all curves are varied between the upper and lower 95% CI values assuming semi-normality with a log transformation. This was necessary because the initial 120 days of the efficacy was not varied and informed from KM

data directly and so estimates after this time use the parameters reported but are rescaled. The central, lower, upper CI values and rescaling were output from analysis in R as described in section 3.3.1.1 of the Company Submission. The log transformation calculations are shown in the Curve fits tab of the cost-effectiveness model.

The parameters and covariance matrices are shown in the Curve fits tab of the cost-effectiveness model. The covariance matrices are used in the model to generate probabilistic estimates of efficacy are shown in Table 44 to Table 59 for the (L)CP curve. As described above, the covariance matrices are not used to calculate efficacy probabilistically for the ILUVIEN arm; this is done with a log transformation assuming semi normality.

(L)CP

Table 44: Exponential covariance matrix for (L)CP curve fit

	rate
rate	[redacted]

Table 45: Weibull covariance matrix for (L)CP curve fit

	shape	scale
shape	[redacted]	[redacted]
scale	[redacted]	[redacted]

Table 46: Log logistic covariance matrix for (L)CP curve fit

	shape	scale
shape	[redacted]	[redacted]
scale	[redacted]	[redacted]

Table 47: Log Normal covariance matrix for (L)CP curve fit

	meanlog	sdlog
meanlog	[redacted]	[redacted]
sdlog	[redacted]	[redacted]

Table 48: Generalised F covariance matrix for (L)CP curve fit

	mu	sigma	Q	P
mu	[redacted]	[redacted]	[redacted]	[redacted]
sigma	[redacted]	[redacted]	[redacted]	[redacted]
Q	[redacted]	[redacted]	[redacted]	[redacted]
P	[redacted]	[redacted]	[redacted]	[redacted]

Table 49: Gamma covariance matrix for (L)CP curve fit

	shape	rate
shape	[redacted]	[redacted]
rate	[redacted]	[redacted]

Table 50: Generalised Gamma covariance matrix for (L)CP curve fit

	mu	sigma	Q
mu	[redacted]	[redacted]	[redacted]
sigma	[redacted]	[redacted]	[redacted]

Q	[redacted]	[redacted]	[redacted]

Table 51: Gompertz covariance matrix for (L)CP curve fit

	shape	rate
shape	[redacted]	[redacted]
rate	[redacted]	[redacted]

Iluvien: fits from day 0

Table 52: Exponential covariance matrix for Iluvien curve fit from day 0 (Not used in base case)

	rate
rate	[redacted]

Table 53: Weibull covariance matrix for Iluvien curve fit from day 0 (Not used in base case)

	shape	scale
shape	[redacted]	[redacted]
scale	[redacted]	[redacted]

Table 54: Log Logistic covariance matrix for Iluvien curve fit from day 0 (Not used in base case)

	shape	scale
shape	[redacted]	[redacted]
scale	[redacted]	[redacted]

Table 55: Log Normal covariance matrix for Iluvien curve fit from day 0 (Not used in base case)

	meanlog	sdlog
meanlog	[redacted]	[redacted]
sdlog	[redacted]	[redacted]

Table 56: Generalised F covariance matrix for Iluvien curve fit from day 0 (Not used in base case)

	mu	sigma	Q	P
mu	[redacted]	[redacted]	[redacted]	[redacted]
sigma	[redacted]	[redacted]	[redacted]	[redacted]
Q	[redacted]	[redacted]	[redacted]	[redacted]
P	[redacted]	[redacted]	[redacted]	[redacted]

Table 57: Gamma covariance matrix for Iluvien curve fit from day 0 (Not used in base case)

	shape	rate
shape	[redacted]	[redacted]
rate	[redacted]	[redacted]

Table 58: Generalised Gamma covariance matrix for Iluvien curve fit from day 0 (Not used in base case)

	mu	sigma	Q

mu	[redacted]	[redacted]	[redacted]
sigma	[redacted]	[redacted]	[redacted]
Q	[redacted]	[redacted]	[redacted]

Table 59: Weibull covariance matrix for Iluvien curve fit from day 0 (Not used in base case)

	shape	rate
shape	[redacted]	[redacted]
rate	[redacted]	[redacted]

B28. The probabilistic sensitivity analysis (PSA) is not performed according to good modelling practice.

a. A 10% standard error (SE) is assumed for many of the parameters included in the PSA. Please estimate the SE based on empirical evidence, or retrieve the SE from the literature, when possible (e.g. for the incidence of adverse event, the distribution of supplemental and subsequent treatments, health state utility values).

Where possible, these have been calculated from the CSR and an option is included to use these.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

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

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Birdshot Uveitis Society.
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Birdshot Uveitis Society (BUS) is a small charity and support group for people with the rare, hard to treat autoimmune chronic posterior uveitis called birdshot chorioretinopathy or birdshot uveitis. BUS was founded in 2009 by two patients who both have birdshot. It was granted charitable status in 2012. It depends on donations and fundraising by its members. BUS received a one-off, no strings attached donation of £10,000 in late 2016 from AbbVie which we have put towards running 'Birdshot Days' (see answer to question 5 below). BUS is run by unpaid volunteers who either have birdshot or who have a family member with it. There are over 680 people registered with BUS. Membership is worldwide, but primarily from the UK. As well as people with birdshot, membership includes healthcare professionals and others with an interest in birdshot. BUS has set up a National Birdshot Research Network. Working with this network, BUS has helped to establish a National Birdshot Database and Bio-resource Centre in Birmingham to provide a foundation for future birdshot research.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None.
5. How did you gather information about the experiences of patients and	• Through continuing regular contact with BUS members through our website. • From our Birdshot Uveitis Society (International) Facebook group of over 1000 members. • From 'Birdshot Days' held for learning and information exchange between birdshot uveitis patients

carers to include in your submission?	and healthcare professionals who treat birdshot uveitis. • From a specific request to members to give their personal experiences of the technology being appraised by NICE, although this response is limited because the technology is not yet licensed for use in uveitis and is not available for NHS treatment of uveitis.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Birdshot uveitis is a bilateral, usually painless, progressive and potentially blinding autoimmune non-infectious form of posterior uveitis. The triggers for it are not fully understood. The initial symptoms are usually floaters and/or blurred vision caused by the presence of inflammatory cells in the vitreous. Other symptoms may include night blindness, impaired vision in low light, delayed light/dark adaptation, defective colour vision, sensitivity to bright lights or glare, a perception of flickering or flashing lights, fluctuating vision, decreased ability to perceive depth, shimmering vision, distorted images and decreased peripheral vision. These effects on vision affect, often profoundly, the ability of birdshot patients to perform many activities of daily living and to continue in work or education. Before being diagnosed with birdshot, patients have considerable anxieties over what is going wrong with their vision. Once diagnosed, other concerns include fear of the possibility of blindness, of not being able to continue to work or to drive, of not being able to see one's children grow up, and of losing one's independence. As a result, patients frequently suffer problems with depression and anxiety, often worsened by the considerable burden of side-effects from the commonly-prescribed medications used to treat birdshot. Currently used treatments are often not well tolerated. Some medications need to be taken at specific times in relation to meals, leading to a daily life governed by taking medication. Frequent clinic visits for treatment monitoring, blood tests and vision checks disrupt life and work for all birdshot patients and their families. Clinic vision checks usually require the eyes to be dilated for examination. This means that the patient cannot drive themselves to and from their appointments and may also need to be accompanied. After eye dilation, patients are likely not to be able to see well enough to resume work, necessitating

	taking the whole day off. Families, friends and employers often find it hard to understand that birdshot patients have a real problem with their sight. It is common for relatives to be in denial about birdshot because they simply do not appreciate the visual problems that patients experience. They also find it hard to understand that changes in behaviour may be more to do with medication taken for birdshot, particularly oral corticosteroids, than for any other reason.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Currently available NHS care for birdshot patients is usually provided in specialised uveitis clinics in tertiary hospitals. Diagnosis can be difficult. Because the condition is rare, there may be delays (years in some cases) in patients reaching specialist uveitis care, during which time their birdshot has continued to progress, adding to the difficulties of getting it under control. Current treatment principles for birdshot are to use high doses of corticosteroid (usually orally but sometimes by injection into the eye) to control the inflammation, then to introduce one or more oral or injectable immunosuppressants as second-line agents to modify the underlying immune dysfunction which is attacking the eye tissues. The oral corticosteroid dose is then slowly tapered with a view to stopping it. In practice, lowering the corticosteroid dose without inducing a disease 'flare' can be very difficult. Many patients have to remain on quite high maintenance corticosteroid doses. Long term use of high-dose oral corticosteroids causes numerous health problems. These include weight gain, fluid retention, osteoporosis and diabetes. Anger, irritability and depression are frequent complaints. Insomnia, restlessness, and unreasonable behaviour, plus tiredness and lack of concentration because of the insomnia, are so common as to be considered normal consequences of high-dose corticosteroids. Persistent stomach pain may require medication. Continued use of corticosteroids can lead to cataract development, which further worsens sight and necessitates lens replacement surgery. Raised intraocular pressure caused by corticosteroids requires daily eyedrops or oral treatments or possibly surgery.

	The immunosuppressants used with corticosteroids as second-line treatment for birdshot all have considerable side-effect profiles. The most common are stomach pain, nausea, vomiting and diarrhoea. Specific immunosuppressants can cause alterations to liver, kidney or bone marrow function, which may mean that treatment has to be stopped and another immunosuppressant tried. Raised blood pressure and raised cholesterol caused by certain immunosuppressants require more medication for control. Suppressing the immune system means that patients are more liable to pick up infections which may not develop as normal. Common immunosuppressant side-effects include fatigue, insomnia, depression, joint and muscle aches and pains, 'pins and needles', tremor, hair thinning, excess body hair, overgrowth of gum tissue and increased skin cancer risk. Plans to have a family may have to be put on hold because of taking medication. The cumulative impact of these side-effects is compounded by the frequent need for more than one immunosuppressant to be used, often alongside large doses of corticosteroids. The biologic adalimumab has recently been approved by NICE for treating non-infectious posterior uveitis, but not as a first- or second-line agent. The consequence of not treating birdshot is progressive sight loss. Several treatment changes may be needed to find a regime which can be tolerated and which can also be shown to work adequately. Usually, patients are otherwise healthy when they are diagnosed with birdshot. Although the medications are prescribed to save vision, treatment can, and does, profoundly affect birdshot patients' health, their quality of life and their relationships. Patients suddenly find that, as well as the medication that they need to take for their eyes, they have to take additional medications for drug-induced side-effects. These medications, in turn, have further side effects. Some BUS members have reported feeling so unwell on treatment that they have considered discontinuing it and letting their birdshot take its course towards blindness.
8. Is there an unmet need for patients with this condition?	Yes. • Need for longer-acting, corticosteroid treatment targeted on the eye, to reduce or eliminate the problems described in question 7, especially for patients who have not responded to, or who cannot tolerate, high-dose oral corticosteroids.

	• Need for an alternative to oral corticosteroid treatment for patients in whom oral corticosteroids are contraindicated, such as diabetes or mental illness.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	"Had Iluvien [fluocinolone acetonide] implants over 3 years ago. Very quick procedure, no pain, minimal recovery time. Started to notice big improvement in vision in 7-10 days. Many of my symptoms reduced or disappeared. My eye pressures remained low throughout. I would highly recommend Iluvien implants. Worked wonders for me. I did not have to take oral corticosteroids and have to experience their negative side-effects." "I had taken many oral immunosuppressants and corticosteroids for around 6 years, all of which I had to stop due to horrendous side-effects. Iluvien implant offered to me in 2016 as my last option at that time. It was and has been completely effective at keeping the retina dry. I had another Iluvien in the other eye and have a small cataract, but it doesn't need attention yet. [Iluvien] has been absolutely life-changing." "I would highly recommend them [Iluvien implants]. Oral prednisolone [corticosteroid] worked but only at super high doses. Eyes got worse with any lower dosage of prednisolone. [On immunosuppressants alone] vision got worse again – 20/200 or more [6/60; legally blind] with thick haze, retinal swelling and scarring. Intraocular steroid injections [gave] intense pain. Iluvien implants cleared the haze. Vision went to 20/80 [6/24] then 20/40 [6/12]. Was able to drive again. [Iluvien] helped with leakage and swelling in upper choroid and retina. Benefits from Iluvien were lack of oral prednisolone side-effects – insomnia, depression, temper – which was huge. Was thinking of giving up all treatment prior to implants due to side-effects, toleration problems and lack of any improvement. [Iluvien] is much better than injections every few weeks. No intolerance issues. Quality of life now is much better than the type of blindness I experienced when my eyes were at their worst."

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	"Slightly bloodshot eyes [after insertion]. Developed cataracts very quickly, which were operated on. [Effects of Iluvien] do not reach the choroid" "Cataract [after first Iluvien] the only side-effect but I have had this removed. [Iluvien] doesn't help the choroid." "Did develop cataracts from the implants."
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Yes. More benefit to: • Patients with birdshot uveitis, because the inflammation in birdshot affects only the eyes. • Patients who are unable to reduce their high doses of oral corticosteroids without their birdshot 'flaring', particularly patients with persistent cystoid macular oedema. • Patients who either cannot tolerate systemic immunosuppressants or who have responded inadequately to them. • Patients whose uveitis inflammation is worse in one eye, as the technology would allow treatment of that eye only.

Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The treatment should be available to all for whom it is judged clinically to be indicated. When the small range of treatments currently used for treating birdshot uveitis either do not work or make patients so ill that treatment has to be stopped, they would prefer that their clinicians and BUS did not have to spend valuable time battling the authorities for permission to use newer treatments. The prospect of sight loss is daunting enough for patients without the additional upset of being told that a possible treatment cannot be used because it is not yet approved for use or because of its cost. It is inequitable and unjust that newer treatments which have been used successfully in other countries are not available to birdshot patients in England.
Other issues	
13. Are there any other issues that you would like the committee to consider?	The technology's innovative device enables a small, continuous dosage of the widely-used corticosteroid fluocinolone acetonide to be released directly into the eye over a period of up to three years. This represents a 'step change' in treatment for non-infectious posterior uveitis. The technology has a long duration of action: around six times longer than a similar corticosteroid intravitreal implant currently available in UK. Use of the technology would reduce the number of patient attendances at clinic and would eliminate the hazards of having repeated injections into the eye. The technology's device provides controlled release of medication to give smooth compliance with treatment without the patient having to remember to take oral medication.

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • Birdshot uveitis greatly affects quality of life • Current birdshot uveitis treatments cause a considerable burden of physical and mental side-effects • Current birdshot uveitis treatments may not control the condition • Long-term use of oral corticosteroids has serious adverse consequences for physical and mental health • Better targeted treatment, such as the technology being appraised, would avoid the known adverse effects of, and contraindications to, oral corticosteroid treatment

Thank you for your time.

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Patient organisation submission

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About you	
1.Your name	[redacted]

2. Name of organisation	Olivia's Vision
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Olivia's Vision is the only uveitis charity in England and Wales supporting, advising and providing information to uveitis patients/carers and their families, while working with the medical profession to further the needs of patients. Olivia's Vision is funded through donations from the general public. It has in excess of 1000 members.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	Via questionnaires and follow up further questions where more info was felt necessary.
Living with the condition	
6. What is it like to live with the condition? What do carers	Of the 137 people who participated the most commonly used phrases were:

experience when caring for someone with the condition?	Terrifying, painful, constant fear of blindness/sight loss or worsening vision. Fear that current treatments will fail. The future has been put on hold for many people who can no longer work or continue with tertiary education due to the physical and mental toll this disease puts on people's lives. The emotional strain has damaged relationships with partners, carers and friends. Many days are taken off work due to pain during flares, side effects of treatments and medical appointments, causing severe anxiety that they will lose their jobs as a consequence, while others have already had to change their career paths. Several are now on benefits having had to stop working/studying completely. "left to rot" was one patient's term Carers feel helpless and anger that treatments are not working.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Insufficient Too little too late Ineffective Short lived success Pace of treatment too slow Not aggressive enough Unwillingness of some medical professionals to fight for them and their sight

	Anger with the system which denies potentially sight saving drugs to uveitis patients which are readily available to those with other autoimmune diseases. Anger that costs are considered more important than vision
8. Is there an unmet need for patients with this condition?	Yes
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Longer lasting than Ozurdex so less frequent injections required Very attractive to those with macular oedema and for patients where immune suppressants are ineffective or can't be tolerated.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	None

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Every patient will benefit from the availability of the technology, but in particular need are those for whom blindness or severe vision loss has already occurred, or is in the immediate/foreseeable future. Those with macular oedema. Patients for whom immunosuppressants are ineffective or can't tolerate the side effects. However, every uveitis patient is entitled to feel that should their current or future drugs fail, that there is an alternative hope.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No

Other issues	
13. Are there any other issues that you would like the committee to consider?	No

Key messages
14. In up to 5 bullet points, please summarise the key messages of your submission: • Immediate need for the technology • Patients are losing their hopes for the future (family/work/education) along with their vision • Uveitis patients must not be denied the technology authorised for other diseases affecting vision • •

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About you	
1.Your name	[redacted]

2. Name of organisation	Royal National Institute of Blind People (RNIB)
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Royal National Institute of Blind People (RNIB), is one of the UK's leading sight loss charities and the largest community of blind and partially sighted people. We recognise everyone's unique experience of sight loss and offer help and support for blind and partially sighted people – this can be anything from practical and emotional support, campaigning for change, reading services and the products we offer in our online shop. We're a catalyst for change – inspiring people with sight loss to transform their own personal experience, their community and, ultimately, society as a whole. Our focus is on giving them the help, support and tools they need to realise their aspirations. We receive funds from the general public, corporations, trusts and foundations, grants from the statutory sector and from the lottery.
4b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and	Through personal experience of customers with birdshot chorioretinopathy (birdshot uveitis), gained by direct discussion of their condition and its treatment, and discussion with our peer charity Birdshot Uveitis Society.

carers to include in your submission?	
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	"I had blurry vision, depth perception was very bad, shimmering halos in both eyes, colours were very dull, difficulty seeing people's faces when sun was behind them, flashes of lights even when eyes were closed." "Floaters, blurred visions, clouds, like a veil coming down over the eye, and flashing zig-zags. It has, thankfully, been painless." Birdshot uveitis is a type of non-infectious, autoimmune chronic progressive posterior uveitis, with the inflammation often relapsing and remitting, with unknown triggers. The onset of the condition is usually gradual and, in the initial stages, a patient may continue to see well but may have problems with night vision and colour vision, and be sensitive to bright lights. How birdshot uveitis affects vision in the long term can be varied. People with milder forms of birdshot can often maintain good sight with little or no treatment. However, more severe cases can be difficult to treat and cause complications which can lead to significant changes in sight, with floaters, cataracts, macula oedema and retinal detachment as possible complications, some of which may result in permanent sight loss if untreated.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	"I have had it [birdshot uveitis] for about eight years. For six years of that I was treated with steroids, which I had to come off as I developed osteoporosis, and then immunosuppressant drugs, which I could only tolerate for a few months at a time because of the side effects. At some points, I needed to attend Moorfields every few weeks, and I live in Leeds." Corticosteroids, injected directly into the eye or taken orally, are the mainstay of uveitis treatment. Oral corticosteroids work well in relieving inflammation, but cause well-documented side effects, particularly at higher doses taken over a prolonged period, including cataracts, glaucoma, weight gain, mood changes (varying from mild to severe), osteoporosis, stomach ulcers and diabetes. Determining a dose that reliably controls the inflammation while reducing side-effects to a tolerable level can be difficult, with additional medication to control these side effects frequently required. Immunosuppressants used either singly or in combination, as a second-line treatment, have a wide range of potential side-effects, in addition to the obvious increased vulnerability to infections. Biologics, such as infliximab or adalimumab are used where immunosuppressants have failed to be effective or tolerated. Dexamethasone implants (Ozurdex) release the drug directly into an eye over the course of six months, and have been shown to be both safe and effective (Pelegrin, 2015), but require more frequent administration than fluocinolone acetonide (FAc) implants.

8. Is there an unmet need for patients with this condition?	Yes. Patients whose uveitis does not respond to, or who are unable to tolerate long-term, high-dose corticosteroid treatment, or immunosuppressant drugs, or for whom treatment is unsuitable because of comorbidities such as diabetes. In addition, some patients have reported that they have considered discontinuing treatment and allowing the condition to progress, rather than have to face the side-effects of oral medication.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	"I have iluvien implants in both eyes, had them done 2 years ago. I had first implant in May 2015 and second in August 2015. Within 10 days of having first implant my symptoms had started to decrease, and same with 2nd implant. So far so good, I don't have the symptoms I had before implants, although I do find I still get glare when the sun is out so I always wear sunglasses. The life of the implant is 2-3 years, nobody really knows, I am back in August for ERG test results, and retinol angiogram, so I guess I'll know more then, but so far all checkups have proved eyes are stable with no signs of new inflammation. My vision is good, although floaters do get on my nerves in bright light. The implant is very effective in keeping down inflammation in the retina, apparently this is the part of the eye that's hard to treat, doctors are not quite sure as yet if the implant can reach the choroid, only time and more data will tell." “I’ve had implants in both eyes for about two and a half years, and they’ve kept my retinas dry. One eye does have a cataract, but it isn’t serious enough to operate on yet – a cataract in the other eye developed before the implants and was removed before. I did get a single flare-up in my choroid, after I was treated

	for kidney stones, which needed a course of injections to treat. I think the two were connected as I'd had 18 months before that without problems. I've not had any issues with my eye pressures. There is no comparison with the old treatment; the implants have meant I'm not constantly in the hospital and my eyes are stable." Bajwa. Aziz and Foster (2014) concluded "The data suggest that fluocinolone acetonide implant (0.59 mg) helps to control inflammation in otherwise treatment-refractory cases of birdshot retinochoroidopathy. It is associated with significant side effects of cataract and ocular hypertension requiring treatment." Burkholder, et al (2013) concluded that "The FAc implant is effective in controlling inflammation and reducing the need for systematic immunosuppressive therapy; however, eyes of patients with birdshot chorioretinitis appeared to have a more robust IOP [intraocular pressure] response to the implant than patients with other types of posterior and panuveitis." FAc implant use for treating other types of macular oedema, such as diabetic macular oedema "has been associated with increased patient satisfaction and a lower treatment burden with FAc versus others using frequent intravitreal injections" (Quhill, 2015) and, given the positive response by patients using implants, it is likely the same would be true of their use for birdshot uveitis.

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	"The implants will without doubt give you cataracts, mine grew very quickly in both eyes, I have had cataract surgery in both eyes. Eye pressure can also increase with implants, but mine have always been normal." It is acknowledged that use of FAc implants, as with any course of corticosteroid treatment, leads to a significantly increased risk of developing cataracts and more moderately increased risk of elevated intraocular pressure (Saedon, Anand and Yang, 2017), albeit that this risk appears reduced for birdshot uveitis patients (Burkholder, et al, 2013).
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Those who live a great distance away from the tertiary clinics that provide specialist uveitis care – use of the implants will have a huge impact on their ability to live less fragmented lives, and improve treatment compliance by eliminating the possibility of appointments being missed, whether that is due to a patient DNA or clinic cancellation, over the three-year period that the device is active or omission of an oral medication. It will also reduce the risk that accompanies repeated intravitreal injections. This will have the added benefit of increasing clinic capacity by reducing demand for appointments. Those whose uveitis has not responded to or who are unable to tolerate high-dose oral corticosteroids or immunosuppressants, whose side-effects are unable to be controlled. Because the drug is delivered

	locally, the dosage is far lower than traditional treatments, largely obviating the need for control of side-effect symptoms. Those whose uveitis is occurring in one eye – allowing for the localised treatment of the inflammation with a single intervention, rather than high systemic doses of corticosteroids.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Use of the FAc implant will improve compliance with treatment, and therefore outcomes for, those who are less able to understand or remember their treatment – those with dementia, mental health problems, and those with language difficulties – by providing a less intensive treatment plan that does not depend on taking regular oral medication. It will also provide better access to treatment for patients living in lower socioeconomic groups or who are homeless, who would otherwise be required to travel frequently to what may be a geographically distant tertiary clinic at their own expense and during working hours.
Other issues	
13. Are there any other issues that you would like the committee to consider?	• A. Bajwa, K. Aziz and C. S. Foster, "Safety and efficacy of fluocinolone acetonide intravitreal implant (0.59 mg) in birdshot retinochoroidopathy," *Retina,* vol. 34, no. 11, pp. 2259-2268, 2014.

- B. M. Burkholder, J. Wang, J. P. Dunn, Q. D. Nguyen and J. E. Thorne, “Post-operative outcomes following fluocinolone acetonide implant surgery in patients with Birdshot chorioretinitis and other types of posterior and panuveitis,” *Retina,* vol. 33, no. 8, pp. 1684-1693, 2013.
- L. Pelegrin, M. S. de la Maza, J. Rios and A. Adán, “Long-term evaluation of dexamethasone intravitreal implant in vitrectomized and non-vitrectomized eyes with macular edema secondary to non-infectious uveitis,” *Eye,* vol. 29, pp. 943-950, 2015.
- F. Quhill, “Real-world Experience of Fluocinolone Acetonide (0.2 µg/day) Intravitreal Implant in the Treatment of Diabetic Macular Oedema,” *European Ophthalmic Review,* vol. 9, no. 1, pp. 42-6, 2015.
- H. Saedon, A. Anand and Y. C. Yang, “Clinical utility of intravitreal fluocinolone acetonide (Iluvien®) implant in the management of patients with chronic diabetic macular edema: a review of the current literature,” *Clinical Ophthalmology,* vol. 11, pp. 583-590, 2017.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Controlling birdshot uveitis via oral corticosteroids, immunosuppressants and other second or third-line drugs is a difficult, and sometimes impossible, balancing act between control of the symptoms and minimising side-effects to a tolerable level.

- The side effects of current treatment make managing the condition difficult to bear, taking a toll physically, mentally and emotionally to the point that some have considered stopping treatment and letting the condition progress, to avoid them.
- Frequent travel to tertiary clinics, particularly if they are geographically distant, is disruptive to living a normal life.
- Targeted, localised treatments, particularly ones that last over a number of years, allow for better compliance with treatment, better control of the symptoms of birdshot uveitis with lower drug dose, and a better quality, less disrupted, life for patients.
- Risks, common to corticosteroid use, primarily the certainty of the development of cataracts and a moderate risk of increased IOP, will need monitoring and managing.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

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

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**The Royal College of Ophthalmologists (RCOphth)**

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	**x** an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Ophthalmologists is an independent professional body representing ophthalmologists. It sets and maintains standards of practice in ophthalmology with an overall guiding principle to shape UK eye care for the benefit of patients.
5b. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition,	For the condition of <u>non-infectious uveitis (affecting the posterior segment of the eye)</u> 1. Prevent deterioration or permanent loss of vision by treating inflammation and the complications that result from a chronic uncontrolled state 2. To reduce exposure to other treatments used to treat inflammation such as systemic corticosteroid and immunosuppression which have associated toxicity and effects on morbidity

or prevent progression or disability.)	
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	1. Reduction in intraocular inflammation (as per standardised grading system (Standardised uveitis nomenclature (SUN)) or maintained control of inflammation graded by: • Anterior chamber (AC) cells or flare • Vitreous haze • Absence of new chorioretinal lesions/retinal vascular lesions Clinical trials in uveitis often use a 2 step reduction in activity to define treatment success and a 2 step increase in activity to define treatment failure 2. Resolution of macular oedema secondary to inflammation and prevention of recurrence 3. Ability to reduce systemic treatment use • Oral corticosteroid to safer long-term dose (<10mg/day) or withdrawal completely • Reduction in systemic immunosuppression (number of agents/dose of each agent(s))
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – there are many medications being used off licence and two now being used per NICE TA460, (Dexamethasone implant and Adalimumab injections) however the nature of the disease is to last many years and or lifelong. A long acting adjunct to Adalimumab or an alternative to repeated short term Dexamethasone implant is needed. Further treatment approach are also needed for patients unresponsive to currently used systemic medications including immunosuppression and biologic (adalimumab) therapy.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Non-infectious uveitis (NIU) is treated with local and/or systemic therapy: • <u>Systemic treatment:</u> Corticosteroid therapy and often second line immunosuppression treatment (if successful or tolerated) with option to escalate therapy to biologic treatment in patients reaching NICE criteria for adalimumab in NIU. The efficacy is often limited by systemic toxicity

	• Local treatment: Stepwise ladder approach with corticosteroid therapies, starting with topical application before moving to peri-ocular injections and then intravitreal injections of which the dexamethasone implant (Ozurdex) is the only licenced mediation as per NICE approval (TA460). This has a 4-6 month duration of effect so repeated injections are commonly needed.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	NICE TA460 is used to guide treatment including inclusion criteria and exit criteria for these therapies.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	There is no defined pathway of care worldwide for non-infectious uveitis, this is partly due to the majority of agents, for example second line immunosuppressives being used off-licence. There is significant global variation in the agents used, doses and duration of treatment and role of local therapy. However, there is broad consensus across the UK and world that inflammation in the eye should not go undertreated as the consequences are vision threatening. All clinicians will work their way up a treatment ladder starting with simple agents and moving onto immunosuppression and eventually biologic therapy (adalimumab). Local therapy such as Ozurdex and the implant being considered herein have a role in unilateral disease and as an adjunct to treatment or for local treatment where systemic treatment is not tolerated. NICE TA 460 has helped to define the stepwise ladders ‘top rungs’ e.g. when the corticosteroid for bilateral disease or topical drops for unilateral disease have failed to achieve disease quiescence/control.
• What impact would the technology have on the current pathway of care?	The current technology is likely to fit into the current pathway as a longer acting alternative to Ozurdex dexamethasone implant. As the major difference between the two is duration of action, if the patient has tolerated and shown success with Ozurdex therapy BUT required repeat injections to maintain quiescence, then this technology should have similar anti-inflammatory success with a much longer duration of action. Reducing the need for multiple repeated injections is more tolerable for the patient and decreases the intravitreal injection procedure risks of endophthalmitis and subsequent vision loss.

	By achieving long-term disease control through local treatment it may avoid/reduce the need for systemic therapy.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	
• How does healthcare resource use differ between the technology and current care?	If assumptions are made that the implant has a 36 month duration of action after injection versus a 4-6 month duration of action for a Ozurdex dexamethasone implant then it could be expected to that one intravitreal injection could replace 4-6 Ozurdex injections. The resource used on the day of injections would be no different between the two. Followup appointments after an Ozurdex are at least 3-4 in over 6 months, whereas if quiescence was achieved then appointments may be 4-6 monthly for this technology. Outpatient appointments for the fluocinolone implant could be 10-12 in 3 years versus 20+ for the Ozurdex implant.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Tertiary level uveitis care in specialised services.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No extra investment needed, facilities are already available for administration of intravitreal medications, including dexamethasone implant. Staff are already trained in use of this technology as it is given for a different indication (diabetic macular oedema)
11. Do you expect the technology to provide clinically	

meaningful benefits compared with current care?	
• Do you expect the technology to increase length of life more than current care?	No – even though the technology may reduce the use of some second line immunosuppressives and systemic corticosteroids there is no published evidence in the uveitis field that this could improve life expectancy
• Do you expect the technology to increase health-related quality of life more than current care?	Yes - for the following reasons: 1. Reduced numbers of intravitreal injections when compared to Ozurdex implants given over the expected duration of action (2-3 years) – decreased rates of injection related complications, less appointments 2. Reduced use of systemic corticosteroids and secondary immunosuppressives – decreased toxicity levels, need for blood testing, steroid related complications such as osteoporosis, hyperglycaemia, hypertension 3. Reduced fluctuations in disease quiescence – the flare up of disease that occurs when an Ozurdex implant wears off should not occur – each episode of macula oedema could result in permanent retinal anatomical changes
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Not to our knowledge
The use of the technology	

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	<u>Compared to use of shorter acting intravitreal steroid (Ozurdex):</u> • Longer-duration of action would achieve far fewer injections and risks associated with each injection • Long-term disease control without recurrences achieving disease stability <u>Compared with systemic corticosteroid:</u> • Avoidance of long-term morbidity risks with this therapy including obesity, osteoporosis, diabetes, hypertension, cardiovascular disease, mood and sleep disturbance • Less frequent outpatient attendances • Corticosteroids are major cause of morbidity in uveitis and significantly affect patient quality of life. Local treatment, achieving control and allowing long-term safe systemic steroid dose/withdrawal is much more acceptable to a significant proportion of patients. <u>Compared with systemic immunosuppression:</u> • No need for frequent monitoring blood tests (6-12 weekly) • No systemic risk of toxicity or increased risk of infection • Less frequent outpatient attendances <u>Potential concomitant treatments:</u> • Pressure lowering medications • Cataract surgery <u>Acceptability of Intravitreal therapy:</u> • Intravitreal injections very well tolerated by most patients. Very low risk of intra-procedural complications and very low risk of infection • Outpatient clean injection room procedure – does not need admission or theatre environment • Procedure takes <10minutes

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Similar to NICE TA460 for Ozurdex (Dexamethasone Implant) - Rules for starting: • Diagnosis of non-infectious uveitis (NIU) involving the posterior segment • Phakic or pseudophakic, not to be used if aphakic • Requires controlled intra-ocular pressure • Active or chronic non-infectious uveitis with worsening vision or high-risk of blindness • Response shown to previous Ozurdex implant but recurrence of uveitis requiring further longer-acting treatment No additional testing – NIU will have been confirmed as part of diagnostic investigations. Rules for stopping: 1 or more of the following • New active inflammatory chorioretinal or inflammatory retinal vascular lesions, or both or • A 2-step increase in vitreous haze or anterior chamber cell grade • Worsening of best corrected visual acuity by 3 or more lines or 15 letters • Uncontrolled intraocular pressure/advanced glaucoma
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the	As detailed above: • Reduced risk of intravitreal injection related complications • Reduced number of hospital appointments • Reduced number of blood tests • Reduced corticosteroid related side effects e.g. obesity, osteoporosis etc

quality-adjusted life year (QALY) calculation?	• Reduced risk of toxicity resulting from second line immunosuppression e.g. hepatotoxicity from methotrexate or nephrotoxicity from cyclosporin
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes – No other treatment available for uveitis offers the promise of up to 3 years of disease control with a single application and no systemic side effects.
• Is the technology a 'step-change' in the management of the condition?	Yes – see answer above
• Does the use of the technology address any particular unmet need of the patient population?	There are unmet treatment needs in patients with uveitis including: • Patients with NIU where immunosuppression is ineffective or poorly tolerated who have active disease and require further therapy. Long-term corticosteroid therapy (>7.5mg/day) is associated with significant health risk and is inappropriate in this group. • Population of uveitis patients with disease in one eye with worsening vision and high risk of blindness who do not qualify for biologic treatment.

	• Biologic therapy is ineffective in a proportion of patients with NIU – there is an unmet need for alternative treatment in patients failing to achieve disease control with biologic therapy. • There is currently no available long-acting intravitreal steroid therapy for NIU (Ozurdex activity is up to 6mo in clinical practice). Patients currently receive local steroid therapy alone or in combination with systemic therapy and may undergo regular, repeated intravitreal steroid injections, with fluctuations in control between injections. A long-acting device would significantly change the treatment approach and strategy. • Population of patients with uveitis on systemic medication with uncontrolled uveitis disease and/or systemic toxicity from standard therapy. Technology offers potential for treatment of condition, using long-acting steroid therapy and avoiding exposure to long term systemic therapy including corticosteroid, immunosuppression and biologic therapy.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects: 1. Cataract – may require cataract surgery. This is a recognised complication of chronic uveitis and steroid therapy (local and systemic). Patients may develop cataract or worsening of existing cataract. No long-term effect on QoL predicted. 2. Raised pressure – may require 1 or more pressure lowering topical therapy in addition to treatment for uveitis. Risk of glaucoma if untreated high pressure and very small proportion may need surgical intervention for raised pressure. These side effects are not expected to be significantly worse than those experienced by a patient receiving 4-6 Ozurdex dexamethasone implants over the 3 year possible duration of action – and may be less.
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	There is limited uveitis specialist experience of use of technology in real-world in NHS in UK. There has been a large 36 month Phase 3 study of a Fluocinolone implant – the 12 month results were published in October 2018. These results are described below, however this is not the same implant as the technology considered in this application – the trial was conducted using a 0.18mg Fluocinolone implant and the technology being considered is a previously commercially available preparation at 0.19mg Fluocinolone. It is our opinion they are very similar in efficacy and expected side effects but that the difference may have been made for commercial reasons around licencing etc. Jaffe GJ, Foster S, Pavesio C, Paggiarino D, Riedel GE, Effect of an Injectable Fluocinolone Acetonide Insert on Recurrence Rates in Noninfectious Uveitis Affecting the Posterior Segment: 12-Month Results, Ophthalmology (2018), doi: https://doi.org/10.1016/ j.ophtha.2018.10.033. "The 6-month (28% and 91%) and 12-month (38% and 98%) uveitis recurrence rates were significantly lower (P<0.001) with FAi versus sham, respectively. Fewer recurrences per study eye (mean of 0.7 versus 2.5), lower incidence of ≥15 letter decrease in best corrected visual acuity (14% vs 31%),and reduced systemic (19% vs 40%) and local (7% vs 62%) uveitis adjunctive treatments were observed with Fai versus sham, respectively. FAi had higher rates of cataract. Intraocular pressure-lowering treatment use was similar. No deaths, treatment-related study discontinuations, or unanticipated safety signals were observed through 12 months."

• If not, how could the results be extrapolated to the UK setting?	We believe these results can be extrapolated to a clinical setting in a similar fashion to the trial data for dexamethasone implants were extrapolated at the time of that technology appraisal..
• What, in your view, are the most important outcomes, and were they measured in the trials?	Trials focussed on disease control and ability of the technology to prevent recurrence of uveitis activity and assessed safety outcomes which include visual acuity. Therefore, we feel the most important outcomes were measured.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Although the 36 month trial has concluded, only the 12 month data has been published so far. Iluvein implants have been in use for some years in the UK for other indications (NICE TA301 – Diabetic macular oedema) without unexpectedly high rates intraocular pressure in pseudophakic eyes.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	No real-world data yet for use of technology in uveitis
Equality	

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.

- Control of inflammation in non-infectious uveitis affecting the posterior segment of the eye can prevent sight loss in a working age population
- Current treatment strategies rely on long term systemic corticosteroids and use of potentially toxic immunosuppressives
- Local corticosteroid intravitreal injections have been proven to reduce the burden of systemic treatment and preserve vision
- There is an unmet need for a long-acting (up to 36 months), intravitreal corticosteroid therapy
- Identifiable population who can benefit from this technology based on an expansion of existing NICE TA460 guidelines

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Archana Pradeep**
2. Name of organisation	**University Hospitals of Nottingham**

3. Job title or position	**Consultant Ophthalmologist (Uveitis and Inflammatory eye diseases)**
4. Are you (please tick all that apply):	☐ a specialist in the treatment of people with this condition
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	**I do not have anything to add**
The aim of treatment for this condition	

7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent progression / improve the clinical outcome/ prevent disability (to save sight)
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Reduction in the degree of inflammation (reduction in macular oedema/vitritis/vasculitis)
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	With a range of anti-inflammatory medications (local and systemic)
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes UK based: NICE CKS, NICE TA 460,BMJ best medical practice, Scottish uveitis network guideines ,College of Optometrists guidelines, Guidelines developed in local units (for example ,Birmigham, Manchester, Bristol)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	No standard care pathway is defined although there are variations in practice between professionals in NHS. Recently an expert working group (2017)was formed in the UK with a view to unify practice.
• What impact would the technology have on the current pathway of care?	Widen treatment options, Better outcome measures, Improved HRQoL
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes Infact the same drug is used for a different eye condition (Diabetic Macular Oedema) and approved by NICE (TA301).It is currently not approved by NICE for use in non-infectious posterior uveitis.

• How does healthcare resource use differ between the technology and current care?	No extra resources needed except the availability of the drug itself.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Specialist clinics provided in secondary/tertiary care
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Monetary funds for the medication itself
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
• Do you expect the technology to increase length of life more than current care?	No. N/A to life expectancy

• Do you expect the technology to increase health-related quality of life more than current care?	Yes. Visual impairment is known to affect quality of life of patients as well as their carers because of loss of independence.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would be appropriate (and the only option) in uveitis patients in whom systemic treatment is contraindicated/ not tolerated.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	The technology will not be more difficult to use than current care. As the implant effect is deemed to last for at least 36 months, it is hoped to reduce the need for additional treatments (which is currently every 6 months with a shorter acting implant device) and facilitate fewer hospital review visits.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	The technology will be used based on the clinical indication and treatment response. No additional testing is required.
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Yes Improved patient satisfaction with regards to fewer hospital visits, less time off work, reduce burden on cares,fewer injection procedures itself.
17. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes

impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes (In the clinically indicated patient group)
• Does the use of the technology address any particular unmet need of the patient population?	Yes. Longer duration of disease control with less relapses until the effect of the medication lasts Treatment option in patients who cannot tolerate/ contraindication of systemic treatment Treatment option in patients who do not respond to conventional treatment
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effect profile is low and comparable to that of current available treatment options (ie: of short acting intravitreal steroid implant) Side effects management will require additional treatments which can affect the QoL in the interim (for example having additional drops treatment/cataract surgery).

Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Not in regular settings due to lack of approval of the medication for treatment of uveitis by UK professional body. Use of the technology in UK is only through successful independent funding request approvals . Current standard of care in UK practice is local steroids, systemic steroids and disease modifying immunomodulatory agents tailored to the each patient needs.
• If not, how could the results be extrapolated to the UK setting?	As above
• What, in your view, are the most important outcomes, and were they measured in the trials?	Time taken for recurrence of uveitis (since the drug implantation), Relapse rate, Visual acuity, Improvement in central retinal thickness, Reduction/ Cessation of systemic treatment. Yes they were measured in the trials.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Surrogate outcomes (imputed recurrence rate) were used as primary outcomes. Yes they do predict long term outcomes ie recurrences
• Are there any adverse effects that were not apparent in clinical trials	No

but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	Yes. Two Phase 3 trials have been conducted to assess the safety and efficacy of the implant for the treatment of posterior uveitis. The primary endpoint of both trials include prevention of recurrence of posterior uveitis at six months, with patients being evaluated for three years. The preliminary results were presented at an international conference and the publication is awaited in peer reviewed journal. Longer term outcome data awaiting to be published.
21. How do data on real-world experience compare with the trial data?	Real world data is awaiting to be generated as the drug is not readily available for the indicated use. Personal and other clinicians' anecdotal evidence shows that this is an effective treatment when there is recurrence or persistence of inflammation.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

22b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

23. In up to 5 bullet points, please summarise the key messages of your statement.

The technology will be a great addition to the treatment of non infectious posterior uveitis as it would

- Improve patient outcome measures
- Improve quality of life
- Increase patient satisfaction
- Unique - longer acting agent for persistent disease
- Cost effective

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……A.Pradeep…….

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NICE National Institute for Health and Care Excellence

Patient expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

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- Your response should not be longer than 10 pages.

About you	
1.Your name	Amanda Jacobs
2. Are you (please tick all that apply):	☑ a patient with the condition? ☐ a carer of a patient with the condition?

	☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Birdshot Uveitis Society
4. Did your nominating organisation submit a submission?	☑ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☑ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐
7. How did you gather the information included in your statement? (please tick all that apply)	☑ I have personal experience of the condition ☑ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I was diagnosed with birdshot uveitis in January 2010. It has been a frightening experience for me. Not so much the actual eye condition, which is painless, but I have been terrified that I will go blind, and because I have had such a lot of difficulty with the actual treatment. The medicines have made me ill to the point where I can no longer take them. Life for the last eight years has been a continuous round of hospital appointments, dealing with my eye issues, as well as doctor's appointments dealing with the side-effects from the drugs that have been used to treat me. I was unable to find satisfactory treatment close to home, so I have ended up travelling hundreds of miles to get the treatment I have needed, spending large amounts of time and money on train travel and hotel accommodation. It has totally disrupted my family life. It has been as if my life has been put on hold. Holidays have had to be cancelled and I have often had to turn down invitations because I have felt too unwell to attend. This has not only affected me, but also my entire family.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	The care available on the NHS has been very good. The problem has been that the choice of drugs which are currently commonly used to treat my condition have made me ill and caused me to suffer extremely unpleasant side-effects. On oral corticosteroids, I could not sleep, I was manic, I could not rest, I felt permanently jet-lagged, and they have also given me osteoporosis: a condition of thinning bones which is also hard to treat. I will have to live with brittle bones for the rest of my life, which is quite a daunting prospect. After 10 months on tacrolimus, the side-effects became intolerable. I had severe 'pins and needles' firing all over my body. On mycophenolate mofetil, after a period of several months, I developed shingles, so I had to stop taking it while I got better from that. When I resumed taking it, I found I had developed an allergic reaction to the drug, with constant diarrhoea, so again I could not carry on with that treatment. I have had some success with an Ozurdex (dexamethasone) ocular steroid implant, except it stopped working after about seven or eight months.
10. Is there an unmet need for patients with this condition?	Yes, there is definitely an unmet need. The treatments commonly available have many unpleasant side-effects which affect many patients. None of the current treatments is ideal.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	The Iluvien implant, my most recent treatment which I have had in both eyes, has been nothing short of miraculous. I received the implants in each eye one month apart in April/May 2016 and they've kept my retinas dry. There is no comparison with the old treatments: the implants have meant I'm not constantly in the hospital and my eyes are stable. The bonus of this treatment is it treats just the eye, and not the rest of the body.

	As far as I am concerned, there are no side-effects from the Iluvien apart from cataracts, which is a common occurrence anyway, and easy to deal with. The Iluvien implants have meant far fewer hospital visits; a much better family life; my daily life no longer revolves around taking medication and when to eat; I don't suffer any dreadful medicines side-effects. I didn't realise how bad the side-effects were until I came off the drugs and I didn't realise the impact that my treatment was having on other members of my family. Having Iluvien implants means that I got both my life and my family back.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	The disadvantages of the Iluvien implants are that you may develop cataracts and you may develop raised pressure in the eyes. Before I was given my first Iluvien implant I had already had cataract surgery in one eye, and I will soon need to get my other eye done. I have not had any raised eye pressure issues with Iluvien, so this has not been a problem for me.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	• Patients with birdshot uveitis who do not have other systemic illnesses benefit particularly from a targeted treatment for the eyes. • Patients with cystoid macular oedema, because the Iluvien resolves this very effectively. • Patients who find it difficult to comply with complicated medicine-taking regimes. • Patients with any mental health issues, including depression, whose mental health problems would be made worse with the current treatments.

Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	No.
Other issues	
15. Are there any other issues that you would like the committee to consider?	No.
Key messages	

16. In up to 5 bullet points, please summarise the key messages of your statement:

- This technology is life-changing and empowering: I have got my life back
- It is cost-effective: two injections once every three years, which in the long run would save the NHS money
- Significantly reduced numbers of hospital visits, freeing up busy eye clinic time
- Reduced side-effects stop patients feeling awful, help them live a normal life and forget that they have a sight-robbing chronic disease
- I am able to work and I am able to be a valued member of society

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient expert statement

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

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Alison Richards**
2. Are you (please tick all that apply):	**x**☐ a patient with the condition? ☐ a carer of a patient with the condition? ☐ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	Olivia's Vision
4. Did your nominating organisation submit a submission?	**x**☐ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x**☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐
7. How did you gather the information included in your statement? (please tick all that apply)	x☐ I have personal experience of the condition x☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with this condition is challenging and sometimes frightening. You live life day to day with the constant fear that tomorrow, you could lose your sight. There is no cure for sight threatening uveitis and the current treatments that are available can result in additional problems, such as increased ocular pressure with steroid and increased risk of infection with immunosuppressants. The steroidal treatment available to patients, at present, offers a short term solution. Treatments require me to be constantly at clinic (1 - 2 times each week), for consultations and treatment. This causes strain on the whole family. To get me to appointments, my husband takes time off work and I have to make arrangements for my three children. Current treatments for me of 5mg oral steroid and mycophenolate mofetil daily, with triamcinolone or Ozurdex added, were only effective for about five to seven weeks, then they would fail and my vision deteriorate. I could not work, drive or care for my young family at these times. The constant need for triamcinolone acetonide and Ozurdex injections direct into the eye resulted in increased ocular pressure and cataract. I needed three surgeries (cataract and stent, trabeculectomy and revised trab) to solve these issues, which nearly cost me my sight. At this point, I received Iluvian. Constant uncertainty and the frequent visits to hospital take their toll, not only on me but the whole family. Alongside my

	personal fears, there was a financial impact on my family as I was unable to work before my Iluvian implant. I add below the transcript of the talk I gave to the Birmingham uveitis information group, PINGU, about my uveitis and Iluvian. Hello! My name is Alison. I'm a 47 year old mom of three… a 13 year old boy, Samuel, and 5 year old twins, Jack and Annabella. Not forgetting, a wife to Steve for nearly 25 years. Tonight, I'm here to give you a patient's view and perspective on life before and life after my Iluvian implant. I just want to stress that I'm not a professional or specialist in eye diseases, and this is specifically about my experiences. I've had PIC for about 25 years, which is nearly half my life. In the beginning, I wasn't told it was PIC, just that I had had bleeds at the back of my eye. Treatments back then were limited and nowhere near as advanced as those we have available to us today, so my only option was to have two operations to try to stop the bleeds which, unfortunately, resulted in the total loss of central vision in my right eye. I then went into what I now believe is remission, or a non-flare period in my PIC story. For about 10 years, I enjoyed a normal life, established my career, worked and travelled a lot and had our fantastic children, generally, a wonderful life. When the twins were about a year old, I noticed flashing lights appearing in my left eye (my good eye) and a gradual deterioration in my vision followed. I went to New Cross eye department twice but was sent away, because they couldn't see anything wrong and at this point, I could see okay on the eye chart. I knew that there was something wrong, so I persisted. To cut a very, very long story short, I came to Professor Denniston via the wonderful Ms Thalumas. Immediately after my first consultation, I felt assured that I was in good hands. Finally, someone was listening to me and could tell me what was happening with my eyes. By this point, however, I had lost so much vision that I couldn't see well enough to drive, read or watch TV. My lowest point, at this time, was not being able to perform as well as I wanted to as a mom. I remember having the twins in their high chairs, trying to feed them some yogurt, and missing their mouths with the food. I can laugh at this now, but at the time, this nearly broke me. I then

started a cycle of treatment that continued for about three years. It was established by a process of elimination, that high doses of oral steroids, intravenous steroids, avastin injections and immunosuppressants did not restore my sight to a functioning level. It was only after my first triamcinolone injection directly into my eye, that my sight was restored to what I refer to as a usable, workable level. By this, I mean that I can read, drive, watch TV and do all the things I normally would do, if just a little differently, with some moderate adjustments.

My life then became a pattern of injections. A cycle, you could say, that I could predict to the week, if not the day. A triamcinolone injection would last about 6-7 weeks. My sight would then start to deteriorate to a non-functioning level. I would then get an appointment with Prof Denniston for scans, checks and then another injection. This was always arranged quickly and Prof Denniston, whenever possible (and that was most of the time) got my many scans and treatments arranged together. However, I had one year old twins who needed childcare, someone was needed to take me to the hospital, and someone was needed to collect my eldest from school. My life was dictated by my constant need for treatment. Even when I was given an Ozurdex implant, this only gave me a couple of weeks extra sight over the triamcinolone and as it was a slow release treatment, it took about 7 days to restore my sight. Effectively, for three years, I had 6 weeks of workable sight followed by 3 weeks of drastically reduced vision.

This had a massive impact on my life, not only for me but for my family. I could not work, so our income was much reduced. I was totally reliant on my husband, in-laws, dad and sister. I was very aware of the stress and worry that I was causing everyone; it was a horrible feeling as I knew they all wanted to be there for me. I stopped going out with friends as I was worried that they would get fed up of asking me how things were going and I couldn't give them a positive answer. In my head at that time, it was better just to avoid taking about it.

Then things took a further turn and became more complicated. As result of many, many, many injections of steroids, there was a consequence. My eye pressure started to increase more and more. Initial treatments were eye drops, followed by laser treatment, then an operation to put a stent in place in my trabecular mesh. These treatments were just proverbial sticking plasters and very soon, the pressure in my good eye reached 60! You know you're in trouble when your consultant looks a little shocked, pops out for advice and six consultants come back into the room. The care, as always, was second to none; I was admitted on the spot and operated on the very next day. Many follow up appointments in the next few

	weeks revealed that this operation was failing and a revision trabeculectomy was performed. There were a few more complications that followed with me, at one point, having to travel back from Devon to get urgent treatment. This was an awful time for my family and me. Not only was I at the QE at least once a week, but also at the City hospital. My life, and that of my family, revolved around me and my appointments. We couldn't plan anything like days out, social events and a most needed holiday. Personally, this put a massive strain on us as a family. One thing I knew for sure that helped us get through all of this was the knowledge that I was getting the best care in world at the QE and with the wonderful Mr Pandy at The City Eye Hospital. Enough with the doom and gloom. Here is where my story took a huge turn for the better. At my next PIC appointment, Professor Denniston advised that he had obtained the approval and funding for me to have an Iluvian implant. For this, I cannot thank him enough! The procedure, for me as a patient, is very similar to that of an injection or an Ozurdex implant. I think possibly the needle size is larger, but I didn't notice that, other than I felt more pressure as it was pushed in. It was definitely not painful at all. (I'm a great believer that you can't have too many numbing drops and I always ask for more). I did suffer a complication after the injection, but I think this was case specific due to the recent operations I had had due to my pressure issues. I developed retinal folds, which after three weeks, corrected themselves. After the first three weeks, I have not looked back. It is amazing! I have gone from being in clinic up to three times a week, down to just a three monthly check up. I have needed no further injections for nearly two years. My quality of life has been transformed; we are able to have wonderful uninterrupted family time, I'm helping with homework and we're having fun together. I'm able to start reading a book without the fear of not being able to finish it. I'm back working part time, so we are able to do those nice little extras like going out for a meal or treating the kids. I feel confident to go out with my friends and enjoy myself, not worried the conversation is all about me and my blooming eyes. My confidence in life has returned and I'm back to being me, enjoying life, back to exercising and eating well. **I FEEL NORMAL!** A last point is just to say how grateful I and my family are to the NHS, particularly to Professor Denniston (and his team) and also Mr Pandy for working so hard and saving my sight. I don't have the words to convey how much I appreciate all you have done. Thank you !

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	Current treatments with steroid are a short term fix to a lifelong incurable condition. Injecting higher dose steroids multiple times directly into the eye can result in major complications that require further treatments such as pressure lowering eye drops and glaucoma surgery. High ocular pressure is then a potential threat to sight, along with the uveitis. I needed glaucoma surgery before Iluvian because of tri !amcinolone but the literature says that when Iluvian raises pressure, the majority of patients can be managed effectively with drops thus reducing this threat to vision. Current steroid treatments are only effective for relatively short periods of time, and do not give any respite in the treatment process. Despite the risks of Iluvian, patients and carers who attend PINGU, (Birmingham's patient, carer and professionals' information group) were excited about this treatment when I, OV, and two uveitis professors gave a presentation about it. One patient member summed up the attitude of the group when he emailed his support after our presentation: *I am fortunate in that my episodes are acute, usually every four or five years or so. When they occur, they are in my right eye only and are painful and distressing. However, my symptoms are relatively short-lived and easily treated with drops. In short, I am fortunate in that I can 'live with' my episodes when they occur, in the knowledge that symptoms will disappear after a few weeks.* *However, I know of several fellow sufferers (in our patients' group) who suffer from uveitis in both eyes and whose condition is chronic. I cannot imagine what it must be like to have the chronic 'version' of the condition in one eye, let alone both eyes.* *I fully support the submission to NICE for acceptance of the Iluvian implant form of treatment. A slow release of steroid is clearly much more effective than regular injections and, as such, is proven to enhance the well-being of sufferers of this form of uveitis.* A second patient, detailing her 36 years of sarcoidosis with uveitis, included a description of her experience with a course of high dose oral steroid:

	I spent the next few years intermittently taking prednisolone whenever I had a flare up. What my family had to live with were the side effects - the unexplained (roid rage) the irritation from my constant hunger which saw my weight balloon, the morphing of my body where I developed a body builders buffalo hump across the bridge of my shoulders, the bruising and tearing of my thinned skin and the utter exhaustion as my adrenaline constantly crashed from over exertion. Life was tense. A third patient, a young man with severe pan uveitis, asked us after the presentation, 'How much does this cost?' When we were told, the patient group wondered that this appraisal process was even necessary. Sight threatening uveitis is rare and patients are scared that they cannot easily access treatments which could help them because they don't have a major disease like diabetic retinopathy, macular degeneration or RA for which clinical trials provide evidence of effectiveness.
10. Is there an unmet need for patients with this condition?	There is a definite unmet need. Patients desperately need a longer term treatment solution that can avoid further complications due to the side effects of immune suppressants. Our quality of life will be drastically improved due to eye sight stability and peace of mind.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	There are a number of advantages: 1. Drastic reduction in the number of direct ocular steroid injections. 2. Reduces the risk of further complications due to side effects of current treatments. 3. Reduction in clinic appointments. 4. Dramatic cost savings to the NHS. 5. Possibly the most important, getting quality of life back. Security of sight enables a return to work and feeling normal.

Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	I am not a clinician, but I have had no issues nor see any disadvantages of the new treatment. It's given me a 'normal' life. With steroid being the fastest way to stop inflammation, many patients already have to deal with cataract and a number will be steroid responders so these potential side effects don't make much difference to many of us.
Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	I am not an expert on every macular condition and do not wish to exclude any group of patients that could benefit from this treatment. I can, however, draw from my twenty five years of personal knowledge on Punctate Inner Choroidopathy (PIC). It is difficult to ascertain at the start of a diagnosis, the best course of treatment for an individual patient. However, if the individual is presenting with a long term "flare up" that persists over a twelve month period, I believe that this new technology would be an amazing treatment. It would reduce risks of further complications due to side effects and improve quality of life due to sight stability.

	If this new treatment is approved, it does concern me how the criteria to access it may be drawn up. I was in a critical sight loss situation. Having already lost all central sight in my right eye, my left eye was losing vision every six weeks. I had nearly also lost my vision in my left eye, due to an ocular pressure of 60, a consequence of the need for constant steroid injections. Coupled with this, I had three young children to support and I was unable to work. People like me, in a desperate situation, are likely to benefit most but it would be terrible to have to be in as much need as I was before this new treatment is offered. There are other groups of patients who will benefit more. For patients without systemic underlying disease which requires immune suppressants, this treatment removes the side effects and risks of those drugs. To be told that to preserve your sight, you must take a powerful drug and practice birth control, can be devastating. This implant allows some patients the basic human right to have children instead of choosing which they want most – sight or children. Patients who struggle to keep on track with immune suppressants or a self-injected biologic either through side effects or personal mismanagement will also benefit. The only patients I can see who will benefit less are those with severe underlying disease who will still need the alternative treatments and those whose uveitis does respond well to long term treatment with steroid.
Equality	
14. Are there any potential equality issues that should be taken into account when	In regard to equality issues, I cannot see issues for equality in gender, race, sexuality disability etc.

considering this condition and the technology?	
Other issues	
15. Are there any other issues that you would like the committee to consider?	
Key messages	

16. In up to 5 bullet points, please summarise the key messages of your statement:

- Greatly improved quality of life – normality.
- Decreased fear of sight loss.
- Lessons the risk of further complications.
- Reduction in clinic appointments
- Cost effective, NHS /State/Patient

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

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in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis

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

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None.

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Academic in confidence (AiC) data are highlighted in yellow throughout the report.

Rider on responsibility for report

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

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Contributions of authors

Rob Riemsma acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Xavier Pouwels acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Svenja Petersohn, Willem Witlox, Dhwani Shah and Nigel Armstrong acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Annette Chalker, Vanesa Huertas Carrera and Heike Raatz acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Alastair Denniston contributed to the writing of the report and provided clinical advice. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Abbreviations

AC	Anterior chamber
ADA	Adalimumab
AE	Adverse events
AIC	Akaike information criterion
AWMSG	All Wales Medicines Strategy Group
BCVA	Best corrected visual acuity
BD	Behçet's disease
BI	Budget impact
BIC	Bayesian information criterion
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CE	Cost effectiveness
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CFT	Central foveal thickness
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMO	Cystoid macular oedema
CRD	Centre for Reviews and Dissemination
CrI	Credible interval
CS	Company's submission
CSR	Clinical study report
DEX 350	Dexamethasone 0.35 mg
DEX 700	Dexamethasone 0.7 mg
DMO	Diabetic macular oedema
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
ETDRS	Early Treatment Diabetic Retinopathy Study
EUR	Erasmus University Rotterdam
FAc	Fluocinolone acetonide
FDA	Food and Drug Administration
HADS	Hospital anxiety and depression scale
HLA	Haplotype association
HR	Hazard ratio
HRQoL	Health-related quality of life
HRU	Healthcare resource use
HTA	Health technology assessment
IC	Indirect comparison
ICD	International classification of diseases
ICER	Incremental cost effectiveness ratio
IOP	Intraocular pressure
ITT	Intention to treat
KSR	Kleijnen Systematic Reviews
LCP(H)	Limited current practice based on HURON
LCP(VI)	Limited current practice based on VISUAL I
LCP(VII)	Limited current practice based on VISUAL II
LOCF	Last observation carried forward
LogMAR	Logarithm of the minimum angle of resolution,
LYG	Life year gained
MeSH	Medical subject headings
MHRA	Medicines and Healthcare Products Regulatory Agency

MTC	Mixed treatment comparison
NA	Not applicable
NEI	National Eye Institute
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
[redacted]	
NMA	Network meta-analysis
NR	Not reported
NSAID	Non-steroidal anti-inflammatory drug
OCT	Optical coherence tomography
OR	Odds ratio
OS	Overall survival
PAS	Patient access scheme
PICOS	Population, intervention, comparators, outcomes, study
PRESS	Peer review of electronic search strategies
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRN	Pro re nata (as needed)
PSIU	Posterior segment-involving uveitis
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
QALY(s)	Quality-adjusted life year(s)
QoL	Quality of life
RCT	Randomised controlled trial
RR	Relative risk; risk ratio
SAE	Serious adverse events
ScHARR	School of Health and Related Research
SD	Standard deviation
SE	Standard error
SF-36	Short form 36
SHTAC	Southampton Health Technology Assessments Centre
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of product characteristics
STA	Single technology appraisal
SUN	Standardisation of uveitis nomenclature
TA	Technology assessment
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor
UK	United Kingdom
UMC	University Medical Centre
USA	United States of America
VA	Visual acuity
VFQ-25	Visual function questionnaire-25
VH	Vitreous haze
VKH	Vogt-Koyanagi-Harada syndrome
WPAI	Work productivity and activity impairment
WHO	World Health Organisation
WTP	Willingness to pay

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1. SUMMARY

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

The NICE scope describes the decision problem as the clinical and cost effectiveness of fluocinolone acetonide ocular implant within its marketing authorisation for treating recurrent non-infectious uveitis. The anticipated license is for [redacted].

The main trial, PSV-FAI-001, included patients with chronic [redacted].

The description of the comparators in the NICE scope is as follows:

- Periocular or intravitreal corticosteroid injections
- Intravitreal corticosteroid implants including dexamethasone intravitreal implant (in line with NICE Technology Appraisal 460)
- Systemic corticosteroids
- Systemic immunosuppressive therapies, including but not limited to, azathioprine, methotrexate, cyclophosphamide, ciclosporin, tacrolimus, mycophenolate mofetil (and mycophenolic acid) (with the exception of ciclosporin, none of the listed immunosuppressive therapies currently have a marketing authorisation in the UK for this indication)
- TNF-alpha inhibitors including adalimumab (in line with NICE Technology Appraisal 460)
- Best supportive care (when all other treatment options have been tried)

In the submission, the company ignores most comparators listed in the NICE scope, and presents only one comparator: Current practice/limited current practice ((L)CP). The company claims that (L)CP, as used in the PSV-FAI-001 trial, is reflective of the various treatment options in the UK. However, the ERG does not agree with this statement for three reasons (see also Chapter 4.3 of this report):

1. The only difference between the two trial arms is that patients in the intervention arm received a fluocinolone acetonide (FAc) implant and patients in the control arm received a sham injection, all other treatments that were allowed in both treatment arms were the same. Therefore, the comparison in the PSV-FAI-001 trial is FAc plus (L)CP versus (L)CP.
2. Patients in both arms were tapered off from any systemic corticosteroids or immunosuppressants, or topical steroids to control uveitis within three months following Day 1 of the trial. Therefore, after completion of the tapering-off phase, the comparison is essentially FAc versus no treatment until first recurrence. This is particularly problematic for chronic patients, where a recurrence is likely as soon as treatment stops. In the intervention arm the original treatment is replaced by FAc implant immediately, while in the control arm the original treatment is replaced with no treatment. This is likely to produce a bias in favour of FAc.
3. The control arm is a constrained version of current practice. For active unilateral disease – particularly if this included macular oedema – local treatment would be common practice. However, for bilateral disease many clinicians would opt for systemic therapy (which was not allowed within the trial unless local had failed). In the HURON trial the clinician could use either local or systemic therapy as they felt appropriate. Therefore, it could be argued that (L)CP in the HURON trial is closer to current UK practice, than (L)CP in the PSV-FAI-001 trial. This is likely to produce a bias in favour of FAc since 59 (67.8%) patients in the FAc implant arm and 31 (73.8%) patients in the sham arm had bilateral disease at baseline.

The main issue with the decision problem is the response of the company to the outcome 'recurrence of uveitis'. It was not adequately assessed in the PSV-FAI-001 trial because the vast majority of recurrences were imputed from the prescription of 'prohibited medication', [redacted]. Given that prohibited medications included systemic treatments such as steroids or immunosuppressants and systemic treatment is more commonly prescribed for those with bilateral disease it cannot be ruled out that much of the prescription of prohibited medication was not for a relapse of the study eye, but for either a deterioration in the underling autoimmune disease or in the fellow eye. This problem is compounded by the fact that all systemic treatments, which accounted for the treatment of 50% of patients in each arm at baseline, were tapered off at the start of the trial. Therefore, it would not be surprising if any underlying autoimmune condition or the condition of the fellow eye worsened, thus requiring the re-administration of the withdrawn treatment. To make matters worse the underlying cause of the uveitis was not captured, as the company stated in the response to clarification letter. Indeed, the company admit in the response to the clarification letter that: '…recurrence was likely overestimated, since some patients could have received systemic corticosteroids or immunosuppressants to treat conditions other than uveitis.' The direction of any bias is difficult to assess, although there is the possibility of a bias in favour of FAc in that a higher proportion of patients in the sham arm had bilateral disease: 59 (67.8%) vs. 31 (73.8%).

Therefore, the ERG believes that the evidence presented in the CS is not a good reflection of the decision problem defined in the final scope.

1.2 Summary of clinical effectiveness evidence submitted by the company

In their submission the company focusses on results from the PSV-FAI-001 trial. PSV-FAI-001 (NCT01694186) is a 36-month Phase 3, multinational, randomised, double-blind, sham-controlled trial to assess the efficacy and safety of a fluocinolone acetonide (FAc) intravitreal implant in the management of patients with [redacted]. The trial followed a parallel group design and the treatment arms were: 0.19 mg fluocinolone acetonide implant which delivers FAc into the vitreous humour for 36 months versus sham injection followed by standard practice. The study included 129 patients from six countries (USA, India, Israel, UK, Germany and Hungary), with 20 patients from the UK (16 (18.4%) in the FAc arm and four (9.5%) in the sham arm).

The primary efficacy analysis was performed on the intention-to-treat (ITT) population at six months and compared the proportion of patients, in the treatment and control groups, who did not have a recurrence of uveitis in the study eye in the six months following Day 1.

For the primary endpoint ITT analysis, data on recurrence of uveitis was imputed as follows:

- A patient who had not previously experienced a recurrence and did not have the required eye examination data for assessing recurrence at Month six (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) for any reason was considered as having a recurrence.
- A patient who had not previously experienced a recurrence and takes a prohibited concomitant medication (systemic or local in the study eye) at any time during the study prior to Month six (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) was considered as having a recurrence.

In terms of recurrence of uveitis in the study eye, results showed statistically significant benefits of FAc over sham injections at six (27.6% vs 90.5%), 12 (37.9% vs 97.6%) and [redacted] However, most recurrences were imputed, so the effectiveness of

each treatment arm is likely to be underestimated. However, we do not know how this influences the relative effectiveness of FAc versus sham injection.

[redacted]experienced recurrence of uveitis in the fellow eye [redacted] 86.4% vs 74.2% at 12 months [redacted]. There was a clear effect in terms of time to first recurrence of uveitis in favour of FAc when compared to sham injection. In terms of visual acuity in the study eye, results seem to favour FAc over sham injection. However, the significance of the results in terms of visual acuity is not reported. It is therefore very possible that none of these results show a statistically significant difference. Also, in terms of the need for further corticosteroid treatment, results favour FAc over sham injection; but the significance of the results is not reported. Health-related quality of life was not assessed in the PSV-FAI-001 trial.

[redacted].

In terms of adverse events, [redacted] The most common ocular TEAEs associated with FAc implant were cataract ([redacted] for FAc versus [redacted] for sham injection) and intraocular pressure increased (IOP) ([redacted] for FAc versus [redacted] for sham injection).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The company submission (CS) and response to clarification provided sufficient details for the ERG to appraise the searches for eligible studies. Searches were carried out in accordance with the NICE guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4 using a good range of databases. Additional searches of HTA agencies, clinical trials registries, conference proceedings and reference checking were reported.

However, no attempt was made to search for most comparators mentioned in the scope (periocular or intravitreal corticosteroid injections, intravitreal corticosteroid implants other than dexamethasone, systemic corticosteroids, systemic immunosuppressive therapies, and TNF-alpha inhibitors other than adalimumab) or to make any comparison (direct or indirect) with these comparators. Only two comparators were included in the literature search performed by the company: adalimumab and dexamethasone. However, the company decided not to perform an indirect comparison with these two remaining comparators. Therefore, the only comparison presented in the company submission (CS), is FAc versus (L)CP from the PSV-FAI-001 trial. The company argues that "the sham injection arm of PSV-FAI-001 is considered largely representative of current practice in the UK for the treatment of uveitic flares and recurrence" (CS, page 83). However, the ERG does not agree with this (see above, Chapter 1.1).

The PSV-FAI-001 trial does not provide evidence for the use of FAc as first-line treatment. All patients in the trial had received treatment with systemic corticosteroid or other systemic therapies during the 12 months prior to enrolment. A comparison with adalimumab is relevant if the committee believes FAc is a relevant third-line treatment option. Regarding best supportive care, our clinical expert advised that best supportive care (BSC; i.e. the absence of active treatment) is very rare in active disease. The ERG believes that the most likely place of FAc in the treatment pathway is in second-line alongside dexamethasone (see Figure 2.1 in Chapter 2 of this report), which makes intraocular dexamethasone the most appropriate comparator.

Results from the PSV-FAI-001 trial show that FAc has significant benefits when compared to sham injection in terms of recurrence of uveitis. However, what was reported as recurrence of uveitis was largely prescription of so-called 'prohibited medication', which as highlighted in the critique of the decision problem, is not an adequate measure of this outcome. This is because its prescription is likely to be indicated for a number of reasons other than recurrence of uveitis in the study eye, including recurrence in the fellow eye and deterioration of an underlying autoimmune condition. It is also unclear whether (L)CP is representative of UK clinical practice, and the CS did not present any comparisons with another active treatment for [redacted] (e.g. dexamethasone, corticosteroids or immunosuppressants). In addition, most recurrences in the trial were imputed, so the effectiveness of each treatment arm is likely to be underestimated. However, we do not know how this influences the relative effectiveness of FAc versus sham injection.

Overall, there is a significant beneficial effect of FAc versus (L)CP and our clinical expert pointed out that there is extensive experience with the risks of cataract and raised IOP associated with FAc in other eye conditions. Therefore, the benefit-risk ratio for FAc (when compared to no treatment) seems good. However, the size of the effect of FAc is unclear due to the imputation methods and the comparator used in the trial.

1.4 Summary of cost effectiveness evidence submitted by the company

Three systematic literature reviews (SLR) were performed with the objective to identify and select relevant: 1) cost effectiveness analysis (CEA) studies including [redacted], 2) health-related quality of life (HRQoL) and utility studies in patients affected with recurrent non-infectious uveitis, and 3) resource use and costs studies including [redacted]. None of the identified studies considered the cost effectiveness of fluocinolone acetonide (FAc) implant, nor the effect of FAc implants on health-related quality of life. The literature search yielded one study that contained costs and resource use sourced in the UK, which was TA460.

The company developed a de novo Markov cohort state transition model comprising five health states: 'on treatment', 'subsequent treatment', 'remission', 'permanent blindness' and 'death'. This model structure was suggested by the assessment group commissioned in TA460. All patients entered the model in the 'on treatment' health state. Patients who were still on treatment and did not experience a recurrence of uveitis for a period of two years transitioned to the 'remission' health state. Upon recurrence of uveitis in both the 'on treatment' and 'remission' health states, patients transitioned to the 'subsequent treatment' health state. In the 'subsequent treatment' health state, patients were at risk of transitioning to the 'permanent blindness' health state. This implies that patients had to fail first-line treatment before being at risk of becoming permanently blind. Death was an absorbing health state, all patients in all health states were subject to age-matched UK general population mortality probabilities.

The cost effectiveness model considered patients affected by [redacted]. This was in line with the anticipated marketing authorisation.

The intervention, FAc, a long lasting (36 months) implant for the treatment of [redacted], was considered as per its anticipated licensed indication. In the cost effectiveness model, it was assumed patients would receive only one implant. The comparator consisted of limited clinical practice ((L)CP), as implemented in the sham placebo arm of the PSV-FAI-001 trial. This implied that (L)CP did not include any treatment for [redacted] because systemic immunosuppressant therapies and steroidal treatments were prohibited for all study participants. Supplemental treatments were included at the beginning of the cost effectiveness model in both study arms. Supplemental treatments were the treatments that patients received at study initiation but that were prohibited during the trial follow-up. These treatments were tapered off in the first three months of the follow-up.

The analysis took a NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and health benefits. The cycle length of the model was two weeks with a lifetime time horizon (51 years in the base-case analysis). A half-cycle correction was not applied.

Treatment effectiveness was based on the PSV-FAI-001 trial and the literature. The PSV-FAI-001 trial informed the time to first recurrence, which informed the proportion of patient in the 'on treatment', 'remission' (after two years) and 'subsequent treatment' health states. The company digitised the Kaplan-Meier (KM) curves of both arms of the PSV-FAI-001 trial to reconstruct the individual patient level data representing time to first recurrence. In the FAc arm, a piecewise model was used to estimate time to first recurrence. During the first 120 days of the cost effectiveness model, the digitised KM curve of the PSV-FAI-001 trial directly informed time to first recurrence while a parametric time-to-event model was fitted to the remainder of the KM curve and was used for the remainder of the time horizon. In the (L)CP arm, time to first recurrence was informed by a parametric time-to-event model that was fitted from the start of the digitised KM data. The following distributions were fitted to the KM data in both treatment arms: exponential, Weibull, log-logistic, lognormal, gamma, Gompertz, generalised gamma, and generalised F. For its base-case analysis, the company selected the exponential distribution for the FAc arm and the log-logistic distribution for the (L)CP arm based on visual inspection and statistical fit (the exponential distribution had the best statistical fit statistics after the 120 days cut-off in the FAc arm and the log-logistic distribution had the best statistical fit statistics in the (L)CP arm). The company assumed that all patients who were still on treatment after two years and who did not experience a recurrence yet would enter the 'remission' health state. The transition probability from the 'subsequent therapy' to the 'permanent blindness' health state was informed by Dick et al. (annual rate of 0.0066). Alternative rates were used in scenario analyses. The transition probability to the 'death' health state from all other health states was equal to the general UK population mortality probability.

The main source of evidence informing the probability of experiencing treatment-related adverse events (AEs) was the PSV-FAI-001 trial. All treatment-related AEs that occurred in at least 5% of patients in either treatment arm were included in the cost effectiveness model. Patients were at risk of experiencing AEs in each cycle of the 'on treatment' and 'remission' health states of the cost effectiveness model.

There was no quality of life data collected in the PSV-FAI-001 trial and none of the studies identified in the SLR provided utility values in accordance with the NICE reference case. For the 'on treatment' and 'remission' health state utility values, the company mapped VFQ-25 data from the MUST trial to EQ-5D data, using the same regression equation as in TA460 (based on the HURON trial). The 'permanent blindness' health state utility value (0.38) was based on Czoski-Muray et al., as in TA460. The company assumed that patients in the 'remission' health state accrued age-matched UK general

population utility values. There were no utility decrements for experiencing adverse events included in the cost effectiveness model.

The costs included in the model were acquisition and administration costs of the intervention, monitoring costs, costs of subsequent treatment, costs of permanent blindness and costs of managing adverse events. The list price of a FAc implant was £5,500, but the company assumed a patient access scheme (PAS) price of a FAc implant of [redacted] in its base-case analysis. Administration costs of the implant were £99.58, totalling treatment costs of FAc to [redacted]. There were no acquisition or administration costs associated with (L)CP. Monitoring visits were assumed to take place at weeks six and 12, and then every 12 weeks in the 'on treatment' health state. Supplemental treatment costs were applied to the first 12 weeks of the model. These costs were different for FAc and (L)CP and were based on the distribution of treatments that patients received at study initiation in the PSV-FAI-001 trial. Transition costs were applied upon transition to the 'subsequent treatment' health state in the FAc arm but not in the (L)CP arm. The distribution of treatments used to calculate these transition costs was based on the distribution of supplemental treatments. In the 'subsequent treatment' health state, patients received a mix of immunosuppressant and systemic steroid treatment; monitoring visits were assumed to take place every six weeks. Transition costs were applied when patients transitioned to the 'permanent blindness' health state, such as the costs of registration as a blind person, the costs of low vision aids, low vision rehabilitation and the costs of residential care. The costs of the 'permanent blindness' health state included monitoring visits every six weeks and the costs of depression, hip replacement and community care. AE costs were applied in the 'on treatment' and 'remission' health states.

The deterministic base-case cost effectiveness results of treatment with FAc versus (L)CP amounted to a deterministic incremental cost effectiveness ratio (ICER) of £7,183 per quality-adjusted life year (QALY) gained. FAc was associated with larger QALY gains ([redacted]) and higher costs than (L)CP ([redacted]). The main share of the [redacted] QALY increment stemmed from the larger accrual of QALYs in the 'remission' health state in the FAc arm compared to (L)CP ([redacted] versus [redacted]).

The company performed probabilistic sensitivity analysis (PSA), deterministic sensitivity analyses (DSA), as well as scenario analyses. The probabilistic ICER (1,000 iterations) of FAc versus (L)CP was [redacted] per QALY gained. FAc resulted in [redacted] QALY gained and incremental costs of [redacted] versus (L)CP. Based on the DSA, the most influential parameters on the cost effectiveness results were the 'subsequent treatment' health state utility value, the 45-54 years age matched utility value (which informed the 'remission' health state utility), and the 'on treatment' health state utility value.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The majority of the cost effectiveness searches in the CS were well documented and easily reproducible, and were carried out in line with the NICE guide to the methods of technology appraisal. Searches were reported for a good range of databases. Additional searches of conference proceedings, HTA agencies and reference checking were also reported.

In the absence of cost effectiveness analyses evaluating FAc for the treatment of [redacted], the ERG agrees that a de novo cost effectiveness analysis was necessary. The ERG is concerned about several assumptions underlying the model structure even though it was informed by a previous technology assessment (TA460). The major concern of the ERG is that the company aimed at modelling the consequence of (the treatment of) uveitis in a single eye. The ERG believes that considering both eyes is necessary to fully capture the impact of vision loss on health-related quality of life, survival and costs, especially when patients suffer from, or are at risk of developing, bilateral disease, as is the case for

uveitis patients. The ERG further questions the validity of other structural assumptions such as the definition of the 'remission' health state, the lack of transition from the 'on treatment' to the 'permanent blindness' health state, and the lack of transition from the 'subsequent treatment' to the 'remission' health state.

The population considered in the cost effectiveness model was narrower than the one defined in the NICE final scope. The company did not provide the subgroup analyses listed in the final scope.

In its base-case analysis, the company considered the cost effectiveness of a single FAc implant while re-treatment with subsequent implants would likely be considered for patients who responded to the first FAc implant. There is scarce and indirect evidence showing that there is a low probability of FAc implant removal due to adverse events. Additionally, the ERG wondered whether (L)CP was representative of UK clinical practice for the treatment of [redacted]. A major concern of the ERG was the lack of comparison with dexamethasone intravitreal implant and other comparators listed in the NICE final scope.

The ERG is concerned by the estimation of the time to first recurrence in the company's cost effectiveness model because, as stated in the critique of the decision problem, it is unclear what the relationship is between recurrence of uveitis and prescription of prohibited medication, which was used to impute recurrence. Due to this, the number of recurrences may have been overestimated. This may lead to a biased estimation of time to first recurrence, of which the direction and magnitude is unknown. Additionally, the company identified a 'drop' (around 120 days) in the KM curve representing time to first recurrence of FAc. Due to this 'drop', the company used a piecewise model to estimate time to first recurrence for FAc but used a standard parametric time-to-event model for (L)CP. Using different approaches to model the effectiveness of the comparators might impact outcomes regardless of clinical effectiveness. Another uncertainty concerns the representativeness of this 'drop' for UK clinical practice, as this 'drop' may be caused by trial characteristics and may not represent a change in the hazard function due to treatment effectiveness on recurrence of the disease. Uncertainty in the estimation of time to first recurrence was also raised by the use of digitised KM curves instead of the individual patient level data. Finally, uncertainty remains concerning the effectiveness of FAc implants after three years, and concerning the rate of incidence of permanent blindness in the current patient population.

The available evidence shows that the long-term safety profile of FAc implants is sparse and indirect. The probability of adverse events leading to long-term health impact seems low.

The HRQoL of [redacted] (treated with FAc implants) remains uncertain, because HRQoL data were not collected in PSV-FAI-001 trial and the literature does not provide utility values meeting the NICE reference case requirements. The ERG was further concerned about the representativeness of the utility values obtained from the literature because these were based on a patient population who had different characteristics than the PSV-FAI-001 trial population. Additionally, the population on which the mapping algorithm was developed and the one on which the mapping algorithm was applied were not similar, which may lead to a bias in the EQ-5D estimations. Finally, the health benefits obtained in both treatment arms were overestimated because disutility for adverse events were not included in the company's base-case analyses and because the company used health state utility values that may have exceeded the age-adjusted UK general population utility values.

The main concern of the ERG regarding the estimation of resource use and costs relates to the estimation of the costs of permanent blindness. These costs were obtained from an age-related macular degeneration population, and contained costs of hip replacement, community care, and residential care,

which may not be relevant cost items for the current population given their age. The ERG further wondered about the representativeness of the treatment costs in the subsequent treatment health states since the company assumed that 50% of patients would not receive treatment in this health state. Costs associated with [redacted] treatment may have been underestimated due to the omission of monitoring visits in the remission health state and of blood tests during immunosuppressive treatment in the subsequent treatment health state. The ERG also identified multiple errors in the cost calculations incorporated in the company's cost effectiveness model.

The probabilistic sensitivity analysis (PSA) did not include the rate of permanent blindness; in addition, all parameters included in the PSA, with the exception of FAc and (L)CP parametric time-to-event models, had standard errors equalling to 10% of the mean. The omission of the rate of permanent blindness in the PSA may lead to an underestimation of uncertainty, while using 10% of the standard error of the mean does not reflect the true parameter uncertainty surrounding the parameter estimates. The ERG is concerned that the scenarios presented by the company do not reflect all uncertainties related to structural and methodological assumptions and choices. For instance, the company did not explore the consequences of using utility decrements for adverse events.

The ERG identified multiple errors in the implementation of the cost effectiveness model, which raises doubts concerning the quality of the performed internal validation. Additionally, the company did not provide any details about the expert opinions' elicitation, consequently, the ERG could not verify the opinion of the experts concerning the face validity of the inputs, assumptions, and results of the company's cost effectiveness model. The ERG is concerned about the non-transparent reporting, and hence the non-reproducibility, of the validation efforts performed using the data from TA460 and about the lack of cross-validation against TA460.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

The company submission (CS) and response to clarification provided sufficient details to ensure that searches were well reported and easily reproducible. Searches were carried out on a good range of databases. The submission reported a wide range of supplementary searches including searches of HTA agencies, clinical trials registries and conference proceedings, along with checking the reference lists of relevant studies.

The submission mainly relies on one randomised controlled trial comparing FAc with (L)CP with three-year follow-up.

1.6.2 Weaknesses and areas of uncertainty

The ERG had some concerns about the language bias of restricting searches to English language only, as this is not in line with current best practice. Further minor errors and limitations were noted in the searching, some of which the company confirmed were due to reporting errors and corrected in their response to clarification. With regard to the remaining limitations, whilst taken individually these were unlikely to have impacted on the overall recall of results, the ERG is unable to say what the overall impact may have been. Unfortunately, the ERG was unable to undertake independent searches and review the results within the STA timeline, as this would be outside of the ERG remit. The broad range of additional searching reported in the CS may have helped improve recall.

The main uncertainty from a clinical effectiveness point of view is the inadequate measurement of the most important outcome, recurrence of uveitis. It remains largely unknown what the effect of FAc is on the rate of recurrence of uveitis because this was often not recorded in the trial and no attempt was made

to differentiate the prescription of medication for the treatment of recurrence from that for any other reason including deterioration in any underlying autoimmune disease. There is also uncertainty regarding the relative effectiveness of FAc versus intraocular dexamethasone, which is not addressed in the company submission.

Regarding the economic model, the major uncertainties concerning the intervention are the proportion of patients who would be eligible to receive multiple implants, the maximum number of implants that a patient could receive, and after how much time on treatment would patients be eligible to receive subsequent implant(s). Another major area of uncertainty concerning the cost effectiveness of FAc is that there was no comparison with another active treatment for [redacted] (e.g. dexamethasone implant, corticosteroids or immunosuppressants). In addition, it is unclear whether (L)CP is representative of UK clinical practice for the treatment of [redacted] patients. There was no quality of life data collected in the PSV-FAI-001 trial. Another major weakness of the company submission is the non-transparent description of model inputs, especially the calculations of the costs, and the multiple errors in the cost effectiveness model.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG incorporated various adjustments to the company's base-case analysis, most importantly the inclusion of dexamethasone as a comparator. All ERG analyses are presented deterministically since the company's model did not allow for a probabilistic comparison of three treatments. The ERG considered that multiple ERG base-case analyses were equally plausible when estimating the cost effectiveness of FAc implant versus dexamethasone implant and (L)CP. Additionally, the ERG considered that multiple assumptions concerning the effectiveness of dexamethasone were plausible. Therefore, the ERG presents its base-case analyses based on three assumptions concerning the effectiveness of dexamethasone. In the first set of analyses, the effectiveness of dexamethasone versus (L)CP was estimated based on the results of TA460 (estimated hazard ratio of 0.456 for dexamethasone versus (L)CP). In the second set of analyses, dexamethasone was assumed as effective as FAc (hazard ratio of 1.0 for dexamethasone versus FAc). In the third set of analyses, a hazard ratio of dexamethasone versus FAc of 0.7 was chosen. The ERG recognises that these analyses are all based on strong assumptions and that their results should be considered carefully. However, the ERG believes that these alternative assumptions concerning the effectiveness of dexamethasone reflect a range of possible outcomes considering the lack of evidence on the comparative effectiveness and cost effectiveness of FAc compared to (L)CP and dexamethasone.

When assuming a hazard ratio of 0.456 for dexamethasone versus (L)CP, the deterministic fully incremental results of all ERG base-case analyses show that FAc extendedly dominated dexamethasone implants. When assuming equal effectiveness between dexamethasone and FAc, dexamethasone led to the same health benefits as FAc but was slightly cheaper than FAc. In this second set of analyses, the ICER of dexamethasone versus (L)CP remained under £30,000 per QALY gained. Finally, when using a hazard ratio of 0.7 for dexamethasone versus FAc, FAc was extendedly dominated by dexamethasone. In this third set of analyses, the ICERs of dexamethasone versus (L)CP remained under £26,000 per QALY gained. In all ERG base-case analyses, the deterministic ICERs of FAc versus (L)CP remained under £31,000 per QALY gained. Apart from adding dexamethasone as a comparator, the most influential adjustment made by the ERG in its base-case analyses were fixing errors in the company base-case, reducing the 'permanent blindness' health state costs for patients younger than 65, including utility decrements for AEs, and assuming the administration of multiple FAc implants.

The scenarios performed by the ERG illustrate the influence of three major areas of uncertainty in the current assessment: the influence of alternative health state utility values, the inclusion of adverse event utility decrements, and the assumptions concerning treatment effectiveness after three years.

In conclusion, the uncertainty surrounding the cost effectiveness of FAc implant is substantial; mainly because relevant comparators for this assessment have not been included, the lack of reliable effectiveness data, the lack of utility data concerning the population of interest, and not including utility decrements for adverse events.

2. BACKGROUND

2.1 Critique of company's description of underlying health problem.

In the CS,[1] the company emphasises uveitis as a potentially sight-threatening condition whose complications can be responsible for a fifth of all legal blindness and is the leading cause of visual impairment in the United Kingdom (UK).[2, 3]

The company describes uveitis as the inflammation of the components of the eye that are comprised in the uvea, which includes the iris, ciliary body, and choroid.[4] According to the Standardisation of Uveitis Nomenclature, the differentiation of types of uveitis is based on the affected eye structure.[5] The company has made [redacted] the focus of the submission due to the increased likelihood of experiencing an irreversible complication such as glaucoma or retinal damage.[3, 6] The company states that [redacted] comprises intermediate, posterior and panuveitis but that some cases of anterior uveitis, where the posterior segment of the eye is affected as well could also be considered to be a form of [redacted] (no reference provided in the CS). The company provided a picture to illustrate the anatomical classification of uveitis (see CS, Figure 1, page 19).[3, 7] Our clinical expert pointed out that the figure may be misleading as the labelling suggests that the anatomical classification is based on a sequence of structures moving from back to front, which it is not. As described in the background posterior uveitis means primarily affecting the retina and/or choroid, intermediate uveitis means primarily affecting the vitreous etc.

The company states that an estimate regarding the epidemiology of [redacted] in England had not been identified but that in Europe 3.8 per 10,000 people have uveitis and in the US 91% of the uveitis cases are non-infectious.[8, 9] According to the NICE scope slightly more people, i.e. 4.8 per 10,000, have uveitis in the European Union. The company cites a retrospective review of referrals to the Manchester Uveitis Clinic (MUC) and suggests that based on the proportions of posterior, intermediate, and panuveitis in the MUC study the posterior segment of the eye is affected in 54% of cases of uveitis.[10] The company then concludes that based on this information and the adult population size of England approximately 8,500 prevalent cases of [redacted] with 51 new cases per year can be expected and refers to section 3.12 of the CS for further details. However, section 3.12 of the CS does not exist and it is unclear how these estimates were calculated. The company feels that its estimate of 8,500 prevalent cases is confirmed by the estimate from Santen (in their comment on the draft scope for TA460[11]) that "between 1,500 and 5,000 people are diagnosed with non-infectious uveitis intermediate or posterior uveitis in England each year" if the numbers for panuveitis should be added to those for non-infectious uveitis intermediate and posterior uveitis.[10, 12]

The ERG feels that data from a tertiary referral centre are not likely to be transferable to the general population in the England; although it may be typical of the population eligible for FAc. The MUC is a specialist uveitis clinic and 77% of the patients seen there came via tertiary referrals.[10] This is likely to affect the disease spectrum seen and may not be comparable between the different studies cited: The MUC study for example also reported the causes of uveitis. And while nearly 20% of the cases at the MUC were infectious or associated to infections, the company claims that 91% of uveitis cases are non-infectious based on a study by Thorne et al.[8] A review by Tsirouki et al.[13] reports that in Western countries anterior uveitis accounts for 50-60% of uveitis in tertiary referral centres, which would be roughly in keeping with the results from the MUC study, but that in primary care settings it accounts for 90% of all cases. Chronic forms of uveitis are also more prevalent in tertiary care centres according to this review with one identified study reporting that 83.4% of cases were acute in community practices and only 34.9% in a university clinic.[13] The ERG feels that using the proportions from the MUC study

is therefore likely to overestimate the size of the population eligible for fluocinolone. The CS further emphasises that most patients who are affected by uveitis are between the working ages of 16-65 years old, with over a third adults between the ages of 16-35.[10]

The CS states that the autoimmune conditions that can be associated with uveitis include ankylosing spondylitis, reactive arthritis, Crohn's disease and ulcerative colitis, psoriasis and psoriatic arthritis, multiple sclerosis, Behçet's disease, sarcoidosis, and juvenile idiopathic arthritis.[10]

2.2 Critique of company's overview of current service provision

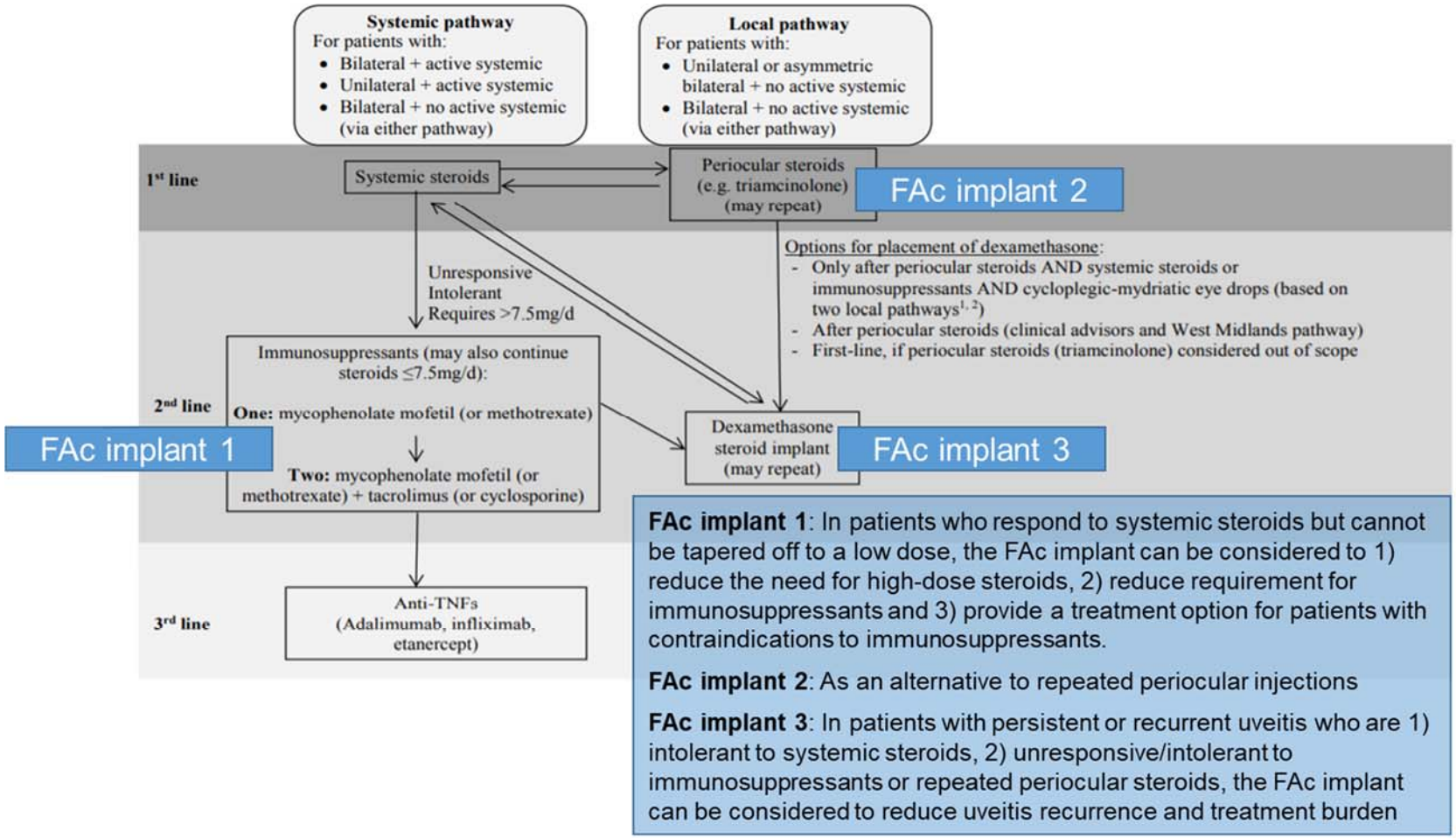
Figure 2.1 shows the treatment pathway for patients with recurrent non-infectious uveitis as presented by the company in the submission.[1] This pathway was based on TA460[14] and was considered by NICE to be representative for the treatment of non-infectious uveitis in England (TA460, Final Appraisal Determination (FAD), page 7[15]). However, the place of fluocinolone acetonide (FAc) in the pathway is unclear. The company submission describes that sustained-release intravitreal implants such as FAc constitute an alternative to periocular steroids and to intravitreal steroid injections and may offer an alternative for patients who may benefit from the dexamethasone implant. The NICE scope lists a wide range of comparators (periocular or intravitreal corticosteroid injections, intravitreal corticosteroid implants including dexamethasone intravitreal implant, systemic corticosteroids, systemic immunosuppressive therapies, TNF-alpha inhibitors including adalimumab and best supportive care), suggesting that FAc may be used as a first, second or third-line treatment. According to expert opinion (Personal communication with A. Denniston, 22 December 2018), it is common practice for periocular steroids to be used before intraocular dexamethasone implant as steroid-related side effects are fewer and the efficacy, though less, may be sufficient.[16] Also, in the event of a dramatic rise in intraocular pressure after periocular steroids, this can be used as an indication to avoid longer-lasting, higher dose exposures of intraocular steroids. This argument is even stronger for the longer acting FAc. This means the most likely place of FAc in the treatment pathway is in second-line alongside dexamethasone.

In the clarification letter we asked the company to specify where in the treatment pathway FAc should be placed (Question A10). In their response, the company provided some suggestions where FAc implant could be considered (see Figure 2.1 of this report). The suggestions included first-line ('FAc implant 2') and second-line ('FAc implant 1' and 'FAc implant 3') options, but not as a third-line alternative. It should be noted, that the company has provided no evidence for the use of FAc in first-line, all patients in the PSV-FAI-001 had received previous treatment. We believe 'FAc implant 3' alongside dexamethasone, is the most likely place of FAc in the treatment pathway, which makes intraocular dexamethasone the most appropriate comparator.

Regarding best supportive care (BSC), our clinical expert advised that BSC (i.e. the absence of active treatment) is very rare in active disease. Local corticosteroid treatment is well-established as first or second-line therapy depending on context, and therefore comparison of FAc to third-line treatments (notably adalimumab) is less relevant.

According to the company treatment decisions will also depend on whether treatment is needed for one or both eyes, i.e. whether the condition is unilateral or bilateral, and whether or not systemic disease is present. The company also notes other variables that will impact treatment decisions, such as whether the uveitis is chronic (i.e. uveitis relapses promptly when therapy is discontinued) or recurrent (i.e. where periods of ocular inflammation are separated by periods without inflammation despite the patient being considered "off-treatment.").[17] The company states that generally local treatment is preferred in patients without systemic disease and in particular if the uveitis is unilateral or highly asymmetric (no reference provided in CS).

Figure 2.1: Treatment of non-infectious uveitis in England



Source: Response to Clarification Letter (Question A10, page 16) and TA460 (ScHARR report, Figure 2, page 22)

TNF = tumour necrosis factor.

Note: Systemic pathway: Treatment pathway proposed for patients with uveitis in one or both eyes in the presence of an active systemic disease or those with severe bilateral uveitis with or without an underlying active systemic condition. Local pathway: Treatment pathway proposed for patients with unilateral uveitis or asymmetrically 'severe' bilateral uveitis with no active systemic condition. Unilateral uveitis may be a first episode or a re-activation of a previous inflammation (flare).

The treatment pathway cited by the company and based on TA460 specifies two different pathways that can be followed for bilateral uveitis without systemic disease – either the local or the systemic pathway.[14] The first-line treatment considered for non-infectious uveitis is corticosteroids, which may be administered systemically or locally.[5, 18] Based on expert opinion (Personal communication with A. Denniston, 26 January 2019), even though the local pathway is acceptable in the case of bilateral uveitis without systemic disease this is uncommon due to (1) patient choice – patients are much more accepting of regular injections to one eye, than to both; and (2) the sense that the overall risk of local therapy is significantly increased if both eyes are treated, which may shift the balance of risk vs benefit towards systemic therapy.

The company describes that when systemic corticosteroids are found to be ineffective for treatment, immunosuppressants can be used instead. However, immunosuppressants are linked to substantial AEs.[19, 20]

The company submission states that "Periocular and intravitreal steroids are effective but provide only short-term control, often requiring repeated injections every three to six months (…)" (CS, page 21).[1] In contrast, the company explains that FAc has a duration of action of up to 36 months and, because of this, a reduction in the number of healthcare appointments and treatment-related burden can be anticipated. According to the company submission, adverse effects resulting from repeated (periocular or intravitreal) injections may include retinal tears, haemorrhage, endopthalmitis, ptosis and fibrosis.[21, 22] The company states that, compared with dexamethasone implant, FAc results in "(…)less fluctuations over time in parameters such as macular oedema and visual acuity over time" (CS, page 22).[1] However, the supporting evidence is a case report of a patient with diabetic macular oedema (DMO) which does not provide sufficient evidence for this statement.

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
Population	Adults with recurrent non-infectious uveitis	[redacted]	The proposed marketing authorisation for the fluocinolone acetonide (FAc) 0.19 mg implant (ILUVIEN®) is restricted to [redacted]	According to the company the population is in line with the expected indication.
Intervention	FAc intravitreal implant in applicator	FAc intravitreal implant (ILUVIEN) in applicator	N/A	The intervention is in line with the scope.
Comparator(s)	• Periocular or intravitreal corticosteroid injections • Intravitreal corticosteroid implants including dexamethasone intravitreal implant (in line with NICE technology appraisal 460) • Systemic corticosteroids • Systemic immunosuppressive therapies, including but not limited to, azathioprine, methotrexate, cyclophosphamide, ciclosporin, tacrolimus, mycophenolate mofetil (and mycophenolic acid) (with the exception of ciclosporin, none of the listed immunosuppressive therapies currently have a	Current practice/limited current practice ((L)CP)	The company model assesses ILUVIEN versus (L)CP, using the pivotal trial comparator (active sham arm with corticosteroids and immunosuppressants for treatment of recurrences). In the event of a recurrence of uveitis both the ILUVIEN and the sham arm patients were allowed to receive: • periocular or intravitreal corticosteroid injections; or • topical corticosteroids as first line treatment. Additionally, systemic immunosuppressants or systematic steroids could also be provided on first-line therapy failure. A previous MTA conducted by NICE recognised the challenges in defining current clinical practice in the UK, given the absence of national treatment guidelines and heterogeneity in both the patient population and subsequent therapies. The nature of the	The company ignores most comparators listed in the NICE scope, and presents only one comparator: (L)CP. The company claims that (L)CP, as used in the PSV-FAI-001 trial, is reflective of the various treatment options in the UK. However, it is not clear from the submission or from the trial CSR which treatments patients in the sham arm of the trial received.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	marketing authorisation in the UK for this indication) • TNF-alpha inhibitors including adalimumab (in line with NICE Technology Appraisal 460) • Best supportive care (when all other treatment options have been tried)		pivotal trial's active sham arm is reflective of the various treatment options in the UK. Therefore, in common with the previous MTA, we have defined our active sham arm comparator as current clinical practice in the UK. We propose not to include best supportive care as a comparator for ILUVIEN. We recognise that best supportive care may also be considered a comparator; however, due to the risk of sight loss associated with uveitis, standard practice is active treatment, rather than supportive only. Indeed, patients in both arms of the pivotal PSV-FAI-001 trial could receive standard practice, including corticosteroids and immunosuppressants, in case of uveitis recurrences. Furthermore, due to the lack of a nationally agreed clinical pathway, it remains a challenge to adequately characterise and quantify best supportive care.	
Outcomes	The outcome measures to be considered include: • recurrence of uveitis (the affected eyes) • visual acuity (the affected eyes) • visual acuity (both eyes) • need for further corticosteroid treatment • mortality • adverse effects of treatment	The company presents evidence on the measures of efficacy against uveitis and its complications that were included in the PSV-FAI-001 trial at 6, 12 and 36 months. The comparator arm was active sham with corticosteroids and immunosuppress-ants for treatment of recurrences. The primary outcome measure was: • Proportion of patients who have a recurrence of uveitis in the study eye	As the relevant data from the PSV-FAI-001 trial is available, the company presented a detailed analysis on recurrence of uveitis (including recurrence rate, time to recurrence and number of recurrences per patient). The data on resolution of macular oedema, based on measurement of CFT, is also presented to demonstrate the efficacy of ILUVIEN against one of the possible complications of uveitis. In addition to the need for further corticosteroid treatment (local or systemic), the	The following outcomes listed in the NICE scope were not reported: • visual acuity (both eyes) • health-related quality of life Health-related quality of life values were incorporated in the cost effectiveness model. These values were

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	• health-related quality of life	within 6 months after receiving study treatment. Additional exploratory outcomes presented include: • Proportion of patients who have a recurrence of uveitis in the study eye within 12 or 36 months • Proportion of patients who have a recurrence of uveitis in the fellow eye (within 6, 12 and 36 months) • Number of recurrences of uveitis (within 6, 12 and 36 months) • Time to recurrence of uveitis (within 6, 12 and 36 months) • Number of supplemental treatments (local or systemic corticosteroids, or systemic immunosuppressants) required to treat recurrences of uveitis (within 6, 12 and 36 months) • Mean change from baseline in BCVA letter score in the study eye (at 6, 12 and 36 months) • Resolution of macular oedema, as measured by OCT imaging (at 6, 12 and 36 months)	use of systemic immunosuppressive medication was also captured in the PSV-FAI-001 trial and is presented in this submission. Health-related quality of life data was not available from the PSV-FAI-001 trial or the PSV-FAI-005 trial and is not presented in the clinical effectiveness section; however, it is incorporated into the economic model.	informed by the literature, and UK age matched general population utility values. Additionally, VFQ-25 values from the MUST trial were mapped to EQ-5D values, using a mapping algorithm developed based on the HURON trial.
Subgroups to be considered	If evidence allows, consideration will be given to subgroups according to: • Type of uveitis (acute or chronic; single incident or recurrent; posterior	No subgroup analyses performed	The description of clinical effectiveness and base-case cost effectiveness model aligns with the expected marketing authorisation for ILUVIEN; [redacted]	The company declined to do subgroup analysis based on the type of uveitis. Subgroup analysis for baseline visual acuity and

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG Comment
	segment, posterior, intermediate or pan uveitis) • Baseline visual acuity • Previous treatment history Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.		[redacted]. Therefore, subgroup analysis based on the type of uveitis as described in the final NICE scope (acute or chronic; single incident or recurrent; posterior segment, posterior, intermediate or pan uveitis) is not considered appropriate. While the manufacturer acknowledges that the subgroups analysis for: • Baseline visual acuity • Previous treatment history are potentially relevant to the decision problem, there is insufficient clinical data available to consider them in the appraisal. Nonetheless, descriptive analysis of the primary PSV-FAI-001 endpoint only (proportion of patients with recurrence of uveitis at 6 months) is presented in this submission (prior treatment history) and Appendix E (baseline visual acuity)	previous treatment history were not done due to limited data availability.

Source: CS, Table 1, pages 10-14.

BCVA = best corrected visual acuity; FAc = fluocinolone acetonide; MTA = multiple technology assessment; N/A = not applicable; NICE = National Institute for Health and Care Excellence; [redacted]; NHS = National Health Service; (L) CP = limited current practice; OCT = optical coherence tomography; PAS = patient access scheme.

3.1 Population

The population defined in the scope is: Adults with recurrent non-infectious uveitis.[23] The population in the CS is limited to '[redacted]'.[1]

According to the company the decision problem addressed in the company submission has a narrower population than the NICE scope, and is in line with the expected license indication for fluocinolone acetonide (FAc). However, [redacted]

Therefore, the relevant population for this appraisal is unclear.

The population included in the main trial for the submission (PSV-FAI-001) is patients with chronic [redacted]. In the response to the clarification letter (page 14), the company states that "chronic disease relapses promptly when therapy is discontinued", while the "key feature of recurrent acute disease is the presence of episodes of active inflammation separated by periods of no inflammation when not on therapy".[24]

[redacted]

3.2 Intervention

The intervention (fluocinolone acetonide (FAc)) is in line with the scope.

A single FAc implant contains 0.19 mg of the active ingredient (fluocinolone acetonide) and delivers a continuous, low dose of the medication (0.2 µg of FAc per day) into the vitreous humour over 36 months. The implant is administered through intravitreal injection.

Following FAc injection, patients should be monitored for potential initial complications related to the injection procedure, such as endophthalmitis, increased intraocular pressure (IOP), retinal detachments, and vitreous haemorrhages or detachments. Biomicroscopy with tonometry should be performed between two and seven days after the implant injection. Immediate IOP measurement may be performed at the discretion of the treating ophthalmologist. Thereafter it is recommended that patients are monitored at least quarterly for potential complications, due to the extended duration of FAc release. Patients who have FAc implanted in a phakic eye should be closely monitored for cataract development and may require cataract surgery with intraocular lens implantation.

3.3 Comparators

The description of the comparators in the NICE scope is as follows:

- Periocular or intravitreal corticosteroid injections
- Intravitreal corticosteroid implants including dexamethasone intravitreal implant (in line with NICE Technology Appraisal 460)
- Systemic corticosteroids
- Systemic immunosuppressive therapies, including but not limited to, azathioprine, methotrexate, cyclophosphamide, ciclosporin, tacrolimus, mycophenolate mofetil (and mycophenolic acid) (with the exception of ciclosporin, none of the listed immunosuppressive therapies currently have a marketing authorisation in the UK for this indication)
- TNF-alpha inhibitors including adalimumab (in line with NICE Technology Appraisal 460)
- Best supportive care (when all other treatment options have been tried)

In the submission, the company ignores most comparators listed in the NICE scope, and presents only one comparator: Current practice/limited current practice ((L)CP). The company claims that (L)CP, as used in the PSV-FAI-001 trial, is reflective of the various treatment options in the UK.

However, it is not clear from the submission or from the PSV-FAI-001 trial Clinical Study Report (CSR) which treatments patients in the sham arm of the trial received. Therefore, the comparator is unclear. In addition, patients in the intervention arm could also receive the same (L)CP as patients in the control group. Therefore, the trial is actually: FAc+(L)CP versus (L)CP, making it impossible to find data for a comparison of FAc vs. any single comparator specified in the scope

3.4 Outcomes

The NICE final scope lists the following outcome measures:

- recurrence of uveitis (the affected eyes)
- visual acuity (the affected eyes)
- visual acuity (both eyes)
- need for further corticosteroid treatment
- complications of uveitis
- mortality
- adverse effects of treatment
- health-related quality of life.

Most of these were assessed in the PSV-FAI-001 trial. However, the first and most important outcome, 'recurrence of uveitis' was not adequately assessed in the sense that the vast majority of recurrences were imputed from the prescription of 'prohibited medication', up to [redacted]. Given that prohibited medications included systemic treatments such as steroids or immunosuppressants and systemic treatment is more commonly prescribed for those with bilateral disease it cannot be ruled out that much of the prescription of prohibited medication was not for a relapse of the study eye, but for either a deterioration in the underling autoimmune disease or in the fellow eye. This problem is compounded by the fact that all systemic treatments, which accounted for the treatment of 50% of patients in each arm at baseline, were tapered off at the start of the trial. Therefore, it would not be surprising if any underlying autoimmune condition or the condition of the fellow eye worsened, thus requiring the re-administration of the withdrawn treatment. To make matters worse the underlying cause of the uveitis was not captured, as the company stated in the response to the clarification letter. Indeed, the company admit in the response to clarification letter that: "…recurrence was likely overestimated, since some patients could have received systemic corticosteroids or immunosuppressants to treat conditions other than uveitis."[24] The direction of any bias is difficult to assess, although there is the possibility of a bias in favour of FAc in that a higher proportion of patients in the sham arm had bilateral disease: 59 (67.8%) vs. 31 (73.8%).[24]

Health-related quality of life was not assessed and visual acuity was only assessed for the affected eye, not for both eyes.

Health-related quality of life values were incorporated in the cost effectiveness model. These values were informed by the literature ('permanent blindness' health state), and UK age matched general population utility values ('remission' health state). Additionally, Visual Functioning Questionnaire-25 (VFQ-25) values from the MUST trial[25] were mapped to EuroQol – 5 dimensions (EQ-5D) values ('on treatment' and 'subsequent treatment' health states). This mapping algorithm was developed by the

assessment group (AG) of TA460. The AG estimated the relationship between VFQ-25 and EQ-5D data based on individual patient level data from the HURON trial.[26]

3.5 Other relevant factors

In a previous technology appraisal (TA301: ILUVIEN in chronic DMO[27]) a PAS was applied to the cost of the FAc implant, which had been agreed with the Department of Health. In the current assessment [redacted].

[redacted]

.

The company claims FAc is innovative, because it is the only long-lasting (up to 36 months) ocular implant for patients with [redacted]End-of-life criteria are not applicable to FAc (CS, page 73), and the company does not expect the use of FAc to raise any equality issues (CS, page 24).[1]

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

4.1.1 Searches

The following paragraphs contain summaries and critiques of all searches related to clinical effectiveness presented in the company submission. The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.[28] The submission was checked against the single technology appraisal (STA) specification for company/sponsor submission of evidence.[29] The ERG has presented only the major limitations of each search strategy in the report, further limitations are listed in Appendix 1.

The company submission stated that a comprehensive systematic literature review was undertaken to assess the clinical effectiveness and safety of fluocinolone acetonide implant (Iluvien), adalimumab subcutaneous injection and dexamethasone intravitreal implant for adults with [redacted]. Searches were undertaken in September 2018. Search strategies were reported in Appendix D of the CS for the following databases: Embase, MEDLINE, MEDLINE In-Process, Cochrane's CENTRAL, CDSR and Clinical Answers databases. Searches contained terms for both RCTs and observational studies and were limited to English language publications.

Supplementary searches were reported for the following conference proceedings from January 2016-September 2018: The Royal College of Ophthalmologists Annual Congress, European Society of Ophthalmic Plastic and Reconstructive Surgery, American Academy of Ophthalmology, European Society of Retina Specialists, the Association for Research in Vision and Ophthalmology and the International Ocular Inflammation Society. Searches to identify ongoing, discontinued or completed clinical trials were reported for Clinicaltrials.gov, the International Clinical Trials Registry Platform and the European Union's Clinical trials Register, in addition to this HTA agency websites including NICE, SMC and All Wales Medicines Strategy Group (AWMSG) were searched in order to identify other relevant publications not identified by the main literature searches.

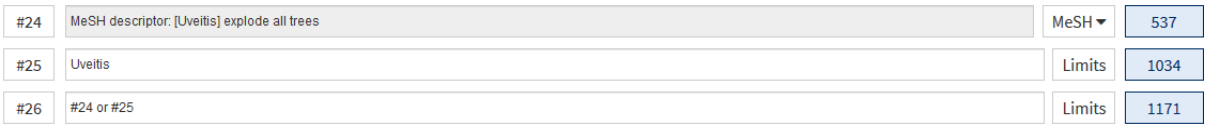
ERG comment:

- The majority of searches were clearly structured and documented. Missing data regarding the supplementary searches were provided at clarification.
- The ERG noted that both an RCT and observational studies filter were applied to the Cochrane library searches of CDSR and CENTRAL. As stated in the MECIR (Methodological Expectations of Cochrane Intervention Reviews) Manual "Use specially designed and tested search filters where appropriate including the Cochrane Highly Sensitive Search Strategies for identifying randomized trials in MEDLINE, but do not use filters in pre-filtered databases e.g. do not use a randomized trial filter in CENTRAL or a systematic review filter in DARE."[30]. The inclusion of these filters may result in unnecessarily restricting the results retrieved. However, given the breadth of the searches reported this is unlikely to have impacted on the overall recall of results.
- In the request for clarification letter the ERG asked the company to confirm whether the searches reported in Appendix D were also intended to inform the following: indirect and mixed treatment comparisons, non-RCT evidence and adverse events. The company responded that "the searches were intended to inform indirect and mixed treatment comparisons as well as to identify non-RCT evidence and adverse events. However, the search results of the SLR couldn't inform an

indirect/mixed treatment comparison nor was any relevant non-RCT evidence identified. The adverse events reported in the pivotal study, PSV-FAI-001, were the only identified source for adverse events data".[24]

- The ERG was concerned that strategies reported in Appendix D contained searches for only three comparators; adalimumab, dexamethasone and "best supportive care". Whilst this was in line with the comparators listed in the exclusion table (Appendix D table 4), this was not in line with the NICE final scope. The ERG queried what effect this may have had on the overall recall of results and the company provided the following response: "This search strategy was adopted in order to be in line with the search strategy applied in TA460. All relevant results were captured through this approach."[24] The ERG remains concerned regarding this approach – see Chapter 4.1.2 of this report for further comments.
- The ERG was concerned that limiting the clinical effectiveness searches reported in Appendix D to English language only may have introduced potential language bias. Current best practice states that "Whenever possible review authors should attempt to identify and assess for eligibility all possibly relevant reports of trials irrespective of language of publication".[31]
- The ERG noted both a limited use of synonyms and a failure to use subject headings in all reported strategies for the comparators adalimumab and dexamethasone. Without rerunning the searches, the ERG is unable to say what effect this may have had on the overall recall of results, the broad range of supplementary searches reported may have guarded against some loss of recall.
- The Cochrane Library search for clinical effectiveness and all subsequent sections omitted free text terms for uveitis, relying solely on MeSH. A free text search for uveitis, without synonyms, returns 1,034 records compared to 537 when searching using MeSH alone. Combined, these two search lines retrieve 1,171 records (see Figure 4.1). However, any loss of recall may have been mitigated by the searches reported for other databases, which used both free text and subject headings for the condition facet.

Figure 4.1: Cochrane Library search strategy



- When viewed individually the limitations listed above may not have had a significant impact, but when combined the ERG is unable to say what the impact may have been on the overall recall of results. Unfortunately, the ERG was unable to undertake independent searches and review the results within the STA timeline, as this would be outside of the ERG remit. However, the broad range of additional searching reported in the SR may have mitigated against some loss of recall particularly in the case of RCTs, and the ERG (including the clinical expert) are not aware of any significant omissions.

4.1.2 Inclusion criteria

The eligibility criteria used in the search strategy for randomised controlled trials (RCTs) and non-RCTs is presented in Table 4.1.

Table 4.1: Eligibility criteria for the identification of studies describing the clinical effectiveness of treatments for non-infectious posterior uveitis

	Inclusion criteria	Exclusion criteria
Population	[redacted] • Eligible populations will be considered for inclusion regardless of type of [redacted] (i.e. active or inactive uveitis; unilateral or bilateral uveitis; presence or absence of uveitis-related systemic disease or previous treatments for uveitis).	• Paediatric patients • Infectious uveitis • Uveitis as part of masquerade syndrome • Non-human studies
Interventions	Fluocinolone acetonide (FAc) (Medidur™, pSivida)	Intervention of interest not reported
Comparators	• Adalimumab (Humira®) • Dexamethasone (Ozurdex®)	Comparators of interest not reported
Outcomes	The outcome measures to be considered include: • Time to recurrence (the affected eye). • The number of recurrences (the affected eye). • The number of supplemental ocular treatments to manage recurrences (the affected eye). • The visual acuity (the affected eye).	Studies that do not report outcomes of interest

	Inclusion criteria	Exclusion criteria
Study design	• Randomised and non-randomised trials • Longitudinal cohort studies • Registries	• Pharmacokinetics studies • Cost effectiveness studies • Clinical trial registry entry only • Reviews, editorial, letter or comment • Case control studies • Narrative reviews • Clinical guidelines • Editorials • Letter • Opinion pieces
Language restrictions	English language only	Studies published in languages other than English
Date restrictions	Inception to present	None
Source: Table 4, Appendix D of the CS		

ERG comment: The full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised is reported in appendix D of the CS. However, the information from appendix D (seven publications included) does not correlate with the information in the CS (four publications included). In addition, the CS only includes two studies (PSV-FAI-001 and PSV-FAI-005) and it is unclear what the four included publications are. Therefore, we asked the company to explain the study inclusion process in the clarification letter (Question A12). The company responded that "the statement on page 26 that four publications were identified in the systematic literature review (SLR) represents an error. The SLR identified publications" (Clarification response to Question A12).[24] Therefore, we still do not know the correct number, but it is most likely that the correct number is seven publications. One publication (Erckens, 2012[32]) looked at adalimumab, which may or may not be a relevant comparator depending on the expected place of FAc in the treatment pathway. Two of these publications (Jaffe 2008[33] and Taban 2008[34]) looked at Retisert, a fluocinolone acetonide intravitreal implant (0.59 mg) designed to release fluocinolone acetonide locally to the posterior segment of the eye at a nominal initial rate of 0.6 μg/day, decreasing over the first month to a steady state between 0.3 to 0.4 μg/day over approximately 30 months. The European Medicines Agency application for a marketing authorisation for Retisert was withdrawn on 16 July 2017. The remaining four publications (Jaffe 2017,[35] Pavesio 2018 (No reference provided), Nguyen 2018 (No reference provided) and Suhler 2018 (No reference provided)) are conference abstracts of study PSV-FAI-001, which is included in the CS.

In the literature search, the company included two comparators: adalimumab and dexamethasone. The NICE scope included the following other comparators: periocular or intravitreal corticosteroid injections, intravitreal corticosteroid implants other than dexamethasone, systemic corticosteroids, systemic immunosuppressive therapies, and TNF-alpha inhibitors other than adalimumab. we asked the company to explain why none of the other comparators listed in the scope were included in the search (Question A11 in the Clarification Letter). The company responded that "the decision to not specifically search for periocular or intravitreal corticosteroid injections, intravitreal corticosteroid implants other than dexamethasone, systemic corticosteroids, systemic immunosuppressive therapies, and TNF-alpha inhibitors other than adalimumab, was due to search strategy applied in TA460. Therefore, the search strategy for this submission was designed to only capture evidence for potentially relevant comparators.".[24] Basically, the company did not search for any evidence at all for most of the comparators in the scope. In addition, they decided not to perform an indirect comparison with the two remaining comparators that were included in the literature search: dexamethasone or adalimumab. The ERG believes searches for all comparators mentioned in the scope should have been performed and that a comparison with dexamethasone is definitely necessary. A comparison with adalimumab is relevant if the committee believes FAc is a relevant third-line treatment option.

From the description of the literature review in appendix D, it is clear that a full search of the evidence according to the NICE scope was not performed. The description of the systematic review in appendix D is incomplete, it does not match the NICE scope and it does not match the information in the main company submission.

4.1.3 Critique of data extraction

In appendix D of the company submission the company states that "Data were extracted by a single reviewer and then checked by a second reviewer".[36]

ERG comment: Although the company stated that two reviewers were involved in the data extraction of included studies, it is unclear how discrepancies were resolved (e.g. use of a third reviewer).

Although it is good practice to include this detail when reporting a systematic review, we believe that overall the data extraction was carried out appropriately.

4.1.4 Quality assessment

In section 3 of appendix D of the CS, the company describes the results of the quality assessment of the studies included for clinical evidence.[36] The results of the quality assessment of trial PSV-FAI-001 are reported in Table 9 (page 50-51) of the CS.[1] This assessment was performed against the checklist developed by Downs and Black (1998).[37] The checklist includes 27 items describing external validity, internal validity, selection bias, confounding and statistical power. No quality assessment is reported for the trial PSV-FAI-005.

ERG comment: Trial PSV-FAI-001 is a randomised controlled trial therefore the recommended risk of bias assessment tool would be the Cochrane Collaboration's tool.[38] The instrument developed by Downs and Black is recommended for the assessment of the methodological quality of non-randomised controlled trials. The critical difference between the tools is that the Cochrane Collaboration's tool includes items on the judgement on the specific randomisation and allocation concealment method that was employed in the trial. In addition, as with data extraction, it is normally recommended that two reviewers are involved in quality assessment to reduce the potential for error and bias. Similarly, best practice advises that a third reviewer is employed when resolving discrepancies. It was not reported in the CS how quality assessment of trial PSV-FAI-001was carried out.

4.1.5 Evidence synthesis

The CS focusses on one clinical trial, the PSV-FAI-001trial. Therefore, no evidence synthesis was performed.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Included studies

Two RCTs were included to assess the safety and efficacy of FAc compared to sham injection in patients with [redacted] (PSV-FAI-001 and PSV-FAI-005). These are listed in Table 4.2.

Table 4.2: Included clinical effectiveness studies

Study name	Intervention	Comparator	Patient population	Reference
PSV-FAI-001 (completed)	FAc Intravitreal Implant with 0.19 mg fluocinolone acetonide releasing 0.2 µg/day	Sham injection	Patients with chronic [redacted]	Month-36-CSR[1]
PSV-FAI-005 (ongoing)	FAc Intravitreal Implant with 0.19 mg fluocinolone acetonide releasing 0.2 µg/day	Sham injection	Patients with chronic [redacted]	Month-12-CSR[39]

The main difference between the two trials is that the PSV-FAI-001 trial offers more mature data compared to PSV-FAI-005 (36 months follow-up versus 12 months follow-up) and was conducted internationally (also in the UK), while PSV-FAI-005 was conducted solely in India. They were complementary Phase 3 trials using similar methods. Therefore, the company focusses on results from the PSV-FAI-001 trial.

ERG comment: As the PSV-FAI-001 provides longer follow-up data than PSV-FAI-005, it seems reasonable to focus on PSV-FAI-001.

4.2.2 Methodology of included studies

The methodology of the two FAc studies that provided effectiveness data is described in Table 4.3.

PSV-FAI-001 (NCT01694186) is a 36-month Phase 3, multinational, randomised, double-blind, sham-controlled trial to assess the efficacy and safety of a fluocinolone acetonide (FAc) intravitreal implant in the management of patients with chronic [redacted]. The trial followed a parallel group design and the treatment arms were: 0.19 mg fluocinolone acetonide implant which delivers FAc into the vitreous humour for 36 months versus sham injection followed by standard practice.

The protocol allowed investigators to treat patients prior to entry to meet study inclusion criteria. The objective of prior treatment was to obtain a relatively quiet eye prior to enrolment. If a patient was receiving systemic corticosteroids or immunosuppressants, or topical steroids to control uveitis prior to study enrolment, that patient had such treatment discontinued within three months following Day 1, in a manner that followed the standard practice for discontinuing the specific treatment.

Other than during the initial tapering-off or in case of uveitis recurrence (see below), the following concomitant medications were not permitted during the study: oral, systemic, injectable, or topical steroids; and systemic immunosuppressants. In the event of a uveitis recurrence in either eye, intra- or peri-ocular corticosteroid injections, or topical medications would have been administered as first-line local therapy in accordance with the protocol. Investigators would have considered treatment with topical steroids as first-line therapy for a recurrence that involved only an increase in anterior chamber cells with no increase in vitreous opacity. Systemic treatment with immunosuppressants or steroids was only to be used if local therapy failed.

The study included 129 patients from six countries (USA, India, Israel, UK, Germany and Hungary), with 20 patients from the UK (16 (18.4%) in the FAc arm and four (9.5%) in the sham arm).

For patients with unilateral uveitis, the study eye was the affected eye. For patients with bilateral uveitis, the study eye was the more severely affected eye meeting the inclusion/exclusion criteria. For patients with symmetrical uveitis, the study eye was the right eye. The protocol permitted any local ocular treatment of the non-study (fellow) eye at the discretion of the investigator.

Eligible patients were males or females aged at least 18 years, who had been diagnosed with unilateral or bilateral chronic [redacted] for at least 12 months prior to randomisation. During the 12 months prior to enrolment, the study eye should have received treatment with systemic corticosteroid or other systemic therapies given for at least three months, and/or at least two intra- or peri-ocular administrations of corticosteroid for the management of uveitis, or the study eye experienced at least two separate recurrences of uveitis requiring systemic, intra- or peri-ocular injection of corticosteroid. At the time of enrolment, the study eye was to have <10 anterior chamber cells/high powered field, vitreous haze ≤grade 2 and visual acuity of at least 15 letters on the early treatment diabetic retinopathy study chart. Patients with a history of posterior uveitis only, that was not accompanied by vitritis or macular oedema were excluded.

The PSV-FAI-001 trial offers more mature data compared to PSV-FAI-005 (36 months follow-up versus 12 months follow-up) and was conducted internationally (also in the UK), while PSV-FAI-005 was conducted solely in India. Therefore, the company focusses on results from the PSV-FAI-001 trial.

ERG comment: As mentioned in Chapter 2 of this report, when discussing the place of FAc in the treatment pathway, the PSV-FAI-001 trial does not provide evidence for the use of FAc as first-line

treatment. All patients in the trial had received treatment with systemic corticosteroid or other systemic therapies during the 12 months prior to enrolment.

Table 4.3: Summary of methodology for the PSV-FAI trials

Study	PSV-FAI-001	PSV-FAI-005 (ongoing)
Location	Phase 3, randomised, sham-controlled, double-blind, multi-centre study conducted in 49 study centres in the US, India, Israel, UK, Germany and Hungary.	Phase 3, randomised, sham-controlled, masked, multi-centre study conducted in 15 study sites in India.
Population	Patients with chronic [redacted]	Patients with chronic [redacted]
Eligibility criteria for participants	Eligible patients were males or females aged at least 18 years, who had been diagnosed with unilateral or bilateral chronic [redacted] for at least 12 months prior to randomisation. During the 12 months prior to enrolment, the study eye should have received treatment with systemic corticosteroid or other systemic therapies given for at least 3 months, and/or at least 2 intra- or peri-ocular administrations of corticosteroid for the management of uveitis, or the study eye experienced at least 2 separate recurrences of uveitis requiring systemic, intra- or peri-ocular injection of corticosteroid. At the time of enrolment, the study eye was to have <10 anterior chamber cells/high powered field, vitreous haze ≤grade 2 and visual acuity of at least 15 letters on the early treatment diabetic retinopathy study chart.	NR
Interventions	FAc Intravitreal Implant with 0.19 mg fluocinolone acetonide releasing 0.2 µg/day (n=87). The implant was administered to the study eye by injection through the pars plana using a preloaded applicator with a 25-gauge needle. Each implant was implanted on day 1 of the study and delivered a constant dose of FAc over 36 months; Sham injection (n=42). The sham applicator consisted of an empty 1ml syringe attached to a blunt 14-gauge needle without FAc. On day 1 of the study the sham applicator was gently pressed against the study eye to provide the patient with the perception that an intravitreal injection was being performed.	FAc Intravitreal Implant with 0.19 mg fluocinolone acetonide releasing 0.2 µg/day; Sham injection.
Permitted and disallowed concomitant medication	Concomitant medications: The following concomitant medications were not permitted during the study, other than during the initial 3-month tapering-off period or in case of uveitis recurrences: Oral, systemic, injectable or topical steroids	NR

Study	PSV-FAI-001	PSV-FAI-005 (ongoing)
	Systemic immunosuppressants	
Reported outcomes specified in the decision problem	• Proportion of patients who had a recurrence of uveitis in the study eye within 6, 12 and 36 months following treatment • Mean change from baseline in BCVA letter score in the study eye (at 6months, 12 months, or 36 months) • Number of supplemental treatments required to treat recurrences of uveitis (within 6 months, 12 months, or 36 months) • Mortality • Ocular and non-ocular adverse effects of treatment	• Proportion of patients who had a recurrence of uveitis in the study eye within 6, 12 and 36 months following treatment • Mean change from baseline in BCVA letter score in the study eye (at 6 months, 12 months, or 36 months) • Number of supplemental treatments required to treat recurrences of uveitis (within 6 months, 12 months, or 36 months) • Mortality • Ocular and non-ocular adverse effects of treatment
All other reported outcomes	• Proportion of patients who had a recurrence of uveitis in the fellow eye (within 6, 12 or 36 months following treatment) • Number of recurrences of uveitis (within 6, 12 or 36 months) • Time to recurrence of uveitis (within 6, 12 or 36 months) • Resolution of macular oedema, as measured by optical coherence tomography imaging (at 6, 12 or 36 months)	• Proportion of patients who had a recurrence of uveitis in the fellow eye (within 6, 12 or 36 months following treatment) • Number of recurrences of uveitis (within 6, 12 or 36 months) • Time to recurrence of uveitis (within 6, 12 or 36 months • Resolution of macular oedema, as measured by optical coherence tomography imaging (at 6, 12 or 36 months) • Safety: Pregnancies, laboratory test abnormalities (screening only), vital signs, physical examination (screening only), and concomitant medications
Pre-planned subgroups	Subgroup analyses, using descriptive statistics only, were performed on the primary efficacy endpoint for the ITT population at Month 6. Analyses were performed to determine the treatment effect within specific subgroups of interest, and to determine if the treatment effect is consistent across different subgroup levels.	NR

Source: CS, Table 3 to 5, pages 26 to 41.

BCVA = best corrected visual acuity; FAc = fluocinolone acetonide; ITT = intention-to-treat; [redacted].

4.2.3 Baseline characteristics

The demographics and baseline disease characteristics of patients enrolled in PSV-FAI-001 are summarised in Table 4.4. Baseline characteristics for patients enrolled in PSV-FAI-005 are not reported.

At baseline, approximately half of the patients were receiving systemic treatments to control active/ persistent uveitis.

Table 4.4: Baseline demographics and disease characteristics for PSV-FAI-001 (ITT population)

PSV-FAI-001	FAc (n=87)	Sham (n=42)	Total (n=129)
Age (years)			
Mean (SD)	48.3 (13.90)	48.3 (13.71)	48.3 (13.79)
Median (range)	48.0 (20,77)	48.0 (18,73)	48.0 (18,77)
Age categories (years), n (%)			
≤20	1 (1.10)	2 (4.8)	3 (2.3)
20 to<40	24 (27.6)	8 (19.0)	32 (24.8)
40 to<60	40 (46.0)	22 (52.4)	62 (48.1)
≥60	22 (25.3)	10 (23.8)	32 (24.8)
Sex, n (%)			
Male	37 (42.5)	13 (31.0)	50 (38.8)
Female	50 (57.5)	29 (69.0)	79 (61.2)
Race, n (%)			
White	60 (69.0)	26(61.9)	86(66.7)
Black	4 (4.6)	3 (7.1)	7 (5.4)
Asian	21 (24.1)	12 (28.6)	33(25.6)
Other	2 (2.3)	1 (2.4)	3(2.3)
Ethnicity, n (%)			
Hispanic or Latino	3 (3.4)	3 (7.1)	6(4.7)
Not Hispanic or Latino	84 (96.6)	39 (92.9)	123 (95.3)
Study Eye, n (%)			
Right eye	46 (52.9)	19 (45.2)	65(50.4)
Left eye	41 (47.1)	23 (54.8)	64 (49.6)
Systemic treatment to control uveitis, n (%)			
Not receiving systemic treatment	43 (49.4)	21 (50.0)	64 (49.6)
Receiving systemic treatment			
Corticosteroid therapy	27 (31.0)	13 (31.0)	40 (31.0)
Immunosuppressive therapy	17 (19.5)	8 (19.0)	25 (19.4)
Duration of uveitis (years)[a]			
Mean (SD)	7.8 (6.69)	5.6 (6.82)	7.1 (6.79)
Median (range)	5.9 (1,28)	2.8 (1, 30)	4.0 (1, 30)
Duration of uveitis categories (years), n (%)			
<2	15 (17.2)	14 (33.3)	29 (22.5)
2 to 5	25 (28.7)	16 (38.1)	41 (31.8)
>5	47 (54.0)	12 (28.6)	59 (45.7)
Number of recurrences in the study eye within 12 months prior to screening, n (%)			
≤2	65 (74.7)	34 (81.0)	99 (76.7)
>2	21 (24.1)	8 (19.0)	29 (22.5)
Lens status, n (%)			
Phakic	42 (48.3)	21 (50.0)	63 (48.8)
Cataract present[b]	25 (59.5)	9 (42.9)	34 (54.0)
Aphakic	0	0	0
Pseudophakic	45 (51.7)	21 (50.0)	66 (51.2)

PSV-FAI-001	FAc (n=87)	Sham (n=42)	Total (n=129)
History of vitrectomy, n (%)			
Yes	8 (9.2)	7 (16.7)	15 (11.6)
No	79 (90.8)	35 (83.3)	114 (88.4)
History of incisional surgery to control elevated IOP, n (%)[c]			
History collected[c]	56 (64.4)	24 (57.1)	80 (62.0)
Yes[d]	5 (8.9)	0	5 (6.3)
History not collected	31 (35.6)	18 (42.9)	49 (38.0)
BCVA (letters)			
Mean (SD)	66.9 (15.49)	64.9 (15.53)	66.3 (15.47)
Median (range)	70.0 (19, 89)	65.0 (21, 99)	68.0 (19,99)
Vitreous haze			
Absent (0)	22 (25.3)	8 (19.0)	30 (23.3)
Trace (0.5)	26 (29.9)	13 (31.0)	39 (30.2)
1+	29 (33.3)	19 (45.2)	48 (37.2)
2+	10 (11.5)	2 (4.8)	12 (9.3)
Anterior chamber cells			
0	54 (62.1)	20 (47.6)	74 (57.4)
0.5+	23 (26.4)	13 (31.0)	36 (27.9)
1+	10 (11.5)	8 (19.0)	18 (14.0)
2+	0	1 (2.4)	1 (0.8)
IOP (mmHg)			
Mean (SD)	13.9 (3.12)	13.6 (3.15)	13.8 (3.12)
Median (range)	14.0 (6, 21)	13.0 (8, 20)	14.0 (6, 21)
Severity of oedema, n (%)			
CSFT<300 microns	37 (42.5)	14 (33.3)	51 (39.5)
CSFT >300 microns	48 (55.2)	27 (64.3)	75 (58.1)

Source: CS, Table 6, pages 42-44.

BCVA = best-corrected visual acuity; CSFT = central subfield thickness; FAc = fluocinolone acetonide; IOP = intraocular pressure; ITT = intention-to-treat; SD = standard deviation

a For partial uveitis onset dates, a missing month was imputed as January, and a missing day was imputed as the first of the month.

b Only assessed for eyes with a lens status of phakic. Percentages were based on the number of phakic eyes.

c Incisional surgery history was collected following the approval of protocol version 5.0 and was not collected for patients that enrolled in the study prior to the amendment's approval.

d Percentage is based on the number of patients with incisional surgery history collected.

ERG comment: Patients in the FAc arm were relatively more often male (42.5%) compared to those in the sham injection arm (31%). Mean duration of uveitis was longer in the FAc arm (7.8 years) compared to patients treated with sham injection (5.6 years) and disease duration of more than five years was more common in the FAc arm (54%) compared to the sham injection arm (28.6%). More patients receiving FAc presented with cataract than patients receiving sham injection (59.5% and 42.9%, respectively).

4.2.4 Statistical analyses

The primary efficacy analysis was performed on the ITT population at six months and compared the proportion of patients, in the treatment and control groups, who did not have a recurrence of uveitis in the study eye in the six months following Day 1. Odds ratios (OR) and 95% confidence intervals (CI) of no recurrence for FAc compared to sham injection were calculated using the Mantel-Haenszel method.

The same inferential analysis employing the same methods as for the primary analysis was performed for the per-protocol (PP) population to assess recurrence at Month six. Additionally, the same analysis was performed for both the intention-to-treat (ITT) and PP populations to assess recurrence in the exploratory analyses conducted at Months 12 and Month 36. No adjustment of type I error was performed.

For the primary endpoint, data on recurrence of uveitis was imputed in a conservative manner, as follows:

- A patient who had not previously experienced a recurrence and did not have the required eye examination data for assessing recurrence at Month six (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) for any reason was considered as having a recurrence.
- A patient who had not previously experienced a recurrence and takes a prohibited concomitant medication (systemic or local in the study eye) at any time during the study prior to Month six (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) was considered as having a recurrence.

Two sensitivity analyses were performed around the aforementioned data imputation:

1. Rather than being considered as having a recurrence, a patient who had not previously experienced a recurrence and did not have the required eye examination data was considered as NOT having a recurrence.
2. A tipping point analysis was performed, whereby FAc-treated patients with missing data were considered as having a recurrence, while sham-treated patients with missing data were considered as NOT having a recurrence.

Additionally, for missing data due to any reason, sensitivity analyses were conducted using multiple imputation methods.

The ITT and safety populations included all randomised patients, who were analysed according to the treatment they were randomised to receive (ITT) or treatment actually received (safety).

Analysis on the PP population was supplementary to the ITT analysis and was performed for all efficacy endpoints. The PP population was defined separately for Month six, Month 12 and Month 36 analyses and excluded all patients in the ITT population who:

- Received systemic treatment for recurrence of uveitis in the fellow eye
- Experienced an imputed endpoint at six months (or 12 or 36 months)
- Failed screening, without exemption, but received FAc
- Had a major protocol deviation

The analysis populations are summarised in Table 4.5.

Table 4.5: Analysis populations in the PSV-FAI-001 trial

Analysis Population	FAc (n=87), n (%)	Sham (n=42), n (%)	Total (n=129), n (%)
Safety	87 (100)	42 (100)	129 (100)
ITT	87 (100)	42 (100)	129 (100)
PP at Month 6	[redacted]	[redacted]	[redacted]
PP at Month 12	52 (59.8)	13 (31.0)	65 (50.4)
PP at Month 36	[redacted]	[redacted]	[redacted]

Source: CS, Table 7, pages 48-49. FAc = fluocinolone acetonide; ITT = intention-to-treat; PP = per-protocol

ERG comment: The statistical analysis methods were appropriate and the imputation methods were conservative as they assumed a negative outcome (recurrence) for patients with a missing eye examination or who had not previously had a recurrence and received a prohibited systemic or local concomitant medication in the study eye prior to the study month. Two further sensitivity analyses making different assumptions about imputing missing data were also performed.

4.2.5 Results

4.2.5.1 PSV-FAI-001

We will discuss the results in the order the outcome measures were listed in the NICE scope:

- recurrence of uveitis (the affected eyes)
- visual acuity (the affected eyes)
- visual acuity (both eyes)
- need for further corticosteroid treatment
- complications of uveitis
- mortality
- adverse effects of treatment
- health-related quality of life

Recurrence of uveitis (the affected eyes)

Recurrence of uveitis in the study eye, assessed in the intention-to-treat (ITT) population at 6 months following FAc or sham injection was the primary endpoint of the PSV-FAI-001 study, while recurrence of uveitis in the study eye at 12 and 36 months were exploratory endpoints. Results are shown in Table 4.6.

Table 4.6: PSV-FAI-001 study (ITT and PP populations): Patients experiencing recurrence of uveitis in the study eye up to 36 months

Time point	FAc arm n (%)	Sham arm n (%)	Odds ratio of no recurrence (95% CI)	P value (continuity corrected Chi-square test)
ITT population	N = 87	N = 42		
Recurrence at 6 months	24 (27.6)	38 (90.5)	24.94 (8.04, 77.39)	<0.001
Observed	1 (1.1)	12 (28.6)	–	–
Imputed	23 (26.4)	26 (61.9)	–	–
Missing data	[redacted]	[redacted]		
Prohibited medication	[redacted]	[redacted]		
Systemic steroid or immunosuppressant	[redacted]	[redacted]		
Intra/peri-ocular steroid	[redacted]	[redacted]		
Topical steroid	[redacted]	[redacted]		
12 months	33 (37.9)	41 (97.6)	67.09 (8.81, 511.05)	<0.001
Observed	3 (3.4)	12 (28.6)	–	–
Imputed	30 (34.5)	29 (69.0)	–	–

Time point	FAc arm n (%)	Sham arm n (%)	Odds ratio of no recurrence (95% CI)	P value (continuity corrected Chi-square test)
Missing data	[redacted]	[redacted]		
Prohibited medication	[redacted]	[redacted]		
Systemic steroid or immunosuppressant	[redacted]	[redacted]		
Intra/peri-ocular steroid	[redacted]	[redacted]		
Topical steroid	[redacted]	[redacted]		
36 months	[redacted]	[redacted]	[redacted]	[redacted]
Observed	[redacted]	[redacted]	[redacted]	[redacted]
Imputed	[redacted]	[redacted]	[redacted]	[redacted]
Missing data	[redacted]	[redacted]		
Prohibited medication	[redacted]	[redacted]		
Systemic steroid or immunosuppressant	[redacted]	[redacted]		
Intra/peri-ocular steroid	[redacted]	[redacted]		
Topical steroid	[redacted]	[redacted]		
PP population				
Recurrence at 6 months	[redacted]	[redacted]		
Observed	[redacted]	[redacted]	[redacted]	[redacted]
Imputed	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence at 12 months	[redacted]	[redacted]		
Observed	[redacted]	[redacted]	[redacted]	[redacted]
Imputed	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence at 36 months	[redacted]	[redacted]		
Observed	[redacted]	[redacted]	[redacted]	[redacted]
Imputed	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS, Table 10, pages 52-53 and clarification response Table 11, pages 43-44.
CI: confidence interval; FAc = fluocinolone acetonide; ITT: intention-to-treat

Recurrence of uveitis could be observed on ophthalmological examination or imputed in case of the patient not completing the required examination or receiving prohibited medication, Table 4.6 provides a breakdown of recurrence by type. [redacted] In the FAc arm, there were [redacted] recurrences due to missing data [redacted], one (1.1%) at 12 months [redacted].

ERG comment: The imputation rates of missing recurrence data at the six, 12, and 36 month assessments were high, especially in the FAc arm. At six months 23/24 (95.8%) of the FAc arm and

26/38 (68.4%) of the sham arm recurrences were imputed due to the use of prohibited medicines. These patients were assumed to have had a recurrence which means that the recurrence rates are likely to be overestimated in both arms. Two sensitivity analyses making different assumptions about imputing recurrence data were performed but both provided the same OR and 95% CI as the primary ITT analysis. However, this was because only data from patients with a missing month six assessment were imputed so the original results did not change. Data from patients taking prohibited medications were not imputed which consisted of most of the imputations. The PP population analysis excluded patients with missing assessments, or who used prohibited medications but these results are not reliable as they are based on a smaller sample which no longer reflects the randomised treatment groups. The ITT results should be considered to be the primary results but given the high proportion of imputed outcomes they should be treated with caution.

In addition to recurrence of uveitis in the study eye, the company also reported the recurrence rate in the fellow eye, the number of recurrences per study eye, and time to first uveitis recurrence in the study eye. These results are summarised in Tables 4.7 and 4.8 and in Figure 4.2.

Table 4.7: PSV-FAI-001 study: Patients experiencing recurrence of uveitis in the fellow eye up to 36 months

	FAc arm (n=59)	Sham arm (n=31)
Patients experiencing recurrence of uveitis in the fellow eye up to 36 months		
Recurrence at 6 months, n (%)	[redacted]	[redacted]
Protocol-defined recurrence	[redacted]	[redacted]
Imputed recurrence	[redacted]	[redacted]
No recurrence within 6 months, n (%)	[redacted]	[redacted]
Recurrence at 12 months, n (%)	51 (86.4)	23 (74.2)
Protocol-defined recurrence	14 (23.7)	4 (12.9)
Imputed recurrence	37 (62.7)	19 (61.3)
No recurrence within 12 months, n (%)	8 (13.6)	8 (25.8)
Recurrence at 36 months, n (%)	[redacted]	[redacted]
Protocol-defined recurrence	[redacted]	[redacted]
Imputed recurrence	[redacted]	[redacted]
No recurrence within 36 months, n (%)	[redacted]	[redacted]

Source: CS, Section 2.6.1.2, pages 53-54; CSR 6m, page 105; CSR 12m, page 113; and CSR 36m, page 111.
FAc = fluocinolone acetonide;
Note: Patients with no recurrence prior to Month 6, 12 or 36 who did not have recurrence assessed at Month 6, 12 or 36 (for any reason) or who took a prohibited systemic or local concomitant medication prior to Month 6, 12 or 36 were counted as having a recurrence of uveitis.

[redacted] experienced recurrence of uveitis in the fellow eye [redacted] 86.4% vs 74.2% at 12 months [redacted].

Table 4.8: PSV-FAI-001 study (ITT population): Number uveitis recurrences in the study eye up to 36 months

	FAc arm (n=87)	Sham arm (n=42)
Number of recurrences per patient at 6 months		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Number of recurrences per patient at 12 months		
Mean (SD),	0.7 (1.22)	2.5 (1.67)
Median (min, max)	0.0 (0,7)	2.0 (0,8)
Number of recurrences per patient at 36 months		
Mean (SD)	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]
Number of recurrences per patient at 36 months, n (%)		
0	[redacted]	[redacted]
1	[redacted]	[redacted]
2	[redacted]	[redacted]
3	[redacted]	[redacted]
4	[redacted]	[redacted]
5	[redacted]	[redacted]
>5	[redacted]	[redacted]

Source: CS, Table 11, page 54.
FAc = fluocinolone acetonide; ITT = intention-to-treat; max = maximum; min = minimum; SD = standard deviation

In the ITT population, the mean number of uveitis recurrences per study eye was [redacted], 0.7 vs 2.5 at 12 months [redacted].

[redacted] 4 2 PSV-FAI-001 study (ITT population): Time to first Recurrence of uveitis in the study eye (up to 36 months and beyond)

[redacted]

[redacted]

Source: CS, Figure 5 (page 55), and Response to Clarification Letter (Question A34)
FAI: fluocinolone acetonide intravitreal; ITT: intention-to-treat

[redacted]

ERG comment: There is a clear effect in terms of time to first recurrence of uveitis in the study in favour of FAc when compared to sham injection. However, the relevance of this comparison is not clear and these results include imputed recurrences in both treatment arms.

Visual acuity (the affected eyes)

Mean BCVA (expressed as ETDRS letters) in the study eye at baseline and at six, 12 and 36 months is shown in Table 4.9.

[redacted]

Table 4.9: PSV-FAI-001 study (ITT population): BCVA (ETDRS letters) in the study eye at baseline and Months six, 12 and 36

Visit	FAc arm (n=87)	Sham injection arm (n=42)
	Value	Value
Baseline^		
n	87	42
Mean (SD)	66.9 (15.49)	64.9 (15.53)
Median (range)	70.0 (19,89)	65.0 (21,99)
Month 6		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]
Month 12		
n	85	39
Mean (SD)	72.8 (13.25)	69.2 (18.35)
Median (range)	76.0 (33,90)	73.0 (0,97)
Month 36		
n	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]

Source: CS, Table 13, page 57.
BCVA = best-corrected visual acuity; ETDRS = Early Treatment Diabetic Retinopathy Study; FAc = fluocinolone acetonide; ITT = intention-to-treat; SD = standard deviation

ERG comment: Results seem to favour FAc over sham injection. However, no between-arm statistical analysis was performed so the significance of the results in terms of visual acuity is not reported. It is therefore very possible that none of these results show a statistically significant difference between FAc and sham treatment.

Visual acuity (both eyes)

Visual acuity (both eyes) was not assessed in the PSV-FAI-001 trial.

Need for further corticosteroid treatment

[redacted]

Table 4.10: PSV-FAI-001 study (ITT population): Number of supplemental treatments within 36 months by type of treatment

Outcome	Study eye	
	FAc arm (n=87)	Sham arm (n=42)
Systemic steroid or immunosuppressant		
Total no. of supplemental treatments	[redacted]	[redacted]
No. of patients with ≥1 supplemental treatment	[redacted]	[redacted]
No. of supplemental treatments per patient		
0, n (%)	[redacted]	[redacted]
1, n (%)	[redacted]	[redacted]
2, n (%)	[redacted]	[redacted]
3, n (%)	[redacted]	[redacted]
4, n (%)	[redacted]	[redacted]
5, n (%)	[redacted]	[redacted]
>5, n (%)	[redacted]	[redacted]
Intra/peri-ocular steroid (study eye)		
Total no. of supplemental treatments	[redacted]	[redacted]
No. of patients with ≥1 supplemental treatment	[redacted]	[redacted]
No. of supplemental treatments per patient		
0, n (%)	[redacted]	[redacted]
1, n (%)	[redacted]	[redacted]
2, n (%)	[redacted]	[redacted]
3, n (%)	[redacted]	[redacted]
4, n (%)	[redacted]	[redacted]
5, n (%)	[redacted]	[redacted]
>5, n (%)	[redacted]	[redacted]
Topical steroid (study eye)		
Total no. of supplemental treatments	[redacted]	[redacted]
No. of patients with ≥1 supplemental treatment	[redacted]	[redacted]
No. of supplemental treatments per patient		
0, n (%)	[redacted]	[redacted]
1, n (%)	[redacted]	[redacted]
2, n (%)	[redacted]	[redacted]
3, n (%)	[redacted]	[redacted]
4, n (%)	[redacted]	[redacted]
5, n (%)	[redacted]	[redacted]
>5, n (%)	[redacted]	[redacted]

Source: CS, Table 12, page 56.
CI = confidence interval; FAc = fluocinolone acetonide; ITT = intention-to-treat

ERG comment: Again, results favour FAc over sham injection; but the statistical significance of the results is not reported.

Complications of uveitis

Complications of uveitis are reported under adverse events (see Chapter 4.2.6 of this report).

Mortality

[redacted]

Adverse effects of treatment

Adverse effects of treatment are reported in Chapter 4.2.6 (adverse events) of this report.

Health-related quality of life

Health-related quality of life was not assessed in the PSV-FAI-001 trial.

Other outcomes

In addition to the outcomes specified in the NICE scope, the CS also reported results for macular oedema and vitreous haze and anterior chamber cell count.

In the ITT population, 40 patients in the FAc arm and 23 patients in the sham arm had macular oedema in the study eye at baseline; one patient in the FAc arm was not evaluable. [redacted]

[redacted]. Table 4.11 presents the number of patients in the safety population with [redacted].

Table 4.11: PSV-FAI-001 study (safety population): Vitreous haze and anterior chamber cell count in the study eye at baseline and Months six, 12 and 36

Arm	FAc arm, n (%)			Sham arm (n=42), n (%)		
Grade	**Absent**	**Trace**	**Grade ≥1+**	**Absent**	**Trace**	**Grade ≥1+**
Anterior chamber cells						
Baseline (n= 86 for ILUVIEN and n= 42 for sham)	53 (61.6)	23 (26.7)	10 (11.6)	20 (47.6)	13 (31.0)	9 (21.4)
Month 6 (n= 87 for ILUVIEN and n= 42 for sham)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 (n= 85 for ILUVIEN and n= 39 for sham)	73 (85.9)	10 (11.8)	2 (2.4)	28 (71.8)	5 (12.8)	6 (15.4)
Month 36 (n= 72 for ILUVIEN and n= 34 for sham)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitreous haze						
Baseline (n= 87 for ILUVIEN and n= 42 for sham)	22 (25.3)	26 (29.9)	39 (44.8)	8 (19.0)	13 (31.0)	21 (50.0%)
Month 6 (n= 87 for ILUVIEN and n= 42 for sham)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12 (n= 85 for ILUVIEN and n= 39 for sham)	70 (82.4)	12 (14.1)	3 (3.5)	27 (69.2)	6 (15.4)	6 (15.4)
Month 36 (n= 72 for ILUVIEN and n= 34 for sham)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS, Table 14, page 61.
FAc = fluocinolone acetonide; ITT = intention-to-treat

4.2.5.2 PSV-FAI-005

PSV-FAI-005 is an ongoing Phase 3, multicentre, randomised, masked (outcomes assessors), controlled study to evaluate the safety and efficacy of either FAc or sham injection in patients with chronic [redacted]. The FAc implant contains 0.19 mg FAc and releases FAc at a nominal rate of approximately 0.2µg/day over the course of 36 months.

The primary efficacy and safety analyses at Months six and 12 are available and additional efficacy and safety analyses will be conducted at Month 36 (April 2020). The primary efficacy endpoint was defined as the proportion of patients who had a recurrence of uveitis in the study eye within six months after receiving study treatment. The updated analysis of uveitis recurrence at 12 months is presented in Table 4.12 (proportion of patients experiencing a recurrence in the study eye) and Table 4.13 (the number of uveitis recurrences in the study and fellow eye)

Table 4.12: PSV-FAI-005 (ITT and PP populations): Proportion of patients with recurrence of uveitis in the study and fellow eyes within 12 months

	Study Eye		Fellow Eye	
Outcome, n (%)	**FAc**	**Sham injection**	**FAc**	**Sham injection**
ITT (n)	**101**	**52**	**66**	**31**
Recurrence within 12 months, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Protocol-defined recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Imputed recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Missing data	[redacted]	[redacted]	-	-
Prohibited medication or rescue med.	[redacted]	[redacted]	-	-
Systemic steroid or immunosuppr.	[redacted]	[redacted]	-	-
Intra/peri-ocular steroid	[redacted]	[redacted]	-	-
Topical steroid	[redacted]	[redacted]	-	-
No recurrence within 12 months, n (%)				
Difference from sham injection[a]			-	-
Odds ratio	[redacted]	-	-	-
95% confidence interval	[redacted]	-	-	-
P value	[redacted]	-	-	-
PP (n)	**77**	**25**	**51**	**14**
Recurrence within 12 months, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Protocol-defined recurrence	[redacted]	[redacted]	[redacted]	[redacted]
Imputed recurrence	[redacted]	[redacted]	[redacted]	[redacted]
No recurrence within 12 months, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Difference from sham injection[a]				
Odds ratio	[redacted]	[redacted]	[redacted]	[redacted]
95% confidence interval	[redacted]	[redacted]	[redacted]	[redacted]
P value	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS, Table 21, pages 69-70.
FAc = fluocinolone acetonide; ITT: intention-to-treat; med. = medication; PP = Per Protocol.

Table 4.13: PSV-FAI-005 (ITT population): Number of recurrences of uveitis in the study and fellow eyes through Month 12

Outcome	Study eye		Fellow eye	
	FAc	Sham injection	FAc	Sham injection
ITT (N)	**101**	**52**	**66**	**31**
Total number of recurrences	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients with at least 1 recurrence in 12 months	[redacted]	[redacted]	[redacted]	[redacted]
Number of recurrences per patient				
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]
Number of recurrences per patient, n (%)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]
>5	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS, Table 20, page 70.
FAc = fluocinolone acetonide; ITT, intention-to-treat; SD, standard deviation

ERG comment: Results for trial PSV-FAI-005 in terms of recurrence of uveitis seem similar to those of trial PSV-FAI-001.

4.2.6 Adverse events

4.2.6.1 Ocular treatment-emergent adverse events - study eye

General ocular and TEAEs for the study eye are described in Table 4.14. [redacted]

Table 4.14: PSV-FAI-001 study (Safety population): Overall summary of ocular treatment-emergent adverse events for the study eye through Month 36 visit

Number of patients with:	FAc (N=87), n (%)	Sham (N=42), n (%)	Total (N=129), n (%)
Any TEAE	[redacted]	[redacted]	[redacted]
Any serious TEAE	[redacted]	[redacted]	[redacted]
Any study treatment- related TEAE	[redacted]	[redacted]	[redacted]
Any study treatment- related serious TEAE	[redacted]	[redacted]	[redacted]
Any TEAE leading to treatment discontinuation	[redacted]	[redacted]	[redacted]
Any TEAE leading to study discontinuation	[redacted]	[redacted]	[redacted]
Any AE leading to death	[redacted]	[redacted]	[redacted]

Source: CS, Table 16, Page 64.
AE = adverse event; FAc = fluocinolone acetonide; TEAE = treatment-emergent adverse event.

[redacted].

A full list of ocular TEAEs and treatment-related ocular TEAEs in the study eye affecting >5% of patients in either treatment group occurring over the 36-month follow-up period is shown in Table 4.15.

Table 4.15: PSV-FAI-001 study (Safety population): Ocular TEAEs and treatment-related ocular TEAEs in the study eye affecting >5% of patients in either treatment group occurring over the 36-month follow-up period

System Organ Class Preferred Term	Study eye ocular TEAEs by preferred Term			Study eye treatment-related ocular TEAEs by preferred term		
	FAc Implant (N=87) n (%)	Sham Injection (N=42) n (%)	Total (N=129) n (%)	FAc Implant (N=87) n (%)	Sham Injection (N=42) n (%)	Total (N=129) n (%)
Eye disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anterior chamber flare	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cataract	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cataract subcapsular	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Conjunctival haemorrhage	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cystoid macular oedema	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eye pruritus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eyelid ptosis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

System Organ Class Preferred Term	Study eye ocular TEAEs by preferred Term			Study eye treatment-related ocular TEAEs by preferred term		
	FAc Implant (N=87) n (%)	Sham Injection (N=42) n (%)	Total (N=129) n (%)	FAc Implant (N=87) n (%)	Sham Injection (N=42) n (%)	Total (N=129) n (%)
Foreign body sensation in eyes	[redacted]					
Iridocyclitis						
Macular fibrosis						
Macular oedema						
Ocular discomfort						
Ocular hyperaemia						
Photopsia						
Posterior capsule opacification						
Uveitis						
Vision blurred						
Visual acuity reduced						
Visual impairment						
Vitreous floaters						
Vitreous opacities						
Investigations						
Intraocular pressure increased						
Infections and infestations						
Conjunctivitis						
General disorders and administration						
Pain						

Source: S, Appendix F, Table 1.
AE = adverse event; FAc = fluocinolone acetonide; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event

4.2.6.2 Ocular treatment-emergent adverse events - fellow eye

[redacted]

[redacted] period (see Table 4.16). A summary of detailed TEAEs affecting the fellow eye is shown in Table 4.17.

Table 4.16: PSV-FAI-001 study (Safety population): Overall summary of ocular treatment-emergent adverse events for the fellow eye through Month 36 visit

Number of patients with:	FAc (N=87) n (%)	Sham (N=42) n (%)	Total (N=129) n (%)
Any TEAE	[redacted]	[redacted]	[redacted]
Any serious TEAE	[redacted]	[redacted]	[redacted]
Any study treatment- related TEAE	[redacted]	[redacted]	[redacted]
Any study treatment- related serious TEAE	[redacted]	[redacted]	[redacted]
Any TEAE leading to treatment discontinuation	[redacted]	[redacted]	[redacted]
Any TEAE leading to study discontinuation	[redacted]	[redacted]	[redacted]
Any AE leading to death	[redacted]	[redacted]	[redacted]

Source: CS, Table 17, Page 65.
AE = adverse event; FAc = fluocinolone acetonide; TEAE = treatment-emergent adverse event.

Table 4.17: PSV-FAI-001 study (safety population): Ocular TEAEs in the fellow eye affecting >5% of patients in either treatment group occurring over the 36-month follow-up period

System Organ Class Preferred Term	FAc Implant (N=87) n (%)	Sham Injection (N=42) n (%)	Total (N=129) n (%)
Eye disorders	[redacted]	[redacted]	[redacted]
Anterior chamber cell	[redacted]	[redacted]	[redacted]
Cataract	[redacted]	[redacted]	[redacted]
Conjunctival haemorrhage	[redacted]	[redacted]	[redacted]
Cystoid macular oedema	[redacted]	[redacted]	[redacted]
Dry eye	[redacted]	[redacted]	[redacted]
Eye inflammation	[redacted]	[redacted]	[redacted]
Eye pain	[redacted]	[redacted]	[redacted]
Iridocyclitis	[redacted]	[redacted]	[redacted]
Macular fibrosis	[redacted]	[redacted]	[redacted]
Macular oedema	[redacted]	[redacted]	[redacted]
Posterior capsule opacification	[redacted]	[redacted]	[redacted]
Uveitis	[redacted]	[redacted]	[redacted]
Visual acuity reduced	[redacted]	[redacted]	[redacted]
Visual impairment	[redacted]	[redacted]	[redacted]
Vitreous floaters	[redacted]	[redacted]	[redacted]
Vitreous opacities	[redacted]	[redacted]	[redacted]
Investigations	[redacted]	[redacted]	[redacted]
Intraocular pressure increased	[redacted]	[redacted]	[redacted]

System Organ Class Preferred Term	FAc Implant (N=87) n (%)	Sham Injection (N=42) n (%)	Total (N=129) n (%)
Nervous system disorders	[redacted]	[redacted]	[redacted]
Visual field defect	[redacted]	[redacted]	[redacted]
Source: CS< appendix F, Table 2. AE = adverse event; FAc = fluocinolone acetonide; TEAE = treatment-emergent adverse event			

4.2.6.3 Non-ocular treatment-emergent adverse events

[redacted] (See Table 4.18). [redacted].

Table 4.18: PSV-FAI-001 study (safety population): Overall summary of non-ocular treatment-emergent adverse events through month 36 visit

Number of patients with	FAc (N=87) n (%)	Sham (N=42) n (%)	Total (N=129) n (%)
Any TEAE	[redacted]	[redacted]	[redacted]
Any serious TEAE	[redacted]	[redacted]	[redacted]
Any study treatment- related TEAE	[redacted]	[redacted]	[redacted]
Any study treatment- related serious TEAE	[redacted]	[redacted]	[redacted]
Any TEAE leading to treatment disc.	[redacted]	[redacted]	[redacted]
Any TEAE leading to study disc.	[redacted]	[redacted]	[redacted]
Any AE leading to death	[redacted]	[redacted]	[redacted]
Source: CS, Table 18, page 66. AE: adverse event; disc. = discontinuations; FAc = fluocinolone acetonide; TEAE: treatment-emergent AE.			

[redacted] (see Table 4.19).

Table 4.19: PSV-FAI-001 study (safety population): Non-ocular TEAEs and treatment-related non-ocular TEAEs affecting >5% of patients in either treatment group occurring over the 36-month follow-up period

System Organ Class Preferred Term	Non-ocular TEAEs by preferred term			Treatment-Related non-ocular TEAEs by preferred term		
	FAc Implant (N=87) n (%)	Sham Injection (N=42) n (%)	Total (N=129) n (%)	FAc Implant (N=87) n (%)	Sham Injection (N=42) n (%)	Total (N=129) n (%)
Cardiac disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Palpitations	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infections and infestations				[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Viral upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Immune system disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Contrast media reaction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metabolism and nutrition disorder	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vitamin D deficiency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vascular disorders				[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
General disorders and administration site conditions				[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Respiratory, thoracic and mediastinal disorders				[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatric disorders				[redacted]	[redacted]	[redacted]
Depression	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endocrine disorders				[redacted]	[redacted]	[redacted]
Hypothyroidism	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: CS, Appendix F, Table 3.
AE = adverse event; FAc = fluocinolone acetonide; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

4.2.6.4 Intraocular pressure

[redacted] (see Table 4.20).

Table 4.20: PSV-FAI-001 (safety population): Increase in IOP in the study eye over 36 months of follow-up

	Treatment-emergent IOP increased			Treatment-related treatment-emergent IOP increased		
	FAc (N=87) n (%)	Sham (N=42) n (%)	Total (N=129) n (%)	FAc (N=87) n (%)	Sham (N=42) n (%)	Total (N=129) n (%)
Total	[redacted]					
Mild						
Moderate						
Severe						

Source: CS, Table 19, page 67.
FAc = Fluocinolone acetonide; IOP = intraocular pressure

[redacted]

4.2.6.5 Cataract

[redacted] A summary of cataract events in the study eye is provided in Table 4.21.

Table 4.21: PSV-FAI-001 (safety population): Cataract in the study eye over 36 months of follow-up

	Treatment-emergent cataract			Treatment-related treatment-emergent cataract		
	FAc (N=87) n (%)	Sham (N=42) n (%)	Total (N=129) n (%)	FAc (N=87) n (%)	Sham (N=42) n (%)	Total (N=129) n (%)
Cataract	[redacted]					
Mild						
Moderate						
Severe						

Cataract subcapsular	[redacted]											
Mild	[redacted]											
Moderate	[redacted]											
Severe	[redacted]											
Source: CS, Table 20, page 68. FAc = Fluocinolone acetonide												

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

As described in Chapter 4.1.2 of this report, most of the comparators mentioned in the NICE scope (periocular or intravitreal corticosteroid injections, intravitreal corticosteroid implants other than dexamethasone, systemic corticosteroids, systemic immunosuppressive therapies, and TNF-alpha inhibitors other than adalimumab) were not included in the literature searches. Therefore, no attempt was made to make any comparison (direct or indirect) with these comparators.

Only two comparators were included in the literature search performed by the company: adalimumab and dexamethasone. However, the company decided not to perform an indirect comparison with these two remaining comparators. In the response to the clarification letter (Question A37) the company stated that "A meta-analysis comparing the FAI insert with dexamethasone insert was not performed, as it was not considered appropriate due to the very different patient populations enrolled in the HURON trial compared with PSV-FAI-001 and the fact that the HURON trial did not specifically report the outcomes of patients in whom the posterior segment of the eye was affected".[24]

ERG comment: The ERG believes searches for all comparators mentioned in the scope should have been performed and that looking at the treatment pathway dexamethasone is the most relevant comparator. A comparison with adalimumab is relevant if the committee believes FAc is a relevant third-line treatment option.

Regarding a comparison between dexamethasone and FAc, we agree that there are considerable differences between the HURON trial (dexamethasone vs (L)CP) and the PSV-FAI-001 trial (FAc vs (L)CP), in terms of populations, treatments and outcome measures. Nevertheless, dexamethasone is the most relevant comparator and the PSV-FAI-001 and HURON trials offer the best opportunity to make an indirect comparison between the two treatments. Therefore, some attempt at an indirect comparison should be made. We will present results of an indirect comparison of FAc versus dexamethasone in Chapter 5.3 of this report.

The company argues that "the sham injection arm of PSV-FAI-001 is considered largely representative of current practice in the UK for the treatment of uveitic flares and recurrence" (CS, page 83).[1] However, the ERG does not agree with this statement. First of all, the comparison in the PSV-FAI-001 trial is FAc plus (L)CP versus (L)CP. The only difference between the two trial arms is that patients in the intervention arm received a FAc implant and patients in the control arm received a sham injection, all other treatments that were allowed in both treatment arms were the same.

Secondly, patients in both arms were tapered off from any systemic corticosteroids or immunosuppressants, or topical steroids to control uveitis within three months following Day 1 of the trial. Therefore, after completion of the tapering-off phase, the comparison is essentially FAc versus no treatment until first recurrence. This is particularly problematic for chronic patients, where a recurrence is increasingly likely after treatment stops. In the intervention arm, the original treatment is replaced by FAc implant immediately, while in the control arm, the original treatment is replaced with no treatment. Thirdly, the control arm is a constrained version of current practice. For active unilateral disease –

particularly if this included macular oedema – local treatment would be common practice. However, for bilateral disease many clinicians would opt for systemic therapy (which was not allowed within the trial unless local had failed). In the HURON trial the clinician could use either local or systemic therapy as they felt appropriate. Therefore, it could be argued that (L)CP in the HURON trial is closer to current UK practice, then (L)CP in the PSV-FAI-001 trial.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

No indirect comparison was performed.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No further additional work regarding clinical effectiveness was performed. An attempt at an indirect comparison of dexamethasone implant versus FAc implant is presented in Chapter 5.3.

4.6 Conclusions of the clinical effectiveness section

Most of the comparators mentioned in the NICE scope (periocular or intravitreal corticosteroid injections, intravitreal corticosteroid implants other than dexamethasone, systemic corticosteroids, systemic immunosuppressive therapies, and TNF-alpha inhibitors other than adalimumab) were not included in the literature searches. Therefore, no attempt was made to make any comparison (direct or indirect) with these comparators. Only two comparators were included in the literature search performed by the company: adalimumab and dexamethasone. However, the company decided not to perform an indirect comparison with these two remaining comparators. Therefore, the only comparison presented in the CS, is FAc versus (L)CP from the PSV-FAI-001 trial. The company argues that "the sham injection arm of PSV-FAI-001 is considered largely representative of current practice in the UK for the treatment of uveitic flares and recurrence" (CS, page 83).[1] However, the ERG does not agree with this statement for three reasons (see also Chapter 4.3 of this report):

1. The only difference between the two trial arms is that patients in the intervention arm received a FAc implant and patients in the control arm received a sham injection, all other treatments that were allowed in both treatment arms were the same. Therefore, the comparison in the PSV-FAI-001 trial is FAc plus (L)CP versus (L)CP.
2. Patients in both arms were tapered off from any systemic corticosteroids or immunosuppressants, or topical steroids to control uveitis within three months following Day 1 of the trial. Therefore, after completion of the tapering-off phase, the comparison is essentially FAc versus no treatment until first recurrence. This is particularly problematic for chronic patients, where a recurrence is expected as soon as treatment stops. In the intervention arm the original treatment is replaced by FAc implant immediately, while in the control arm the original treatment is replaced with no treatment.
3. The control arm is a constrained version of current practice. For active unilateral disease – particularly if this included macular oedema – local treatment would be common practice. However, for bilateral disease many clinicians would opt for systemic therapy (which was not allowed within the trial unless local had failed). In the HURON trial the clinician could use either local or systemic therapy as they felt appropriate. Therefore, it could be argued that (L)CP in the HURON trial is closer to current UK practice, then (L)CP in the PSV-FAI-001 trial.

Therefore, the ERG believes that the evidence presented in the CS is not a good reflection of the decision problem defined in the final scope.

PSV-FAI-001 (NCT01694186) is a 36-month Phase 3, multinational, randomised, double-blind, sham-controlled trial to assess the efficacy and safety of a fluocinolone acetonide (FAc) intravitreal implant in the management of patients with chronic [redacted]. The trial followed a parallel group design and the

treatment arms were: 0.19 mg fluocinolone acetonide implant which delivers FAc into the vitreous humour for 36 months versus sham injection followed by standard practice. The study included 129 patients from six countries (USA, India, Israel, UK, Germany and Hungary), with 20 patients from the UK (16 (18.4%) in the FAc arm and four (9.5%) in the sham arm).

The primary efficacy analysis was performed on the ITT population at six months and compared the proportion of patients, in the treatment and control groups, who did not have a recurrence of uveitis in the study eye in the six months following Day 1.

For the primary endpoint, data on recurrence of uveitis was imputed in a conservative manner, as follows:

- A patient who had not previously experienced a recurrence and did not have the required eye examination data for assessing recurrence at Month six (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) for any reason was considered as having a recurrence.
- A patient who had not previously experienced a recurrence and takes a prohibited concomitant medication (systemic or local in the study eye) at any time during the study prior to Month six (or Month 12 or Month 36 for the Month 12 or 36 analyses, respectively) was considered as having a recurrence.

In terms of recurrence of uveitis in the study eye, results showed significant benefits of FAc over sham injections at six (27.6% vs 90.5%), 12 (37.9% vs 97.6%) and [redacted] However, most recurrences were imputed, so the effectiveness of each treatment arm is likely to be underestimated. However, we do not know how this influences the relative effectiveness of FAc versus sham injection.

[redacted] experienced recurrence of uveitis in the fellow eye [redacted] 86.4% vs 74.2% at 12 months [redacted]. There was a clear effect in terms of time to first recurrence of uveitis in favour of FAc when compared to sham injection. In terms of visual acuity in the study eye, results seem to favour FAc over sham injection. However, the significance of the results in terms of visual acuity is not reported. It is therefore very possible that none of these results show a statistically significant difference. Also, in terms of the need for further corticosteroid treatment, results favour FAc over sham injection; but the significance of the results is not reported. Health-related quality of life was not assessed in the PSV-FAI-001 trial.

[redacted].

In terms of adverse events, [redacted]

Overall, there is a significant beneficial effect of FAc versus (L)CP and our clinical expert pointed out that there is extensive experience with the risks of cataract and raised IOP associated with FAc in other eye conditions. Therefore, the benefit-risk ratio for FAc (when compared to no treatment) seems good. However, the size of the effect of FAc is unclear due to the imputation methods and the comparator used in the trial.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

This section pertains mainly to the review of cost effectiveness analysis studies. However, the search section (5.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the company submission. Therefore, the following section includes searches for the cost effectiveness analysis review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness presented in the company submission.

5.1.1.1 Searches for cost effectiveness analysis review

The CS reported that searches were carried out in September 2018. Searches were not limited by date or language. Searches were carried out on the following databases from inception to 11 Sept 2018: Embase, MEDLINE, MEDLINE In-Process. CDSR, CENTRAL and Cochrane Clinical Answers via The Cochrane Library and EconLit. Where appropriate, searches contained filters adopted from previous searches, CRD and HTA publications. Searches were carried out in line with the NICE 2013 guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.[40] Supplementary searches of the NICE, SMC and AWMSG websites were conducted along with searches of the following conference proceedings for 2016-2018: The Royal College of Ophthalmologists Annual Congress, European Society of Ophthalmic Plastic and Reconstructive Surgery, American Academy of Ophthalmology, European Society of Retina Specialists, The Association for Research in Vision and Ophthalmology, International Ocular Inflammation Society and ISPOR annual European and International meetings. The CS also reported that the reference lists of relevant studies were checked to ensure that all relevant economic studies were captured.

5.1.1.2 Measurement and valuation of health effects

The CS reported that searches were carried out in September 2018. Searches were limited by English language and carried out on the following databases from inception to 28 Sept 2018: Embase, MEDLINE, MEDLINE In-Process. CDSR, CENTRAL and Cochrane Clinical Answers via The Cochrane Library. Where appropriate, searches contained filters adopted from previous searches, CRD and HTA publications. Searches were carried out in line with the NICE 2013 guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.[40] A supplementary free text internet search was conducted to identify further eligible studies and reference lists of relevant studies were checked to identify further studies.

5.1.1.3 Cost and healthcare resource identification, measurement and valuation

The CS reported that searches were carried out in September 2018. Searches were limited by English language and carried out on the following databases from inception to 25 Sept 2018: Embase, MEDLINE, MEDLINE In-Process. CDSR, CENTRAL and Cochrane Clinical Answers via The Cochrane Library and EconLit. Where appropriate, searches contained filters adopted from previous searches, CRD and HTA publications. Searches were carried out in line with the NICE 2013 guide to the methods of technology appraisal Sections 5.2.2 and 5.2.4.[40] Further to reference checking, the CS reported that a supplementary search of the grey literature would be conducted "including a search of relevant conference programs and a review of HTA websites (e.g. NICE, SMC and AWMSG)".[41]

ERG comments:

- The majority of searches were clearly structured and documented. Missing data regarding the supplementary searches were provided at clarification.
- The ERG noted that the Embase cost effectiveness search strategy appeared to contain an error in the costs filter in line #22. Lines #2 and #3 appeared to have been missed in this combination. The company reported that this was due to a reporting error and provided the original strategy confirming that this had no effect on the overall recall of results.
- As previously reported in Section 4.1.1., the Cochrane Library searches for cost effectiveness, health-related quality of life (HRQoL) and Resource identification omitted free text terms for uveitis, relying solely on MeSH, the same limitations will apply.
- The ERG queried the tense used in the reporting of the supplementary searches reported for the Resource identification section (Appendix I) and the company confirmed that "searches of the HTA websites for NICE, SMC and AWMSG have been conducted in September 2018. The websites were each searched for any uveitis related technology assessments using uveitis as the search term".[24]

5.1.2 Inclusion/exclusion criteria used in the study selection

The in- and exclusion criteria for the SLR on cost effectiveness studies, utilities, and resource use and costs are presented in Table 5 of Appendix G,[42] Table 4 of Appendix H,[43] and Table 5 of Appendix I,[41] respectively.

5.1.3 Included/excluded studies in the cost effectiveness review

The SLR on cost effectiveness studies yielded two full publications[44, 45] and two published abstracts[46, 47]. The SLR on cost effectiveness studies yielded two full publications[44, 45] and two published abstracts[46, 47]. Twenty-five studies [25, 44, 45, 48-69] were identified by the search for utilities, six of them reported EuroQol – 5 dimensions (EQ-5D) or EuroQol-visual analog scale (EQ-VAS) values[25, 44, 48-50, 62] and two reported VFQ-25 values.[25, 48] The search for costs and resource use studies identified five studies [44, 46, 70-72] (two publications reported results from the same study)[70, 71], of which one reported UK-related costs and resource use data.[44]

5.1.4 Conclusions of the cost effectiveness review

The CS provides an overview of the included cost effectiveness, health-related quality of life, and resource use and costs studies. The company considered TA460 to be the most relevant source to inform the model structure, and resource use and costs of the current assessment.[14] None of the HRQoL studies were deemed consistent with the NICE reference case.

ERG comment: The ERG agrees that TA460 may be a useful source to inform the current assessment and that none of the identified HRQoL studies meet the NICE reference case requirements.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

Table 5.1: Summary of the company's economic evaluation (with signposts to CS)

	Approach	Source/Justification	Signpost (location in CS)
Model	Markov cohort state transition model	In line with model approach in TA460	Section B.3.2.2

	Approach	Source/Justification	Signpost (location in CS)
States and events	On treatment, subsequent therapy/end of first line therapy, remission, permanent blindness and death	In line with a scenario analysis in TA460	Section B.3.2.2
Comparators	FAc implant and limited clinical practice	Reflective of the treatment strategies compared in PSV-FAI-001	Section B.3.2.3
Population	Patients with [redacted].	Reflective of patients included in PSV-FAI-001	Section B.3.2.1
Treatment effectiveness	Time to first recurrence was estimated through a piecewise model for FAc and a standard parametric time-to-event model for (L)CP. Patients in the subsequent treatment health state were subject to a constant probability of becoming blind. Both the disease and treatment did not influence the probability of death, all patients were subject to UK general population mortality probability in all health states.	Time to first recurrence was informed by PSV-FAI-001, the probability of blindness was informed by Dick et al. UK life tables informed the UK general population mortality probability.	Sections B.3.3.1 to B.3.3.4
Adverse events	Treatment-related AE were included in the cost effectiveness model.	AEs occurring in at least 5% of patients in any treatment arm of PSV-FAI-001 were included in the cost effectiveness model.	Sections B.3.3.5, B.3.4.4 and B.3.5.5
Health related QoL	'On treatment' and 'subsequent treatment' health state utility values were obtained by mapping the VFQ-25 estimates from the MUST trial. The 'permanent blindness' health state utility value was obtained from the literature. Patients in the 'remission' health state were assumed to have the same quality of life as age-matched UK general population utility values.	The mapping algorithm used to map the MUST utility values was obtained from TA460 and based on the individual patient level data from the HURON trial. The 'permanent blindness' utility value was obtained from Czoski-Murray et al. and the utility values used for the 'remission' health state were obtained from Janssen and Szende.	Section B.3.4
Resource utilisation and costs	The costs included in the model were acquisition and administration costs of the intervention, monitoring costs, costs of supplemental and subsequent treatment, costs of permanent blindness and costs of managing	The proportion of patients receiving supplemental and subsequent treatment was based on PSV-FAI-001. Resource use were	Section B.3.5

	Approach	Source/Justification	Signpost (location in CS)
	adverse events. Unit prices were based on the National Health Service (NHS) reference prices, Personal Social Services Research Unit (PSSRU) and Monthly Index of Medical Specialities (MIMS).	mainly informed by TA460.	
Discount rates	Discount of 3.5% for utilities and costs.	As per NICE reference case	Table 26
Subgroups	No subgroup analysis was performed.	Not in line with the NICE scope which mentions subgroup analyses based on type of uveitis (acute or chronic; single incident or recurrent; posterior segment, posterior, intermediate or pan uveitis), baseline visual acuity, and previous treatment history.	Section B.3.9
Sensitivity analysis	Both DSA and PSA were performed as well as scenario analyses	As per NICE reference case	Sections B.3.8
AE = adverse events; FAc = fluocinolone acetonide; (L)CP = (limited) current practice; NICE = National Institute for Health and Care Excellence; [redacted] = VFQ-25 = visual function questionnaire 25.			

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.2: NICE reference case checklist

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Population	As per NICE scope	Partly	The population included in the current analysis is narrower than specified in the NICE scope. Subgroup analyses were not performed.
Comparator(s)	Therapies routinely used in the National Health Service (NHS), including technologies regarded as current best practice	No	There were no comparisons performed against dexamethasone intravitreal implant and other treatments mentioned in the NICE final scope.
Type of economic evaluation	Cost-utility analysis	Yes	As per NICE reference case

Elements of the economic evaluation	Reference Case	Included in submission	Comment on whether *de novo* evaluation meets requirements of NICE reference case
Perspective on costs	NHS and Personal Social Services (PSS) perspective	Yes	As per NICE reference case
Perspective on outcomes	All health effects on individuals	Yes	As per NICE reference case
Time horizon	Lifetime horizon	Yes	As per NICE reference case
Synthesis of evidence in outcomes	Systematic literature review (SLR)	Yes	As per NICE reference case
Measure of health effects	Quality adjusted life years (QALYs)	Yes	As per NICE reference case
Source of data for measurement HRQoL	Reported directly by patients and/or carers.	No	The 'permanent blindness' utility value was obtained from a sample of healthy participants. Patients in the MUST trials had different patient characteristics than patients included in PSV-FAI-001.
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population.	Partly	It is unclear which tariffs have been used to value the EQ-5D utilities of the 'permanent blindness' health state.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes	As per NICE reference case
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes	As per NICE reference case
Sensitivity analysis	Probabilistic modelling	Yes	As per NICE reference case

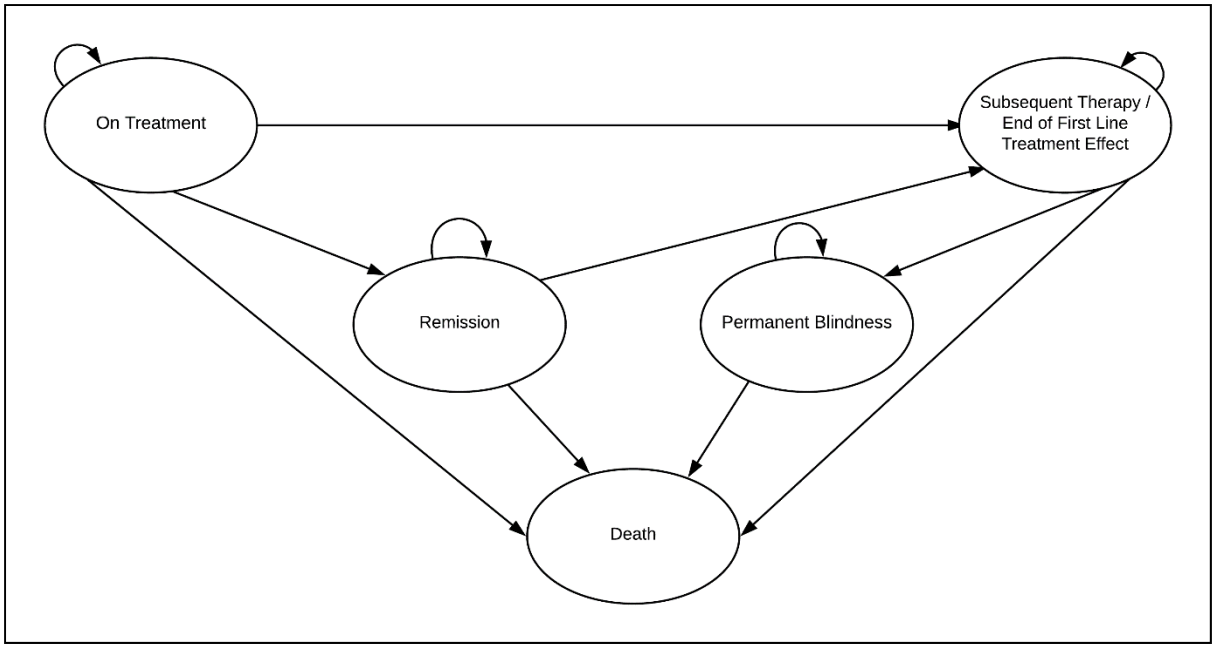
AEs = Adverse events; HRQoL = health-related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSA = probabilistic sensitivity analysis; PSS = Personal Social Services; QALY = quality-adjusted life year; SLR = systematic literature review

5.2.2 Model structure

The company developed a de novo Markov cohort state transition model. The model comprised five health states, i.e. on treatment, subsequent therapy/end of first line treatment effect (referred to as subsequent therapy in the remainder of this report), remission, permanent blindness and death (Figure 5.1). This model structure was proposed by the appraisal group for TA460;[1] but the 'remission' health state was not used in the appraisal group's base-case analysis due to a lack of evidence regarding long-term treatment effectiveness.

Patients entered the cost effectiveness model in the 'on treatment' health state and transitioned to 'subsequent therapy' upon disease recurrence in the study eye. After having experienced a recurrence, patients could not reach the 'remission' health state anymore. In the company's model, remission was defined as no recurrence for more than two years. It reflects remission from ocular disease in the study eye, in line with the outcomes of PSV-FAI-001.[1] In the 'remission' health state, patients' outcomes were considered akin to the general population. It was further assumed that a patient's treatment must fail before their condition can escalate to blindness. As a consequence, only patients in the state 'subsequent therapy' could transition to permanent blindness.

Figure 5.1: Model structure



Source: Based on Figure 10 of the CS[1]

ERG comment: The concerns of the ERG relate to a) the modelling of recurrence and remission based on changes in the study eye; b) the remission state; c) transition to permanent blindness; d) not being able to achieve remission after a recurrence.

a) Modelling in ophthalmology should, if the other eye is not already blind, consider both eyes in order to fully capture the impact of vision loss on health-related quality of life, survival and costs. This is especially true if the disease is or becomes bilateral, which is the case for uveitis. The ERG could not assess the impact of this model flaw. The assumption that patients in the remission health state are akin to the general population seems however unrealistic given the proportion of patients with bilateral disease in the PSV-FAI-001 study (59 (67.8%) patients in the implant arm and 31 (73.8%) patients in the placebo sham arm, Alimera Sciences' Response to clarification question A13[24]). In addition, treatment of patients with bilateral disease is different than for patients with unilateral disease (see Section 5.2.4).

b) Patients entered the remission state after two years if no recurrence had taken place. In response to clarification question B3,[24] the company clarified this period was chosen based on the analysis suggested in TA460,[1] and corroborated with clinical advice. The ERG requested scenario analyses in which the proportion of patients (0%, 10%, 25%, 50%, 75%) and the cut-off value (3, 5, 10, 20 years) for entering the 'remission' health state were varied. In response to clarification question B3, the company provided the latter analyses.[24] In the ERG's base-case analyses, the remission

health state has been removed, because according to the ERG the definition of remission is uncertain and the assumption that patients in the remission health state are akin to the general population is unrealistic (see Section 5.3).

c) The model does not allow for transition to permanent blindness from the on treatment state. This is consistent with observations in the PSV-FAI-001 study, but inconsistent with TA460. According to the clinical expert consulted by the ERG, in practice FAc may be administered to patients with lower vision than in the study. Therefore, in the ERG's base case analyses the transition from on treatment to permanent blindness is modelled as was done in TA460.

d) After a recurrence, patients enter the subsequent therapy state. It was assumed in the model that patients in this health state could not achieve remission. The company stated, in response to clarification question B2, that this transition was not included due to a lack of data.[24] The costs and quality of life in the subsequent therapy state are a weighted average of patients who have active, and inactive uveitis. This is discussed in more detail in Section 5.2.9.

5.2.3 Population

In line with its anticipated marketing authorisation, FAc was considered in the cost effectiveness model for the treatment of patients with [redacted], who displayed a history of [redacted] and who had received either systemic therapy for three months or at least two intra- or peri-ocular administrations of corticosteroids during the previous 12 months.[1] Parameters for the patient population were aligned to this proposed indication and derived from PSV-FAI-001: the starting age was 48.3 years, and the proportion males 38% (Table 25 of the CS [1]). Subgroups analyses requested in the final scope (type of uveitis (acute or chronic; single incident or recurrent; posterior segment, posterior, intermediate or pan uveitis), baseline visual acuity, previous treatment history) were not considered.

ERG comment: The main concerns of the ERG relate to: a) the inclusion of adults with [redacted], while the scope describes the population as "adults with recurrent non-infectious uveitis", b) not considering the subgroups listed in the final scope.

a) As mentioned in Section 3.1, the population included the cost effectiveness model is narrower than the one defined in the NICE scope. Furthermore, the relevant population for this appraisal is unclear since the marketing authorisation for the UK has not been granted yet.

b) The company did not perform the subgroups analyses mentioned in the final scope, i.e. by type of uveitis (acute or chronic; single incident or recurrent; posterior segment, posterior, intermediate or pan uveitis), baseline visual acuity, and previous treatment history due to limited availability of data.

5.2.4 Interventions and comparators

FAc implant, a long lasting (36 months) implant for the treatment of [redacted], was considered as per its anticipated licensed indication. In the cost effectiveness model, it was assumed a patient would receive only one implant, at the start of the analysis, which would not be removed, even after it was "empty" after 36 months. In the final scope the following comparators are listed: peri-ocular or intravitreal corticosteroid injections, intravitreal corticosteroid implants including dexamethasone intravitreal implant (in line with NICE TA460), systemic corticosteroids, systemic immunosuppressive therapies, TNF-alpha inhibitors including adalimumab (in line with NICE TA460), and best supportive care (when all other treatment options have been tried). In the company submission, only one comparator was

considered, i.e. limited clinical practice ((L)CP), which reflected the treatments received in the sham placebo arm in PSV-FAI-001.[1] In this study, oral, systemic, injectable, or topical steroids, and systemic immunosuppressants were not allowed other than during the initial tapering-off (first three months of the trial) or in case of uveitis recurrence. In case of recurrence, treatment consisted of periocular or intravitreal steroids, and if these failed with systemic steroids or immunosuppressants.

An overview of the treatments administered during tapering off is presented in Table 27 of the CS.[1] An overview of the treatments provided for recurrences can be found in Table 28 in the CS.[1] Treatments administered in the 'subsequent therapy' health state, i.e. after the initial treatment of the recurrence, consisted of immunosuppressant therapies and systemic prednisolone. The proportion of patients who received systemic steroids or immunosuppressants in the cost effectiveness model is presented in Table 44 in the CS.[1]

ERG comment: The main concerns of the ERG relate to: a) the intervention modelled as a once only implant; b) the intervention modelled as an implant that would not be removed; c) the comparators which are not in line with the final scope; d) (L)CP may not be reflective of UK practice.

a) In response to clarification question B4, the company stated that, in clinical practice, patients who have no contraindications and are likely to benefit from retreatment would most probably be retreated after 36 months, when the effectiveness of the initial implant begins to decline.[24] This was supported by the clinical expert consulted by the ERG. For this reason, although the experience with retreatment is low, the ERG explored retreatment in a scenario analysis. See Section 5.3 for details.

b) In response to clarification question A35, the company states that the implant is non-bioerodable and designed to stay in the eye. If complications arise, the implant can be removed by vitrectomy. This was not observed in PSV-FAI-001, but did occur in the FAME trials in diabetic macular oedema. In the FAME trials three patients had to have the study implant removed – two due to increased IOP and one due to a visual disturbance caused by the implant. All three patients were in the 0.5µg/day treatment group (N=393). In patients with increased intraocular pressure, removal of the implant resulted in a prompt decrease in IOP.[24] Because of the indirect evidence, low probability of occurrence and apparent lack of long-term health impact the ERG did not include implant removal in its analyses.

c) The company did not include dexamethasone intravitreal implant as a comparator in the analysis. Their argument, in response to clarification question A37, is a lack of evidence to perform an indirect comparison with the FAc implant.[24] The ERG agrees that an indirect comparison is not possible due to differences in populations and outcomes between the trials (Section 4.3). The ERG performed analyses with dexamethasone intravitreal implant as a comparator considering different assumptions regarding the effectiveness of dexamethasone (see Section 5.3.1). Apart from the dexamethasone intravitreal implant, the other treatment options mentioned in the final scope were only considered during the tapering-off and after a recurrence, in both the intervention and (L)CP, but not as separate direct comparators. The ERG asked for these comparisons in question A37, but the company refused to perform the requested analyses (Sections 4.3 and 4.4).[24]

d) The clinical expert consulted by the ERG questioned the inclusion of some of the medications provided during tapering off and for recurrences as these did not seem to relate to uveitis. In addition, the treatment of a recurrence with local steroids, and systemic treatment if this fails, may not reflect UK practice for patients with bilateral disease. These patients may immediately receive systemic treatment upon a recurrence. Moreover, for patients with persistent disease, tapering off

oral, systemic, injectable, or topical steroids, and systemic immunosuppressants may not reflect clinical practice.

5.2.5 Perspective, time horizon and discounting

The analysis took an NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% were applied to both costs and benefits. The model cycle length was two weeks with a lifetime time horizon (51 years in the base-case analysis). A half-cycle correction was not applied.

ERG comment: At the end of the time horizon, 2% of the patients are still alive. The ERG considered this a sufficient approximation of a lifetime time horizon. Perspective and discounting were also in line with the NICE reference case.

5.2.6 Treatment effectiveness and extrapolation

The treatment effectiveness was informed by the PSV-FAI-001 trial and the literature.[73]

5.2.6.1 Time to first recurrence

Patients transitioned from the 'on treatment' to the 'subsequent therapy' health state when they experienced a recurrence of the disease. This transition was informed by the time to first recurrence as measured in the PSV-FAI-001 trial.[74] The company digitised the Kaplan-Meier (KM) curves of both arms of the trial to reconstruct the individual patient level data representing time to first recurrence.

For FAc, the company initially fitted parametric time-to-event models to the observed data in order to estimate time to first recurrence. However, due to their poor visual fit, time to first recurrence was directly informed by the KM curve for the first 120 days of the cost effectiveness model. After 120 days, a parametric time-to-event model, fitted to the remainder of the KM curve, informed time to first recurrence. The company justified using the 120 days cut-off by stating that it identified [redacted]. After 120 days, the following distributions were fitted to the KM data: exponential, Weibull, log-logistic, lognormal, gamma, Gompertz, generalised gamma, and generalised F. The company selected the exponential distribution, which showed the best statistical fit, for its base-case analysis based on visual inspection and statistical fit.

For (L)CP, time to first recurrence was informed by a parametric time-to-event model that was fitted from the start of the digitised KM data of the sham placebo arm of PSV-FAI-001. The following distributions were fitted: exponential, Weibull, log-logistic, lognormal, gamma, Gompertz, generalised gamma, and generalised F. The company selected the log-logistic distribution, which showed the best statistical fit, for its base-case analysis based on visual inspection and statistical fit. Figures 5.2 and 5.3 present the KM curves and the fitted parametric time-to-event models for FAc and (L)CP. Alternative parametric time-to-event models were used in scenario analyses.

[redacted] 5.2 Kaplan-Meier curve and fitted time-to-event models (after 120 days) in the FAc arm

Source: CS, Figure 13[1]
Exp = exponential; Gen. Gamma = generalised gamma; Gen. F = generalised F; L. logistic = log-logistic

[redacted] 5.3 Kaplan-Meier curve and fitted time-to-event models in the (L)CP arm

Source: CS, Figure 15[1]
Exp = exponential; Gen. Gamma = generalised gamma; Gen. F = generalised F; L. logistic = log-logistic

5.2.6.2 Remission

The company assumed that all patients who were still on treatment after two years (e.g. who had not experienced a recurrence) would enter the 'remission' health state. Approximately [redacted] of patients transition to the 'remission' health state in the FAc and (L)CP arm respectively. In the 'remission' health state, patients' time to first recurrence was based on the parametric time to event models described above.

5.2.6.3 Blindness

The company assumed that patients who were in the 'on treatment' or 'remission' health states could not transition to the 'permanent blindness' health state. This implies that patients had to experience a recurrence of the disease before being at risk of becoming permanently blind. Hence, only patients in the 'subsequent therapy' could transition to the 'permanent blindness' health state. The transition probability from the 'subsequent therapy' to the 'permanent blindness' health state was informed by Dick et al. (annual rate of 0.0066).[73] Alternative rates were used in scenario analyses.

5.2.6.4 Mortality

The company assumed that uveitis does not influence the mortality risk of patients. Hence, the transition probability to the 'death' health state from all health states was equal to the general UK population mortality probability (based on UK life tables).[75]

ERG comment: The main concerns of the ERG relate to: a) the suitability of the time to first recurrence data from the PSV-FAI-001 trial for the current assessment, b) the use of digitised KM curves from

PSV-FAI-001 instead of using the individual patient data to inform time to first recurrence, c) the assumption that the treatment effect of FAc continues after three years, d) [redacted], e) the use of different approaches to model time to first recurrence for FAc and (L)CP, and f) the rate of incidence of 'permanent blindness'.

a) The company stated that the model aimed to reflect uveitis in a single eye.[1] However, recurrences were imputed when patients used prohibited systemic treatments. The company acknowledged this assumption may lead to an overestimation of the number of recurrences. The concerns of the ERG surrounding the definition and estimation of time to first recurrence expressed in Sections 3.4 and 4.2.5 also apply to this section. The ERG was not able to estimate the direction and magnitude of the bias introduced by these assumptions.

b) The company fitted parametric time-to-event models to the digitised KM curves of the PSV-FAI-001 trial. This may induce imprecision in the estimation of time to first recurrence. In response to clarification question B6, the company estimated time to first recurrence based on the individual patient data.[24] This resulted in slightly longer mean time to first recurrence in both treatment arms. The ERG will use the parametric time-to-event models fitted to the individual patient data in its base-case analyses.

c) The transition to the 'subsequent treatment' health state for FAc was extrapolated beyond the three-year time horizon of the PSV-FAI-001 trial. The FAc implant however does not release active substance after three years. The company acknowledged in response to clarification question B7 that there is uncertainty concerning the treatment effectiveness of FAc after three years and showed that assuming no treatment effect after three years, i.e. all patients transitioned to the 'subsequent therapy' health state, increased the incremental cost effectiveness ratio (ICER) of FAc versus (L)CP.[24] The ERG thinks this assumption may be too conservative and will assume that, after three years, the probability of recurrence in the FAc arm will be equal to the probability of recurrence in the (L)CP arm. The assumption of no treatment effect after three years is explored in the ERG's scenario analyses.

d) [redacted] The company further justified the use of a piecewise model due to the fluctuation in the hazard function. Upon request of the ERG, the company investigated the use of parametric time-to-event models fitted from the start of the follow-up to the FAc arm (instead of after 120 days) but did not consider to use of one of those parametric time-to-event models in its base-case analysis because they did not provide a good fit to the data.

The ERG agrees, based on visual inspection of these curves, that these parametric time-to-event models may not be suitable to represent time to first recurrence for FAc, based on the available evidence. Additionally, almost all fitted parametric time-to-event models from the start of the follow-up are most likely overestimating the time to first recurrence since they estimate mean time to first recurrence exceeding three years in the FAc arm.

The ERG requested the company to explore the use of spline models to estimate time to first recurrence since these are more flexible than the models fitted by the company (clarification question B9e).[24] This request was declined by the company.

[redacted], the estimated time-to-first recurrence in the FAc arm is likely a biased representation of the effectiveness of FAc in clinical practice. The ERG is however unable to quantify the direction and magnitude of this bias. The estimation of the effectiveness of FAc therefore remains uncertain.

e) The company used different approaches to model time to first recurrence in each treatment arm (piecewise model in the FAc arm and parametric time-to-event model in the (L)CP arm). These might impact outcomes regardless of clinical effectiveness. However, the 'standard' parametric time-to-event models (fitted from the start of the follow-up) do not provide realistic estimations of time to first recurrence in the FAc arm (see point d)). The ERG will use the same approach as the company to estimate time to first recurrence because the models used by the company seem to provide the most accurate estimation of time to first recurrence, based on the available evidence.

f) As emphasised in TA460, there is limited evidence to inform the rate of incidence of permanent blindness in [redacted] patients. The ERG will explore the influence of alternative blindness rates in scenario analyses, using the same rates as in TA460.[14]

5.2.7 Adverse events

The main source of evidence informing the probability of experiencing treatment-related adverse events (AEs) was the PSV-FAI-001 trial.[74] All treatment-related AEs that occurred in at least 5% of patients in either treatment arm were included in the cost effectiveness model. Patients were at risk of experiencing AEs in each cycle of the 'on treatment' and 'remission' health states of the cost effectiveness model. Table 32 of the CS provides an overview of the probability of experiencing each AE per treatment arm.[1]

ERG comment: The main concern of the ERG relates to whether AEs caused by the FAc implant itself should be included for the entire time that the implant is in the patients' eyes.

The company submission does not differentiate between AEs that were caused by the active substance (fluocinolone acetonide) and the delivery vehicle (the implant itself), while the active substance is delivered for three years and the implant is not supposed to be removed during the patients' life time.[24] The company clarified in response to question B11 that the cause of the AEs (either the active substance or the implant itself) was not registered. The company also acknowledged in response to question A35 that there is a very small risk of intra-ocular issues caused by the device and that vitrectomy was performed in three patients in the FAME trials (trials in which FAc implants were used to treat diabetic macular oedema) because of increased IOP (N=2) and visual disturbance caused by the implant (N=1). Increased IOP was resolved by vitrectomy.[24] Because of the sparse and indirect evidence, the low probability of occurrence and the apparent lack of long-term health impact the ERG did not include implant removal in its analyses.

5.2.8 Health-related quality of life

The utility values were obtained from the literature for all health states as HRQoL data was not collected in the PSV-FAI-001 trial.

5.2.8.1 Health-related quality of life data identified in the review

None of the identified studies reported utility values meeting the NICE reference case requirements.

5.2.8.2 On treatment and subsequent therapy health state utility values

No studies reporting EQ-5D utilities based on the UK tariff were found during the SLR. Therefore, the company argued it was most appropriate to map the VFQ-25 data from the MUST trial to EQ-5D data, using the same regression equation as used in TA460.[12] The mapped utility values of the implant arm (Retisert: fluocinolone acetonide intravitreal implant, 0.59 mg) at 24 months was used for the 'on treatment' health state, and the mapped baseline utility value was used for the 'subsequent treatment' health state.

5.2.8.3 Permanent blindness health state utility value

For the 'permanent blindness' health state, the company used the utility value (0.38) reported in TA 460.[14] This utility value was based on a weighted average of utility values reported in Czoski-Murray et al.[76] In addition, another value reported by Brown et al. (0.57),[77] which was also identified in TA460,[12] was used in a scenario analysis.

5.2.8.4 Remission health state utility value

The company assumed that patients who entered the remission health state did not experience any HRQoL detriment because of or related to uveitis and therefore accrued age-matched UK general population utility values.[78]

5.2.8.5 Adverse event related disutility values

Adverse event related disutilities were not taken into account in the economic model. The company stated that including disutilities for AEs would constitute double counting.

A summary of all utility values used in the cost effectiveness model is provided in Table 5.3.

Table 5.3: Health state utility values

Health state	Utility value (mean)	Lower bound	Upper bound	Justification	Reference
On treatment	0.818	0.654	0.982	MUST trial VFQ-25 to EQ-5D mapped value at 24 months[a]	MUST trial[25]
Subsequent therapy	0.759	0.607	0.911	MUST trial VFQ-25 to EQ-5D mapped value at baseline[a]	MUST trial[25]
Permanent blindness	0.38	0.304	0.456	As per TA460	Czoski-Murray[76]
Remission: Ages 45-54	0.885	0.684	1.000	Clinical opinion – Age matched utilities.	Janssen and Szende[78]
Remission: Ages 55-64	0.810	0.648	0.972		Janssen and Szende[78]
Remission: Ages 65-74	0.773	0.618	0.928		Janssen and Szende[78]

Health state	Utility value (mean)	Lower bound	Upper bound	Justification	Reference
Remission: Ages 75+	0.703	0.562	0.844		Janssen and Szende[78]
Source: Based on Table 39 of the CS.[1] [a]) Based on mapping algorithm from TA406 EQ-5D utility = 0.4454059 + VFQ-25 score * 0.0051322					

ERG comment: The main concerns of the ERG relate to: a) the lack of HRQoL data collection in PSV-FAI-001, b) the representativeness of utility values, c) mapping VFQ-25 data from the MUST trial, d) the non-inclusion of disutility for AEs, and e) the 'on treatment' and 'subsequent treatment' health state utility values may exceed age-adjusted UK general population utility values.

a) The company did not collect any HRQoL data in PSV-FAI-001. Therefore, the HRQoL of [redacted] treated with FAc implants remain uncertain, especially when considering that the literature does not provide utility values meeting the NICE reference case requirements.

b) There is uncertainty whether the utility values used in the company's cost effectiveness model are representative of the population included in the current decision problem. Firstly, the 'on treatment' and 'subsequent treatment' utility values were based on the MUST trial[25] in which 1) patients received a higher dosage of FAc through their implants (FAc 0.59 mg instead of FAc 0.19 mg), 2) 20% of patients received systemic treatment (which was prohibited in PSV-FAI-001), 3) patients were allowed to be treated bilaterally with FAc implants (prohibited in PSV-FAI-001), and 4) the proportion of patients with oedema at baseline was lower (41% in MUST versus 56.5% in PSV-FAI-001). These patient and trial characteristics may all influence the quality of life of patients; however, the direction and magnitude of the bias incurred by these differences is difficult to quantify.

   Secondly, the patients in the 'remission' health state were assumed to have utility values equal to age-adjusted UK general population utility values. However, patients may suffer from bilateral disease, auto-immune diseases or adverse events caused by treatment. In response to question B15,[24] the company acknowledged this was the case but argued that these events were captured in the cost effectiveness model because they would lead to treatment with systemic steroids or immunosuppressants and thus to a transition to the 'subsequent therapy' health state. According to the ERG, this argument applies to only some of the health problems patients in remission may experience. The ERG believes the utility used in the 'remission' health state is overestimated.

c) The company used mapped utility values in their base-case analysis for the 'on treatment' and 'subsequent treatment' health states. The population in which the mapping algorithm was developed and the one on which the mapping algorithm was applied were not identical (response to clarification question B16)[24], which may lead to a bias in the EQ-5D estimations.

   EQ-5D utility data based on the US tariff were available from the MUST trial. The mapping algorithm resulted in a fairly similar utility values at 24 months of follow up (0.818 mapped versus 0.83 US tariff) but not for the baseline utility values (0.759 mapped versus 0.81 US tariff) of the MUST trial. The company did not provide an explanation for this discrepancy. Since the utility values in the 'on treatment' and 'subsequent treatment' health states were influential on the results, the ERG decided to investigate the influence on the results of using the EQ-5D data based on the US tariff from the MUST trial instead of the mapped utility values.

d) Utility decrements for AEs were not included in either the company base-case cost effectiveness analysis nor the cost effectiveness model provided with the clarification responses. The ERG thinks the double-counting argument used by the company does not hold because the on treatment utility was based on the baseline utility measured in the MUST trial, and the remission utility was based on general population utility values. The non-inclusion of AEs in the cost effectiveness model is a violation of good modelling practice, leads to an overestimation of health benefits in both arms and may bias the incremental health benefits. Since the company did not provide information on the severity and duration of each AE, appropriate disutility values per AE could not be incorporated in the cost effectiveness model. The ERG explored different assumptions concerning the disutility associated with AEs in its analyses.

e) Health state utility values were not capped to the age-adjusted UK general population utility values and may thus exceed these. In its base-case analysis, the ERG capped the health state utility values of all health states to the age-adjusted UK general population utility values.[78]

5.2.9 Resources and costs

The costs included in the model were acquisition and administration costs of the intervention, monitoring costs, costs of supplemental and subsequent treatment, costs of permanent blindness and costs of managing adverse events.

Unit prices were based on the National Health Service (NHS) reference prices, Personal Social Services Research Unit (PSSRU) and Monthly Index of Medical Specialities (MIMS).

5.2.9.1 Resource use and costs data identified in the review

According to the CS, the SLR identified one study reporting UK relevant resource use and cost information. The identified study had informed TA460[14] and was selected to inform the company's economic analysis.[44] Other studies were not considered relevant as they reported on other countries and interventions not comparable to the FAc implant.

5.2.9.2 Treatment costs (with PAS)

The list price of a FAc implant was £5,500. In its base-case analysis, the company assumed a patient access scheme (PAS) price of [redacted] per implant. Administration costs of the implant were £99.58, totalling treatment costs of FAc to [redacted]. These were applied only once upon treatment start. (L)CP did not have any acquisition or administration costs but did incur costs for supplemental treatment.

Supplemental treatment

During the first 12 weeks on treatment, supplemental treatment costs were applied to represent the tapering-off of previous treatments. The costs of supplemental treatment for FAc and (L)CP were calculated based on the proportion of patients receiving each supplemental treatment as observed in each arm at trial onset in the PSV-FAI-001 trial (CS Table 27[1]). During this phase monitoring visits took place every six weeks. Unit costs were obtained from the MIMS (CS Table 42[1]).

5.2.9.3 Health state and transition costs

An overview of the total costs per health state are presented in Table 5.4. In all health states except the 'remission' health state, monitoring visits took place, the frequency of monitoring differed. Monitoring visits were assumed to include the assessment of visual functioning and potential AEs and a blood test. The cost per visit was £110.48.[79]

On treatment
The 'on treatment' health state costs consisted of a monitoring visit every 12 weeks and the costs of AEs as described below.

Subsequent treatment
In the 'subsequent treatment' health state, acquisition costs of immunosuppressant and steroid treatment and monitoring visits every six weeks were included in the health state costs. The proportion of patients using immunosuppressant or systemic steroid treatments were informed by the PSV-FAI-001 trial while the mix of immunosuppressant and steroid medications informing this calculation were taken from TA460.[14] Prices were obtained from the MIMS.[80]

Transition costs were applied to FAc but not to (L)CP patients upon transition from the 'on treatment' or 'remission' health states to the 'subsequent treatment' health state. This cost was calculated based on resource use at trial onset and MIMS prices.[80]

Permanent blindness
Costs in the 'permanent blindness' health state consisted of monitoring visits every six weeks and cyclic permanent blindness costs. There was also a transition cost applied on the transition to the 'permanent blindness' health state. Cyclic permanent blindness costs contained the costs of depression, hip replacement and community care. The transition costs of becoming permanently blind contained the costs of registration as a blind person, costs of low vision aids, low vision rehabilitation and residential care. All prices stemmed from TA460[14] and were inflated to 2017.

Remission
In remission, only the costs of AEs, which are described below, were applied.

5.2.9.4 Adverse event related costs

Treatment-dependent AE related costs were applied in the 'on treatment' and the 'remission' health states. AEs with a prevalence of ≥5% in any treatment arm were included in the model using the AEs rates reported in PSV-FAI-001 (CS Table 32[1]). Resources use were informed by TA460[14] or estimated by a clinical expert. Prices stemmed from TA460[14], NHS reference prices[79] or PSSRU[81] (CS Table 46[1]).

Table 5.4: Health state and treatment costs with PAS

Health state	FAc	(L)CP	Source
FAc treatment acquisition & administration [a]	[redacted]	£0	CS 3.5.2.1[1]
On treatment			
Supplemental treatment acquisition costs [b]	£99.49	£122.02	CS Table 27[1] CS Table 42[1]
Monitoring costs per cycle	£18.41	£18.41	CS 3.5.3.1[1] CS Table 43[1]
Adverse events costs per cycle	£9.01[c]	£5.25[c]	CS 3.5.4[1] HE Model[82]
Subsequent treatment			
Transition costs to the 'subsequent treatment' health state [a]	£0.77	£0	

Health state	FAc	(L)CP	Source
Acquisition costs of subsequent treatments per cycle	£2.45	£2.45	CS Table 44[1]
Monitoring costs per cycle	£36.83	£36.83	CS 3.5.3.1[1] CS Table 43[1]
Adverse events costs per cycle	£0	£0	HE Model[82]
Permanent blindness			
Transition costs to the 'permanent blindness' health state [a]	£4.952.36	£4.952.36	CS Table 45[1]
Cyclic costs	£46.39	£46.39	CS Table 45[1]
Monitoring costs per cycle	£36.83	£36.83	HE Model[82]
Adverse events costs per cycle	£0	£0	HE Model[82]
Remission			
Adverse events costs per cycle	£9.01[b]	£5.25[b]	CS 3.5.4[1] HE Model[82]

[a] Applied once only
[b] Applied only during the first 12 weeks on treatment
[c] Prices reported in the CS differ from prices applied in the HE model. The price presented here is as applied in the HE model.
(L)CP = (limited) current practice

ERG comment: The main concerns of the ERG relate to: a) potential bias in permanent blindness costs, b) representativeness of subsequent treatment costs, c) treatment-dependent supplemental treatment costs, d) absence of monitoring visits in the remission health state, e) missing blood tests on subsequent immunosuppressive treatment, f) errors and deviations from TA460, g) absence of AEs in subsequent treatment.

a) The ERG is concerned that the cyclic costs of permanent blindness may be biased by the population these were measured in. Sourced from patients with age-related macular degeneration, permanent blindness costs contained costs of hip replacement, community care and residential care. Clinical expert opinion found these items of limited relevance for uveitis patients due to their young age. In their base-case, the ERG excluded these items from the cost of permanent blindness for uveitis patients younger than 65.

b) The ERG is concerned that the costs of subsequent treatment may not be fully representative of the treatment of flares over time. Subsequent treatment costs are composed of immunosuppressants and systemic corticosteroids, applied to 19% and 31% of patients respectively, meaning 50% of patients are not receiving treatment in the 'subsequent treatment' health state. Local steroids are not included in the cyclic subsequent treatment costs although considered first-line treatment for uveitis recurrences. Moreover, through the treatment mix applied, the company makes implicit assumptions about the frequency of recurrences in the 'subsequent treatment' health state and the proportion of patients with uveitis not responsive to local treatment. The proportions of immunosuppressant and systemic steroid treatment were varied in the DSA.

c) The costs of supplemental treatment differ between the treatment arms, in line with the resource use observed at baseline of the pivotal trial [74]. In their clarification response, the company states that "The objective of prior treatment was to obtain a relatively quiet eye prior to enrolment.",[24] but

provided no justification why resource use at baseline would differ between treatment arms. The ERG considers equal costs appropriate and implemented a weighted average of the supplemental costs of FAc and (L)CP in both treatment arms in their base-case.

d) In the 'remission' health state, costs of monitoring were not applied although deemed necessary in patients with a uveitis history, according to expert opinion. In the ERG base-case, the remission health state was not used. However, to reflect the costs of uveitis follow-up in patients in the 'on treatment' health state after two years, monitoring visits were applied every six months as advised by clinical expert opinion. This was implemented in the ERG base-case.

e) In TA460, patients receiving immunosuppressants in the 'subsequent treatment' health state, were assumed to undergo a blood test every second month to monitor the occurrence of AEs.[14] These blood tests were omitted in the CS. The clinical expert consulted by the ERG stated that patients using immunosuppressant drugs are expected to receive a blood test every three months. The ERG incorporated the costs of a blood test every 12 weeks in their base-case.

f) The ERG identified several errors and discrepancies with TA460 in the CS, some of which were amended by the company in their clarification response.[24] The ERG also used some of these amendments in its base-case. In the CS, transition costs to the 'subsequent treatment' health state were only applied to the FAc arm and not the (L)CP arm. The ERG applied treatment-dependent transition costs in the first three years based on data from the primary trial and applied the transition costs of (L)CP to both FAc and (L)CP after three years. The calculation of cyclic and transition costs of permanent blindness was adjusted to be in line with TA460 where residential care occurred as a cyclic cost instead of a transition cost of permanent blindness.[14] The ERG corrected an error in the dosing of mycophenolate mofetil. Moreover, the costs of treatment for macular oedema was changed as it was not considered in line with clinical practice. The ERG implemented two daily doses of 1 mg of mycophenolate mofetil instead of one daily dose. Macular oedema was assumed to be treated with triamcinolone instead of laser photocoagulation, as suggested by the clinical expert consulted by the ERG. The ERG noticed the dosing of bevacizumab was in line with oncological use instead of ocular treatment, and several anaesthetics and disinfectant medications were listed as supplemental treatments and treatment for recurrences, although their use is limited to ocular examinations and procedures. The economic impact of correcting these errors was minimal, therefore, the ERG did not apply adjustments.

g) The company did not apply AE costs in subsequent treatment. This is a conservative assumption that may underestimate the costs of (L)CP.

5.2.10 Cost effectiveness results

The deterministic base-case cost effectiveness results of treatment with FAc versus (L)CP amounted to an ICER of [redacted] per quality-adjusted life year (QALY) gained. FAc was associated with larger QALY gains and higher costs than (L)CP (Table 5.5). The main share of the [redacted] QALY increment stemmed from the larger accrual of QALYs in the 'remission' health state in the FAc treatment arm. The incremental costs of FAc versus (L)CP were [redacted]. This is mainly reflective of FAc acquisition and administration costs (Table 5.6).

Table 5.5: Deterministic base-case results

	Total costs	Total LYs	Total QALYs	ICER (Incremental £/QALY)
(L)CP	[redacted]	[redacted]	[redacted]	
FAc	[redacted]	[redacted]	[redacted]	
Incremental	[redacted]	[redacted]	[redacted]	£7,182.79

Source: Table 49 of the CS[1]
ICER = incremental cost-effectiveness ratio; (L)CP = (limited) current practice; LYs = life years; QALYs = quality-adjusted life-years

Table 5.6: Disaggregated utilities and costs

Item	FAc	(L)CP	Incremental
QALYs			
On treatment	[redacted]	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]	[redacted]
Remission	[redacted]	[redacted]	[redacted]
Permanent blindness	[redacted]	[redacted]	[redacted]
Costs			
Acquisition and administration costs	[redacted]	[redacted]	[redacted]
On treatment: Supplemental treatment costs	[redacted]	[redacted]	[redacted]
On treatment: Monitoring costs	[redacted]	[redacted]	[redacted]
Subsequent treatment: Acquisition costs	[redacted]	[redacted]	[redacted]
Subsequent treatment: Monitoring costs	[redacted]	[redacted]	[redacted]
Permanent blindness: Transition, cyclic and monitoring costs	[redacted]	[redacted]	[redacted]
AE costs	[redacted]	[redacted]	[redacted]

Source: HE Model[82]
AE = adverse event; (L)CP = (limited) current practice; QALY = quality-adjusted life-year

ERG comment: The company did not include dexamethasone intravitreal implant as a comparator in the analysis. Their argument, in response to clarification question A37, is a lack of evidence to perform an indirect comparison with the FAc implant.[24] Apart from the dexamethasone intravitreal implant, the other treatment options mentioned in the final scope are only considered during the tapering-off and after a recurrence, in both the intervention and (L)CP, but not as separate direct comparators. The ERG asked for these comparisons in question A37, but the company refused to perform the requested analyses.[24] Thereby, none of the company analyses compared FAc to an active comparator (see Section 5.2.4. for details).

5.2.11 Sensitivity analyses

Probabilistic sensitivity analysis (PSA) and deterministic sensitivity analysis (DSA) were undertaken and presented by the company. The PSA (1,000 iterations) included patient weight, permanent blindness

rate, the effectiveness of FAc and (L)CP, AE rates, utilities in the 'on treatment', 'permanent blindness', 'subsequent treatment' and 'remission' health states, resource use and costs of permanent blindness, proportions of subsequent corticosteroid and immunosuppressant use, the treatment mix in supplemental and subsequent treatment, administration costs of FAc and AE costs. A standard error (SE) equalling to 10% of the mean was assumed for all parameters. Results of the PSA are shown in Table 5.7; the incremental QALYs were [redacted] and incremental costs were [redacted], resulting in an ICER of [redacted] per QALY gained for FAc versus (L)CP. The probability of FAc being cost effective at a threshold of £20,000 per QALY gained was [redacted].

Table 5.7: PSA results

	Total costs	Total QALYs	ICER (Incremental £/QALY)
(L)CP	[redacted]	[redacted]	
FAc	[redacted]	[redacted]	
Incremental	[redacted]	[redacted]	[redacted]

Source: Table 50 of the CS[1]
ICER = incremental cost-effectiveness ratio; (L)CP = (limited) current practice; QALYs = quality-adjusted life-years

In the DSA, body weight, FAc administration costs, AE costs, costs associated with permanent blindness, monitoring costs, the utilities of the 'on treatment', 'permanent blindness', 'remission' and 'subsequent treatment' health states, AE rates, permanent blindness rate, effectiveness of (L)CP and FAc, proportions of corticosteroid and immunosuppressant in the 'subsequent treatment' health state and the mix of corticosteroid and immunosuppressant drugs used were varied by 20%. The ICERs per QALY of these sensitivity analyses are presented in Table 55 and Figure 21 of the CS.[1] The following parameters were identified as most influential on the cost effectiveness of FAc versus (L)CP:

1. Utility of the 'subsequent treatment' health state
2. 45-54 years age matched utilities (to inform the 'remission' health state utility)
3. Utility of the 'on treatment' health state
4. FAc efficacy
5. 55-64 years age matched utilities (to inform the 'remission' health state utility)

The company performed 10 scenario analyses (Table 5.8). The scenario analyses indicated that the choices regarding the time horizon, the parametric curve of FAc after 120 days, and the removal of the 'remission' health state were major drivers of model results. The use of shorter time horizons resulted in increasingly large ICERs. Most alternative parametric time to event curves for (L)CP and FAc days resulted in increased ICERs. Exceptions were the loglogistic curve for FAc and the log-normal curve for (L)CP which resulted in lower ICERs. The exclusion of the 'remission' health state also increased the ICER of FAc versus (L)CP.

Table 5.8: Scenario analyses

Scenario	Parameter in base case	Parameter in scenario	ICER (Incremental £/QALY)
Base case			[redacted]
1 Time Horizon (years)	51	1	[redacted]

Scenario	Parameter in base case	Parameter in scenario	ICER (Incremental £/QALY)
2 Time Horizon (years)	51	5	[redacted]
3 Time Horizon (years)	51	10	[redacted]
4 Time Horizon (years)	51	20	[redacted]
5 Time Horizon (years)	51	30	[redacted]
6 Time Horizon (years)	51	40	[redacted]
7 Discount rates costs and utilities	3.5%	0%	[redacted]
8 Discount rates costs and utilities	3.5%	6%	[redacted]
9 FAc parametric curve ≥120 days	Exponential	LogNormal	[redacted]
10 FAc parametric curve ≥120 days	Exponential	LogLogistic	[redacted]
11 FAc parametric curve ≥120 days	Exponential	Gompertz	[redacted]
12 FAc parametric curve ≥120 days	Exponential	Gamma	[redacted]
13 FAc parametric curve ≥120 days	Exponential	Generalised Gamma	[redacted]
14 FAc parametric curve ≥120 days	Exponential	Weibull	[redacted]
15 (L)CP parametric curve	Log-Logistic	LogNormal	[redacted]
16 (L)CP parametric curve	Log-Logistic	Gompertz	[redacted]
17 (L)CP parametric curve	Log-Logistic	Gamma	[redacted]
18 (L)CP parametric curve	Log-Logistic	Generalised Gamma	[redacted]
19 (L)CP parametric curve	Log-Logistic	Weibull	[redacted]
20 (L)CP parametric curve	Log-Logistic	Exponential	[redacted]
21 Exclude AEs	Included in costs	Excluded	[redacted]
22 Permanent blindness rate	0.0068 (annual)	0.0038 (annual)	[redacted]
23 Permanent blindness rate	0.0068 (annual)	0.0374 (annual)	[redacted]
24 Permanent blindness utilities	0.38	0.57	[redacted]
25 Remission health state	Yes	No	[redacted]

Source: Table 57 of the CS[1];
AE = adverse event ICER = incremental cost-effectiveness ratio; (L)CP = limited current practice; QALY = quality-adjusted life-year

ERG comment: The main concerns of the ERG concerning the PSA, DSA and scenario analyses are: a) the exclusion of parameters in the PSA, b) the assumed standard error (SE) of 10% of the mean, c) alternative scenarios not explored, e.g. the use of utility decrements.

a) The PSA excluded the rate of permanent blindness. The ERG is concerned that the exclusion of relevant parameters from the PSA would lead to an underestimation of uncertainty.

b) All parameters included in the PSA, with the exception of FAc and (L)CP parametric time-to-event curves, had SEs equalling to 10% of the mean, instead of SEs based on empirical evidence. This assumption does not reflect the true parameter uncertainty surrounding the parameter estimates.

The ERG requested this be amended in their clarification question B28 and the company provided SEs based on empirical evidence for resource use on supplemental and subsequent treatment and AE rates.[24] The ERG did not implement a PSA for their base-cases as the cost effectiveness model provided by the company did not support the probabilistic analysis of a fully incremental comparison of three comparators.

c) The ERG is concerned that the scenarios presented in the CS do not reflect all uncertainties related to structural and methodological assumptions and choices. For instance, no scenarios assessed the impact of using a time-to-event curve for FAc from the start of the follow up as was done for the comparator. Likewise, the possibility of additional implants after three years of effective treatment was not explored. The company also did not explore the consequences of using utility decrements for adverse events. In their clarification response, the company provided scenario analyses regarding the fitting of a time-to-event curve from the start for FAc and scenarios regarding the time of transition into remission.[24]

5.2.12 Model validation and face validity check

The company undertook efforts to validate the cost effectiveness model and the cost effectiveness estimates for FAc and (L)CP. The internal validity of the model was tested through a technical review including an assessment of cell-by-cell input calculations, formulae and visual basic code. Calculations and assumptions were further validated by entering data from TA460[14] and Squires[44] into the company model and comparing the reported outcomes with the calculated results. Comparisons were made for total life-years (LYs) in the dexamethasone and (L)CP arms, and LYs and QALYs accrued on treatment. The results obtained from the company model were similar to those reported in TA460.[14]

Face validity checks were performed for some aspects of the economic model. A clinical advisory board held in October 2018 validated the model approach, and the health state utility of the 'remission' health state was validated by an expert.

The external validity of the model was assessed through a comparison with the PSV-FAI-001 trial.[74] Modelled median time to recurrence was compared to the reported median time to recurrence. These were 640 and 657 days for estimated and observed recurrence on FAc, and 70 and 70.5 days on (L)CP.

ERG comment: The main concerns of the ERG relate to a) internal validation issues, b) the reporting of the face validity checks, c) the reproducibility of validation with data from TA460, d) the absence of cross validation.

a) The ERG identified several errors in the implementation of the model and the company identified additional calculation errors when responding to the clarification questions. This raises doubts concerning the quality of the performed internal validation.

b) In multiple sections of the CS, the company refers to clinical expert opinion to support assumptions. Additionally, a clinical advisory board was held in October 2018 to validate the model structure and assumptions. However, no details of the expert opinion elicitation or the advisory board were provided. In response to ERG clarification question B23, the company revealed the identities of the two clinical experts who were solicited.[24] Deviating from best practice as described in ISPOR taskforce 7,[83] the company did not describe the process used to evaluate the face validity, but stated that an overview of questions asked and answers given could not be provided. The clarification response did not specify the attendees, questions asked and answers given at the clinical advisory board. As no information has been made available, the ERG could

not verify the opinion of the experts concerning the face validity of the inputs, assumptions and results of the model.

c) The company described that values obtained from TA460 were entered in the cost effectiveness model to assess the validity of model calculations and assumptions in comparison to TA460. Exact values used were not mentioned, hence the ERG could not confirm the results obtained by the company. The ERG presents a comparison of (L)CP results as observed in TA460 with the CS model and the ERG base-case in Table 5.9.

d) A cross validation of inputs, assumptions and results with TA460 and other relevant models was not conducted. The ERG requested a complete cross validation of assumptions, transition probabilities, health state utility values, costs, and results including life years, quality-adjusted life years and costs. In response to ERG clarification question B24, the company declined to provide a cross-validation against TA460.[24]

Table 5.9: Comparison of (L)CP results with TA460

	TA460	CS base-case	ERG base-case 1
Total LYs	20.529	[redacted]	[redacted]
Total QALYs	14.613	[redacted]	[redacted]
QALYs on treatment	0.620	[redacted]	[redacted]
QALYs on subsequent treatment	17.565	[redacted]	[redacted]
QALYs in remission	0.000	[redacted]	[redacted]
QALYs in permanent blindness	2.343	[redacted]	[redacted]
Total costs	£39,655.21	[redacted]	[redacted]
Drug costs	£2,449.61	[redacted]	[redacted]
Administration and monitoring costs	£17,452.41	[redacted]	[redacted]
AE costs	£5,186.39	[redacted]	[redacted]
Cost of blindness	£14,281.54	[redacted]	[redacted]

Source: HE model,[82] TA460,[14] ERG base-case
AE = adverse event; ICER = incremental cost-effectiveness ratio; (L)CP = (limited) current practice; LYs = life years; QALYs = quality-adjusted life-years

5.3 Exploratory and sensitivity analyses undertaken by the ERG

Table 5.10 summarises the main issues highlighted by the ERG in Section 5.2, indicates the expected direction of bias introduced by these issues and whether these are examined in any analyses or incorporated in the ERG base-case.

Table 5.10: Main ERG critique of company's submitted economic evaluation

Issue	Likely direction of bias introduced in ICER[a]	Addressed in ERG analyses?	Addressed in company analysis?
Model structure (section 5.2.2)			
Uncertainty surrounding the 'remission' health state	+	ERG base-case analyses	Yes
No transition between 'on treatment' and 'permanent blindness' health states	+	ERG base-case analyses	No
Not considering both eyes in the model structure	+/-	No	No
No remission possible after recurrence	+	No	No
Population, interventions and comparators, perspective and time horizon (sections 5.2.3-5.2.5)			
Comparator not in line with final scope	+	ERG base-case analyses	No
Only one FAc implant is modelled	+	ERG base-case analyses	No
(L)CP may not be reflective of UK clinical practice	+	No	No
Treatment effectiveness and extrapolation (section 5.2.6)			
The suitability of the time to first recurrence data from the PSV-FAI-001 trial for the current assessment	+/-	No	No
Use of digitised Kaplan-Meier curves	-	ERG base-case analyses	Yes
Assuming treatment effectiveness of FAc continues after 3 years	+	ERG base-case analyses, scenario analysis 1	Yes
[redacted]	+/-	No	Yes
The use of different approaches to model time to first recurrence in each treatment arm	+/-	No	Yes

Issue	Likely direction of bias introduced in ICER[a]	Addressed in ERG analyses?	Addressed in company analysis?
The uncertainty surrounding the rate of incidence of 'permanent blindness'.	+ and -	Scenario analysis 5	Yes
Adverse events (section 5.2.7)			
No information on the severity of AEs	+/-	ERG base-case analyses, scenario analysis 4	No
Health-related quality of life (section 5.2.8)			
The uncertainty surrounding utility values due to mapping and doubts concerning their representativeness for the current population	+/-	Partially, scenario analysis 2	No
Non-inclusion of utility decrements for AEs	+	ERG base-case analyses, scenario analysis 4	No
Health state utility values may exceed age-matched UK general population utility values	+	ERG base-case analyses	No
Resources and costs (section 5.2.9)			
Multiple errors in the estimation of resource use and costs	-	ERG base-case analyses	Yes
Potential bias in the estimation of the permanent blindness costs	+	ERG base-case analyses	No
Absence of monitoring visits in the 'remission' health state	+	ERG base-case analyses	No

Issue	Likely direction of bias introduced in ICER[a]	Addressed in ERG analyses?	Addressed in company analysis?
Missing blood tests for patients receiving immunosuppressants in the 'subsequent treatment' health state	-	ERG base-case analyses	Yes
Cost effectiveness analyses (sections 5.2.10 and 5.2.11)			
Probabilistic sensitivity analysis: standard errors were assumed to be 10%	+/-	No, since all ERG analyses are presented deterministically	Yes
Validation (section 5.2.12)			
Multiple technical errors in the implementation of the cost effectiveness model	+ and -	ERG base-case analyses	Yes
Lack of details concerning the validation using data from TA460	+/-	No	No
Lack of details concerning the validation by clinical experts	+/-	No	No

Footnotes: [a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the ERG and '+' indicates that the ERG believes this issue likely induces bias in favour of the intervention versus at least one comparator.
AEs = adverse events; ERG = Evidence Review Group; FAc = fluocinolone acetonide; ICER = incremental cost effectiveness ratio; (L)CP = limited current practice; TA = technology appraisal; UK = United Kingdom

Based on all considerations in Section 5.2 (summarised in Table 5.10), the ERG defined multiple base-case analyses, based on different assumptions. These base-cases included multiple adjustments to the original base-case presented in the previous sections. These adjustments made by the ERG form the ERG base-case analyses and were subdivided into three categories (derived from Kaltenthaler et al.[84])

- Fixing errors (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (amending the model where the ERG considers that reasonable alternative assumptions are preferred)

Due to the multiple uncertainties that remain concerning the use of FAc in clinical practice and the impact of AEs on quality of life, the ERG does not present a single ERG base-case analysis but a range of analyses that the ERG deems plausible. These analyses are based on the below-mentioned amendments 1 to 16 (ERG base-case 1). Additionally, the same analysis is presented with the addition of a utility decrement (0.05) for all AEs (amendment 17) (ERG base-case 2). The ERG also combined amendments 1 to 16 with the eventuality that patients may receive multiple FAc implants (amendment 18) (ERG base-case 3). In this ERG analysis, the effectiveness of FAc after three years is assumed to continue for all patients who are still on treatment, i.e. the probability of recurrence after three years in the FAc arm is not equal to the probability of recurrence in the (L)CP arm (amendment 13 removed). Finally, the ERG combined ERG base-case 3 with the AEs disutility of 0.05 (amendment 17) (ERG base-case 4). All ERG analyses include dexamethasone as a comparator.

Fixing errors

1. Error in the calculations of the 'permanent blindness' health state costs (Section 5.2.9).
   The ERG corrected the transition and cyclic costs attributed to the 'permanent blindness' health state.
2. Applying subsequent therapy costs upon transition to the 'subsequent treatment' health state in the (L)CP arm (Section 5.2.9).
   The ERG implemented these transition costs.
3. Error in the calculation of the (L)CP treatment costs calculation (Section 5.2.9).
   The ERG corrected the calculation of the (L)CP treatment costs.
4. Error in the calculation of the 'subsequent treatment' costs in the FAc arm (Section 5.2.9).
   The ERG corrected the calculation of the 'subsequent treatment' costs.

Fixing violations

5. Not considering dexamethasone as a comparator (Section 5.2.4).
   The ERG included dexamethasone as a comparator in its base-case analyses using three different approaches. Section 5.3.1 provides details on how the comparison between dexamethasone intravitreal implant, FAc and (L)CP was performed.
6. Use of digitised KM curve to estimate time to first recurrence (Section 5.2.6).
   The ERG used the individual patient level data to estimate time to first recurrence in both treatment arms.
7. Utility values may exceed age-matched UK general population utility values (Section 5.2.8).
   The ERG capped the health state utility values to the age-matched UK general population utility values.
8. Different supplemental treatment costs for FAc and (L)CP (Section 5.2.9).
   The ERG implemented the same supplemental treatment costs in both treatment arms.

9. Incorrect doses for subsequent and supplemental treatments (Section 5.2.9).
   The ERG corrected these doses in its analyses.
10. Use of a 10% variation to estimate the standard error of all parameters (Section 5.2.11).
    The ERG used empirical information to estimate the standard error of parameters when possible. This amendment does not influence the ERG results since all ERG analyses were performed deterministically.

Matters of judgment

11. Use of the 'remission' health state (Section 5.2.2).
    The ERG removed the 'remission' health state in its analyses and adjusted the frequency of monitoring visits in the 'on treatment' health state after 2 years.
12. No transition from the 'on treatment' to the 'permanent blindness' health states (Section 5.2.2).
    The ERG allowed for the transition from the 'on treatment' to the 'permanent blindness' health states in its analyses. The transition probability was based on the rate reported in Dick et al. (10 year rate of 0.0066).[73] The transition probability from the 'on treatment' to the 'permanent blindness' health state was divided by half for the FAc and dexamethasone intravitreal implants, as done in TA460.[14]
13. Probability of recurrence after three years in the FAc treatment arm (Section 5.2.6).
    The ERG assumed that the probability of recurrence after 3 years in the FAc arm was equal to the probability of recurrence after three years in the (L)CP arm.
14. Correction of the 'permanent blindness' health state costs (Section 5.2.9).
    The ERG applied alternative cyclic costs in the 'permanent blindness' health state to patients younger than 65 years old, omitting several cost components that were not deemed applicable to this age-group.
15. Omission of blood tests in the 'subsequent treatment' health state (Section 5.2.9).
    The ERG corrected the company's implementation of the costs of blood tests. The ERG assumed these costs were incurred every 12 weeks in the 'subsequent treatment' health state for patients receiving immunosuppressants.
16. Cost of transition into subsequent treatment after 3 years (Section 5.2.9).
    Because the ERG assumes the same effectiveness for both treatment arms after 3 years, the ERG also assumes that, upon transition into the 'subsequent treatment' health state, patients will receive the same treatments.
17. The omission of the impact of AEs on quality of life (Section 5.2.8).
    The company did not include the impact of AEs on quality of life. Due to the uncertainty surrounding this assumption, the ERG presents multiple base-case analyses, assuming no disutility associated with AEs and assuming a disutility of 0.05.
18. The omission of the possibility to receive multiple implants (Section 5.2.4).
    There is uncertainty concerning the eventuality that patients may receive multiple FAc implants. Hence, the ERG presents multiple base-case analyses including the economic consequences of implanting multiple FAc implants in patients being on treatment. In these analyses, the effectiveness of FAc after three years is maintained (i.e. adjustment 13 is not applied in this analysis).

Table 6.1 shows how individual adjustments impact the results plus the combined effect of all above-mentioned adjustments simultaneously, resulting in the (deterministic) ERG base-cases. All 'fixing error' adjustments were combined. All 'fixing violations' adjustments were also combined. The 'fixing violations' and 'matter of judgements' adjustments were performed incorporating the 'fixing error'

adjustments given the ERG considered that the 'fixing error' adjustments corrected unequivocally wrong issues.

5.3.1 Details on the comparison with dexamethasone

The ERG agreed that a formal indirect comparison could not be performed between dexamethasone and FAc implant, among other things due to different outcomes reported in the trials (Section 4.3). However, the ERG believes such a comparison may be informative and produced three sets of analyses including dexamethasone as a comparator of FAc and (L)CP.

The first set of analyses including dexamethasone is based on a hazard ratio of dexamethasone versus (L)CP of 0.456. This hazard ratio was applied to the parametric time-to-event model estimating time to first recurrence of (L)CP and was estimated based on the results of dexamethasone versus (L)CP in TA460. In Table 40 of the AG report of TA460, an incremental QALY gained of 0.029 QALY is reported for dexamethasone versus (L)CP.[14] In that assessment, patients were assumed to receive only one dexamethasone implant that was assumed to be effective for 30 weeks. Hence, to compute a hazard ratio of dexamethasone versus (L)CP for the current assessment, the ERG assumed that, over the entire time horizon, a dexamethasone implant would provide a QALY gain of 0.029. The ERG further assumed that this incremental QALY gain was conditional on receiving only one dexamethasone implant that was effective for only 30 weeks. To compute this hazard ratio, equal effectiveness was assumed for dexamethasone and (L)CP after these 30 weeks (based on the (L)CP time to first recurrence curve). Based on these assumptions and the ERG amendments made to obtain ERG base-case 1, the ERG calculated that a hazard ratio of 0.456 for dexamethasone versus (L)CP would be needed to obtain an incremental QALY gain of 0.029 when a single dexamethasone implant would be administered to patients.

The limitations of this calculation are that the same incremental QALY gain of dexamethasone versus (L)CP was assumed between TA460 and the current assessment while different assumptions were made concerning how the effectiveness of dexamethasone was modelled. Additionally, different health state utility values were likely used in TA460 and the current assessment (health state utility values in TA460 were unavailable as they were reported in confidence), and the (L)CP arm of the HURON trial (used to inform TA460) contained a different treatment mix than the (L)CP arm informing the current assessment. These differences have led to different total QALY gains for (L)CP in each assessment (Table 5.9), and, hence, assuming dexamethasone provides the same incremental gain in both assessments is a strong assumption.

In the second set of analyses, equal effectiveness between dexamethasone and FAc was assumed (hazard ratio of 1 for dexamethasone versus FAc). In the third set of analyses, a hazard ratio of dexamethasone versus FAc of 0.7 was chosen. Both hazard ratios were applied to the parametric time to event models informing time to first recurrence for FAc.

Additional assumptions, which apply to all three sets of analyses with the inclusion of dexamethasone in the cost effectiveness model, are the following. For all ERG base-case, multiple dexamethasone implants are administered for the same period of time as FAc is considered active (i.e. three years in ERG base-cases 1 and 2 and unlimited in base-cases 3 and 4). The hazard ratios described above were applied for the same period of time. The acquisition cost of a dexamethasone implant was £870 and the administration cost of the dexamethasone implant was £113.42. The ERG assumed the same model inputs and assumptions as FAc implant for dexamethasone since both treatments are intravitreal corticosteroids implants.

5.3.2 ERG base-case results

The fully incremental deterministic ERG base-case results are presented in Tables 5.11 to 5.13. When assuming a hazard ratio of 0.456 for dexamethasone versus (L)CP, the results show that FAc extendedly dominates dexamethasone. When assuming equal effectiveness between dexamethasone and FAc, the results show that dexamethasone results in the same health benefits but is cheaper than FAC; the ICERs of dexamethasone versus (L)CP remained under £30,000 per QALY gained. When assuming a hazard ratio of 0.7 for dexamethasone versus FAc, the results show that dexamethasone extendedly dominates FAc and that dexamethasone versus (L)CP resulted in ICERs remaining under £26,000 per QALY. In all ERG base-case analyses (independently of the effectiveness of dexamethasone), the ICERs of FAc versus (L)CP remained under £31,000 per QALY gained.

Table 5.11: Deterministic ERG base-case results (based on a hazard ratio of 0.456 for dexamethasone versus (L)CP)

Technologies	Total costs	Total QALYs	Fully incremental costs	Fully incremental QALYs	Fully incremental ICER (£/QALY)	ICER of FAc versus comparator
ERG Base-case 1 (deterministic)						
(L)CP	[redacted]	[redacted]				£12,325
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£5,335
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£12,325	-
ERG Base-case 2 (deterministic)						
(L)CP	[redacted]	[redacted]				£21,531
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£9,457
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£21,531	-
ERG Base-case 3 (deterministic)						
(L)CP	[redacted]	[redacted]				£19,049
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£13,856
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£19,049	-
ERG Base-case 4 (deterministic)						
(L)CP	[redacted]	[redacted]				£30,153
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£22,810
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£30,153	-

ERG = Evidence Review Group; FAc = fluocinolone acetonide implant; ICER = incremental cost effectiveness ratio; (L)CP = (limited) clinical practice; QALY = quality-adjusted life year.

Table 5.12: Deterministic ERG base-case results (assuming the same effectiveness between dexamethasone and FAc)

Technologies	Total costs	Total QALYs	Fully incremental costs	Fully incremental QALYs	Fully incremental ICER (£/QALY)	ICER of FAc versus comparator
ERG Base-case 1 (deterministic)						
(L)CP	[redacted]	[redacted]				£12,325

Technologies	Total costs	Total QALYs	Fully incremental costs	Fully incremental QALYs	Fully incremental ICER (£/QALY)	ICER of FAc versus comparator
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£12,283	Dominated
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
ERG Base-case 2 (deterministic)						
(L)CP	[redacted]	[redacted]				£21,531
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£21,457	Dominated
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
ERG Base-case 3 (deterministic)						
(L)CP	[redacted]	[redacted]				£19,049
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£18,710	Dominated
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
ERG Base-case 4 (deterministic)						
(L)CP	[redacted]	[redacted]				£30,153
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£29,617	Dominated
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-

ERG = Evidence Review Group; FAc = fluocinolone acetonide implant; ICER = incremental cost effectiveness ratio; (L)CP = (limited) clinical practice; QALY = quality-adjusted life year.

Table 5.13: Deterministic ERG base-case results (assuming a hazard ratio of 0.7 for dexamethasone versus FAc)

Technologies	Total costs	Total QALYs	Fully incremental costs	Fully incremental QALYs	Fully incremental ICER (£/QALY)	ICER of FAc versus comparator
ERG Base-case 1 (deterministic)						
(L)CP	[redacted]	[redacted]				£12,325
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	-
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£10,412	£2,297
ERG Base-case 2 (deterministic)						
(L)CP	[redacted]	[redacted]				£21,531
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	-
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£17,843	£3,643
ERG Base-case 3 (deterministic)						
(L)CP	[redacted]	[redacted]				£19,049
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	-

Technologies	Total costs	Total QALYs	Fully incremental costs	Fully incremental QALYs	Fully incremental ICER (£/QALY)	ICER of FAc versus comparator
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£17,239	£12,911
ERG Base-case 4 (deterministic)						
(L)CP	[redacted]	[redacted]				£30,153
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	-
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£25,074	£15,730
ERG = Evidence Review Group; FAc = fluocinolone acetonide implant; ICER = incremental cost effectiveness ratio; (L)CP = (limited) clinical practice; QALY = quality-adjusted life year.						

5.3.3 Additional exploratory analyses performed based on the ERG base-case

Additional sensitivity analyses were performed to examine the potential impact of alternative assumptions on the cost effectiveness estimates. These were performed using the ERG base-case 1 with the exception of scenario 6, which uses ERG base-case 3. Results are presented in Table 6.1 in Section 6. These analyses explore the following uncertainties that were described in previous Sections:

1. FAc and dexamethasone are not effective anymore after three years
   As performed by the company in its response to the clarification letter, the ERG will investigate the influence of assuming no treatment effectiveness at all after three years in the FAc arm.

2. Use US tariff-based utility values from MUST
   This scenario analysis explores the influence on the results of using the EQ-5D data based on the US tariffs, as measured in the MUST trial.[25] These utility values are 0.83 and 0.81 for the 'on treatment' and 'subsequent treatment' health states respectively.

3. Alternative utility value for the 'permanent blindness' health state
   In this scenario analysis, the utility value obtained from Brown et al. (0.57) is used.[77] This scenario analysis was also used in TA460.

4. Incorporate disutility for adverse events
   This scenario investigates the use of a higher utility decrement on the cost effectiveness results, due to the uncertainty surrounding the impact of AEs on the patient's quality of life. In this scenario, each AE was attributed a utility decrement of 0.1.

5. Alternative rate of 'blindness'
   Due to the uncertainty surrounding the rate of developing permanent blindness, the ERG explores the influence of using the rates reported in Durrani et al. (0.0374 annual rate)[85] and Tomkins-Netzer et al. (0.0038 annual rate).[86] These scenarios were also presented in the CS and in TA460.

5.3.4 Subgroup analyses performed based on the ERG base-case

No subgroup analyses were performed.

5.4 Conclusions of the cost effectiveness section

Reviewing the overall evidence, the ERG confirmed that there was no existing cost effectiveness model for FAc implant for the current indication, and thus that development of a de novo model was necessary.

The economic model described in the CS is considered by the ERG to meet the NICE reference case, with the exceptions of (1) the definition of the population included in the cost effectiveness model, (2) the exclusion of comparators that were identified in the scope, (3) the estimation of health state utility values, and (4) the lack of subgroup analyses mentioned in the scope. The ERG was able to perform (scenario) analyses to explore the impact of including one of the omitted comparators (dexamethasone intravitreal implant) and to explore the use of alternative health state utility values on the results but was unable to perform the subgroup analyses.

The majority of the cost effectiveness searches in the CS were well documented and easily reproducible, and were carried out in line with the NICE guide to the methods of technology appraisal.

The company's probabilistic base-case ICERs of FAc implants versus (L)CP was [redacted] per QALY gained. The cost effectiveness results were robust to most scenario analyses and one-way sensitivity analyses conducted by the company. Deterministic sensitivity analyses indicated that the health state utility values were major drivers of model results.

The ERG incorporated various adjustments to the company's base-case analysis, most importantly the inclusion of dexamethasone as a comparator. All ERG analyses are presented deterministically since the company's model did not allow for a probabilistic comparison of three treatments. The ERG considered that multiple ERG base-case analyses were equally plausible when estimating the cost effectiveness of FAc implant versus dexamethasone implant and (L)CP. Additionally, the ERG considered that multiple assumptions concerning the effectiveness of dexamethasone were plausible. Therefore, the ERG presents its base-case analyses based on three assumptions concerning the effectiveness of dexamethasone. In the first set of analyses, the effectiveness of dexamethasone versus (L)CP was estimated based on the results of TA460 (estimated hazard ratio of 0.456 for dexamethasone versus (L)CP). In the second set of analyses, dexamethasone was assumed as effective as FAc (hazard ratio of 1.0 for dexamethasone versus FAc). In the third set of analyses, a hazard ratio of dexamethasone versus FAc of 0.7 was chosen. The ERG recognises that these analyses are all based on strong assumptions and that their results should be considered carefully. However, the ERG believes that these alternative assumptions concerning the effectiveness of dexamethasone reflect a range of possible outcomes considering the lack of evidence on the comparative effectiveness and cost effectiveness of FAc compared to (L)CP and dexamethasone.

When assuming a hazard ratio of 0.456 for dexamethasone versus (L)CP, the deterministic fully incremental results of all ERG base-case analyses show that FAc extendedly dominated dexamethasone implants. When assuming equal effectiveness between dexamethasone and FAc, dexamethasone led to the same health benefits as FAc but was slightly cheaper than FAc. In this second set of analyses, the ICER of dexamethasone versus (L)CP remained under £30,000 per QALY gained. Finally, when using a hazard ratio of 0.7 for dexamethasone versus FAc, FAc was extendedly dominated by dexamethasone. In this third set of analyses, the ICERs of dexamethasone versus (L)CP remained under £26,000 per QALY gained. In all ERG base-case analyses, the deterministic ICERs of FAc versus (L)CP remained under £31,000 per QALY gained. Apart from adding dexamethasone as a comparator, the most influential adjustment made by the ERG in its base-case analyses were fixing errors in the company base-case, reducing the 'permanent blindness' health state costs for patients younger than 65, including utility decrements for AEs, and assuming the administration of multiple FAc implants.

The scenarios performed by the ERG illustrate the influence of three major areas of uncertainty in the current assessment: the influence of alternative health state utility values, the inclusion of adverse event utility decrements, and the assumptions concerning treatment effectiveness after three years.

In conclusion, the uncertainty surrounding the cost effectiveness of FAc implant is substantial; mainly because relevant comparators for this assessment have not been included, the lack of reliable effectiveness data, the lack of utility data concerning the population of interest, and not including utility decrements for adverse events.

6. IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG

6.1 Analyses undertaken by the ERG

In Section 5.3 the ERG base-case analyses were presented, which were based on various changes compared to the company base-case. Table 6.1 shows how individual changes impact the results plus the combined effect of all changes simultaneously. The exploratory scenario analyses are presented in Table 6.2. These are all conditional on the ERG base-case 1, and considering a hazard ratio of 0.456 for dexamethasone versus (L)CP. The scenario analyses based on the alternative assumptions concerning the effectiveness of dexamethasone are presented in Appendix 2. The submitted model file and Appendix 3 contain technical details on the analyses performed by the ERG (e.g. the "ERG" sheet provides an overview of the cells that were altered for each adjustment). Because the company model did not provide the possibility to perform a probabilistic scenario analysis including three comparators, the ERG will present only (fully incremental) deterministic results.

Table 6.1: Deterministic ERG base-case (assuming a hazard ratio of dexamethasone versus (L)CP of 0.456)

Technologies	Total costs	Total QALYs	Fully incremental costs	Fully incremental QALYs	Fully incremental ICER (£/QALY)	ICER of FAc versus comparator
Company base-case						
(L)CP	[redacted]	[redacted]				£7,183
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£4,906
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£7,183	-
Fixing errors						
(L)CP	[redacted]	[redacted]				£2,510
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£716
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£2,510	-
Fixing violations						
(L)CP	[redacted]	[redacted]				£1,502
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£1,502	-
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	-£71,075	Dominating
Matter of judgement: Removing the remission health state: Trace, monitoring costs						
(L)CP	[redacted]	[redacted]				£3,513
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£240
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£3,513	-
Matter of judgement: Create transition from on treatment to Permanent blindness (FAc and dexamethasone rate 50% of (L)CP rate)						
(L)CP	[redacted]	[redacted]				£3,644
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£2,165
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£3,644	-

Technologies	Total costs	Total QALYs	Fully incremental costs	Fully incremental QALYs	Fully incremental ICER (£/QALY)	ICER of FAc versus comparator
Matter of judgement: Effectiveness of FAc after 3 years equal to (L)CP						
(L)CP	[redacted]	[redacted]				£4,221
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£540
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£4,221	-
Matter of judgement: Cost components of permanent blindness removed before 65 years of age: hip replacement, community care and residential care						
(L)CP	[redacted]	[redacted]				£5,354
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£3,595
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£5,354	-
Matter of judgement: Cost component of subsequent treatment added: blood test every 12 weeks for the proportion of patients that receive immunosuppressants						
(L)CP	[redacted]	[redacted]				£2,500
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£707
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£2,500	-
ERG Base-case 1 (deterministic)						
(L)CP	[redacted]	[redacted]				£12,325
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£5,335
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£12,325	-
ERG Base-case 2 (deterministic)						
(L)CP	[redacted]	[redacted]				£21,531
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£9,457
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£21,531	-
ERG Base-case 3 (deterministic)						
(L)CP	[redacted]	[redacted]				£19,049
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£13,856
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£19,049	-
ERG Base-case 4 (deterministic)						
(L)CP	[redacted]	[redacted]				£30,153
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£22,810
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£30,153	-

ERG = Evidence Review Group; FAc = fluocinolone acetonide implant; ICER = incremental cost effectiveness ratio; (L)CP = (limited) clinical practice; QALY = quality-adjusted life year.

Table 6.2: Deterministic scenario analyses conditional on ERG base-case 1

Technologies	Total costs	Total QALYs	Fully incremental costs	Fully incremental QALYs	Fully incremental ICER (£/QALY)	ICER of FAc versus comparator
ERG Base-case 1 (deterministic)						
(L)CP	[redacted]	[redacted]				£12,325
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£5,335
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£12,325	-
FAc and dexamethasone are not effective anymore after 3 years, all patients switch to subsequent treatment						
(L)CP	[redacted]	[redacted]				£24,443
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£15,627
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£24,443	-
Use utility based on the US tariffs (MUST trial) for the 'on treatment' and 'subsequent treatment' health states						
(L)CP	[redacted]	[redacted]				£22,679
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£10,303
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£22,679	-
Alternative 'permanent blindness' health state utility values, Brown et al.						
(L)CP	[redacted]	[redacted]				£14,565
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£6,194
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£14,565	-
Inclusion of adverse events (assumed all AEs incur a disutility value of 0.1)						
(L)CP	[redacted]	[redacted]				£85,084
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£41,574
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£85,084	-
Alternative rates for blindness (Durrani et al. 0.0374 annual rate of blindness)						
(L)CP	[redacted]	[redacted]				£4,465
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£934
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£4,465	-
Alternative rates for blindness (Tomkins-Netzer 0.0038 annual rate of blindness)						
(L)CP	[redacted]	[redacted]				£15,072
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	£6,903
FAc	[redacted]	[redacted]	[redacted]	[redacted]	£15,072	-

ERG = Evidence Review Group; FAc = fluocinolone acetonide implant; ICER = incremental cost effectiveness ratio; (L)CP = (limited) clinical practice; QALY = quality-adjusted life year.

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Appendix 1: Additional limitations of the searches reported in the CS

Additional limitations of the CS searches not covered in the main body of the report:

All sections

- In Appendix D, G, H and I the CS states that "As of Q3 2018, HTA, NHS-EED, and DARE have been removed from the Cochrane database and are no longer publicly available".[36],[42],[43],[41] Whilst these resources are no longer available via the Cochrane Library, their archives are still available from the York CRD website (https://www.crd.york.ac.uk/CRDWeb/). However, given the archival nature of these resources and the additional searches recorded, the ERG feels that these omissions are unlikely to have affected the overall recall of results
- Limited use of synonyms for uveitis, e.g. chorioretinitis, this is unlikely to have affected the overall recall due to the inclusion of both MeSH and free text

Clinical Effectiveness

- The Cochrane Library strategy for both the clinical effectiveness and HRQoL searches reported using the Wiley host interface. The strategies for both cost effectiveness and resource use identification appeared to contain a different search syntax i.e.

  #1 uveitis[MeSH descriptor] **Should display as "MeSH descriptor: [Uveitis] explode all trees"

  #3 ('cost consequence' OR 'cost-benefit analysis'):ti.ab,kw **This line generates an error regarding the use of commas

  The ERG queried this disparity and the company confirmed that this had been a reporting error and had no effect on the recall of results and provided original strategies.

Health-related quality of life

- The Pubmed search appears to contain a translation error in the HRQoL filter, with the $ being used erroneously as the truncation symbol. In Pubmed the * is the accepted truncation symbol, the $ is converted to spaces in search queries. However, both the use of MeSH terms in the Pubmed search and searches of other databases may have mitigated against any loss of recall.

Appendix 2: Results of the scenario analysis based on the alternative assumptions concerning the effectiveness of dexamethasone

Table 1: Results of the ERG scenario's based on ERG base-case 1 and the assumption that the effectiveness of dexamethasone equals the effectiveness of FAc (hazard ratio for dexamethasone versus FAc = 1)

Technologies	Total costs	Total QALYs	Fully incremental costs	Fully incremental QALYs	Fully incremental ICER (£/QALY)	ICER of FAc versus comparator
ERG Base-case 1 (deterministic)						
(L)CP	[redacted]	[redacted]				£12,325
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£12,283	Dominating
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
FAc and dexamethasone are not effective anymore after 3 years, all patients switch to subsequent treatment						
(L)CP	[redacted]	[redacted]				£24,443
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£24,379	Dominated
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Use utility based on the US tariffs (MUST trial) for the 'on treatment' and 'subsequent treatment' health states						
(L)CP	[redacted]	[redacted]				£22,679
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£22,600	Dominating
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Alternative 'permanent blindness' utility values, Brown et al.						
(L)CP	[redacted]	[redacted]				£14,565
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£14,514	Dominating
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Inclusion of adverse events (assumed all AEs incur a disutility value of 0.1)						
(L)CP	[redacted]	[redacted]				£85,084
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£84,790	Dominating
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Alternative rates for blindness (Durrani et al. 0.0374 annual rate of blindness)						
(L)CP	[redacted]	[redacted]				£4,465
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£4,441	Dominating
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-
Alternative rates for blindness (Tomkins-Netzer 0.0038 annual rate of blindness)						
(L)CP	[redacted]	[redacted]				£15,072
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£15,023	Dominating
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-

Technologies	Total costs	Total QALYs	Fully incremental costs	Fully incremental QALYs	Fully incremental ICER (£/QALY)	ICER of FAc versus comparator
ERG = Evidence Review Group; FAc = fluocinolone acetonide implant; ICER = incremental cost effectiveness ratio; (L)CP = (limited) clinical practice; QALY = quality-adjusted life year.						

Table 2: Results of the ERG scenario's based on ERG base-case 1 and the assumption that dexamethasone is more effective than FAc (hazard ratio for dexamethasone versus FAc = 0.7)

Technologies	Total costs	Total QALYs	Fully incremental costs	Fully incremental QALYs	Fully incremental ICER (£/QALY)	ICER of FAc versus comparator
ERG Base-case 1 (deterministic)						
(L)CP	[redacted]	[redacted]				£12,325
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	-
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£10,412	£2,297
FAc and dexamethasone are not effective anymore after 3 years, all patients switch to subsequent treatment						
(L)CP	[redacted]	[redacted]				£24,443
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	-
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£22,929	£14,846
Use utility based on the US tariffs (MUST trial) for the 'on treatment' and 'subsequent treatment' health states						
(L)CP	[redacted]	[redacted]				£22,679
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	-
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£19,382	£4,499
Alternative 'permanent blindness' utility values, Brown et al.						
(L)CP	[redacted]	[redacted]				£14,565
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	-
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£12,262	£2,667
Inclusion of adverse events (assumed all AEs incur a disutility value of 0.1)						
(L)CP	[redacted]	[redacted]				£85,084
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	-
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£62,320	£8,792
Alternative rates for blindness (Durrani et al. 0.0374 annual rate of blindness)						
(L)CP	[redacted]	[redacted]				£4,465
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£3,480	Dominated
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	-

Alternative rates for blindness (Tomkins-Netzer 0.0038 annual rate of blindness)						
(L)CP	[redacted]	[redacted]				£15,072
FAc	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated	-
Dexamethasone 700	[redacted]	[redacted]	[redacted]	[redacted]	£12,840	£3,519
ERG = Evidence Review Group; FAc = fluocinolone acetonide implant; ICER = incremental cost effectiveness ratio; (L)CP = (limited) clinical practice; QALY = quality-adjusted life year.						

Appendix 3: Technical appendix

Description of adjustment	Cells involved
Calculation: costs of permanent blindness: one-off and cyclic costs and application of the transition costs in the (L)CP arm	Data Library'!Q13:R13,'Outcomes Trace'!BR9:BR1444
Trace: Costs of transition into subsequent treatment for (L)CP	Outcomes Trace'!BP9:BP1444
Trace: Costs of on treatment with (L)CP	Outcomes Trace'!BM8:BM1444
Trace: FAC costs for subsequent therapy referring to the discounted Lys	Outcomes Trace'!AA9:AA1444
Curve fit: use of digitized curve vs. IPD	Outcomes Trace'!I8:I1444,'Outcomes Trace'!AX8:AX1444
Capping utility to UK age-matched utility values	Outcomes Trace'!CC8:CD1444,'Outcomes Trace'!CF8:CF1444,'Outcomes Trace'!AN8:AO1444; 'Outcomes Trace'!AQ8:AQ1444
Costs of supplemental treatment equal in FAc and (L)CP, based on weighted average of FAc and (L)CP number of patients	CQ_suppcostsettings
Dose of Mycophenolate mofetil, AE treatment Macular oedema	Data Library'!J22,'Data Library'!R26
Use empirical SE when available	CQ_SE; 'Parameter variation'!G8:G438
Removing the remission health state: Trace, monitoring costs	control_remissionHSused,'Outcomes Trace'!BO8:BO1444,'Outcomes Trace'!Z8:Z1444
Trace: create transition from On treatment to Permanent blindness (FAC rate 50% of (L)CP rate)	Outcomes Trace'!J9:J1444,'Outcomes Trace'!M9:M1444,'Outcomes Trace'!AY9:AY1444,'Outcomes Trace'!BB9:BB1444
Trace: effectiveness of FAC after 3 years equal to (L)CP	Outcomes Trace'!J9:L1444
Cost components of permanent blindness removed before 65 years of age: hip replacement, community care and residential care	Data Library'!R14,'Outcomes Trace'!BR9:BR1444,'Outcomes Trace'!AC9:AC1444
Cost component of subsequent treatment added: blood test every 12 weeks for the proportion of patients that receive immunosuppressants	Data Library'!O213
Cost of transition into subsequent treatment FAc = (L)CP after 3 years	Outcomes Trace'!AA9:AA1444
Patients receive multiple FAc implants, one every 3 years, keep FAc effectiveness	Outcomes Trace'!X8:X1444, ERG_12
Inclusion of adverse events (assumed all AEs incur a disutility value of 0.05)	Data Library'!J52; 'Data Library'!L52;
FAc and dexamethasone are not effective anymore after 3 years, all patients switch to subsequent treatment	Outcomes Trace'!I8:I1444

Use utility based on the US tariffs (MUST trial) for the 'on treatment' and 'subsequent treatment' health states	Data Library'!V11;'Data Library'!V13
Alternative 'permanent blindness' utility values, Brown et al.	Data Library'!V12
Inclusion of adverse events (assumed all AEs incur a disutility value of 0.1)	Data Library'!J52; 'Data Library'!L52;
Alternative rates for blindness (Durrani et al. 0.0374 annual rate of blindness)	Model Control'!F24
Alternative rates for blindness (Tomkins-Netzer 0.0038 annual rate of blindness)	Model Control'!F24
Inclusion of DEX700 as a comparator in all ERG base-cases; =1 based on HR vs (L)CP of 0.44; =2 based on HR vs FAc of 1; =3 based on HR vs FAc of 1.1	Outcomes Trace_DEXLCP' - sheet; 'Outcomes Trace_DEXFAC' - sheet

Additionally, the ERG created the Module ‘ERG’ in the VBA code.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

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

You are asked to check the ERG report from KSR Ltd to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on Monday 18 February 2019** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Description of problem	Description of proposed amendment	Justification of proposed amendment	ERG Response
Comparators and ITC The ERG commented that searches for all comparators mentioned in the scope should have been performed and that dexamethasone is the most relevant comparator. The ERG also stated that the company "ignores" most comparators listed in the scope. The ERG further commented that an attempt on an ITC with dexamethasone should have been made.	The company disagrees that searches should have been conducted for all comparators listed in the scope, or that other comparators should be presented in the submission. This is a conscious scientific decision and not an attempt to "ignore" the final scope issued by NICE. The company further disagrees that an ITC with dexamethasone should have been conducted.	The comparators mentioned in the NICE scope reflect an indication broader than the expected licensed indication. The company did not ignore the comparators listed in the scope but due to the expected licensed indication not all these comparators are relevant anymore. TA460 recognised the challenges in defining current clinical practice in the UK, given the absence of national treatment guidelines and heterogeneity in both the patient population and subsequent therapies. Given these challenges, the main comparator used by the Assessment group within this MTA was limited current practice (LCP). This submission applies the same approach. As noted by TA460, an ITC versus dexamethasone or adalimumab is not possible due to the differences in trial design, trial endpoints and study medication. These differences were outlined on page 82-83 in the submission as well as in A37 in the clarification form. Therefore, the company did not decline to conduct an ITC but rather deemed it inappropriate. Therefore, the company deems the assumptions applied by the ERG as unsupported and unscientific, with emphasis on the assumption assuming equivalence. Therefore, it is unsurprising that assuming FAc is less effective than dexamethasone results in a negative cost-effectiveness outcome; however, the ERG should consider this analysis in the context of the evidence supporting this assumption, which is	Not a factual error, the company did ignore most comparators mentioned in the NICE scope.

		non-existent.	
The ERG questioned the comparator used in the PSV-FAI-001 trial, stating on page 28 that "Therefore, the comparator is unclear. In addition, patients in the intervention arm could also receive the same (L)CP as patients in the control group. Therefore, the trial is actually: FAc+(L)CP versus (L)CP, making it impossible to find data for a comparison of FAc vs. any single comparator specified in the scope"	The company would like to note that the use of (L)CP as a comparator is in line with TA460. Also, the fact that patients in the intervention and sham arms could receive additional treatments is in line with other trials in uveitis.	Since both dexamethasone and adalimumab were compared to placebo on a background of additional standard therapy, TA460 focused on a comparison of these drugs vs (L)CP. In this submission, we took a similar approach. Regarding the fact that "patients in the intervention arm could also receive the same (L)CP as patients in the control group", this is also very similar to the VISUAL I and HURON trials. The use of systemic, intravitreal or topical rescue treatments was permitted in both arms of the HURON trial in case of worsening/ recurrence of uveitis. In the VISUAL I trial all patients, regardless of the arm to which they were randomised, received a prednisone burst at study entry that was tapered slowly up to week 15.	Not a factual error.

Description of problem	**Description of proposed amendment**	**Justification of proposed amendment**	**ERG Response**
Recurrence The ERG deems assessment of recurrence as inadequate, due to high imputation rates. For example: "The main issue with the decision problem is the response of the company	The company would like to highlight that recurrence of uveitis was, in fact, adequately assessed in the pivotal PSV-FAI-001 trial. Although [redacted] and [redacted] of patients in the FAc and sham arms, respectively, had an imputed recurrence at 36 months, this was primarily attributed to the use of rescue medication. Imputation of recurrence due to the use of rescue medications ensured that any recurrences treated at the earliest appearance	The degree of imputation, particularly due to patients receiving prohibited (rescue) medication might have been high, but this does not necessarily mean that recurrence was only imputed and was not observed clinically. Indeed, the threshold for defining recurrence according to the protocol was as defined on pages 39	Not a factual error. Our critique of the assessment of recurrence in the PSV-FAI-001 trial is clear.

to the outcome 'recurrence of uveitis'. It was not adequately assessed in the PSV-FAI-001 trial because the vast majority of recurrences were imputed from the prescription of 'prohibited medication', up to [redacted] and [redacted] in the FAc and sham arms respectively at 36 months"	of symptoms were duly recorded.	and 40 of the company submission: • ≥2-step increase in the number of cells in the anterior chamber per high powered field (1.6 × using a 1 mm beam), compared with baseline or any visit time point prior to Month 6 • OR an increase in the vitreous haze of ≥ 2 steps, compared with baseline or any visit time point prior to Month 6 • OR a deterioration in visual acuity of at least 15 letters, compared with baseline or any visit time point prior to Month 6 (or 12 or 36 for the respective analyses) Note this is a very similar definition to that used in the VISUAL I trial of adalimumab, although this also included the appearance of new active inflammatory lesions. If physicians decided to treat patients before these criteria were met to prevent over recurrence, this was recorded as an imputed recurrence due to the use of prohibited (rescue) medication. However, as the ERG noted in its report, some recurrences may have been imputed due to the use of prohibited medications	

		administered for reasons other than treatment of uveitis. It is also important to note that the figures quoted by the ERG as percentage of imputed recurrences ([redacted] and [redacted] in the FAc and sham arms, respectively, at 36 months) are in fact the percentage of patients experiencing an imputed recurrence. As stated in Table 11 in the company submission, at 36 months [redacted] and [redacted] had had more than one recurrence, of which some may have been observed and others imputed. Therefore, the figures quoted by the ERG cannot be interpreted as representing the percentage of imputed recurrences in the PSV-FAI-001 trial.	
The ERG is uncertain regarding the effect of the FAc implant on recurrence rate, e.g. “It remains largely unknown what the effect of FAc is on the rate of recurrence of uveitis because this was often not recorded in the trial and no attempt was made to differentiate the prescription of medication for the treatment of recurrence from that for any other reason including	We propose removing the references to uncertain effect of the FAc implant on recurrence rate.	The effect of FAc on reducing recurrence rate was clearly beneficial when the primary endpoint (including observed and imputed recurrences) was analysed in the ITT population. However, the Per-Protocol analysis excluded patients with an imputed endpoint and there was still a clear beneficial effect of the FAc implant compared to sham, as the number of patients experiencing a recurrence of uveitis was substantially lower with the FAc implant ([redacted] vs [redacted] for sham at 6 months, 5.7% vs 92.3% at 12 months and [redacted] vs [redacted] at 36 months).	Not a factual error. We stand with our critique.

deterioration in any underlying autoimmune disease.”		In addition, to investigate the effects of missing data on the primary endpoint results, sensitivity analyse were provided; all of which used different methods for imputing missing data (including one highly conservative analysis where missing data was assumed to be a recurrence for FAc and assumed to be no recurrence for LCP). All showed the beneficial impact of FAc and most showed increased benefit compared to the primary endpoint definition, so to say that the degree of benefit is uncertain is highly misleading. Although the specific reason for administration of prohibited (rescue) medication was not reported in PSV-FAI-001 trial, there is no good reason to believe that these were largely used for reasons other than the treatment of uveitis. Indeed, such use of rescue medications would constitute a protocol violation. As stated on page 38 of the company submission, the protocol only permitted the use of oral, systemic, injectable, or topical steroids and systemic immunosuppressants during the initial tapering and in case of uveitis recurrence, and the investigators were advised to discuss treatment with the medical monitor before administering any prohibited medication unless it was an	

		emergency. [redacted] This observation supports the notion that prohibited systemic treatments were indeed largely (if not solely) used to treat recurrences of uveitis, rather than other conditions. Therefore, imputation of recurrence in cases of prohibited medication use (or indeed missing data) should be considered as a conservative approach to estimating efficacy of the FAc implant, rather than as a source of uncertainty. Finally, the cost-effectiveness analysis used one of the more conservative methods of imputation. Therefore, it may be that additional clinical benefit may be observed in clinical practice.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Composition of L(CP) and relevance to the UK population The ERG stated that it does not agree	Due to the lack of current treatment guidelines for uveitis and the associated demand for additional effective and possibly steroid–sparing		Not a factual error.

that "the sham injection arm of PSV-FAI-001 is considered largely representative of current practice in the UK for the treatment of uveitic flares and recurrence"	therapies in patients with non-infectious uveitis, the company applied a similar approach used by the AG in TA460.		

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Clinical effectiveness SLR results The ERG commented that the correct number of identified publications within the clinical SLR is unclear, "but it is most likely that the correct number is seven publications."	The correct number of publications identified is indeed seven. As described in A1 in the clarifications document, three additional conference websites had been searched in November 2018 which resulted in three additional conference abstracts eligible for inclusion in the clinical SLR (as listed in A12). This resulted in seven publications in total. All three of these additional conference abstracts present results from the pivotal PSV-FAI-001.	Please see Figure 1 for an overview of study flow and Table 6 for a description of the study and cohort characteristics of the included publications, both in Appendix D.	Not a factual error. Thank you for the clarification.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Statistical analysis The ERG commented that no between-arm statistical analysis was performed to assess significance of	As it has been outlined in the statistical analysis plan for PSV-FAI-001, visual acuity will be expressed as mean change from baseline best corrected visual acuity (BCVA) letter score in each treatment group. Therefore, only		Not a factual error. We state in our report that statistical significance is not reported and "It is

the results in terms of visual acuity. The ERG further points out that therefore none of the results show a statistically significant difference between FAc and sham treatment.	descriptive results are provided. [redacted]		therefore very possible that none of these results show a statistically significant difference between FAc and sham treatment."

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Errors pertaining IOP results in PSV-FAI-001 On page 56, the ERG stated that the proportion of patients who experienced increased IOP in the study eye was similar in the FAc and sham groups ([redacted] vs. [redacted]	The proportion of patients who experienced increased IOP in the study eye was [redacted] in the FAc study arm.	Note that this error was also present in text on page 67 of the company submission.	Thank you for clarifying. As this mistake was copied from the CS, no change to the ERG report has been made.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Errors pertaining to safety data On page 12, the ERG stated that "The most common ocular TEAEs associated with FAc implant were cataract ([redacted] for FAc versus [redacted] for sham injection) and intraocular pressure increased (IOP) ([redacted] for FAc versus [redacted] for sham injection)."	We suggest changing this fragment to "The most common ocular TEAEs occurring in the FAc implant arm were cataract ([redacted] for FAc versus [redacted] for sham injection) and intraocular pressure increased (IOP) ([redacted] for FAc versus [redacted] for sham injection)."	The figures quoted by the ERG do not consider relationship of the adverse event to study treatment. Treatment-related cataracts occurred in [redacted] of patients in the FAc implant groups vs [redacted] in the sham group. Treatment-related increases in intraocular pressure was observed in [redacted] of patients in the FAc implant	Not a factual error. A full list of ocular TEAEs and treatment-related ocular TEAEs in the study eye affecting >5% of patients in either treatment group occurring over the 36-month follow-up period is shown in Table 4.15.

		group and [redacted] in the sham group.	
On page 56, the ERG stated that the proportion of patients who experienced increased IOP in the study eye was similar in the FAc and sham groups ([redacted] vs. [redacted]	The proportion of patients who experienced increased IOP in the study eye was [redacted] in the FAc study arm.	Note that this error was also present in text on page 67 of the company submission.	Thank you for clarifying. As this mistake was copied from the CS, no change to the ERG report has been made.
On page 52, the ERG stated that "There was [redacted] serious ocular TEAE in the study eye affecting two or more patients in the FAc group: cataract (n=[redacted]). Serious ocular TEAEs in the study eye affecting two or more patients in the sham injection group were: macular oedema (n=[redacted]), uveitis (n=[redacted]), and intraocular pressure increased (IOP, n=[redacted])."	We propose amending this to: "The only ocular treatment-emergent serious adverse events affecting the study eye reported in more than 1 subject in the FAc implant group were cataract ([redacted]) subjects in the FAc implant group and [redacted] patients in the sham group); uveitis ([redacted] subjects in the FAc implant group and [redacted] in the sham group) and intraocular pressure increased ([redacted] subjects in the FAc implant group and [redacted] in the sham group). Serious ocular TEAEs affecting the study eye in 2 or more patients in the sham group were uveitis (as specified above), macular oedema ([redacted] in the FAc implant group vs [redacted]) in the sham group) and non-infectious endophthalmitis ([redacted] in the FAc implant group vs [redacted] in the sham group).	Serious treatment-emergent ocular adverse events are listed in Table 12–13 (page 163) of the 36-month CSR and this table was the source of corrected data.	Not a factual error.

Table 4.19 in the ERG report (page 56) the table heading reads “PSV-FAI-001 study (safety population): Non-ocular TEAEs and treatment-related non-ocular TEAEs affecting >5% of patients in either treatment group occurring over the 36-month follow-up period”	The correct table heading should read PSV-FAI-001 study (safety population): Non-ocular TEAEs affecting >5% of patients in either treatment group and treatment-related non-ocular TEAEs occurring over the 36-month follow-up period	Although only non-ocular TEAEs affecting >5% of patients in either treatment group are shown (derived from Table 12–5 in the CSR), this frequency restriction does not apply to treatment-related non-ocular TEAEs (derived from Table 12–12 in the CSR), so the original table caption was misleading. Note this error was also present in Appendix F, which was the source of this table for the ERG report.	Thank you for clarifying. As this mistake was copied from the CS, no change to the ERG report has been made.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Population enrolled in PSV-FAI-001 On page 27, the ERG states the following: “The population included in the main trial for the submission (PSV-FAI-001) is patients with [redacted]. In the response to the clarification letter (page 14), the company states that “chronic disease relapses promptly when therapy is discontinued”, while the “key feature of recurrent acute disease is the presence of	We suggest simply stating that the population included in the main trial for the submission (PSV-FAI-001) is a mixture of patients with [redacted].	Although the PSV-FAI-001 trial was described as conducted in “Subjects With a [redacted]” in the Sponsor’s materials, the trial, in fact. Included a mixture of patients with [redacted] according to the definitions identified in the literature and cited in the clarification letter and the ERG report. According to the trial eligibility criteria provided on page 34 of the company submission, during 12 month prior to enrolment patients had to receive either multiple local treatments or at least 3 month of systemic treatment ([redacted]) or had at least two uveitis recurrences requiring treatment ([redacted]).	Not a factual error. Thank you for clarifying.

episodes of active inflammation separated by periods of no inflammation when not on therapy".24 The number of patients included in the PSV-FAI-001 with [redacted] according to these definitions is unclear."			

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Description of the intervention Throughout the ERG report, there are numerous instances where the ERG refers to fluocinolone acetonide (FAc) as the intervention of interest to this submission, for example on page 27 "The intervention (fluocinolone acetonide (FAc)) is in line with the scope."	The description of the intervention should read FAc implant and, where relevant, FAc 0.19 mg intravitreal implant.	The submission pertains to ILUVIEN, a specific FAc intravitreal implant that contains 0.19 mg of the active ingredient (fluocinolone acetonide) and delivers a continuous, low dose of the medication (0.2 µg of FAc per day) into the vitreous humour over 36 months. It is crucial to distinguish it from other formulations of fluocinolone acetonide (FAc), including other intravitreal implants containing FAc (e.g. Retisert, which contains a higher dose of the drug).	Not a factual error. Thank you for clarifying.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Visual acuity (both eyes) On page 46 of the report, the ERG stated that visual acuity (both eyes) was not assessed in the PSV-FAI-001 trial.	We propose adding that some descriptive data pertaining to visual acuity in the fellow eye are available.	Note that, although not included as an endpoint in the PSV-FAI-001 trial, some descriptive data pertaining to visual acuity in the fellow eye (including change from baseline to Month 36) are available in Table 14.3-4.3 in the 36-month CSR.	Not a factual error. This was not reported in the CS.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Size of the eligible population On page 19 of the ERG report, it states that: “The company states that an estimate regarding the epidemiology of [redacted] in England had not been identified but that in Europe 3.8 per 10,000 people have uveitis and in the US 91% of the uveitis cases are non-infectious.8, 9 According to the NICE scope slightly more people, i.e. 4.8 per 10,000, have uveitis in the European Union. The company cites a retrospective review of referrals to the Manchester Uveitis Clinic (MUC) and suggests that based on the proportions of posterior, intermediate, and panuveitis in the MUC study the posterior segment of the eye is	Please refer to Table 2 in the budget impact document submitted alongside the company submission for details of these calculations.	The budget impact document was originally included in the company submission as section 3.12 and subsequently moved to a separate file, in line with NICE preference. However, the corresponding link in the CS was not updated. The company would like to apologise for this error.	Not a factual error. Thank you for clarifying. As far as we know NICE did share the budget impact document with the ERG.

affected in 54% of cases of uveitis.10 The company then concludes that based on this information and the adult population size of England approximately 8,500 prevalent cases of [redacted] with 51 new cases per year can be expected and refers to section *3.12 of the CS for further details. However, section 3.12 of the CS does not exist and it is unclear how these estimates were calculated*"			

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Inclusion of dexamethasone as a comparator The ERG have included dexamethasone implant as a comparator to ILUVIEN. In the Company Submission (CS) Section 3.2, the company outline why dexamethasone is not an appropriate comparator and also why, if it were appropriate, there are no methods which allow a scientific comparison to be made. Further, the ERG have failed to recognise or engage with these points while describing the CS in	Dexamethasone is not an appropriate comparator and results presented where it is shown as such should be considered with caution. The company believes that there are also substantial issues with the methods used to try and include dexamethasone as a comparator which are discussed individually. Additionally, the company does not believe that the analysis constitutes a formal indirect comparison for the reasons outlined.	As described in the CS, Section 3.2, it was not considered appropriate to include dexamethasone as a comparator because of the key differences between the informing trials (HURON and PSV-FAI-001), these are tabulated in the response to question A37 of the clarification response. These differences in trial design include; an incompatible definition of supplemental therapies, an incompatible definition of (L)CP (the comparator), incompatible primary and	Not a factual error. We have described the shortcomings of an indirect comparison with dexamethasone clearly in our report.

		secondary outcomes measured, different populations, differences in the inclusion criteria, length of time to outcome measurement. Additionally, as described in the CS and in the responses to clarification questions, there is considerable ambiguity in the treatment pathway. Also discussed, was the assumptions that were required for TA460, namely a lack of evidence in the length of efficacy of dexamethasone. TA460 cited a number of these differences between the HURON and VISUAL trials as reason not to conduct an indirect comparison and their methods were considered to produce robust estimates of cost and efficacy. Therefore, using the HURON data to form the calculation of a HR and then apply this to the (L)CP data from PSV-FAI-001 is considered inappropriate given the differences in the populations considered and definitions of (L)CP from these	

		two trials.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Efficacy of dexamethasone The ERG have assumed three definitions of efficacy for Dexamethasone which are based on substantial and unsupported assumptions in all cases. As described in Section 3.2 of the CS and the response to question A37 in the clarification questions, the company do not believe that there is any scientific method by which to estimate the efficacy of the dexamethasone implant in comparison to the ILUVIEN implant.	The company believe that there is no reliable and scientific method by which to estimate the efficacy of dexamethasone in comparison to ILUVIEN and it should therefore have not been included as a comparator in a formal analysis. The method by which the efficacy has been estimated are not considered to be robust and are based on a lack of evidence (where a HR is applied to the efficacy of ILUVIEN) or assumptions and indirect evidence (where a HR is applied to the efficacy of (L)CP).	The ERG acknowledge that the figure of 0.456 as a HR applied to (L)CP is based on some assumptions. These assumptions are also subjective as they are based on the difference in QALYs obtained in a different population (in the HURON trial) than is considered in this submission and the QALYs are estimated with a mapping algorithm. This efficacy outcome is also based on assumed efficacy rather than observed/reported data; due to a lack of evidence, TA460 assumed efficacy for 30 weeks. The HR was calculated assuming that the incremental	Not a factual error. This is clearly described in our report.

		QALYs reported in TA460 were accrued over exactly 30 weeks; this was based on an assumption that dexamethasone has exactly 30 weeks of efficacy (as reported in TA460 the HURON trial lasted for only 24 weeks). The utility values used in TA460 were not collected and reported at either 24 or 30 weeks. The EQ-5D values used in the dexamethasone comparison of TA460 were estimated from an algorithm mapping VFQ-25 to EQ-5D. Therefore, the incremental QALYs upon which this HR is estimated are not from directly measured data. The incremental QALYs reported in TA460 are therefore subject to considerable uncertainty in both their underlying accuracy and the length of time over which they would be truly accrued, yet these have been used as the basis of a measurement of efficacy which is then applied to a different	

		population (in the PSV-FAI-001 trial). Additionally, the populations from which QALYs were obtained in the HURON trial are not the same as the PSV-FAI-001 trial and therefore the generalisability in the incremental QALYs is questionable	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Application of dexamethasone efficacy The ERG have made assumptions about the duration of dexamethasone efficacy in the analyses presented which the company considers to be based on assumptions rather than direct evidence. In the application, no adjustment has been made for the repeated application of the dexamethasone implant; it is assumed completely active for the entire 30 weeks. Additionally, where these have been applied, they are contradictory with methods that were recommended for the company follow in the clarification questions.	If it were appropriate to consider dexamethasone as a comparator and there were a reliable method by which to estimate the magnitude of efficacy compared to ILUVIEN, the company propose that direct evidence should be used to inform the length of the efficacy and that this should be in line with the administrations as described by the costing (i.e. every 30 weeks).	The ERG analysis assumes efficacy of 30 weeks, as in TA460 (itself an assumption) however the HR is applied to the (L)CP or ILUVIEN arm with no adjustment for starting treatment. The efficacy estimated for (L)CP and for ILUVIEN gradually decreases as there is only one implant with retreatment is not modelled due to lack of evidence. Applying a HR to this time to event profile assumes that the pattern of the event in the dexamethasone arm is identical despite a	Not a factual error. This is clearly described in our report.

In question B7 of the clarification questions, the ERG ask that as the trial ends at three years for PSV-FAI-001 that there is no reason to extrapolate beyond that time period. However, there are numerous occasions where the implementation of dexamethasone efficacy by the ERG infers no recurrence long after 6 months post treatment.		different treatment schedule and efficacy profile. In ERG base case 1, implants are costed for every 30 weeks up to 150 weeks. At [redacted] weeks there are estimated to be [redacted] of patients still responding to treatment. This same criticism was made about the company's decision to extrapolate beyond the observed time despite the company's decision being made upon review of the observed data from PSV-FAI-001. Additionally, the HR is calculated on the assumption that differences seen in treatments are accrued in exactly 30 weeks and so the presence of patients after [redacted] in the "on treatment" health state violates this assumption and is contradictory with the methods recommended to the company in the modelling of ILUVIEN. Where the ERG implemented a change to the company model whereby a very limited efficacy could be considered after three years (contradictory with observations from PSV-FAI-001), this resulted in a	

		larger ICER. It is reasonable to assume that if the same methodology were followed for the ERG's analysis of dexamethasone that this might result in a reduced ICER, favouring ILUVIEN. Where a HR of 1 is applied to the ILUVIEN arm, implants are costed for up to 150 weeks and after [redacted] weeks [redacted] of patients are reported still responding to treatment. When a HR of 0.7 is applied, this is [redacted] at this time. The source for the assumption that dexamethasone would have the same efficacy or improved efficacy when compared to ILUVIEN is not reported in the ERG report. Given that the dexamethasone implant is considered active for 6 months, it seems implausible that at [redacted] weeks (60 weeks after the last dexamethasone implant) there would be [redacted] of patients "on treatment" which is shown when a HR of 1 is considered (compared to ILUVIEN). Therefore it is considered inappropriate to apply a HR of 1 to the ILUVIEN arm especially as the	

		source of evidence supporting an assumption of equal efficacy has not been reported. Similarly when the HR is reduced to 0.7, at [redacted] weeks there are [redacted] of patients who are “on treatment” which is higher than the ILUVIEN arm. Additionally, the rationale for administering dexamethasone six times is not described in the ERG report.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Inclusion of other comparators The ERG report describes that the company “refused to perform the requested analyses” in relation to including other comparator in a network (other than dexamethasone). The company described why a network including other comparisons was not appropriate and this has been ignored in the reporting of the CS by the ERG.	It is not appropriate to include an indirect treatment comparison for ILUVIEN and systemic corticosteroids and TNF-alpha inhibitors for a number of reasons; incompatible trials, heterogeneity in the patient populations and incompatible positions in the treatment pathway. In Figure 2.1 of the ERG report, the ERG suggest a position for ILUVIEN which suggests that anti-TNF inhibitors are not to be considered comparators for ILUVIEN and so the request for this analysis is contradictory in this report.	Both systemic corticosteroids and TNF-alpha inbhibitors constitute prohibited treatment for ILUVIEN in PSV-FAI-001 and therefore these cannot be used to form a network. The treatment pathway for TA460 also suggests that systemic treatments are likely to be placed after intraoccular treatments. Additionally, both dexamethasone and adalimumab were	Not a factual error.

	Rather than refuse the request, the reasons for not including an indirect comparison were explained in the CS (Sections 1.1 and 3.2) and the clarification response to question A37. These have also been outlined in the response to the first point in this document and include; incompatible primary and secondary outcomes, incompatible comparators, incompatible prohibited therapies and inclusion criteria. Additionally there is considerable ambiguity in the treatment pathway. TA460 cited these differences in the trials that they considered as reason to provide separate comparisons against (differently defined) (L)CP and the company has followed this reasoning.	recommended for patients with uveitis in the posterior segment, whereas ILUVIEN is likely to be indicated for NUI-PS. The AG in TA460 felt it was inappropriate to create a network containing dexamethasone and adalimumab due to differences in; • baseline systemic therapies • rescue therapies • baseline treatments • likely treatment in different populations • heterogeneity in patient populations in terms of active/inactive uveitis • lack of comparable outcomes • no common comparator An SLR was conducted for this submission and no evidence has been sourced which can provide a network for any comparators with ILUVIEN.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Inclusion of disutilties for AEs The source of values used to describe disutilities is not well reported in the ERG report. Further, the method leads to a loss of utilities substantial enough that the implication is that a patient will experience worse quality of life by using an ILUVIEN implant than with systemic immunosuppressants. Additionally, this assumes that all AEs are of the same severity and in response to question B.13, the company clarifies that this is not the case and that ILUVIEN is associated with less severe AEs than (L)CP.	There are a number of issues with the inclusion of common AEs which are listed below: • It is not confirmed that the criteria for reporting AEs for dexamethasone and for ILUVIEN are compatible • It is unknown whether the grading of AEs is compatible. • There is no common measure of HRQoL between the trials • Mortality is not considered and therefore the reduction of 0.1 QALYs per year is quite substantial. Therefore the inclusion of these disutilities does not help with decision making and it is suggested that this should be removed. TA460 did not include disutilities for AEs as they considered that the health state utility values should capture this component. This approach was taken for the CS and as described was deemed appropriate because the health state utilities were based on evidence	All AEs are considered to be associated with a reduction of 0.1 QALYs every cycle. The sum of the probability of experiencing an AE is [redacted] per cycle so this is multiplied and applied to the proportion on treatment. This equates to a reduction of [redacted] QALYs every cycle, [redacted] every year (assumes 26 cycles per year). Given that the difference between "on treatment" and "off treatment" is [redacted] QALYs per year, this value infers that patients will experience improved quality of life if they move straight to systemic treatments. This seems uncertain given the disease progression and the differing AE profiles of ILUVIEN and systemic therapies. This inference also explains why the ICER is so high for this scenario.	Not a factual error. The ERG thinks that the impact of AEs on quality of life was not appropriately captured in the company analyses and therefore provided analyses exploring the potential impact of those events on the results.

	that considered whether a patient was responding to treatment or not.	The source of this disutility is not reported. Its application follows the assumption that all AEs are worth the same. The third most common AE reported for IUVIEN was reduced visual acuity which should ideally be captured in the health state utility which was the original reason for not including disutilities. Jointly was gastrointestinal disorders which could be argued not related to the implant. In the response to question B13.a. it was detailed that only severe AEs would likely result in disutility and that there were 10 more of these events in the (L)CP arm than in the ILUVIEN arm ([redacted]). The descriptions as provided in the CSP for PSV-FAI-001 are listed below: • Moderate AEs : "Discomfort enough to cause some interference with usual activity. Traditionally introduces a low level of inconvenience or concern to the subject and may interfere with	

		daily activities but are usually relieved by simple therapeutic measures." • Severe AEs: "Causes an interruption of the subject's usual daily activity and traditionally requires systemic drug therapy or other treatment." Therefore unless these definitions are comparable between the HURON trial and PSV-FAI-001 it may not be advisable to apply the same utility decrement to all AEs listed.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Transition to permanent blindness from On Treatment In Section 5.2.2, ERG comments that the transition from permanent blindness cannot be made from on treatment. A clinician advised that patients with lower vision than in the PSV-FAI-001 trial may receive the implant and therefore a transition is	The company proposes that the inclusion of this transition is not appropriate as it violates the definition of recurrence that underpins the other transitions in the model and it is not based on observed evidence, but an assumption from TA460 that an intervention might reduce blindness by half.	In the clarification response to question B2.b., it was outlined that the informing trial (PSV-FAI-001) included a definition of recurrence that was based on the change in vision since baseline. This change in vision (worsening) since baseline would result in recurrence	Not a factual error. Including this transition in the cost effectiveness model is a matter of judgement, and has been clearly justified in the ERG report.

included.		being recorded and the modelled patient moving from the “on treatment” to “subsequent treatment” health state regardless of the quality of vision that the patient started treatment with. Unless a patient were to go blind without first experiencing worsening vision (as described in PSV-FAI-001 CSP) then it is not appropriate to include this transition. Additionally, as the ERG acknowledges, the inclusion of this transition is in contrast with the evidence from PSV-FAI-001 in the ILUVIEN arm.	

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG Response**
Subgroup analysis In Section 5.2.3, ERG comments that the company did not provide subgroup analysis as mentioned in the final scope. It is later mentioned (page 80) that the company “refused” to provide this.	The company did not refuse to perform subgroup analysis but described why this was either not possible (i.e the required data had not been collected in a usable format) or that it would not provide robust analysis (with very low n numbers).	In response to question B22 of the clarification questions, the subgroups that were available are described. Not all subgroups were collected and where they were, these were not always available in the detail required (efficacy/events stratified by subgroup for	Not a factual error.

		example) but instead summary figures. Additionally as mentioned in the response to question B22 the overall number of patients in each arm of PSV-FAI-001 (n=87 and n=42 for ILUVIEN and (L)CP respectively) are small and so to further split these group could produce misleading information high in uncertainty. Clinical advice as detailed in this response describes the same issue being true in the exploration of HURON and VISUAL trials and advises that only emergence of real world data can reliably inform these. This has not currently been identified. Therefore, any subgroup analysis would be spurious and be subject to considerable uncertainty rendering it unhelpful in decision making.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Spline Model The ERG report that the company refused to fit a spline model.	The company maintains that they did not refuse but outlined why it was not appropriate, provided justification and an alternative; in the base case a piecewise model was fit to the data which is an appropriate statistical method for data with changing hazards (as seen in the ILUVIEN arm of PSV-FAI-001).	In the response to question B9.e of the clarification questions it is detailed why spline models are not appropriate for extrapolation. This response explains that spline models are appropriate for describing internal data but where extrapolation is required, they are not generally considered correct. As events were observed after the defined cut off period of PSV-FAI-001, the data does require extrapolation beyond the trial time period. A piecewise model (used in the base case) mechanistically describes the process that forms the extrapolated portion of the curve and is therefore more appropriate where extrapolation is required. Spline models only consider up to and including the last observation value meaning that they are of limited use for predictions beyond the trial period.	Not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Duration and severity of AEs ERG states on page 75 that the company did not provide the severity and duration of each AE.	The duration of each AE was not recorded and therefore this could not be provided. Additionally, this was not requested in the clarification letter sent to the Company.		Not a factual error.

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Additional blood test costs On page 76, the ERG state that "The monitoring visits were assumed to include the assessment of visual functioning and potential AEs and a blood test" On page 79, the ERG reports that the cost of blood tests was omitted in the company model. The clinical expert consulted by the ERG confirmed that patients in subsequent therapy were likely to require blood tests every 12 weeks.	The company suggests that this cost of blood tests was included in the monitoring cost as stated in the clarification response to question B20.b and therefore should not be included again.	The addition of blood test costs separate to the monitoring cost constitutes double counting. In the response to question B20.b. the assumption that the cost of a blood test is included and the validation of this assumption by a clinician is outlined. However, the inclusion of an additional cost as a scenario was include. In the ERG report it is stated that the monitoring visit costs are assumed to include blood tests and then later that these costs are omitted by the company which is	Not a factual error. The ERG added blood test costs in the 'subsequent treatment' health state for patients who received immunosuppressants because these were not explicitly costed.

		contradictory.	

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Factual inaccuracies Table 5.4 reports the Supplemental treatment acquisition costs for Iluvien as £99.49 per cycle.	Suggest this be £96.49 as reported in the submission and model		Thank you for highlighting this error, this has been amended in the erratum.
On page 79, the ERG reports that some of the errors (found by ERG) were corrected in the clarification response	Suggest that this reads “all were corrected by the Company in their clarification response”.		Not a factual error.

in collaboration with:

ERASMUS UNIVERSITEIT ROTTERDAM
INSTITUTE OF HEALTH POLICY & MANAGEMENT

Maastricht University

Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis

ERRATUM

This document contains errata in respect of the ERG report in response to the company's factual accuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page nr:	**Change:**
77	In Table 5.4, the ERG mentioned that the supplemental treatment acquisition costs of FAc were £99.49 but these are £96.49

the mix of immunosuppressant and steroid medications informing this calculation were taken from TA460.[14] Prices were obtained from the MIMS.[80]

Transition costs were applied to FAc but not to (L)CP patients upon transition from the 'on treatment' or 'remission' health states to the 'subsequent treatment' health state. This cost was calculated based on resource use at trial onset and MIMS prices.[80]

Permanent blindness
Costs in the 'permanent blindness' health state consisted of monitoring visits every six weeks and cyclic permanent blindness costs. There was also a transition cost applied on the transition to the 'permanent blindness' health state. Cyclic permanent blindness costs contained the costs of depression, hip replacement and community care. The transition costs of becoming permanently blind contained the costs of registration as a blind person, costs of low vision aids, low vision rehabilitation and residential care. All prices stemmed from TA460[14] and were inflated to 2017.

Remission
In remission, only the costs of AEs, which are described below, were applied.

5.2.9.4 Adverse event related costs

Treatment-dependent AE related costs were applied in the 'on treatment' and the 'remission' health states. AEs with a prevalence of ≥5% in any treatment arm were included in the model using the AEs rates reported in PSV-FAI-001 (CS Table 32[1]). Resources use were informed by TA460[14] or estimated by a clinical expert. Prices stemmed from TA460[14], NHS reference prices[79] or PSSRU[81] (CS Table 46[1]).

Table Error! No text of specified style in document**.1: Health state and treatment costs with PAS**

Health state	FAc	(L)CP	Source
FAc treatment acquisition & administration [a]	[redacted]	£0	CS 3.5.2.1[1]
On treatment			
Supplemental treatment acquisition costs [b]	£96.49	£122.02	CS Table 27[1] CS Table 42[1]
Monitoring costs per cycle	£18.41	£18.41	CS 3.5.3.1[1] CS Table 43[1]
Adverse events costs per cycle	£9.01[c]	£5.25[c]	CS 3.5.4[1] HE Model[82]
Subsequent treatment			
Transition costs to the 'subsequent treatment' health state [a]	£0.77	£0	
Acquisition costs of subsequent treatments per cycle	£2.45	£2.45	CS Table 44[1]
Monitoring costs per cycle	£36.83	£36.83	CS 3.5.3.1[1] CS Table 43[1]
Adverse events costs per cycle	£0	£0	HE Model[82]
Permanent blindness			