NICE National Institute for Health and Care Excellence

Fluocinolone acetonide intravitreal implant for treating recurrent non-infectious uveitis

Chair's presentation

2nd appraisal committee meeting

Chair: Peter Selby

ERG: Kleijnen Systematic Reviews

NICE technical team: Kirsty Pitt, Sally Doss

Company: Alimera Sciences

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Fluocinolone acetonide intravitreal implant, Alimera Sciences

Marketing authorisation	Indicated for prevention of relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye
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.

ACD preliminary recommendation

- The committee was minded not to recommend fluocinolone acetonide intravitreal implant as an option for preventing relapse in recurrent non-infectious uveitis affecting the posterior segment of the eye in adults.
- The committee recommends that NICE requests further clarification and analyses from the company, which should be made available for the second appraisal committee meeting, and should include a revised cost-effectiveness model that:
  - considers both eyes
  - compares the fluocinolone acetonide implant with the dexamethasone implant, both as single and repeated implants and
  - includes disutility values calculated based on the length and severity of each adverse event.

[redacted]

Committee's considerations

Issue	Committee's conclusion
Comparators	Dexamethasone is a relevant comparator and should be included in modelling
Clinical trial	• Does not reflect clinical practice in England • Rates of uveitis recurrence likely overestimated
Visual acuity	Possible improvement with fluocinolone implant
Model structure	Should consider both eyes Should not include remission health state Multiple implants should be possible
Treatment effectiveness	No treatment benefit after 3 years with fluocinolone implant
Utility values	Disutilities for adverse events should be modelled based on length and severity of each event
ICERs	Company: £7,183 per QALY gained ERG: £12,325 to £30,153 per QALY gained Scenarios: up to £85,084 with disutility of 0.10 for adverse events

ACD consultation responses

- Consultee comments from:
  - Alimera Sciences (company)
  - Royal College of Ophthalmologists (RCOphth)
  - Birdshot Uveitis Society (BUS)
  - International Uveitis Study Group (IUSG)
- Expert comments from:
  - Archana Pradeep, clinical expert
- Commentator comments from:
  - Allergan
- Web comments:
  - 1 NHS professional

[redacted]

Stakeholder comments

- Clinical trial
  - Trial is representative of clinical practice: systemic immunosuppressants and corticosteroid treatment would be withdrawn in practice and patients monitored for recurrence of uveitis, which would be treated if observed (BUS, RCOphth)
- Comparator
  - Dexamethasone implant is a relevant comparator (IUSG) – benefits of having fewer injections with FAc, and cost of managing disease activity between injections, should be taken into account (RCOphth)
  - Dexamethasone is used for active disease, not prevention (web comment)
- Model
  - Seems unduly sensitive to adverse event modelling (RCOphth)
  - Utility loss of blindness in both eyes is likely to be much higher than in unilateral blindness (Allergan)
  - There is no data from the trials on use in both eyes (web comment)
- More research needed
  - Head to head trial of FAC implant vs dexamethasone implant – modelling long-term outcomes without this increases uncertainty (RCOphth)
  - How long do the effects of the implants last and when is retreatment needed? (clinical expert)

Company comments on ACD

- Rate of recurrence in the trial
  - Same non-study treatments permitted in both arms so affects both treatment groups in trial equally
  - Reduction in recurrence rate in per-protocol population as well
- Trial design and generalisability to NHS clinical practice
  - Protocol advised clinicians to attempt local treatment before systemic, but if necessary systemic treatment could be given
  - Tapering off of systemic corticosteroids once disease is controlled is consistent with NHS clinical practice
  - Further treatment could be given before protocol-defined recurrence if investigator perceived clinical evidence of uveitis recurring
- Comparison with dexamethasone implant
  - Dexamethasone implant is used to treat active disease whereas FAc implant would be used to prevent relapse in recurrent disease

[redacted]

Company's new evidence

Additional clinical evidence requested by committee

- Visual acuity – statistical analysis results

Adapted model:

- Based on ERG base case 1
- Comparison with dexamethasone implant (single and repeated implants)
- Disutilities for adverse events modelled
- Consideration of both eyes in cost comparison analysis

[redacted]

Company's new evidence

Visual acuity statistical analysis

- Statistical analysis was conducted post-hoc
- Mean change from baseline in best corrected visual acuity in the study eye (intent-to-treat population, PSV-FAI-001 study)

	6 months		12 months		36 months	
	FAc implant	Control group	FAc implant	Control group	FAc implant	Control group
N	[redacted]	[redacted]	87	42	[redacted]	[redacted]
Mean Change (SD)	[redacted]	[redacted]	5.8 (14.36)	3.3 (12.78)	[redacted]	[redacted]
Median	[redacted]	[redacted]	5.0	4.0	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	(-39, 49)	(-52, 25)	[redacted]	[redacted]
Difference from sham injection*						
Estimate		[redacted]	2.5			[redacted]
95% CI		[redacted]	(-2.81, 7.82)			[redacted]
P-value		[redacted]	0.353			[redacted]

[redacted] CI, confidence interval; SD, standard deviation.
*Estimate, 95% CI, and P values were based on one-way analysis of variance.

ERG comments

Visual acuity statistical analysis

- Company used parametric method – requires outcome to be normally distributed and standard deviation to be similar in each group
- In this data, all standard deviations are larger than means, suggesting data are skewed and not normally distributed

[redacted]

Company's new evidence

Comparison with dexamethasone implant

- Company used the parametric curve for time to recurrence for FAc implant, condensed to 6 months for the dexamethasone implant
- Assumptions
  - Efficacy of dexamethasone implant over 6 month 'active' period is the same as FAc implant efficacy profile over 3 years
  - Retreatment is permitted on treatment failure rather than after 6 months (dexamethasone implant) or 3 years (FAc implant)
    - Efficacy profile is the same on retreatment

[redacted]

ERG comments

Comparison with dexamethasone implant

- Proportion of patients ‘on treatment’ with 1 FAc implant and 1 dexamethasone implant

  - Rate of relapse for dexamethasone implant is much higher than for FAc implant
  - Large decrease in effectiveness of dexamethasone compared to previous ERG method and TA460
  - In ERG report, parametric curve for dexamethasone assumed to be same as for FAc implant

- Retreatment on treatment failure may be implausible because it potentially increases dose of treatment
  - In analyses allowing for multiple implants, effectiveness and costs may be overestimated

[redacted]

- ***What is the most plausible method of comparison with dexamethasone?***
- ***Is retreatment on treatment failure plausible?***

Company's new evidence

Adverse event disutilities

- Only severe adverse events included
- Rates of adverse events sourced from PSV-FAI-001 study (FAc implant) and HURON study (dexamethasone implant)
- Disutilities identified in literature search for 4 adverse events:

Adverse Event	Disutility (Annual – assumed where not reported)	Indication	Source
Cataract	-0.016	Type 2 diabetes	Lee (2012)
Macular oedema	-0.040	Diabetic retinopathy and diabetic macular oedema	Fenwick (2012)
Visual Impairment	-0.063	Type 2 diabetes	Solli (2010)
Hypertension	-0.009	Mixed	Wang (2014)

- For other adverse events, average disutility of above 4 values (-0.032) used
- Disutility for anxiety related to retreatment with multiple injections also included (0.071 per year for 17.3% of patients, Pochopien 2019)
- Total decrement per year is 0.0006 for FAc implant and 0.0017 for dexamethasone implant

[redacted]

ERG comments

Adverse event disutilities

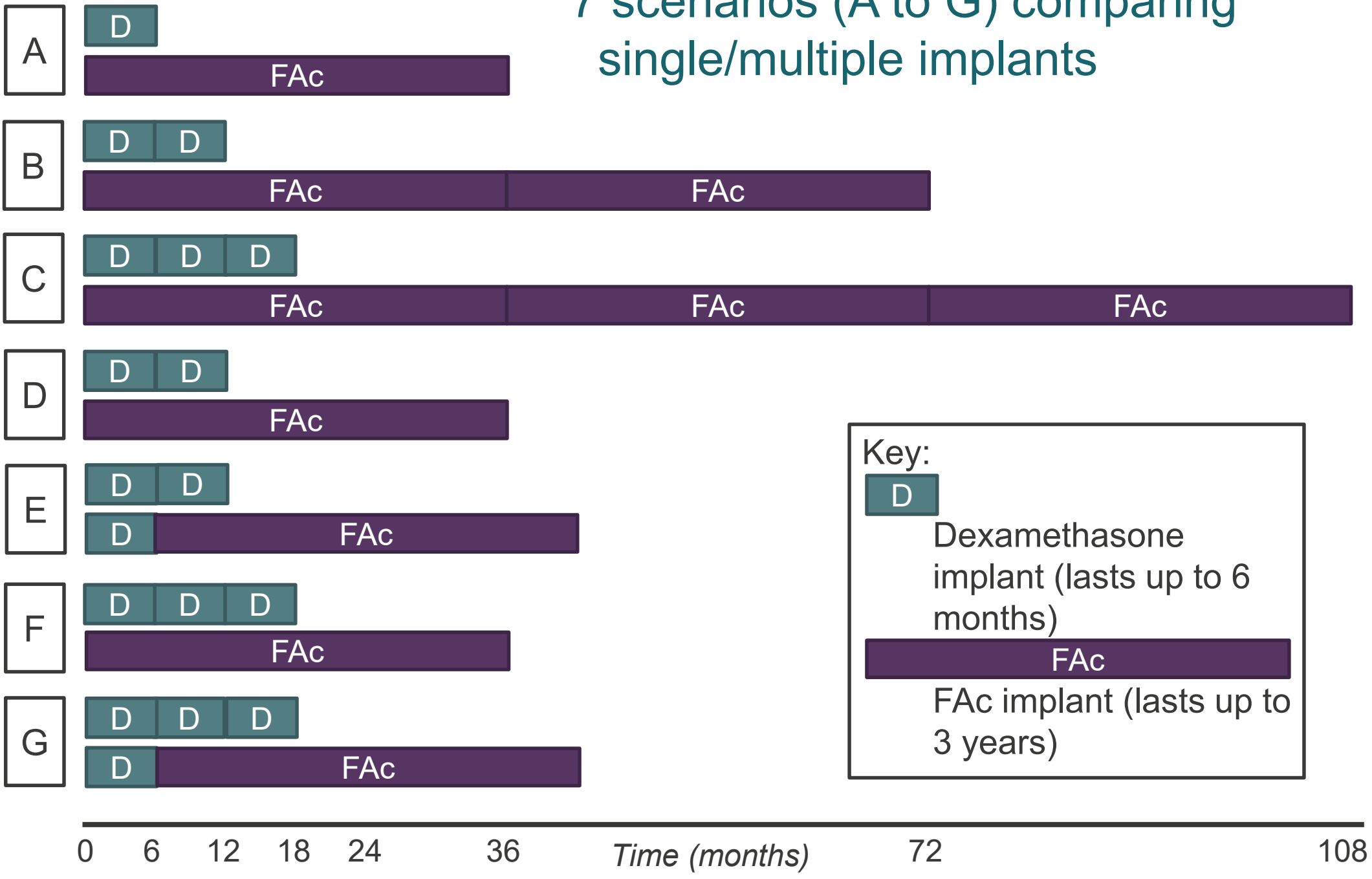
- No detail provided on methods used to identify disutility values associated with adverse events and anxiety related to retreatment
  - *Company provided some more detail in response*
- There are differences in the patient populations between the HURON trial and the population in the scope so adverse event rates from HURON may not be directly applicable to the relevant population for this appraisal

⊙ ***Is the modelling of adverse events reliable?***

[redacted]

Company's new evidence: multiple implants

7 scenarios (A to G) comparing single/multiple implants



Company's results *[corrected]*

No transition to blindness from 'on treatment'

Scenario	Inc. cost	Inc. QALYs	ICER (£/QALY)
A) 1 FAc vs 1 Dex	[redacted]	[redacted]	£13,027
B) 2 FAc vs 2 Dex	[redacted]	[redacted]	£10,989
C) 3 FAc vs 3 Dex	[redacted]	[redacted]	£10,317
D) 1 FAc vs 2 Dex	[redacted]	[redacted]	£7,639
E) 1 Dex+1 FAc vs 2 Dex	[redacted]	[redacted]	£23,126
F) 1 FAc vs 3 Dex	[redacted]	[redacted]	£18
G) 1 Dex+1 FAc vs 3 Dex	[redacted]	[redacted]	£21,971

- Company highlights that for scenarios E and G:
  - treatment for first 6 months is same in both groups and the sample size for the comparison for 6 months onwards is reduced, leading to greater uncertainty
  - because dexamethasone implant lasts 6 months and FAc implant lasts 3 years, retreatment is allowed differently across groups, leading to overestimation of benefit for dexamethasone

[redacted]

Company's results

Transition from 'on treatment' to blindness included

- Rate of blindness = 0.0066 (Dick et al), implemented as in TA460

	Inc. cost	Inc. QALYs	ICER (£/QALY)
A) 1 FAc vs 1 Dex	[redacted]	[redacted]	£16,836
B) 2 FAc vs 2 Dex	[redacted]	[redacted]	£3,047
C) 3 FAc vs 3 Dex	[redacted]	[redacted]	£2,581
D) 1 FAc vs 2 Dex	[redacted]	[redacted]	£9,772
E) 1 Dex+1 FAc vs 2 Dex	[redacted]	[redacted]	£29,461
F) 1 FAc vs 3 Dex	[redacted]	[redacted]	FAc dominates
G) 1 Dex+1 FAc vs 3 Dex	[redacted]	[redacted]	£27,878

⊙ ***Is the fluocinolone acetonide intravitreal implant cost-effective compared with the dexamethasone implant?***

[redacted]

ERG comments

Company's results

- ERG unsure of relevance of the additional analyses – comparing different numbers of dexamethasone implants versus the same amount of FAc implants results in different treatment durations, which leads to larger health benefits with FAc
  - ERG considers comparing 1 FAc implant with 6 dexamethasone implants is more informative, as in ERG report
- Life years gained differ between the 2 groups, although the disease does not affect mortality
  - ERG has concerns about validity of results
  - *Company identified an error in the model and corrected this for results without the transition from 'on treatment' to 'permanent blindness'*

[redacted]

Company's new evidence

Bilateral disease

- Due to lack of data on relationship of efficacy data from PSV-FAI-001 trial to another eye, a full cost-effectiveness analysis is not presented
  - Costs and benefits for the second eye were assumed to be the same as for the modelled eye – model outcomes doubled
  - Total costs for bilateral treatment and proportion estimated to be blind at 5 years are reported

First Eye	Second Eye	Total Cost	Proportion blind at 5 years
1 FAc implant	1 FAc implant	[redacted]	[redacted]
2 FAc implants	2 FAc implants	[redacted]	[redacted]
3 FAc implants	3 FAc implants	[redacted]	[redacted]
1 Dex implant	1 Dex implant	[redacted]	[redacted]
2 Dex implants	2 Dex implants	[redacted]	[redacted]
3 Dex implants	3 Dex implants	[redacted]	[redacted]
1 FAc implant	2 Dex implants	[redacted]	[redacted]
1 FAc implant	3 Dex implants	[redacted]	[redacted]
1 Dex implant, then 1 FAc implant	2 Dex implants	[redacted]	[redacted]
1 Dex implant, then 1 FAc implant	3 Dex implants	[redacted]	[redacted]
Range		[redacted]	[redacted]

ERG comments

Bilateral disease

- ERG considers that more accurate results could have been obtained by including impact of bilateral treatment on visual acuity of both eyes
- Doubling outcomes from the model is not representative of the impact that local and systemic treatment can have on visual acuity when both eyes are affected by uveitis
  - Local treatment would influence visual acuity in treated eye while systemic treatment would influence visual acuity in both eyes

[redacted]

Equality considerations

- New potential equality consideration raised
  - High doses of systemic steroids may adversely affect women's bone density more than men's, so women may benefit more from an alternative intravitreal treatment

[redacted]

Key issues for consideration

- What is the most plausible method of comparison with dexamethasone?
  - Condensing parametric curve for FAc implant into 6 months or assuming curves are the same for both treatments?
- Is retreatment on treatment failure plausible?
- Is the modelling of adverse events reliable?
- Is the fluocinolone acetonide intravitreal implant cost-effective compared with the dexamethasone implant?