NICE National Institute for Health and Care Excellence

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Fluocinolone acetonide ocular implant for treating recurrent non-infectious uveitis

Lead team presentation

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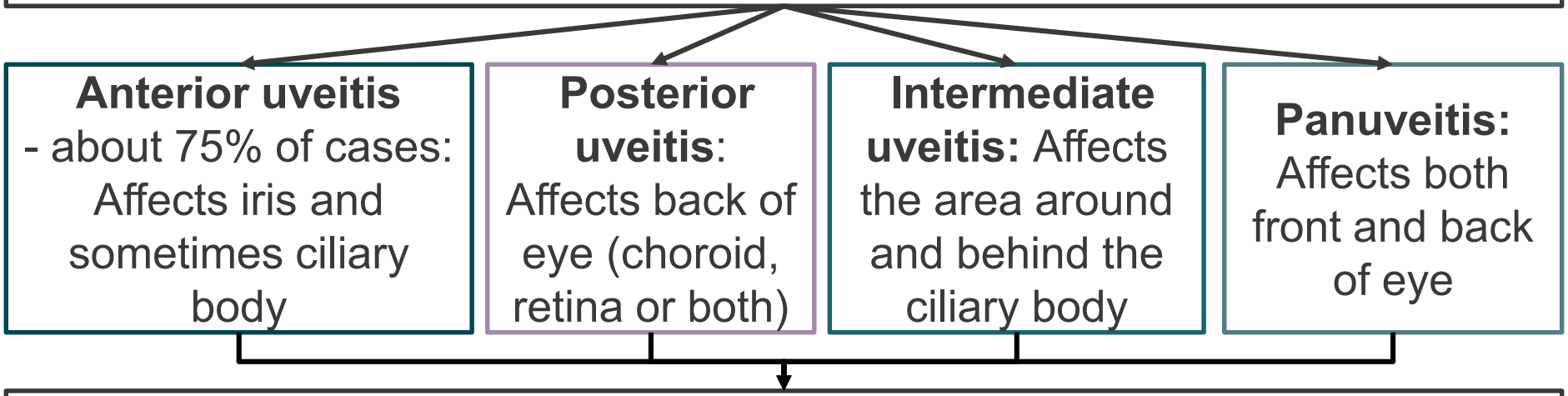
Key issues for consideration: clinical

- At what point in the treatment pathway would fluocinolone acetonide ocular implant (FAc) be used?
  - First line as an alternative to repeated periocular injections?
  - Second line as an alternative or adjunct to systemic steroids or immunosuppressants, or dexamethasone?
  - Would it be used alone or as an adjunct to other treatments?
  - If not first line, what treatments would be used before FAc implant?
- What is the likely benefit of the FAc implant after it has been implanted for 3 years?
- In clinical practice are people likely to receive more than 1 FAc implant?
- Is limited current practice (LCP) in the trial representative of UK clinical practice?
- Are the relevant comparators included?
  - Is dexamethasone a relevant comparator?
- Does the clinical trial provide evidence of the efficacy of FAc implant compared with the most appropriate comparator?
- Is FAc implant effective in preventing recurrence of uveitis?
- What is the effect of the FAc implant on quality of life?

[redacted]

Uveitis background

- Intraocular inflammation that may arise from various causes
- Around 2-5 in 10,000 people affected each year in the UK
  - Usually aged 16-65 at onset and over a third are under 35 years
- 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 sight impairment in UK

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.

[redacted]

Current UK treatment pathway

Non-infectious uveitis

Treatment depends on whether disease is active or inactive, systemic or non-systemic, unilateral or bilateral

Pathway for patients with:
- bilateral uveitis + active systemic disease
- unilateral uveitis + active systemic disease
- bilateral uveitis + no active systemic disease (via either pathway)

Pathway for patients with
- unilateral uveitis or asymmetrical bilateral uveitis + no active systemic disease
- bilateral uveitis + no active systemic disease (via either pathway)

1st line: systemic steroids

1st line: periocular steroids (may repeat)

FAc

2nd line: Immunosuppressants (may also continue steroids ≤7.5mg/d):
- One: mycophenolate mofetil (or methotrexate)
- Two: mycophenolate mofetil (or methotrexate) + tacrolimus (or cyclosporine)

FAc

2nd line: Dexamethasone implant (may repeat) (**recommended in TA460 for active disease with worsening vision and a risk of blindness**)

FAc

3rd line: Anti-TNFs (adalimumab (**recommended in TA460**), infliximab, etanercept)

FAc = Potential place of fluocinolone acetonide ocular implant

Comments from patients and professionals [1]

- Common uncertainties and fears: worsening vision or eventual blindness; continuity of work or education; impact on personal independence, social life, relationships
  - "Terrifying, painful, constant fear of blindness/sight loss or worsening vision...Many days are taken off work...causing severe anxiety that they will lose their jobs as a consequence" [patient organisation]
- Control of uveitis may preserve vision, delay or prevent its deterioration
- Local and systemic treatments can be burdensome and disruptive. Physical and mental side effects can be long term and need extensive monitoring.
  - "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...used to treat me…It has totally disrupted my family life." [patient expert]
  - "Plans to have a family may have to be put on hold because of taking medication." [patient organisation]
  - "Was thinking of giving up all treatment prior to implants due to side-effects, toleration problems and lack of any improvement." [patient organisation]

Comments from patients and professionals [2]

- Unmet need for more treatment options and adjuncts to current therapies
  - "Treatments require me to be constantly at clinic (1 - 2 times each week), for consultations and treatment...Current treatments [of daily oral steroids and immunosuppressants plus dexamethasone implant] were only effective for about five to seven weeks, then they would fail and my vision deteriorate." [patient expert]
  - "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" [professional organisation]
- Expectation is that a fluocinolone implant is appropriate when a patient has a good response to a dexamethasone implant but recurrence requires longer acting treatment
  - "Even when I was given a [dexamethasone] implant...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." [patient expert statement]
- Side effects of cataracts and raised intraocular pressure are familiar to this patient group from current treatments
  - Side effects with FAc implant not expected to be worse than with 4-6 dexamethasone implants over 3 years

Comments from patients and professionals [3]

- Long-acting nature of treatment may be less onerous for patients and reduce the need for systemic treatments
  - "The bonus of this treatment is it treats just the eye, and not the rest of the body...[My] daily life no longer revolves around taking medication and when to eat...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." [patient expert statement]
  - "I have gone from being in clinic up to three times a week, down to just a three monthly check up." [patient expert statement]
  - "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". [patient organisation]

Decision problem - population

	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

ERG comments

- 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

[redacted]

Decision problem - comparators

Final scope issued by NICE	Company's submission	Rationale if different
• 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 (LCP)	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 implant 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

[redacted]

ERG comments on comparators

- None of the comparators in the scope included in the submission
- ERG considers searches should have been performed for all comparators in scope
- Company considered not appropriate to compare HURON trial (dexamethasone implant vs LCP) 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**

[redacted]

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

[redacted]

Note: The trial intervention was a 0.18 mg fluocinolone acetonide implant. The implant considered in this appraisal is 0.19 mg fluocinolone acetonide. RCOphth opinion is that they are very similar in efficacy and expected side effects.

PSV-FAI-001 Study

Baseline characteristics

	FAc implant (n=87)	LCP (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)

PSV-FAI-001 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 (%)	LCP (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 defined as ≥2-step increase in the number of cells in the anterior chamber per high powered field OR increase in vitreous haze of ≥2 steps OR deterioration in visual acuity of at least 15 letters

Recurrence of uveitis 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 (oral, systemic, injectable or topical steroids and systemic immunosuppressants)

→ **Company and ERG agree that recurrence rates are likely overestimated**

PSV-FAI-001 trial results

Time to recurrence in study eye (ITT population)

[redacted]

ERG comments

- [redacted]

[redacted]

PSV-FAI-001 trial results

Supplemental treatments required to treat recurrences of uveitis

Number of supplemental treatments within 36 months by type of treatment

Outcome	Study eye	
	FAc implant (n=87) n, %	LCP (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

[redacted]

PSV-FAI-001 trial results

Visual acuity

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

ERG comment: No between group statistical significance tests reported

Adverse events

	FAc implant (N=87) n, %	LCP (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 LCP group.
[redacted]

[redacted]

ERG comments on trial

- Size of the effect of FAc implant 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
- Health-related quality of life data not available from the trial
- PSV-FAI-001 trial does not provide evidence for use of FAc implant 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 implant+LCP and LCP
- In both groups, systemic and local steroids or systemic immunosuppressants were tapered off after 3 months
  - After 3 months, comparison is FAc implant 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

Key issues for consideration: clinical

- At what point in the treatment pathway would fluocinolone acetonide ocular implant (FAc) be used?
  - First line as an alternative to repeated periocular injections?
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  - Is dexamethasone a relevant comparator?
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[redacted]

Cost effectiveness

Key issues for consideration: cost

Intervention and comparators

- If dexamethasone is a relevant comparator, what is the likely effectiveness of dexamethasone compared with FAc implant and LCP?
  - Hazard ratio of 0.456 compared with LCP?
  - Hazard ratio of 1 or 0.7 compared with FAc implant?

Model structure

- Should a 'remission' health state be included in the model?
- Should a transition between 'on treatment' and 'permanent blindness' be possible?
  - If so, what should be used as the rate of blindness? 0.0066 (Dick et al), 0.0374 (Durrani) or 0.0038 (Tomkins-Netzer)*?

Utility values

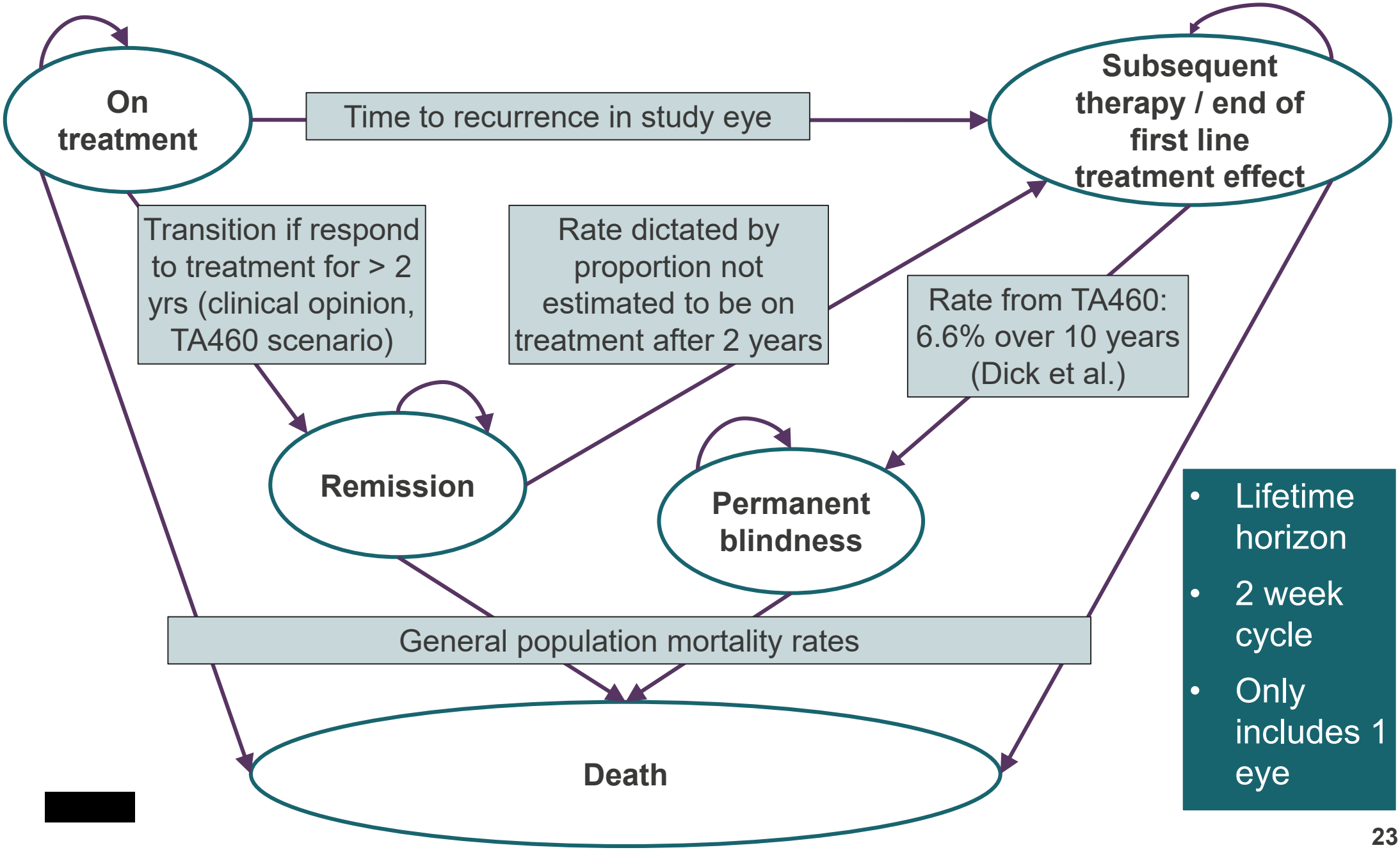
- Should utility values from the MUST trial mapped from VFQ-25 to EQ-5D be used for the 'on treatment' and 'subsequent therapy' health states?
- Should disutilities for adverse events be included in the modelling?
  - If so, what disutility should be included? 0.05 or 0.1?

General

- Is the FAc implant innovative?
- Are there any equality considerations?

*corrected at committee meeting

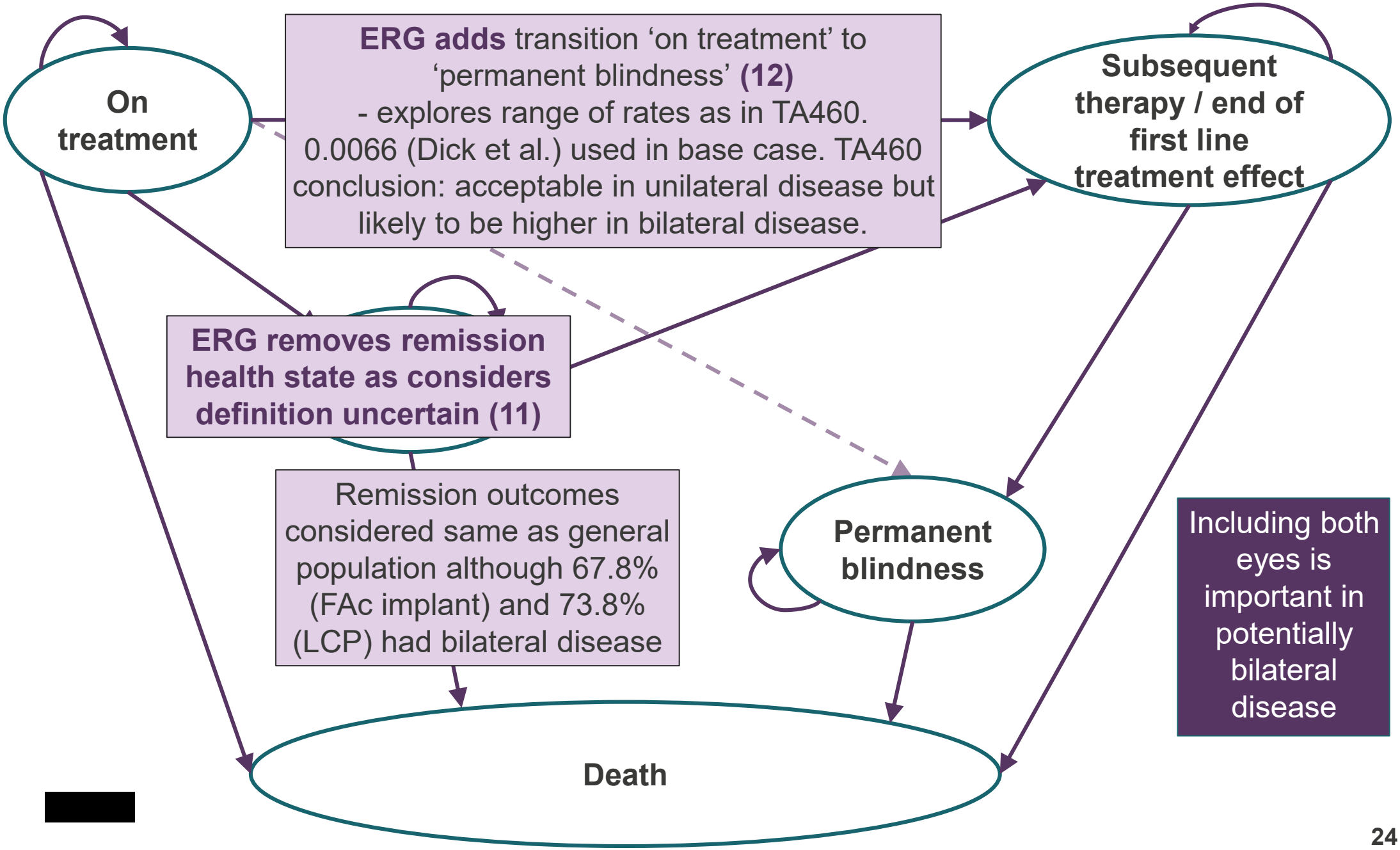
Company's Markov model



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

[redacted]

ERG comments: model structure



[redacted]

Treatment effectiveness in the model

Time to recurrence

FAc implant 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.

[redacted]

LCP 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 LCP 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)**

[redacted]

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 (higher strength)

Health state	Mean utility value	Source
On treatment	0.818	VFQ-25 (Visual Function Questionnaire) 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

[redacted]

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 implant treatment allowed	Unilateral treatment only
Lower proportion with oedema at baseline	Higher proportion with oedema at baseline

- 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 is 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

[redacted]

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)**

[redacted]

Company's base case results (deterministic)

All results include PAS for FAc implant

- In company submission

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

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

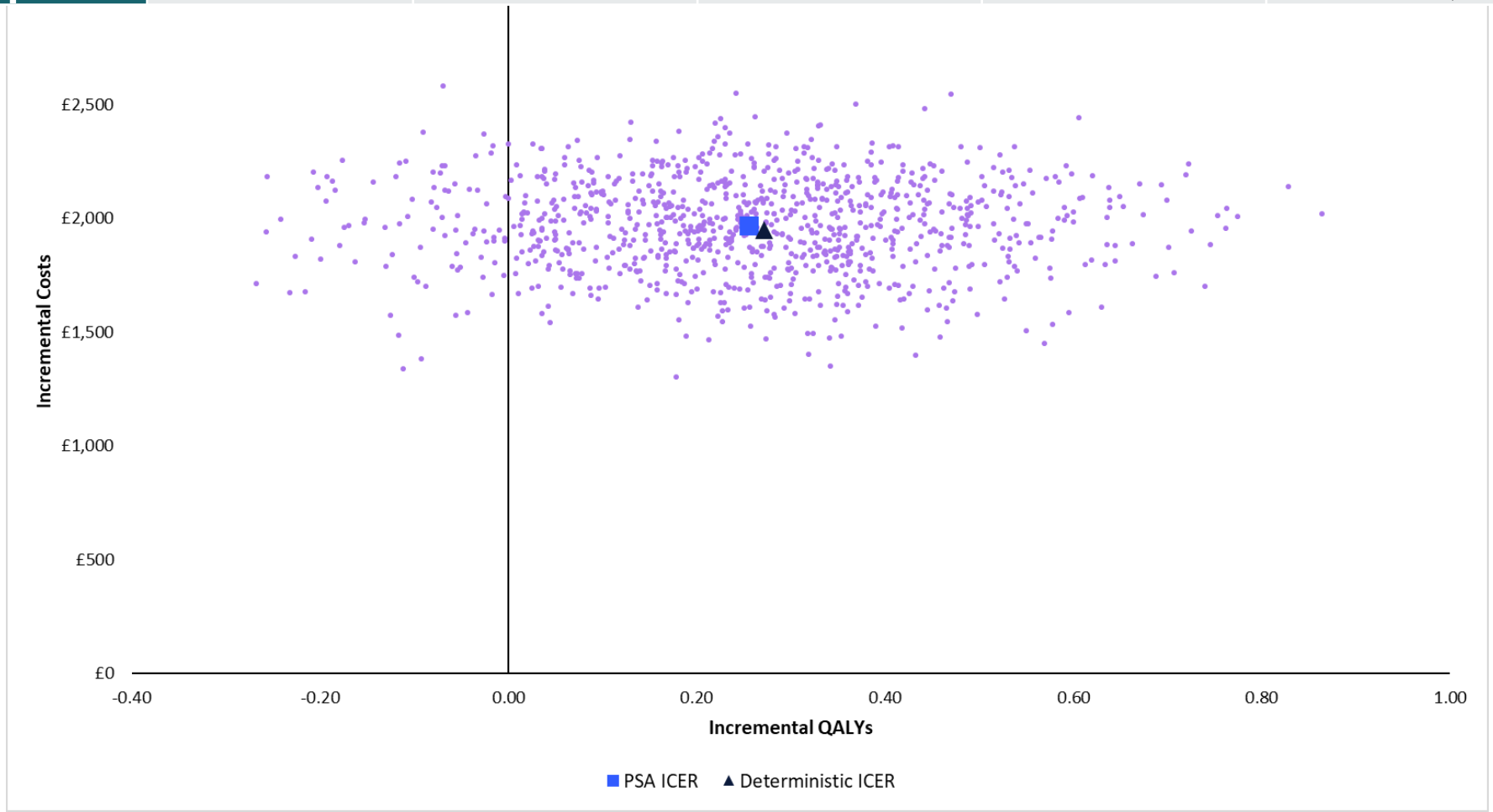
	Total costs	Total QALYs	Inc. cost	Inc. QALYs	ICER (£/QALY)
LCP	[redacted]	[redacted]			
FAc implant	[redacted]	[redacted]	[redacted]	[redacted]	£1,072

[redacted]

Company's probabilistic sensitivity analysis

On base case included in submission

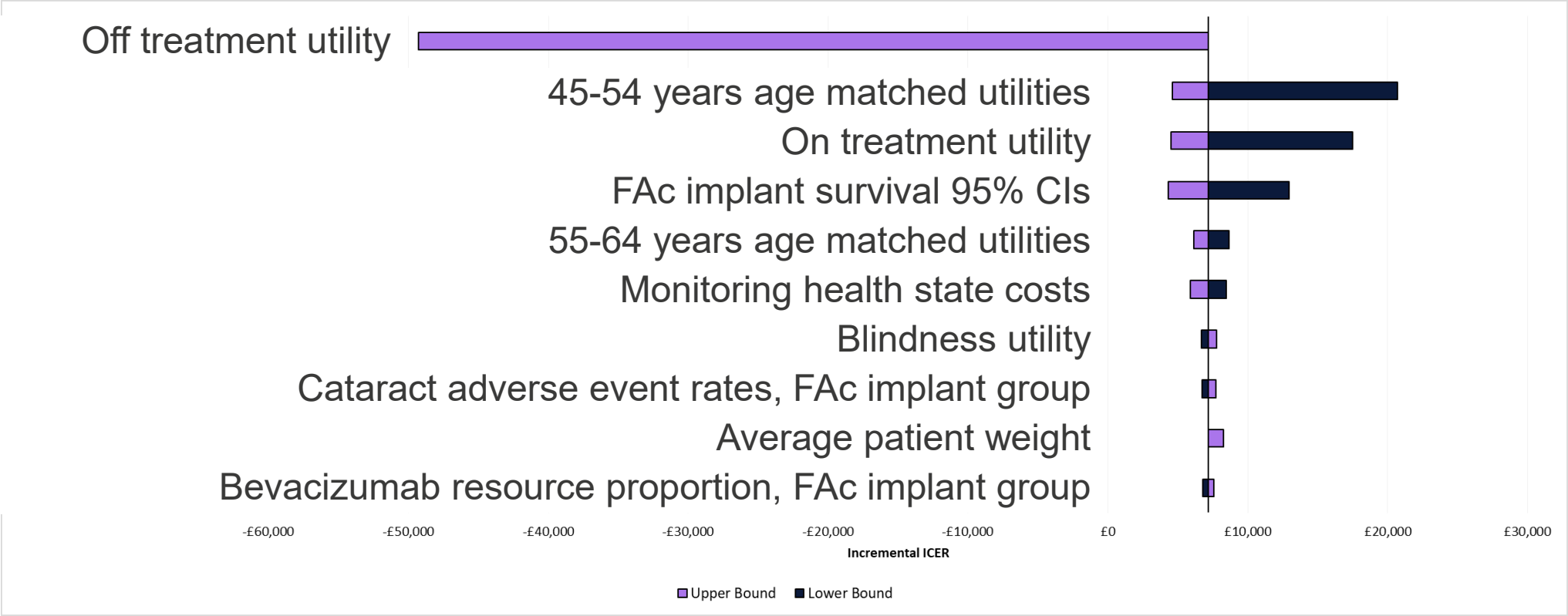
Mean results	Total costs	Total QALYs	Inc. cost	Inc. QALYs	ICER (£/QALY)
LCP	[redacted]	[redacted]			
FAc implant	[redacted]	[redacted]	[redacted]	[redacted]	£7,702



[redacted]

Company's deterministic sensitivity analysis

On base case included in submission



[redacted]

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 LCP

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 LCP 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 implant

[redacted]

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 implant after 3 years made equal to LCP
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 LCP

Technologies	Total costs	Total QALYs	Incremental costs	Incremental QALYs	Fully inc. ICER (£/QALY)	ICER FAc vs comparator
Company base-case						
LCP	[redacted]	[redacted]				£7,183
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£4,906
FAc implant	[redacted]	[redacted]	[redacted]	[redacted]	£7,183	-
Errors corrected (1-4)						
LCP	[redacted]	[redacted]				£2,510
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£716
FAc implant	[redacted]	[redacted]	[redacted]	[redacted]	£2,510	-
Corrections for NICE reference case, scope or best practice (1-10)						
LCP	[redacted]	[redacted]				£1,502
FAc implant	[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; LCP = limited clinical practice; QALY = quality-adjusted life year, ext. dominated = extendedly dominated

[redacted]

*corrected after committee meeting

ERG exploratory analyses: results [2]

Assuming hazard ratio of 0.456 for dexamethasone vs LCP

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)						
LCP	[redacted]	[redacted]				£3,513
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£240
FAc implant	[redacted]	[redacted]	[redacted]	[redacted]	£3,513	-
Create transition from on treatment to permanent blindness (annual rate 0.0066) (1-4, 12)						
LCP	[redacted]	[redacted]				£3,644
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£2,165
FAc implant	[redacted]	[redacted]	[redacted]	[redacted]	£3,644	-
Effectiveness of FAc implant after 3 years equal to LCP (1-4, 13)						
LCP	[redacted]	[redacted]				£4,221
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£540
FAc implant	[redacted]	[redacted]	[redacted]	[redacted]	£4,221	-
Cost components of permanent blindness removed before 65 years of age (1-4, 14)						
LCP	[redacted]	[redacted]				£5,354
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£3,595
FAc implant	[redacted]	[redacted]	[redacted]	[redacted]	£5,354	-
Cost of blood test every 12 weeks when receiving immunosuppressants (1-4, 15)						
LCP	[redacted]	[redacted]				£2,500
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£707
FAc implant	[redacted]	[redacted]	[redacted]	[redacted]	£2,500	-

ERG base-case results (deterministic)

Assuming hazard ratio of 0.456 for dexamethasone vs LCP

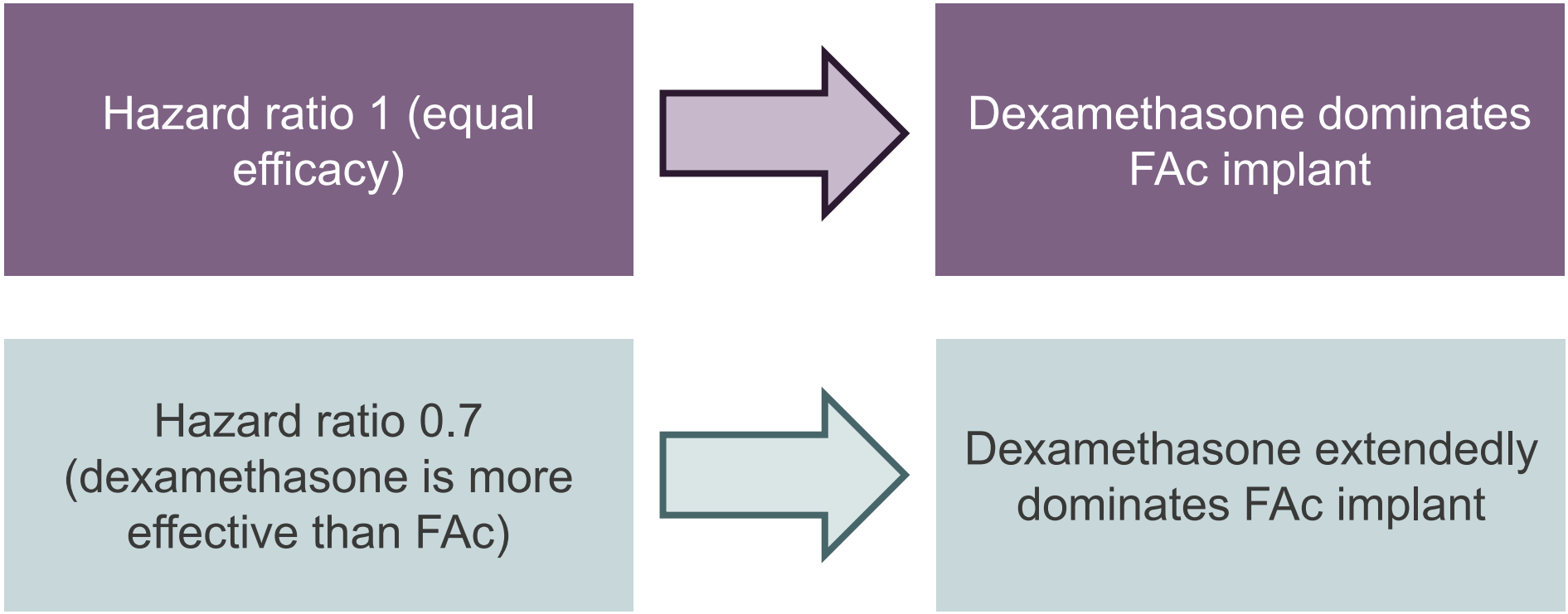
Technology	Total costs	Total QALYs	Fully inc. costs	Fully inc. QALYs	Fully inc. ICER (£/QALY)	ICER of FAc versus comparator
ERG base case 1 (1-16)						
LCP	[redacted]	[redacted]	-	-		£12,325
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	£5,335
FAc implant	[redacted]	[redacted]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

FAc, fluocinolone acetonide implant; ICER, incremental cost effectiveness ratio; LCP, 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 implant:



ERG scenario analyses based on base case 1	Technology	Fully incremental ICER (£/QALY)	ICER of FAc versus comparator
ERG base-case 1	LCP		£12,325
	Dexa 700	Ext. dominated	£5,335
	FAc implant	£12,325	-
FAc and dexamethasone are not effective anymore after 3 years, all patients switch to subsequent treatment	LCP		£24,443
	Dexa 700	Ext. dominated	£15,627
	FAc implant	£24,443	-
Use utility based on the US tariffs (MUST trial) for the 'on treatment' and 'subsequent treatment' health states	LCP		£22,679
	Dexa 700	Ext. dominated	£10,303
	FAc implant	£22,679	-
‘Permanent blindness' health state utility value from Brown et al. (0.57) (preferred in TA460)	LCP		£14,565
	Dexa 700	Ext. dominated	£6,194
	FAc implant	£14,565	-
Inclusion of disutility for adverse events (assumed all AEs incur a disutility value of 0.1)	LCP		£85,084
	Dexa 700	Ext. dominated	£41,574
	FAc implant	£85,084	-
Rate for blindness (Durrani et al. 0.0374 annual –study included population with severe and often bilateral uveitis)	LCP		£4,465
	Dexa 700	Ext. dominated	£934
	FAc implant	£4,465	-
Rate for blindness (Tomkins-Netzer 0.0038 annual – clinical expert to AG in TA460 considered this an underestimate)	LCP		£15,072
	Dexa 700	Ext. dominated	£6,903
	FAc implant	£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

[redacted]

Key issues for consideration: cost

Intervention and comparators

- If dexamethasone is a relevant comparator, what is the likely effectiveness of dexamethasone compared with FAc implant and LCP?
  - Hazard ratio of 0.456 compared with LCP?
  - Hazard ratio of 1 or 0.7 compared with FAc implant?

Model structure

- Should a 'remission' health state be included in the model?
- Should a transition between 'on treatment' and 'permanent blindness' be possible?
  - If so, what should be used as the rate of blindness? 0.0066 (Dick et al), 0.0374 (Durrani) or 0.0038 (Tomkins-Netzer)*?

Utility values

- Should utility values from the MUST trial mapped from VFQ-25 to EQ-5D 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? 0.05 or 0.1?

General

- Is the FAc implant innovative?
- Are there any equality considerations?

*corrected at committee meeting

Additional slides

Time to recurrence

FAc implant group parametric curves

[redacted]

Time to recurrence

FAc implant group fitted exponential curve

[redacted]

ERG base-case results (deterministic)

Assuming hazard ratio of 1 for dexamethasone vs FAc implant

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

FAc, fluocinolone acetonide implant; ICER, incremental cost effectiveness ratio; LCP, 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 implant

Technology	Total costs	Total QALYs	Fully inc. costs	Fully inc. QALYs	Fully inc. ICER (£/QALY)	ICER of FAc versus comparator
ERG base case 1						
LCP	[redacted]	[redacted]	-	-		£12,325
FAc implant	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	-
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	£10,412	£2,297
ERG base case 2						
LCP	[redacted]	[redacted]	-	-		£21,531
FAc implant	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	-
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	£17,843	£3,643
ERG base case 3						
LCP	[redacted]	[redacted]	-	-		£19,049
FAc implant	[redacted]	[redacted]	[redacted]	[redacted]	Ext. dominated	-
Dexa 700	[redacted]	[redacted]	[redacted]	[redacted]	£17,239	£12,911
ERG base case 4						
LCP	[redacted]	[redacted]	-	-		£30,153
FAc implant	[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; LCP, limited clinical practice; QALY, quality-adjusted life year; inc., incremental; ext., extendedly.