Polihexanide eye drops for treating acanthamoeba keratitis in people 12 years and over [ID6497]

For projector – contains **no CON** information

Highly Specialised Technology committee 22nd January 2026

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Polihexanide eye drops for treating acanthamoeba keratitis in people 12 years and over [ID6497]

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Background on acanthamoeba keratitis (AK)

Rare eye infection which can be difficult to treat and may result in vision loss

Causes: Rare but serious parasitic eye infection from a *Acanthamoeba* amoeba affecting cornea.

- Linked to poor contact lens hygiene (use when swimming, overnight wear) in ~90% of cases; also eye trauma

Epidemiology: 0.12 cases per 50,000 per year in the UK*

Diagnosis and classification:

- Acanthamoeba has two life-cycle stages; active motile trophozoite and resilient dormant cyst, making it challenging to treat
- Classified based on level of corneal infiltration but no standardised staging system
- Up to 11% of cases affect both eyes±

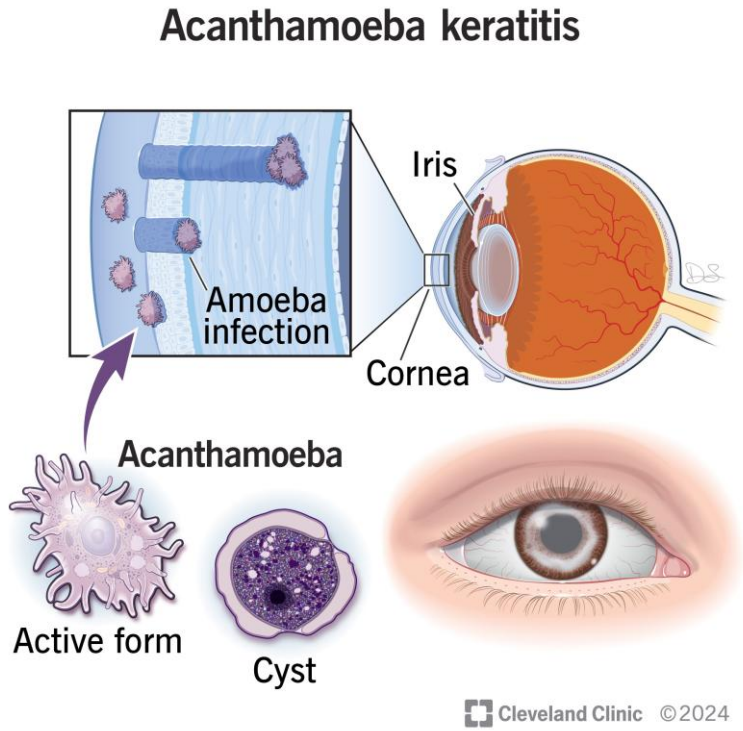
Symptoms: eye pain, intense tearing, light sensitivity, redness or irritation, cloudy or ring-shaped cornea, blurred or clouded vision, deformation of eyeball

- Large physical and mental burden, especially in those with reduced vision

Prognosis: many cases curable with intensive, long-term treatment

- Delayed treatment associated with poorer prognosis, including chance of relapse
- Severe vision loss in up to 25%^ people

see supplementary appendix: stages of AK



Source: *Jasim et al. 2024, ±Acanthamoeba Keratitis (AK) Eye Foundation. ^ Papa et a. 2020

QoL, quality of life

Patient perspectives

Submission from Fight for Sight and patient experts

AK is a physically and emotionally debilitating condition

- Mental wellbeing and quality of life affected by:
  - ❖ Physical symptoms: extreme eye pain, light sensitivity and blurred vision
  - ❖ Psychological symptoms: social anxiety, isolation, high risk of post traumatic stress disorder, especially after surgery (e.g. eye removal)
- Lack of clinician understanding of the patient experience with high levels of misdiagnosis

Current treatments burdensome and disruptive for patients

- Often require two types of drops which initially need to be applied on an hourly basis (with 5-minute gap between each) during intensive phase (~24 days) → can be highly painful and difficult to tolerate
- Polihexanide 0.8 mg/ml is a monotherapy → more convenient but:
  - Still needs hourly administration during the intensive phase (19 days) → may cause compliance issues
  - May be easier to tolerate but potential toxicity and side effects from eye drops remain

"AK is a physically painful disease which also causes a great deal of mental distress"

"AK took my vision, my profession, my hobbies, my familiar appearance, my energy and gave me a daily routine with medication, side effects, eye appointments full of anxiety and lost hopes"

"Every tiny light, sound and touch of my face is like a stabbing knife into my exploding eye and head."

"after months of treatment, [and] numerous eye drops I made the decision to have my eye removed"

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AK, acanthamoeba keratitis

Clinical perspectives

Submissions from Royal College of Ophthalmologists (RCOphth) and clinical experts

Rare but sight-threatening corneal infection with poorly defined treatment pathway

- Currently no licenced treatments for AK → current treatment is intensive regimen of off label/unlicensed anti-amoebic therapies (AATs), often in combination regimens, for several months
- Lack of consensus/guidance in standard of care AATs → treatment pathways vary widely but regional guidelines exist.
- Main aim of treatment is to irradicate AK and prevent vision and / or eye loss

Polihexanide 0.8 mg/ml addresses unmet need for AK treatments

- As first licenced treatment for AK, Polihexanide 0.8 mg/ml would standardize treatment, reduce treatment delays and lower risks associated with unlicensed specials (e.g. compounding errors, contamination).
- No additional infrastructure or investment required (lower dose already used in NHS)
- Monotherapy so likely to:
  - ❖ Improve compliance → easier to administer than current options
  - ❖ Reduce treatment burden for patients and healthcare resource: used in 2° care and eye specialist clinics on diagnosis or clinical suspicion of AK, based on clinical history, examination and imaging

"…it is treated as a corneal emergency and affected patients usually require intensive treatment.."

"This technology would provide a valuable addition to the current therapeutic armamentarium of AK."

AK, acanthamoeba keratitis

Equality considerations

Company highlight variable access to AK treatment by location

Company:

- AK currently treated at specialist centres → variable access to treatment centres is a potential driver of health inequalities in AK, particularly because rapid treatment crucial to improve eventual prognosis

- Where is AK currently treated?
- Are there any inequalities that need to be considered for this topic?

Treatment pathway for AK (1)

Mainstay of treatment is topical AATs

OFF LABEL / UNLICENSED ANTI-AMOEBIC THERAPIES (AATs)
Used individually or in combination

Biguanides:
- Chlorhexidine
- Polihexanide 0.2 mg/ml and 0.6 mg/ml

Proposed position for polihexanide 0.8 mg/ml

+

Diamidines
- Propamidine
- Hexamidine

Not cured

Alternative AAT combinations (usually higher dose)

Not cured

SURGERY

Therapeutic surgery

Corneal transplant (keratoplasty): for corneal perforation, non-healing epithelial defects, last resort to eradicate AK (rare).
- Includes deep lamellar keratoplasty (DALK) to replace diseased stroma.

Enucleation: removal of entire eyeball
Evisceration: removal of eye contents

AK assumed irradicated

Optical surgery
- Visual rehabilitation including keratoplasty, DALK, cataract surgery.
- Used in some people to improve sight when AK irradicated

- Does the proposed pathway reflect clinical practice for AK?
- How would "cure" be defined in clinical practice?
- Is polihexanide 0.6 mg/ml used in clinical practice?

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AK, acanthamoeba keratitis; QoL, quality of life

Treatment pathway for AK

No licenced products and lack of standard pathway

- No national guidelines for treating AK → large variation in AAT regimens by centre
- Some AATs need hourly administration day and night in initial treatment period → large QoL impact
- AATs and surgical options used with symptomatic treatments: pain relief, topical corticosteroids and antibiotics for bacterial infections

Company: biguanides often need to be compounded at request, with good manufacturing practice (GMP) not always satisfied → leads to delays in treatment with AATs

EAG: Clinical experts suggest:

- Higher dose polihexanide likely only used in severe cases to avoid ocular surface side effects
- Intensive daily and nightly drops standard care for AK → polihexanide 0.8 mg/ml would be used daily & nightly, especially for moderate to severe AK.
- Polihexanide 0.8 mg/ml would be used as a monotherapy

Technical team: NICE technology appraisals: the manual specifies that relevant comparators "*may also include technologies that do not have regulatory approval for the population defined in the scope if they are considered to be established clinical practice for the population in the NHS*"

- What factors influence the choice of AATs used at first line? Would polihexanide 0.8 mg/ml be the preferred first line option?
- Would polihexanide 0.8 mg/ml be used to treat AK of all severities? If not, how would it be used?
- Would polihexanide 0.8 mg/ml always be used as a monotherapy?
- Would polihexanide 0.8 mg/ml be used at night during the intensive treatment phase?
- To what extent do delays in compounding current AAT regimens and the absence of GMP standards impact outcomes with AK treatments?

AAT, anti-amoebic therapies, AK, acanthamoeba keratitis; QoL, quality of life

Polihexanide 0.8 mg/ml (Akantior, SIFI)

Monotherapy with intensive and continuation phase

Marketing authorisation	• Polihexanide 0.8 mg/ml is indicated for the treatment of Acanthamoeba keratitis in adults and children from 12 years of age. • MHRA licence granted May 2025 • Orphan drug designations by the EMA and FDA
Mechanism of action	• Polyhexanide is a broad-spectrum antimicrobial polymer used as an antiseptic, disinfectant, and wound management agent, effective against bacteria (including MRSA) and fungi, found in contact lens solutions, wound dressings, and catheter flushes. • Dual mechanism of action: a) disrupts cell membranes, b) binds amoebal DNA to block replication.
Administration	One drop in the affected eye according to the following regimen: •Intensive 19-day treatment phase: ❖16 times a day at 1-hour intervals, daytime only, for 5 days ❖8 times a day at 2-hour intervals, daytime only, for a further 7 days ❖6 times a day at 3-hour intervals, daytime only, for a further 7 days •Continuation treatment phase: ❖4 x a day at 4-hour intervals, until cure* and for no longer than 12 months
Price	• List price: £5,960.00 for 30 single-dose vials • List price for 12 months of treatment: [redacted]^ • A patient access scheme has been agreed

*Cure defined as corneal healing, absence of corneal inflammation or no evidence of infection.

^Source: company budget impact test. See supplementary appendix: decision problem

EMA, European Medicines Agency; MHRA, Medicines and Healthcare products Regulatory Agency; FDA, Food and Drug Administration

Key issues

KEY: Change from company base case ICER: small: < £5,000, moderate: £5,000 to £10,000, large: > £10,000, very large: >£500,000

Issue	Resolved?	ICER impact
Exclusion of the ODAK trial comparator from the decision problem and the ITC	No – for discussion	Very large
Validity of the company's indirect treatment comparison	No – for discussion	Unknown
Mean time-on-treatment used from Franch et al. 2024	No – for discussion	Large
AK recurrence in people treated with polihexanide 0.8 mg/ml	No – for discussion	Large
Disutilities associated with long-term complications	No – for discussion	Moderate
Carer disutilities	No – for discussion	Moderate
Carer and patient disutilities associated with the intensive phase	No – for discussion	Small
Hospitalisation during the intensive phase with polihexanide 0.8 mg/ml	No – for discussion	Small
Number of drops of polihexanide 0.8 mg/ml used in the intensive phase	No – for discussion	Small

AK, acanthamoeba keratitis; ICER, Incremental Cost-Effectiveness Ratio; ITC, indirect treatment comparison; ODAK, Orphan Drug for Acanthamoeba Keratitis

Polihexanide eye drops for treating acanthamoeba keratitis in people 12 years and over [ID6497]

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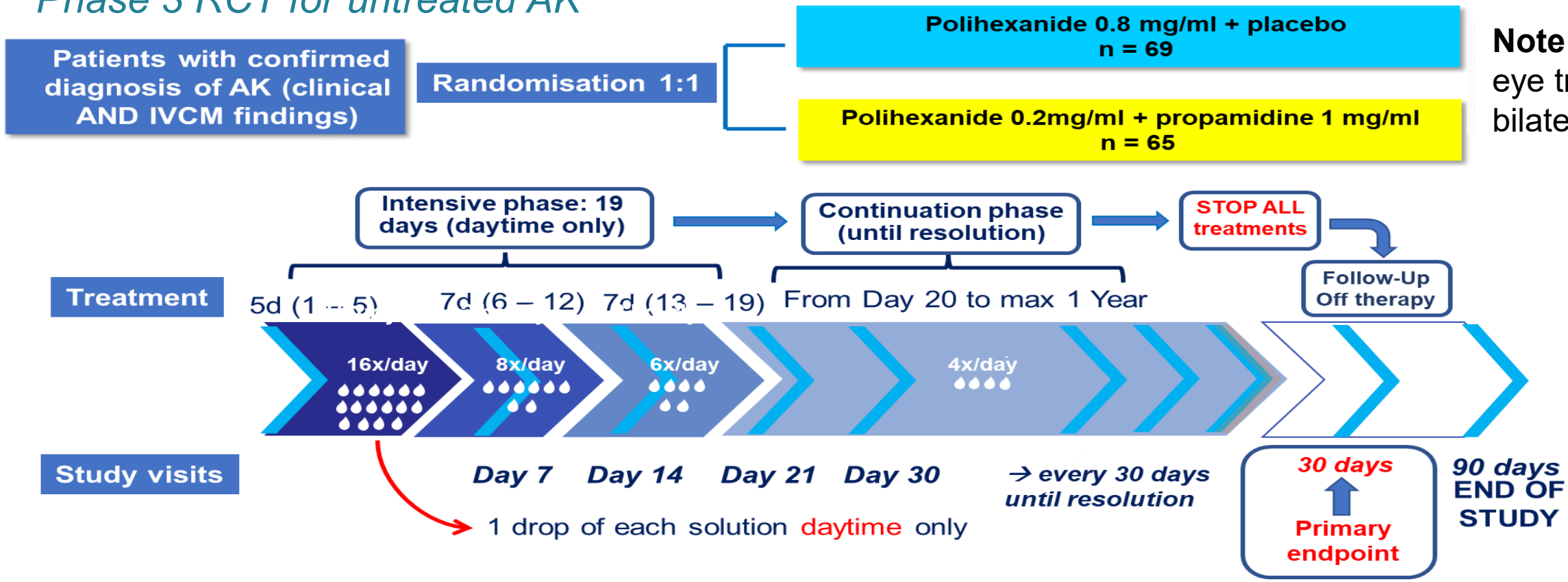
Orphan Drug for Acanthamoeba Keratitis (ODAK) trial design

Phase 3 RCT for untreated AK



Note: Only 1 eye treated if bilateral AK

1° outcome	Medical cure rate (MCR) → % cured 30 days after discontinuing study therapies, within 12m	
Key 2° outcomes	• Time-to-cure • Corneal scarring and ulceration severity • Anterior chamber inflammation • Use of alternative treatment and surgery	• Treatment exposure and AEs • HRQoL (EQ-5D-5L and VFQ-25) • Best-corrected visual acuity (BCVA)
Locations	Italy, Poland and UK (3 UK sites)	

AE, adverse event; AK, acanthamoeba keratitis; d, day; HRQoL, health related quality of life; n, number; IVCM, in vivo confocal microscopy; RCT, randomised controlled trial; VFQ, Visual Function Questionnaire

ODAK trial: key results

Polihexanide 0.8 mg/ml met company's non-inferiority threshold vs 0.2 mg/ml + propamidine

Adjusted 12-month MCR results (full analysis set, [redacted] DCO)

Outcome	Polihexanide 0.8 mg/ml+ placebo (n = 66)	Polihexanide 0.2 mg/ml + propamidine (n = 61)	Intervention vs comparator
Medical Cure Rate (MCR) % (n)	84.8 (56)	88.5 (54)	OR: 0.73 (CI: 0.26 to 2.04), P = 0.544
Test for non-inferiority difference in MCR			-0.04 (CI: -0.16 to 0.09)

Met company criterion for non-inferiority → lower bound of CI above 0.20.

Key secondary outcomes ([redacted] DCO)

- Longer median time to cure in polihexanide 0.8 mg/ml group (140 days) vs comparator (114 days, HR 0.68 (90% CI: 0.49 to 0.94))
- Other 2° outcomes generally not statistically significant
- Both treatments positively impacted HRQoL; slightly higher changes in comparator group

EAG:

- Numerically lower MCR in polihexanide 0.8 group vs comparator: no evidence of clinical benefit over lower doses
- MCR definition fails to capture impact of AK; excluded outcomes with long-term impact on visual acuity after AK cure
- EMA said results do not prove non-inferiority vs comparator. Non-inferiority margin not justified on clinical/statistical grounds

MCR = resolution of symptoms and clinical signs of AK, including cessation of AK and anti-inflammatory treatment for ≥30 days, without need for surgery or change in therapy.
See supplementary appendices for full trial definitions, results 1, 2, 3 and EAG critique 1, 2

CI, confidence interval; DCO, data cut off; EMA, European Medicines Agency; HR, hazard ratio; HRQoL, health related quality of life; MCR, medical cure rate; OR, odds ratio

Key issues: Exclusion of the ODAK trial comparator

Link to supplementary appendix: Distributions from Papa et al.

Company says comparator efficacy over-estimated in ODAK: doesn't reflect NHS outcomes

Background: Company excludes ODAK comparator arm from modelling → uses real world data for comparator arm

Company: Effectiveness of ODAK comparator doesn't reflect NHS outcomes

- Need to compound polihexanide 0.2 mg/ml + propamidine 1 mg/ml in the NHS → leads to delays & worse outcomes vs trial patients with immediate access
- EMA agreed that the trial comparator, manufactured to GMP quality, with immediate availability and a standardised treatment protocol, is not representative of current practice
- Treatments in NHS rely on physician discretion; less consistent outcomes

EAG: disagree with exclusion of ODAK data:

- Clinical experts confirm ODAK comparator reflects UK practice
- Delay between AK diagnosis and treatment initiation reported by the company (17.7 days) is an overestimate; likely only a few days once diagnosed
- Company's Delphi panel suggests ODAK regimen used in 52% AK cases

Base case: 100% of people in comparator arm have polihexanide 0.2 mg/ml + propamidine 1 mg/ml; efficacy based on ODAK trial

Technical team: no company scenarios using BSC as the comparator provided

- What is the appropriate comparator for polihexanide 0.8 mg/ml in the NHS?
- Is it appropriate for ODAK comparator arm data to be disregarded?

Comparators in scope, company submission & ODAK:

Comparator	Scope	Company: pooled AAT combination	ODAK trial
Polihexanide 0.2 mg/ml	✓	✓	
Polihexanide 0.6 mg/ml		✓	
Chlorhexidine	✓	✓	
Propamidine	✓	✓	
Hexamidine	✓	✓	
Polihexanide 0.2 mg/ml + Propamidine	✓	✓	✓

AAT, anti-amoebic therapies; AK, acanthamoeba keratitis; BSC, best supportive care; EMA, European Medicines Agency; GMP, good manufacturing practice

Distributions from Papa et al., ITC methodology, subgroup analyses,

Company's indirect treatment comparison

Company conducted ITC using real world data to inform relative efficacy

Background: Company said ODAK comparator efficacy does not represent real world outcomes, so conducted an ITC:

- Used ODAK as pseudo-single-arm study (to inform intervention efficacy - (see key issue slide)
- Sourced comparator data for pooled AATs in Papa et al. 2020
  - Retrospective cohort study in 227 people with AK treated between 1991 and 2012
- Conducted ITC using propensity scoring analysis (PSA) with overlap weighting (OW)
- Sensitivity analyses varying a) comparator AAT, b) adjustment method, c) matching method, and d) study entry date in Papa et al. show [redacted] to base case ITC

Study	After weighting	
	ODAK	Papa et al.
Effective sample size	65 (98%)	174 (77%)
Events (12-month MCR)	56 (85%)	110 (48%)
Comparison		
Relative risk (95% CI)	**1.75 (1.46 to 2.11)**	

Relative risk over 1 favours polihexanide 0.8 mg/ml over comparator.

*MCR definition in a) ODAK study: AAT discontinued for 30 days, b) Papa et al.: AAT discontinued

ITC aspect	Description
Outcomes	MCR at 12 months*
Prognostic factors adjusted	Age, gender, AK disease stage, prior use of a) corticosteroids, b) antivirals, delay in starting treatment.
Missing data	Patients with missing covariates or outcome data excluded except a) treatment delay (median-imputed), b) age (mean-imputed)

AAT, anti-amoebic therapies; AK, acanthamoeba keratitis; CI, confidence interval; ITC, indirect treatment comparison; MCR, medical cure rate;

Key issues: ITC methodology and relevance

EAG says ITC has high risk of bias

EAG: Company's approach methodologically weak due to:

1. Differences in study design → combining retrospective cohort study (Papa et al) and RCT (ODAK) liable to bias
   - Papa et al based on old data (1991-2012) with methodological limitations (heterogenous treatment regimens, incomplete data)

2. Lack of adjustment for important covariates e.g. contact lens use / differences in baseline populations (severity) → residual confounding?

3. High level of treatment switching in Papa et al. may dilute effect of single AAT → favours polihexanide 0.8 mg/ml? Confounding?

4. Only 2 of 6 covariates imputed, others excluded if missing

Is the ITC appropriate for informing relative efficacy data?

Baseline characteristics in ITC, EAG's naive and adjusted comparisons, Key issue: comparators; Treatment switching

AAT, anti-amoebic therapies; ITC, indirect treatment comparison;

Key issues: ITC methodology and relevance

EAG says ITC unnecessary given direct comparator data exists

EAG: Exclusion of direct comparator data available from ODAK:

- Polihexanide 0.2 mg/ml + propamidine is most common AAT in NHS
- Including may allow connected network for NMA
- Company approach may overestimate effect of polihexanide 0.8 mg/ml
- EAG base case may underestimate effect of polihexanide 0.8 mg/ml as ODAK comparator only represents ~half of NHS standard care
- True treatment effect vs SoC likely to be between these two extremes
- The EMA report did not contain an ITC with a pooled intervention; the comparison is with untreated patients

Comparator data sources explored by EAG

Data source	Provided?
ODAK comparator arm	EAG base case
ODAK comparator as link to the 0.2 mg/ml polihexanide + diamidine subgroup from Papa et al. 2020	Unadjusted comparison only – IPD from ODAK unavailable to EAG
Naïve comparisons: Papa et al. subgroups vs polihexanide 0.8 mg/ml to find plausible range for AAT treatment effect	EAG scenarios vary MCR RR 0.95 to 1.65 (min & max plausible RRs)

Is it appropriate to exclude the ODAK comparator data from the ITC?

Baseline characteristics in ITC, EAG's naive and adjusted comparisons, Key issue: comparators; Treatment switching

AAT, anti-amoebic therapies; EMA, European Medicines Agency; HR, hazard ratio; IPD, individual patient data; ITC, indirect treatment comparison; MCR, medical cure rate; NMA, network meta-analysis; RR, relative risk; SoC, standard of care

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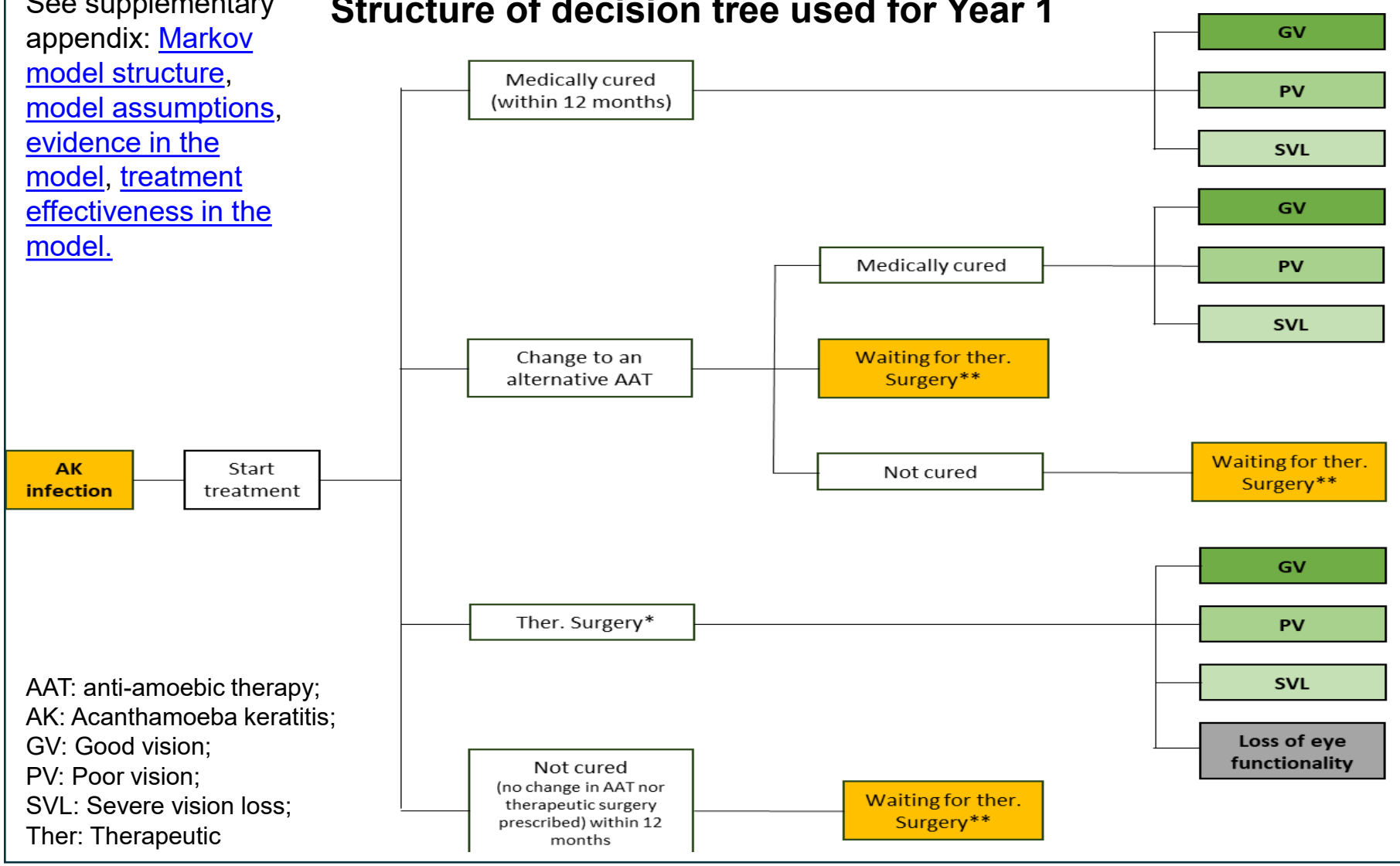
Company's model structure

Company use a hybrid model: Year 1: decision tree, Years 2+: semi-Markov model

See supplementary appendix: Markov model structure, model assumptions, evidence in the model, treatment effectiveness in the model.

Structure of decision tree used for Year 1



AAT: anti-amoebic therapy;
AK: Acanthamoeba keratitis;
GV: Good vision;
PV: Poor vision;
SVL: Severe vision loss;
Ther: Therapeutic

- After Year 1, people enter semi-Markov model in health states at the end of Year 1
- If AK unresolved, remain in AK infection state
- If AK resolved, remain in health state according to their visual acuity until optical surgery, graft failure, AK infection recurrence or death
- If AK reoccurs (post medical / surgical resolution of initial infection), re-enter decision tree for 1 year

EAG: model captures all important health states for AK

Key model aspects: Cycle length 1 year with half-cycle correction, lifetime time horizon (63 years), 3.5% discount rate for health effects and costs.

Key issue: time-to-cure data

Company use treatment duration from Franch et al for polihexanide 0.8 mg/ml; EAG prefer ODAK

Background: drug acquisition costs calculated using dosing regimen and treatment duration:

- Mean treatment duration from Franch et al. 2024 for polihexanide 0.8 mg/ml
- Median time-to-cure from Papa et al. 2020 for pooled AATs

Company: mean duration from Franch et al 2024 represents time that patients exposed to polihexanide 0.8 mg/ml in real-world clinical practice.

EAG: Company's approach unsuitable because:

1. Sample size in Franch et al 2024 study too small (n=11) to be generalisable to clinical practice.
2. Differences in baseline characteristics between retrospective study in Franch et al and ODAK. e.g.
   - Mean age in Franch et al = 41.4 vs 35.2 in ODAK
   - Previous topical corticosteroid treatment in Franch et al = 91% vs. 47% in ODAK
3. Median time-to-cure reported in the ODAK study ensures consistency with outcome from Papa et al.

Base case: median time-to-cure from ODAK for polihexanide 0.8 mg/ml

Scenario: median time-to-cure from ODAK for both modelled arms

Potential time on treatment sources

Arm	Source	Duration (days)	Preferred by
Polihexanide 0.8 mg/ml	Mean treatment duration in Franch et al 2024	101	Company base case
	Median time-to-cure in ODAK (polihexanide 0.8 mg/ml arm)	140	EAG base case
Comparator arm	Median time-to-cure in Papa et al. 2020	152	Company and EAG base case
	Median time-to-cure in ODAK for comparator arm (applied to EAG base case)	114	EAG scenario

AAT, anti-amoebic therapies

Which source is preferred to calculate the number of days on treatment in the model?

Key issue: AK recurrence after polihexanide 0.8 mg/ml

Company: no AK recurrence for polihexanide 0.8 mg/ml; EAG: equal rates between arms

Background: Company assumes:

- AK would not recur in people who had AK resolution after polihexanide 0.8 mg/ml
- AK recurs in a proportion of people after AK resolution on in the AAT arm up to year 15 in the model → based on Delphi panel and 2 case studies

Rates of AK recurrence in company model

Recurrence	Year 1	Year 2+
Polihexanide 0.8 mg/ml	0	0
Pooled AATs	0.1150	0.0300
After therapeutic surgery	0.0327	0.0327
After treatment switch	0.1150	0.0300

Company:

- 0% recurrence for polihexanide 0.8 mg/ml justified [redacted]
- Delphi panel identified smaller risk of recurrence if recurrence doesn't occur within first months of treatment
- AK recurrence modelled up to 15 years based on clinical advice that that this appropriately represents the latest possible timepoint that AK may recur after an initial cure

EAG: conservative to include some level of recurrence after AK resolution on polihexanide 0.8 mg/ml given lack of long-term information

- Company's assumption favours polihexanide 0.8 mg/ml arm

Base case: same recurrence rates after AK resolution in both modelled arms

- Would AK be expected to recur after initial cure with polihexanide 0.8 mg/ml?
- If yes, at the same rate as for people having pooled AAT?

AAT, anti-amoebic therapies; AK, acanthamoeba keratitis

Key issue: Carer disutilities

Company models disutilities for carers based on HST11

See supplementary appendix: utilities in the model

Background: company applies caregivers' disutility based on values used in HST11 (Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations)

- For graft failure, caregiver disutility adjusted by % having further procedures after a graft failure as reported by the Delphi panel.

Company: caregiver disutilities based on HST11 → similar disease burden associated with managing chronic visual impairment.

EAG: clinical experts support inclusion of caregiver disutilities ***Scenarios***: excluding carer disutility.

Caregiver disutilities in company model

Event	Utility decrement	Duration (days)
Intensive treatment phase (pooled AATs only)	-0.04	19.00
Therapeutic surgery	-0.04	121.75
Optical surgery	-0.04	121.75
Graft failure	-0.014	141.70
Severe vision loss or loss of eye functionality	-0.04	–

Technical team: Inherited retinal dystrophies (HST11) affect both eyes, typically from childhood, and ultimately lead to near-total blindness → not comparable to AK (company models 48% cured at 12 months with current AATs, only 1 eye affected)

- Is it appropriate to include a disutility for caregivers of people with AK?
- If yes, are the disutilities from HST11 translatable to this appraisal?

AAT, anti-amoebic therapies; AK, acanthamoeba keratitis; HST, highly specialised technology; RPE, Retinal Pigment Epithelium

Key issue: modelling intensive treatment phase

Concerns with company's modelling of disutilities, hospitalisation and number of drops

Background: company models polihexanide 0.8 mg/ml as daytime monotherapy only → in line with licence

EAG: Clinical advisers: polihexanide 0.8 mg/ml would be used daily & nightly, especially for moderate to severe AK.

- EAG raise key issues for intensive treatment phase:

Company	EAG	Impact
a) Disutilities for intensive treatment phase apply to pooled AAT arm only Higher burden of care for AATs (overnight treatment with multiple therapies) vs polihexanide 0.8 mg/ml Carer disutilities accepted in HST 11	***Base case:*** patient and carer disutilities in intensive treatment phase apply to both arms	Small
b) Hospitalisation costs apply to 26.6% AAT arm only Current AAT regimens need admission to improve compliance & outcomes → N/A for polihexanide 0.8 mg/ml (monotherapy with daytime administration)	Likely also hospitalised for nighttime treatment with polihexanide 0.8 mg/ml. ***Base case:*** hospitalisation costs in 26.6% both arms	Small
c) Costs for daytime only administration in the intensive phase: in line with the licence (max 16 drops).	Clinical advisers: max 24 drops over 3 – 5 days in intensive phase ***Scenario:*** 24 drops/ day for 2, 3, 4 or 5 days	Small

During the intensive treatment phase in the model:

- Should disutilities be included for polihexanide 0.8 mg/ml? If yes for both patients and carers?
- Would people having polihexanide 0.8 mg/ml be hospitalised? If yes, is the EAG's proportion plausible?
- Would polihexanide 0.8 mg/ml be used both daily and nightly? If yes, for how many days?

AAT, anti-amoebic therapies; AK, acanthamoeba keratitis; HST, highly specialised technology

Other key issues identified by the EAG

Concerns with modelling disutilities for long-term complications

Background	Company	EAG	Impact
Disutilities modelled for long term complications following AK resolution	Short duration (12 months) of ODAK trial could not capture long-term implications of AK	Company's approach is double counting → complications of AK captured in trial EQ-5D • Disutilities applied to people with good vision, who are assumed to have general population utility → lacks face validity ***Base case:*** exclude disutilities for long-term complications for all health states	Moderate

- What impact do long term complications of AK have on quality of life?
- Should disutilities be included in the model for long term complications of AK?

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AK, acanthamoeba keratitis

Summary of company and EAG base case assumptions

Comparator data source is main driver of difference between base cases

Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
Comparator	Pooled AATs based on distribution in Papa et al.	Polihexanide 0.2 mg/ml + propamidine 1 mg/ml (ODAK comparator)
Relative efficacy (risk ratio)	1.75 (ITC: ODAK vs Papa)	0.96 (ODAK)
Time-on-treatment data for polihexanide 0.8 mg/ml	Mean based on Franch et al. 2024	Median based on ODAK trial
AK reoccurrence after polihexanide 0.8 mg/ml	Does not reoccur	Same chance of AK reoccurrence in both arms
Disutilities for on-going long-term conditions	Included for all health states	Excluded for all health states
Patient and carers disutilities associated with the intensive treatment period with polihexanide 0.8 mg/ml	Excluded	Included
Proportion hospitalised during the intensive treatment phase with polihexanide 0.8 mg/ml	Excluded	26.60%

AAT, anti-amoebic therapies; AK, acanthamoeba keratitis; N/A, not applicable; ITC, indirect treatment comparison;

Distribution of life years from the Markov model

EAG model predicts more favourable outcomes for comparator arm than company's model

Undiscounted life years in each health state in the company and EAG's model 12 months onwards

Model	Treatment	AK	Good vision	Poor vision	Severe vision loss	Loss of eye functionality
Company	Polihexanide 0.8 mg/ml	1.10	35.53	3.52	1.44	3.51
	Pooled AAT	1.65	22.67	3.36	3.23	13.05
EAG	Polihexanide 0.8 mg/ml	1.52	34.83	3.50	1.48	3.74
	Polihexanide 0.2 mg/ml + propamidine 1 mg/ml	1.52	35.58	3.51	1.38	3.15

EAG model predicts longer time with good vision and shorter time with severe vision loss and loss of eye functionality → driven by better MCR rate for the comparator in ODAK than the company's ITC

- Which model outputs are most reflective of clinical practice for people having AATs in the NHS?

AAT, anti-amoebic therapies; AK, acanthamoeba keratitis; ITC, indirect treatment comparison; MCR, medical cure rate

Company base case

Company's base-case results after clarification, using PAS for polihexanide 0.8 mg/ml

Strategy	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£/QALY)	INHB at £20K	INHB at £30K
Deterministic									
Pooled AAT	[redacted]	22.37	14.76	-	-	-	-	-	-
Polihexanide 0.8 mg/ml	[redacted]	22.65	17.31	[redacted]	0.28	2.56	[redacted]	[redacted]	[redacted]
Probabilistic									
Pooled AAT	[redacted]	22.37	14.81	-	-	-	-	-	-
Polihexanide 0.8 mg/ml	[redacted]	22.65	17.31	[redacted]	0.27	2.50	[redacted]	[redacted]	[redacted]

AAT: anti-amoebic therapy; ICER; incremental cost-effectiveness ratio; INHB: incremental net health benefit; LYG; life years gained; PAS: patient access scheme; QALYs; quality-adjusted life years.

Cumulative changes in EAG base case

EAG's preferred model assumptions applied to the company base case (PAS for polihexanide 0.8 mg/ml)

	Scenario	Inc. cost (£)	Inc. QALYs	ICER (£) (Δ from company base case)	INHB £20K	INHB £30K
Company's base case		[redacted]	**2.56**	[redacted]	[redacted]	[redacted]
1	Include comparative results from ODAK → polihexanide 0.8 mg/ml versus polihexanide 0.2 mg/ml + propamidine 1 mg/ml	[redacted]	0.10	[redacted]	[redacted]	[redacted]
2	Median time to cure from ODAK for polihexanide 0.8 mg/ml	[redacted]	2.54	[redacted]	[redacted]	[redacted]
3	AK recurrence may occur in people treated with polihexanide 0.8 mg/ml	[redacted]	1.71	[redacted]	[redacted]	[redacted]
4	Exclude disutilities for on-going long-term conditions	[redacted]	2.03	[redacted]	[redacted]	[redacted]
5	Include disutilities (patients and caregivers) associated with the intensive treatment period with polihexanide 0.8 mg/ml	[redacted]	2.54	[redacted]	[redacted]	[redacted]
6	26.60% treated with polihexanide 0.8 mg/ml hospitalised during intensive phase	[redacted]	2.56	[redacted]	[redacted]	[redacted]
EAG's base-case deterministic (1 + 2 + 3 + 4 + 5 + 6)		[redacted]	**-0.11**	[redacted]	[redacted]	[redacted]
EAG's base-case probabilistic (1 + 2 + 3 + 4 + 5 + 6)		[redacted]	**-0.20**	[redacted]	[redacted]	[redacted]

ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; QALY, quality-adjusted life year

EAG scenario analyses on company base case

	Theme	Scenario	Inc. costs (£)	Inc. QALYs	ICER £/QALY	Impact to the ICER (%)
Company's base-case			[redacted]	2.56	[redacted]	-
1.	AK recurrence after cure	No AK recurrence with pooled AAT	[redacted]	2.05	[redacted]	30%
2.		Same for polihexanide 0.8 mg/ml & pooled AAT	[redacted]	1.71	[redacted]	58%
3.	Comparator = polihexanide 0.2 mg/ml + propamidine (ODAK RR)		[redacted]	0.20	[redacted]	2753%
4.	Relative risk for MCR (RR from ODAK = 0.96 RR from Papa et al. =1.75)	0.95	[redacted]	0.05	[redacted]	6151%
5.		1.05	[redacted]	0.55	[redacted]	412%
6.		1.15	[redacted]	0.98	[redacted]	183%
7.		1.25	[redacted]	1.34	[redacted]	103%
8.		1.35	[redacted]	1.65	[redacted]	62%
9.		1.45	[redacted]	1.92	[redacted]	38%
10.		1.55	[redacted]	2.16	[redacted]	21%
11.		1.65	[redacted]	2.37	[redacted]	9%
12.	Exclude disutilities for on-going long-term conditions		[redacted]	2.03	[redacted]	26%
13.	Polihexanide treatment costs from ODAK median time-to-cure		[redacted]	2.54	[redacted]	43%
14.	26.6% with polihexanide 0.8 mg/ml hospitalised		[redacted]	2.56	[redacted]	1%
15.	Intensive phase disutilities applies to:	Patients and carers	[redacted]	2.54	[redacted]	1%
16.		Patients only	[redacted]	2.54	[redacted]	1%
17.		Carers only	[redacted]	2.55	[redacted]	0%

AAT, anti-amoeba therapy; AK, acanthamoeba keratitis; ICER, incremental cost-effectiveness ratio; MCR, medical cure rate; QALY, quality adjusted life year; RR, relative risk

EAG scenario analyses on EAG base case

Scenario applied to EAG's base-case		Inc. costs (£)	Inc. QALYs	ICER £/QALY	Change to ICER	INHB at £20K /QALY)	INHB at £30K /QALY)
EAG's base-case		[redacted]	-0.11	[redacted]		[redacted]	[redacted]
1.	General population mortality for all health states	[redacted]	-0.10	[redacted]	+10%	[redacted]	[redacted]
2.	Exclude disutilities for intensive treatment phase in polihexanide 0.8 mg/ml	[redacted]	-0.09	[redacted]	+22%	[redacted]	[redacted]
3.	Including disutilities for on-going long-term conditions	[redacted]	-0.14	[redacted]	-21%	[redacted]	[redacted]
4.	Exclude for caregiver disutilities	[redacted]	-0.09	[redacted]	+22%	[redacted]	[redacted]
5.	Median time-to-cure from ODAK for both arms	[redacted]	-0.13	[redacted]	-15%	[redacted]	[redacted]
24 drops polihexanide 0.8 mg/ml drops per day (1 per hour) for:							
6.	2 days	[redacted]	-0.11	[redacted]	-4%	[redacted]	[redacted]
7.	3 days	[redacted]	-0.11	[redacted]	-	[redacted]	[redacted]
8.	4 days	[redacted]	-0.11	[redacted]	-	[redacted]	[redacted]
9.	5 days	[redacted]	-0.11	[redacted]	+4%	[redacted]	[redacted]
Costs for polihexanide 0.2 mg/ml and 0.6 mg/ml and chlorhexidine 0.2 mg/ml (unlicenced AATs)							
10.	Costs increase X3	[redacted]	-0.11	[redacted]	-2%	[redacted]	[redacted]
11.	Costs increase X2	[redacted]	-0.11	[redacted]	-1%	[redacted]	[redacted]
12.	Costs decrease X2	[redacted]	-0.11	[redacted]	0%	[redacted]	[redacted]
13.	Costs decrease X3	[redacted]	-0.11	[redacted]	+1%	[redacted]	[redacted]

AAT, anti-amoeba therapy; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; QALY, quality adjusted life year;

Polihexanide eye drops for treating acanthamoeba keratitis in people 12 years and over [ID6497]

- ❑ Background and key issues
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ✓ **Summary**

NICE National Institute for Health and Care Excellence

Key issues

KEY: Change from company base case ICER: small: < £5,000, moderate: £5,000 to £10,000, large: > £10,000, very large: >£500,000

Issue	Resolved?	ICER impact
Exclusion of the ODAK trial comparator from the decision problem and the ITC	No – for discussion	Very large
Validity of the company's indirect treatment comparison	No – for discussion	Unknown
Mean time-on-treatment used from Franch et al. 2024	No – for discussion	Large
AK recurrence in people treated with polihexanide 0.8 mg/ml	No – for discussion	Large
Disutilities associated with long-term complications	No – for discussion	Moderate
Carer disutilities	No – for discussion	Moderate
Carer and patient disutilities associated with the intensive phase	No – for discussion	Small
Hospitalisation during the intensive phase with polihexanide 0.8 mg/ml	No – for discussion	Small
Number of drops of polihexanide 0.8 mg/ml used in the intensive phase	No – for discussion	Small

AK, acanthamoeba keratitis; ICER, Incremental Cost-Effectiveness Ratio; ITC, indirect treatment comparison; ODAK, Orphan Drug for Acanthamoeba Keratitis

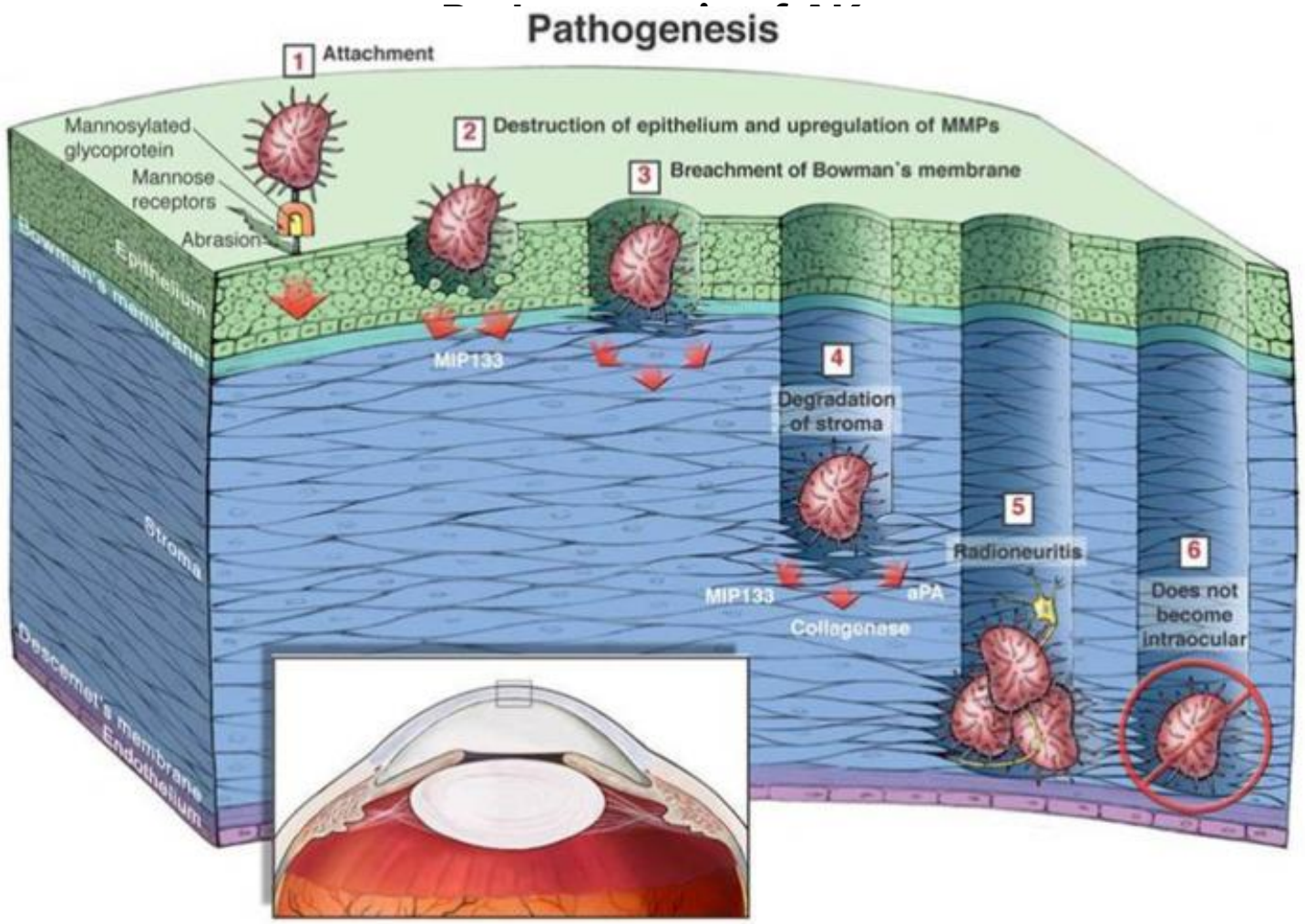
Polihexanide eye drops for treating acanthamoeba keratitis in people 12 years and over [ID6497]

Supplementary appendix

NICE National Institute for Health and Care Excellence

Background on acanthamoeba keratitis

Stages defined by level of corneal infiltration



Link to main slides: background

AK, acanthamoeba keratitis; MIP Mannose-Induced Protein; aPA, acanthamoeba plasminogen activator

Stages of AK in the company submission

Stage 1: corneal epithelium: nonspecific symptoms (dry eyes, foreign body sensation, photophobia, blurred vision, tearing, moderate pain and eye redness)

Stage 2: ≥1 epithelial defects, infiltrating perineural (area surrounding corneal nerves) or stroma, causing severe ocular pain

Stage 3: Infiltration of cornea.

- ≥1 features of Stage 2 and infiltration of cornea from deep stromal involvement.
- Corneal ulceration can occur.
- If untreated or therapy resistant can lead to corneal perforation or infection spreading into adjacent eye tissue, causing severe scleritis and vision loss

Source: *Wanis, H.A. et al. (2021), ^The Brain Tumour Charity

Decision problem

Link to main slides: technology

	Final scope	Company	EAG comments
Population	Adults and children from 12 years of age with AK	No change	Generally, reflects AK patients in NHS
Comparators	Used individually or in combination: • Polihexanide 0.2 mg/ml • Chlorhexidine • Propamidine • Hexamidine	Pooled AAT comparator used individually or in combination • reflects heterogeneity of treatment classes and regimens in NHS given lack of SoC. • Also includes polihexanide 0.6 mg/ml → Delphi panel identified use in small % of AK cases	Disagree with company's choice to exclude: • Comparator from ODAK (polihexanide 0.2 mg/ml + propamidine 1 mg/ml) • Subgroups of cohort study: polihexanide 0.2 mg/ml +/- diamidine, diamidine, combined AAT (polihexanide 0.2 mg/ml + chlorhexidine + diamidine)
Outcomes	Clinical resolution rate, time-to-cure, visual acuity, reduction of symptoms (e.g.: pain, swelling, redness), AEs, HRQoL	As per scope	-

AAT, anti-amoeba therapy; AE, adverse event; AK, acanthamoeba keratitis; HRQoL, health related quality of life; AK, acanthamoeba keratitis; SoC, standard of care

Analysis populations and definitions in the ODAK trial

	0.8 mg/ml polihexanide + placebo	0.2 mg/ml polihexanide + 1 mg/ml propamidine	All subjects	Used in company submission: 0.8 mg/ ml polyhexanide results only
Safety Analysis Set (ITT population)	69	65	134	Baseline characteristics, treatment discontinuation and AEs
Full Analysis Set	66	61	127	All other clinical outcomes
Per Protocol Analysis Set	62	57	119	Sensitivity analysis around the primary outcome, protocol deviations

Definitions in the ODAK trial

MCR (medical cure rate): resolution of symptoms and clinical signs of AK, including cessation of AK and anti-inflammatory treatment for ≥30 days, without need for surgery or change in therapy.

- Pre-defined non-inferiority margin in ODAK of 20% vs comparator arm justified by company:
  - Statistically: uses historical data to ensure that >50% standard treatment effect vs placebo
  - Clinically: small delay in response from using monotherapy would not be expected to cause blindness or serious morbidity, given the slow progression of AK and the close monitoring in practice.

BCVA (best corrected visual acuity) or Snellen:

- Numerator = distance from the chart, typically 20 feet
- Denominator = distance at which a person with "normal" vision can read smallest line clearly read.

LogMAR: 0.0 = normal vision (20/20 Snellen) with each 0.1 step indicating a doubling/halving of visual detail

- Lower LogMAR scores indicate better vision; higher scores indicate poorer vision.

AAT, anti-amoeba therapy; AE, adverse event; AK, acanthamoeba keratitis; ITT, intention to treat; LogMAR, logarithm of the Minimum Angle of Resolution

ODAK baseline characteristics

Link to main slides: ODAK results

Summary of patients' baseline characteristics in ODAK trial (full analysis set, n=127)

Characteristic		Polihexanide 0.8 mg/ml + Placebo (N = 66)	Polihexanide 0.2 mg/ml + Propamidine 1 mg/ml (N = 61)
Age, years	Mean (SD)	35.2 (13.2)	38.3 (14.4)
Age group (years), n (%)	15 - 35	36 (54.6)	28 (45.9)
	36 - 73	30 (45.5)	33 (54.1)
Sex	Male, n (%)	27 (40.9)	26 (42.6)
BCVA, n (%)	≥ 6/6	59 (96.7)	49 (92.5)
	< 6/6–6/12	1 (1.6)	3 (5.7)
	6/15–6/30	1 (1.6)	1 (1.9)
Risk factors for AK	CL wear, n (%)	64 (97.0)	58 (95.1)
	Ocular trauma	3 (4.6)	2 (3.3)
Days from (Mean (SD)):	Symptom onset	33.5 (39.2)	36.9 (55.0)
	1st keratitis treatment	12.0 (22.2)	13.5 (22.3)
Prior medications, n (%)	Antibiotics	56 (84.8)	50 (82.0)
	Antivirals	18 (27.3)	19 (31.1)
	Antifungals	1 (1.5)	0 (0.0)
	Corticosteroids (any cause)	31 (47.0)	20 (32.8)
Disease stage at baseline, n (%)	Stage I	14 (21.2)	8 (13.1)
	Stage II	41 (62.1)	46 (75.4)
	Stage III	11 (16.7)	7 (11.5)
Bilateral disease, n (%)	Present	10 (15.2)	4 (6.6)
Refractive error at baseline, n (%)	Myopia	55 (85.9)	49 (81.7)
	Hyperopia	8 (12.5)	7 (11.7)
	Emmetropia	1 (1.6)	4 (6.7)

EAG: measurements taken ≥2 days before dosing → introduce differences as condition is time-sensitive?

- Most baseline characteristics broadly similar across arms
- Higher % aged 15-35 in 0.8 mg/ml arm → known prognostic factor
- Other imbalances (prior corticosteroid use, % bilaterial disease) not prognostic.
- Higher % bilateral disease than expect in NHS practice

AK, acanthamoeba keratitis; BCVA, baseline best corrected visual acuity, CL, contact lens; n, number; SD, standard deviation

ODAK trial results: secondary outcomes in the model

Outcome	Polihexanide 0.8 mg/ml + placebo (n = 66)	Polihexanide 0.2 mg/ml + propamidine 1 mg/ml (n = 61)	Intervention vs comparator	In model
MCR at 12 months, % (n)	84.8 (56)	88.5 (54)	OR: 0.73 (95% CI: 0.26 to 2.04), P = 0.544	Yes – treatment response rate
Median Time-to-Cure (days)	140	114	HR: 0.68 (90% CI: 0.49 to 0.94), P = 0.048	EAG base case (intervention data only), EAG scenario (both arms)
BCVA at 12 month visit				
BCVA ≥20/40 (logMAR ≤0.3)	86.54% (45 / 52)	87.23% (41 / 47)	NR	Yes – 0.8 mg/ml results only. Used in model for good vision, poor vision and severe vision loss
BCVA ≥20/200 and <20/40 (logMAR ≤1.00 and >0.3)	11.54% (6 / 52)	12.77% (6 / 47)		
BCVA <20/200 (logMAR >1.00)	1.92% (1 / 52)	NR		
EQ-5D-5L VAS: Mean change (n = number assessed/number missing)	17.9 (SD 19.6) (n = 60/5)[a]	18.8 (SD 20.0) (n=52/9)	P = 0.366	Yes – cross walked to EQ-5D-3L

BCVA, Best corrected visual acuity; CI, confidence intervals; HR, hazard ratio; LogMAR, logarithm of the Minimum Angle of Resolution; MCR, medical cure rate; NR, not reported; OR, odds ratio; SD, standard deviation; VAS, Visual Analogue Scale

ODAK trial results: other secondary outcomes (1)

Outcome	Polihexanide 0.8 mg/ml + placebo (n = 66)	Polihexanide 0.2 mg/ml + propamidine 1 mg/ml (n = 61)	Intervention vs comparator
Mean change in BCVA (LogMAR) from baseline	-0.293 (SD 0.469) (n = 64)	-0.251 (SD 0.326) (n = 60)[a]	Mean difference: 0.05 (90% CI: -0.06 to 0.16), P = 0.444
Corneal Scarring at end of study n (%)	33 (50)	30 (49.2)[f]	OR: 1.14 (95% CI: 0.55 to 2.36), P = 0.734
Corneal ulceration at end of study n (%)	4 (6.1)	3 (4.9)	OR: 1.09 (95% CI: 0.22 to 5.47), P = 0.917
Anterior chamber inflammation (no inflammation) n (%)	62 (93.9)	50 (82)	OR: 0.65 (95% CI: 0.14 to 3.11), P = 0.651
Any adjunctive therapy n (%)	30 (45.5)	25 (41)	Not Reported
Post randomisation corticosteroid use n (%)	11 (16.7)	13 (21.3)	Not Reported

BCVA, Best corrected visual acuity; CI, confidence intervals; HR, hazard ratio; n, number; MCR, medical cure rate; OR, odds ratio; SD, standard deviation; VAS, Visual Analogue Scale

ODAK trial results: other secondary outcomes (2)

Outcome	Polihexanide 0.8 mg/ml + placebo (n = 66)	Polihexanide 0.2 mg/ml + propamidine 1 mg/ml (n = 61)	Intervention vs comparator
EQ-5D-5L: Least squares (90% CI)	1.34 (1.20 to 1.48)	1.38 (1.23 to 1.53)	P = 0.772
EQ-5D-5L: Pain/discomfort dimension n (%)			
No pain or discomfort	41 (63.1)	37 (60.7)	Not reported
Slight pain or discomfort	14 (21.5)	10 (16.4)	
Severe pain or discomfort	0 (0)	1 (1.6)	
Extreme pain or discomfort	0 (0)	0 (0)	
VFQ-25 Composite Score: Mean Change (n = number assessed/number missing)	23.5 (SD 19.4) (n = 60/5)	23.7 (SD 19.7) (n = 55/6)	P = 0.655
VFQ-25 mean ocular pain score (SD)	86.8 (17)	88.8 (19.5)	Not reported

CI, confidence interval; n, number; SD, standard deviation; VFQ, visual Function Questionnaire

ODAK adverse events

Link to main slides: ODAK results

Summary of adverse events across treatment arms (safety analysis set)

Adverse event outcome	Polihexanide 0.8 mg/ml + placebo (n=69)	Polihexanide 0.2 mg/ml + propamidine 1 mg/ml (n=65)
≥1 Adverse event	31 (44.9), 83	29 (44.6), 69
≥1 Serious adverse event	0 (0.0), 0	0 (0.0), 0
Any adverse event leading to death	0 (0.0), 0	0 (0.0), 0
Adverse events by severity		
Mild	24 (34.8), 46	24 (36.9), 50
Moderate	12 (17.4), 30	11 (16.9), 13
Severe	4 (5.8), 7	5 (7.7), 6
Adverse events by causality		
Not related	11 (15.9), 17	13 (20.0), 29
Unlikely related	10 (14.5), 13	11 (16.9), 19
Possibly related	13 (18.8), 35	8 (12.3), 12
Probably related	8 (11.6), 18	6 (9.2), 9
Related	0 (0.0), 0	0 (0.0), 0
Adverse events by action taken with study treatment		
Dose increased	5 (7.2), 7	0 (0.0), 0
Dose not changed	24 (34.8), 48	23 (35.4), 57
Dose reduced	0 (0.0), 0	0 (0.0), 0
Drug interrupted	11 (15.9), 16	6 (9.2), 6

EAG:

- safety data not reported by grade using a standard criteria (e.g. CTCAE)
- AE rates generally similar between treatments
- Limited long-term follow up
- Re-evaluation using CIOMS criteria identified 4 SAEs in 3 patients, including corneal perforation, corneal transplant, and visual impairment, suggesting potential underestimation of serious harm at the time of original analysis.

AE, adverse event; CIOMS, Council for International Organizations of Medical Sciences; CTCAE, Common Terminology Criteria for Adverse Events; N, number; SAE, serious adverse event

Link to main slides: ODAK results

ODAK trial: EAG comments (1)

Concerns over ODAK study → no statistically significant advantages observed for polihexanide 0.8 mg/ml in clinical and patient reported outcomes and concerns over risk of bias

Outcome	EAG comment
MCR	Concerns MCR defintion fails to capture impact of AK: 1. Exclusion of some outcomes with long-term implications on vision after cure (e.g. HRQoL, visual function, structural sequelae such as corneal scarring) 2. Patient reported QoL → reading, mobility, and emotional well-being domains did not fully normalise with AK cure 3. Corneal scarring linked to poor visual acuity
Time-to-Cure	Long time-to-cure → QoL impact with raises queries over clinical meaningfulness of the MCR?
BCVA	Not stratified by key clinical variables (e.g. corneal scarring) → unclear whether visual improvements limited to less severe disease or fewer structural complications
Corneal Scarring	Company post-hoc analysis: higher MCR (93.9%) and better BCVA (LogMAR of 0.07) with vs without corneal scarring (MCR of 77.4% and LogMAR of 0.31). Likely represents differences in baseline severity → more severe disease = more risk of scarring and treated and followed up more intensively.
Anterior chamber inflammation	High missing data at end of study in comparator arm. Potential confounding by use of adjunctive anti-inflammatory medications
Adjunctive & corticosteroid therapy	Adjunctive therapies may impact clinical and patient reported outcomes, especially those sensitive to inflammation. 12-month MCR comparable between groups with and without corticosteroid use (95.8% vs. 92.9% and 81.8% vs. 76.9%, respectively, P = 1 for both analyses)
HRQoL results	May not fully capture symptom burden, particularly ocular pain but no alternative measure available

AK, acanthamoeba keratitis; BCVA, Best corrected visual acuity; HRQoL, health related quality of life; LogMAR, logarithm of the Minimum Angle of Resolution; MCR, medical cure rate; QoL, quality of life

Link to main slides: ODAK results

ODAK trial: EAG comments (2)

EAG: EMA raised concluded the following:

1. Polihexanide 0.8 mg/ml cannot be called non-inferior to the active comparator in the ODAK trial because:
   - Non-inferiority margin (0.2) in ODAK cannot be justified on clinical or on statistical grounds
   - No evidence of clinical benefit over lower doses for 0.8 mg/ml dose
   - Differences between the finished product in clinical trials and commercially that cannot be resolved
   - No data on treatment and outcome of fellow eye for bilateral disease, and no measures taken to prevent treatment mistakes

2. Polihexanide 0.8 mg/ml performs better than no anti-amoebic treatment (when compared with historical data of 'untreated' patients)
   - No ITC with Papa 2020 provided in EMA submission → treatment benefit established using external control group of 'untreated' patients → simple pooling of 56 'untreated' patients from 37 case reports and case series published between 1970 and 1995, identified by company SLR
   - Used untreated RWE historical cure rates (19.6%), plus 30.7% boost (estimated 'trial effect' bias)
   - Approach considered valid but graded as low certainty of evidence with inherent bias.

EMA, European Medicines Agency; ITC, indirect treatment comparison; RWE, real world evidence; SLR, systematic literature review

Distribution of comparator treatments used for costs and effects in the company's model

AAT distribution obtained from the Delphi panel and Papa et al.

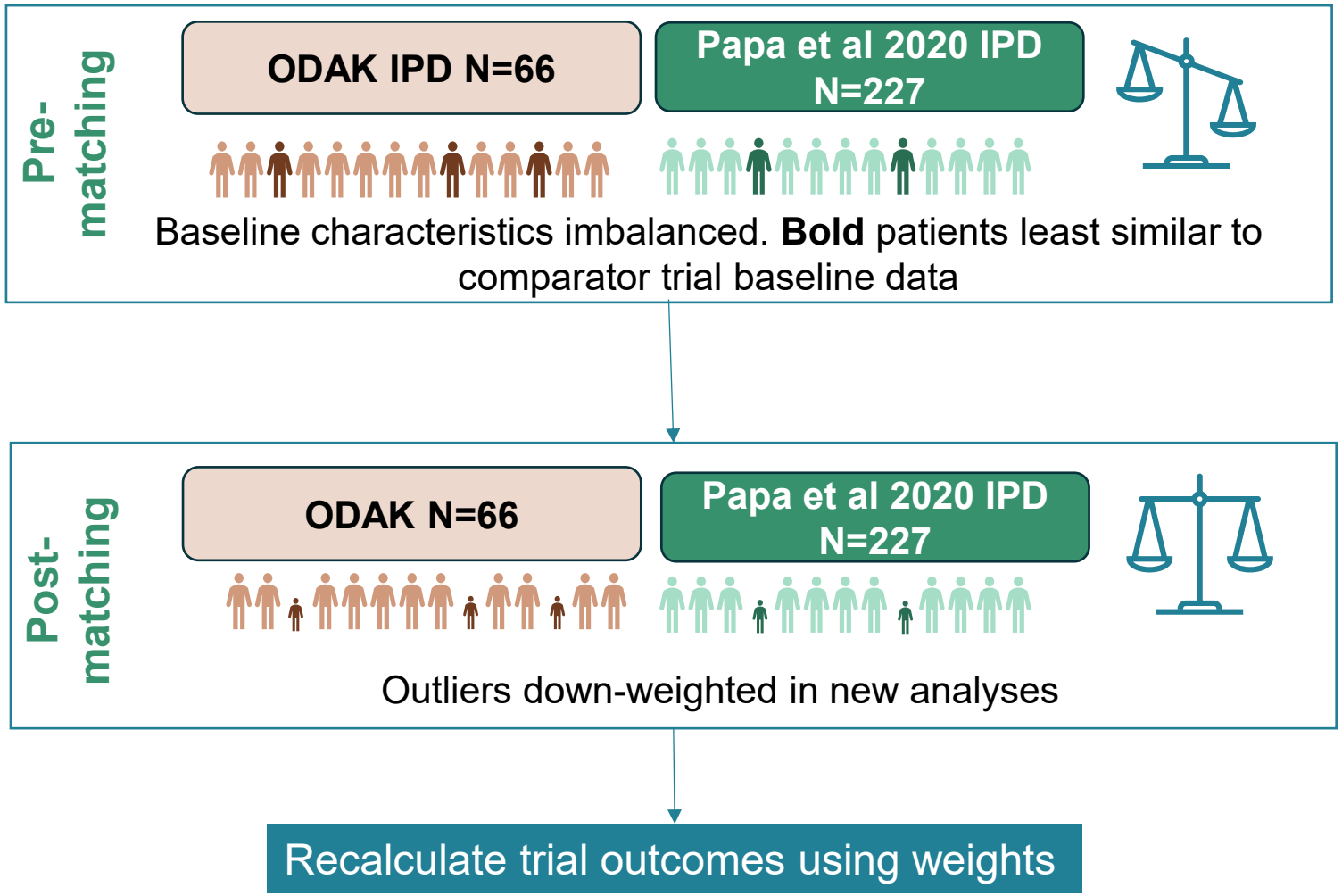
AAT distribution	Delphi panel	Papa et al., 2020
	Mean (90% CI)	Mean
Polihexanide 0.2 mg/ml + Propamidine 1 mg/ml	52.3 (43.9, 60.8)	48.90
Polihexanide 0.2 mg/ml monotherapy	14.5 (11.2, 17.7)	19.38
Chlorhexidine 0.2 mg/ml + diamidine	13.7 (10.7, 16.7)	9.25
Polihexanide 0.6 mg/ml monotherapy	8.5 (5.1, 11.9)	1.32
Polihexanide 0.6 mg/ml + diamidine	6.5 (4.4, 8.5)	2.64
Diamidine monotherapy	1.9 (1.1, 2.7)	11.01
Chlorhexidine 0.2 mg/ml monotherapy	1.4 (0.7, 2.2)	6.17
Polihexanide 0.2 mg/ml + chlorhexidine + diamidine	0.9 (0.5, 1.2)	0.88
Polihexanide 0.2 mg/ml + chlorhexidine	0.3 (0.2, 0.4)	0.44

AAT, anti-amoebic therapy; CI, confidence interval

Company's ITC methodology: PSM with overlap weighting (OW)

Propensity score matching (PSM) with OW uses all patient data for both trials

Methodology of the PSM



- Propensity score capturing all patient characteristics generated for each person for both trials
- Overlap weighting means all trial participants contribute data to the analyses → outliers are downweighed not removed
- Other methods of adjustment considered (average treatment effect, average treatment effect of treated) → OW deemed most balanced and stable weighting scheme, minimising extreme weights and maximising comparability.

Effective sample size (ESS) in company's ITC before and after matching

ESS	ODAK	Papa et al
Before matching	66	227
After matching	64.8 (98%)	174 (76.7%)

NICE

ESS, effective sample size; IPD, individualised patient data; ITC, indirect treatment comparison; N, number; PSM, propensity score matching

Link to main slides: Company's ITC

Company's ITC sensitivity analyses (1)

Results of company's ITC using Papa subgroups and untreated AK patients from the SLR

[redacted]

Relative risk over 1 favours polihexanide 0.8 mg/ml vs comparator.

Note: untreated AK patients outside of NICE scope

Sensitivity ITC results for the comparison to Papa full cohort, subjects since 2005, and since 2000

[redacted]

AAT, anti-amoeba therapy; AK, acanthamoeba keratitis; BCVA, Best corrected visual acuity; ESS, effective sample size; chlor, chlorhexidine; CI, confidence interval; HRQoL, health related quality of life; LogMAR, logarithm of the Minimum Angle of Resolution; poli, polihexanide; MCR, medical cure rate; RR, relative risk; SLR, systematic literature review; QoL, quality of life

Link to main slides: Company's ITC

Company's ITC sensitivity analyses (2)

Sensitivity ITC results using different weighting methods and imputations

ESS, effective sample size; CI, confidence interval; ITC, indirect treatment comparison; PSA, probabilistic sensitivity analysis; RR, relative risk

Relative risk over 1 favours polihexanide 0.8 mg/ml over comparator.

Results of EAG's naïve and adjusted risk ratios for 12-month MCR

Summary of naïve and adjusted risk ratios for MCR across treatment arms in ODAK and Papa et al. 2020 in ascending order of RR (RR>1 favours polihexanide 0.8 mg/ml)

Study	Arm	Sample size	% cured	Naïve RR	Adjusted RR
ODAK	Polihexanide 0.8 mg/ml	66	84.8%	Ref	Ref
	Polihexanide 0.2 mg/ml + propamidine	61	88.5%	0.96	NC
ODAK/Papa groups pooled	PHMB + diamidine pooled (EAG approach #2)	175	70.9%	1.20*	NC
Papa et al. (publication defintion of cure)	Other combined	38	63.2%	1.34*	NC
	Blended AAT	227	60.8%	1.40*	NC
	PHMB + diamidine	114	61.4%	1.38*	NC
	Diamidine monotherapy	25	60.0%	1.41*	NC
	PHMB monotherapy	50	58.0%	1.46*	NC
Papa et al. (company defintion of cure)	PHMB + diamidine	111	55.0%	1.54*	1.40*
	Blended AAT	227	43.6%	[redacted]*	1.75*
	Chlorhexidine 0.2 mg/ml ± propamidine	35	40.0%	2.12*	1.79*

Company's base case deemed an overestimation by EAG → scenarios vary RR in 0.10 increments between 0.96 and 1.65

*p<0.05. Bold denotes company base case ITC. The EAG were unable to calculate the adjusted RRs due to lack of IPD, these are denoted NC.

AAT, anti-amoebic therapy; ITC, indirect treatment comparison; MCR, medical cure rate; NC, not calculable; PHMB, polihexamethylene biguanide; RR, relative risk

Link to main slides: EAG ITC critique

Treatment switching in ODAK and Papa et al.

Proportion of people switching treatment in ODAK and Papa et al.

Study	Arm	% switched
ODAK	Polihexanide 0.8 mg/ml	3%
Papa et al	Polihexanide 0.2 mg/ml	25%
	Polihexanide 0.2 mg/ml + diamidine	48%
	Diamidine	88%
	Other combinations	53%

Baseline characteristics before and after matching in the company's ITC

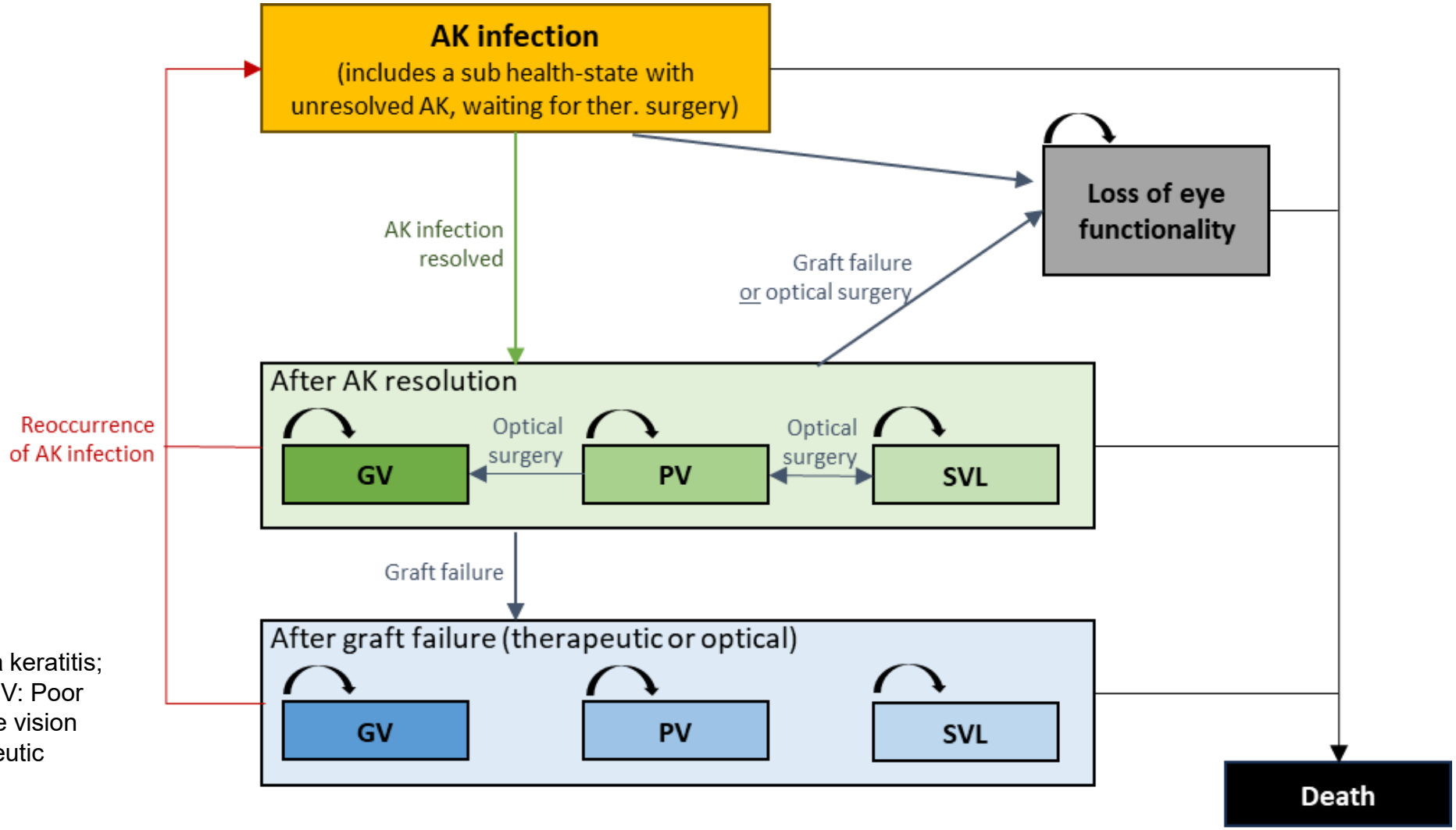
	Before adjustment			After adjustment		
	ODAK	Papa et al.	SMD	ODAK	Papa et al.	SMD
Effective sample size	66	227		64.8 (98.2%)	174 (76.7%)	-
Age	-	-	-	-	-	-
Mean (SD)	35.2 (13.2)	35.7 (13.8)	0.037	34.9 (13.0)	34.9 (14.1)	0
Median (min, max)	33.5 (15.0, 73.0)	33.0 (13.0, 76.0)		33.0 (15.0, 73.0)	32.0 (13.0, 76.0)	
Gender	-	-	-	-	-	-
Male	40.9	44.1	0.065	40.6	40.6	0
Female	59.1	55.9		59.4	59.4	
AK disease						
Stage 3	16.7	27.3	0.258	18.8	18.8	0
Prior use of corticosteroids	47.0	44.5	0.050	45.2	45.2	0
Prior use of antivirals	25.8	44.9	0.408	30.0	30.0	0
Delay in starting treatment	-	-	-	-	-	-
Mean (SD)	33.5 (39.2)	44.9 (48.4)	0.259	35.6 (41.3)	35.6 (36.7)	0
Median (min, max)	19.0 (1.0, 177.0)	30.0 (0.0, 330.0)		21.0 (1.0, 177.0)	28.0 (0.0, 257.0)	

CS, company submission; SD, standard deviation; SMD, standardised mean difference

Company's model structure

Company use semi-Markov model for years 2+ in model

Structure of semi-Markov used for Years 2+



AK: Acanthamoeba keratitis; GV: Good vision; PV: Poor vision; SVL: Severe vision loss; Ther: Therapeutic

Company's model assumptions

Defintion of visual impairment in the company's model

Visual impairment	Definition
AK infection	Patients with AK infection (not resolved)
Good vision (GV)	Patients who achieved a resolution of the AK infection (with or without therapeutic surgery) with BCVA ≥20/40 (logMAR ≤0.3)
Poor vision (PV)	Patients who achieved a resolution of the AK infection (with or without therapeutic surgery) with BCVA ≥20/200 and <20/40 (logMAR ≤1.00 and >0.3)
Severe vision loss (SVL)	Patients who achieved a resolution of the AK infection (with or without therapeutic surgery) with BCVA <20/200 (logMAR >1.00)
Loss of eye functionality	Patients who lose the eye functionality due to unresolved, severe AK, surgical procedures such as evisceration and enucleation, or in the event that patients do not undergo further procedures after a graft failure

Technology affects **costs** by:

- Drug acquisition costs (higher price vs monotherapy comparator treatments)
- Removing hospitalisation costs vs. comparator arm.
- Affecting costs associated with therapeutic and optical surgeries, and resource use and costs associated with AK infection, visual acuity and loss of eye functionality

Technology affects **QALYs** by changing the:

- Utility associated with AK infection and best corrected visual acuity
- Disutilities associated with events
- Caregiver disutilities

Assumptions with greatest **ICER** effect:

- Varying discount rate applied to outcomes
- Varying the relative risk for 12- month MCR
- Varying the duration of treatment (days)

AK, acanthamoeba keratitis; BCVA, Best corrected visual acuity; ICER, Incremental Cost-Effectiveness Ratio; LogMAR, logarithm of the Minimum Angle of Resolution; MCR, medical cure rate; QALY, quality adjusted life year

How company incorporated evidence into model

Link to main slides: model structure

Input	Assumption and evidence source
Baseline characteristics	ODAK trial for age, % male and mean body weight
Intervention	Polihexanide 0.8 mg/ml → regimen according to MA (see technology slide)
Comparator	Pooled AAT with Delphi panel distributions (see supplementary appendix)
Efficacy	See supplementary appendix
Utilities	• Health state utilities: ODAK EQ-5D-5L, cross walked to 3L • Disutilities for long-term complications of AK: published literature • One-off disutility for with intensive treatment and key milestones: literature, past HSTs and assumptions • Caregiver disutilities: HST11
Adverse events	No cost, resource use or disutility associated with AEs → similar reported rates between arms in ODAK
Resource use and costs	• Off label AAT costs: company's Market Intelligence Report. Distribution: Delphi panel • Costs per treatment course calculated based on number of bottles required. • Costs of subsequent treatment in both arms = pooled AAT treatment costs • One off costs: concomitant medication, therapeutic and optical surgery, graft failure • Hospitalisation during intensive treatment phase for 26.60% of the AAT arm only.
Mortality	Increased mortality risk for people cured with poor vision, cured with severe vision loss and people who lose functionality in the affected eye from Christ et al., (2008)

HST 11: Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations)

AAT, anti-amoebic therapy; AE, adverse event; AK, acanthamoeba keratitis; HST, highly specialised technology; MA, marketing authorisation

Treatment effectiveness in the company's model (1)

Efficacy input	Polihexanide 0.8 mg/ml	Pooled AATs	Further info
12-month MCR	MCR from ODAK: 84.85%	ITC RR (1.75)*: 48.37%.	***Company scenarios:*** Replace ODAK data for intervention in ITC with real world data from Franch et al (11 patients (12 eyes) treated with polihexanide 0.8 mg/ml): • #1: RR = [redacted] (95% CI: [redacted] to [redacted]), all base case covariates adjusted • #2: RR = [redacted] (95% CI: [redacted] to [redacted]), age and sex not adjusted. ***EAG prefers:*** MCR from ODAK for comparator arm (88.5%)
Change to new AAT	3.55%	[redacted]%	• Assumes that 23.4% of those not cured at 12 months change to new AAT (Delphi panel) • Same clinical resolution rate as initial response to AAT ([redacted]%)
Therapeutic surgery	2.50%	[redacted]%	• Assumes 21.5% of those not cured at 12 months undergo surgery (Delphi panel) • Mean surgery waiting time = 141.7 days (Delphi panel) • Type and distribution of surgery from Delphi panel
Optical surgery	41.9% with poor vision, 46% with severe vision loss		• % having surgery + type and distribution based on Delphi panel. • Mean waiting time for surgery 365.25 days (UK clinician)

* Calculated by dividing the ODAK MCR (84.85%) by [redacted] (RR from ITC for pooled AATs)

NICE AAT, anti-amoebic therapy; ITC, indirect treatment comparison; MCR, medical cure rate; RR, relative risk;

Treatment effectiveness in the model (2)

Efficacy input	Further info
BCVA	• Post pharmacological treatment: 12-month ODAK assessment data for polihexanide 0.8 mg/ ml • BCVA post therapeutic surgery depends on surgery type: distributions based on Robaei et al. 2015, Delphi panel and assumptions UK Delphi panel informs outcomes after: • optical surgery (improve, worsen or same BCVA range, lose eye functionality) • graft failure (good vision, poor vision, severe vision loss, lose eye functionality)
Graft failure	• Yearly probability of graft failure after therapeutic and optical keratoplastasty up to 3 years post surgery based on KM curves in Veugen et al. 2023 → applies to Markov model (Years 2+) only

BCVA, Best corrected visual acuity; KM, Kaplan-Meier

Link to main slides: Carer utilities

Utility values in the company's model

Health state utility values in the company's model

Health state	Utility	Source
Baseline utility + cured with good vision	0.902	General population utility (age and sex adjusted)
Disutilities applied in the model		
AK infection	-0.249	Assumption based on utility value in good vision (MMRM on ODAK data; [redacted]) population minus the average baseline utility from the ODAK trial ([redacted])
Cured with poor vision	-0.106	MMRM using GV as an intercept based on the ODAK trial data
Cured with severe vision loss	-0.123	MMRM using GV as an intercept based on the ODAK trial data
Loss of eye functionality	-0.248	Rentz et al.

AK, Acanthamoeba keratitis; MMRN, mixed model repeated measures; GV, good vision

Caregiver disutilities applied in the model

Event	Utility decrement	Duration (days)
Intensive treatment phase	-0.04	19.00
Therapeutic surgery	-0.04	121.75
Optical surgery	-0.04	121.75
Graft failure	-0.014	141.70
Severe vision loss or loss of eye functionality	-0.04	–

One off disutilities associated with events

Event	Disutility	Durations
Insomnia during intensive treatment phase	-0.280	24.00 (only comparator arm)
Therapeutic surgery	-0.140	121.75
Graft rejection	-0.248	141.70
Optical surgery	-0.140	121.75

Key model outputs

Health state occupancy over time in the company's model after clarification

AK: Acanthamoeba keratitis; GV: Good vision; PV: Poor vision; SVL: Severe vision loss

Link to main slides: Key model outputs

Decision making framework (1)

What are committee's preferred assumptions?	Details
Comparator	Pooled AATs informed by ITC, or ODAK comparator (polihexanide 0.2 mg/ml + propamidine 1 mg/ml)?
Time on treatment for polihexanide 0.8 mg/ ml	Franch et al or ODAK?
AK recurrence with polihexanide 0.8 mg/ml	Does or doesn't reoccur? At same or different rate to pooled AATs?
Disutilities from long-term complications	Include or exclude?
Carer disutilities	Include or exclude?
Disutilities for intensive phase	Include or exclude? For patients, carers or both?
Hospitalisation costs during the intensive phase	Include for polihexanide 0.8 mg/ml?

AAT, anti-amoeba therapy; AK, acanthamoeba keratitis; ITC, indirect treatment comparison

Decision making framework (2)

<table>
<tr><th colspan="2">What are committee's preferred assumptions?</th></tr>
<tr><td rowspan="2">What is the committee's preferred ICER threshold?</td><td>If yes, recommend for routine commissioning? (considering uncertainty, inequalities, innovation etc that might impact decision if close to threshold):</td></tr>
<tr><td>Could key uncertainties be sufficiently resolved during period of managed access? If so:</td></tr>
<tr><td>Should QALYs be weighted for severity and if so which weighting?</td><td rowspan="2">• Has company made a managed access proposal? Is this considered feasible?
• Are any updates or amendments required to the managed access proposal?
• Has committee answered the questions in NICE's feasibility assessment?
• What is committee's preferred threshold for managed access?
• Which ICERs/assumptions represent committee's lower/upper end of uncertainty?</td></tr>
<tr><td>What is the committee's preferred ICER? (if this is a range, please state whether the committee want the lower, upper, or midpoint of range to be below threshold)</td></tr>
<tr><td rowspan="2">Is the ICER below preferred ICER threshold?</td><td>If not, is chair's action appropriate*?</td></tr>
<tr><td>What, if any, are the key remaining uncertainties?</td></tr>
</table>

*That is, if NHSE have indicated they are willing to consider a commercial deal, and the company submit an ICER ≤ committee's preferred threshold using committee preferred assumptions, would committee be happy for the chair to approve this outside of a formal committee meeting?

QALY, quality adjusted life-year; ICER, incremental cost-effectiveness ratio