

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to stakeholders:

[Access the **final scope** and **final stakeholder list** on the NICE website.](#)

- 1. Company submission from SIFI SpA:**
 - a. Full submission
 - b. Summary of Information for Patients (SIP)
- 2. Clarification questions and company responses**
- 3. Patient group, professional group, and NHS organisation submissions from:**
 - a. Fight for Sight
 - b. Royal College of Ophthalmologists
- 4. Expert personal perspectives from:**
 - a. Miss Lana Fu, consultant ophthalmologist – clinical expert, nominated by SIFI S.p.A
 - b. Mr Darren Shu Jeng Ting, consultant ophthalmologist – clinical expert nominated by Royal College of Ophthalmologists (see item 3b*)
 - c. Mr Joe Beer – patient expert, nominated by Fight for Sight
- 5. External Assessment Report** prepared by Birmingham Centre for Evidence and Implementation Science
 - a. Addendum
- 6. External Assessment Report – factual accuracy check**

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Company evidence submission

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Abbreviations

Abbreviation	Definition
AAT	Anti-amoebic therapy
AE	Adverse event
AK	<i>Acanthamoeba</i> keratitis
BCVA	Best-corrected visual acuity
BNF	British National Formulary
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organisations of Medical Sciences
COMP	Committee for Orphan Medicinal Products
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CUP	Compassionate use programme
DALK	Deep lamellar keratoplasty
DNA	Deoxyribonucleic acid
DSA	Deterministic sensitivity analysis
DSAEK	Descemet's Stripping Automated Endothelial Keratoplasty
DSU	Decision Support Unit
EEPRU	Policy Research Unit in Economic Evaluation of Health and Care Interventions
EMA	European Medicines Agency
EPAR	European public assessment report
ESA	Employment and Support Allowance
FAS	Full analysis set
FDA	Food and Drug Administration
GBP	Great British Pounds
GMP	Good manufacturing practice
GV	Good vision
HCRU	Healthcare resource use
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HSK	Herpes Simplex keratitis
HST	Highly specialised technology
HSUV	Health-state utility value
HSV	Herpes simplex virus
ICER	Incremental cost-effectiveness ratio
INHB	Incremental net health benefit
IPD	Individual patient data
IQR	Interquartile range
IRP	International recognition procedure

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Abbreviation	Definition
ISPOR-SMDM	International Society of Pharmacoeconomics and Outcomes Research and Society for Medical Decision Making
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IVCM	In vivo confocal microscopy
LogMAR	Logarithm of the minimum angle of resolution
LYG	Life years gained
MCR	Medical cure rate
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed model repeated measures
NA	Not applicable
NAS	New Active Substance
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drug
ODAK	Orphan Drug for Acanthamoeba Keratitis
PAS	Patient access scheme
PCR	Polymerase chain reaction
PIM	Promising Innovative Medicine
PIP	Personal Independence Payment
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PSA	Propensity scoring analysis
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
PTSD	Post-traumatic stress disorder
PV	Poor vision
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
RWD	Real-world data
RWE	Real-world evidence
SAE	Serious adverse event
SAP	Statistical analysis plan
SLR	Systematic literature review
SMDM	Society for Medical Decision Making
SOC	System organ class
STA	Single technology appraisal
SVL	Severe vision loss
TEAE	Treatment-emergent adverse events
Ther	Therapeutic
TSD	Technical support document

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Abbreviation	Definition
VAS	Visual analogue scale
VBA	Visual Basic for Applications
VFQ	Visual Functioning Questionnaire
VRQoL	Vision-related quality of life questionnaire
WHO	World Health Organisation
WTP	Willingness-to-pay threshold

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

1.1 *Decision problem*

This submission addresses the clinical and cost-effectiveness of polihexanide 0.8 mg/ml within its full marketing authorisation for the treatment of *Acanthamoeba* keratitis (AK) in adults and children from 12 years of age. The decision problem addressed in this submission is provided in Table 1 which outlines any differences from the National Institute for Health and Care Excellence (NICE) final scope.¹

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults and children from 12 years of age with AK	Adults and children from 12 years of age with AK	NA
Intervention	Polihexanide 0.8 mg/ml	Polihexanide 0.8 mg/ml	NA
Comparator(s)	Used individually or in combination: • Polihexanide 0.2 mg/ml • Chlorhexidine • Propamidine • Hexamidine	A pooled AAT comparator in which the following are used individually or in combination: • Polihexanide 0.2 mg/ml • Chlorhexidine • Propamidine • Hexamidine • Polihexanide 0.6 mg/ml	The proposed comparator is in line with the NICE final scope, comprising compounded/off label polihexanide 0.2 mg/ml, chlorhexidine and diamidines (propamidine and hexamidine) used individually or in combination. This reflects findings from a Delphi Panel conducted in the UK, which informs the distribution of the comparator. Compounded polihexanide 0.6 mg/ml is also included as part of the pooled AAT comparator as a small proportion of patients who had received this treatment were identified in a UK-based Delphi panel which is used to inform this submission. A pooled comparator is presented to reflect the heterogeneity of treatment classes and regimens received by patients in UK clinical practice in the absence of a SoC.
Outcomes	The outcome measures to be considered include: • Clinical resolution rate • Time-to-cure • Visual acuity • Reduction of symptoms (for example: pain, swelling, redness) • Adverse effects of treatment • Health-related quality of life	The outcome measures include: • Clinical resolution rate • Time-to-cure • Visual acuity • Reduction of symptoms (pain as captured in health-related quality of life measures, corneal scarring, ulceration severity and anterior chamber inflammation) • Adverse effects of treatment	The outcomes presented are in line with the NICE final scope. Pain was not measured as a distinct outcome in the pivotal ODAK trial; however, the EQ-5D-5L includes a domain on pain/discomfort and the VFQ-25 includes a measure of ocular pain. ² Reduction of symptoms is also addressed in this submission through inclusion of data on corneal scarring, ulceration severity and anterior chamber inflammation from the ODAK trial. As such, all outcomes listed in the NICE final scope are captured in the outcomes presented in Section 2.

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	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
		Health-related quality of life	
Economic analysis	- Cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. - The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. - Costs will be considered from an NHS and Personal Social Services perspective. - The cost effectiveness analysis should include consideration of benefit in best and worst seeing eyes.	- Cost-effectiveness of polihexanide 0.8 mg/ml is expressed in terms of incremental cost per quality-adjusted life year. - A lifetime horizon is used in the model and the base case perspective is NHS and Personal Social Services. - The cost-effectiveness model includes consideration of the worst seeing eye only.	The results, time horizon and perspective of the economic analysis for polihexanide 0.8 mg/ml are in line with the NICE reference case.³ A simple PAS is proposed in this submission (see Table 2 below). The pivotal source of efficacy data for polihexanide 0.8 mg/ml is the ODAK trial, which reports outcomes only for the worst seeing eye.⁴ There are no data available to support a best seeing eye cost-effectiveness analysis of polihexanide 0.8 mg/ml and this has therefore not been presented.
Subgroups to be considered	No subgroups were proposed in the final scope.	No subgroups are considered in this submission.	In line with its anticipated marketing authorisation (MA), polihexanide 0.8 mg/ml is intended to offer the first approved treatment for the entire AK patient population aged 12 years and over.
Special considerations including issues related to equity or equality	NA	NA	SIFI strongly believes in equity of access, and therefore it should be ensured that people with AK who are eligible within the regulatory label are not restricted access to new therapies.

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Abbreviations: AAT: anti-amoebic therapy; AK: *Acanthamoeba* keratitis; MA: marketing authorisation; NA: not applicable; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PAS: Patient access scheme; SoC: standard of care; UK: United Kingdom.

Source: NICE, 2025 (Final Scope Document [ID6497]).¹

1.2 Description of the technology being evaluated

Table 2 summarises the technology (polihexanide 0.8 mg/ml) being evaluated in this submission.

Table 2: Technology being appraised

UK approved name and brand name	Approved name: Polihexanide 0.8 mg/ml Brand name: Akantior®
Mechanism of action	Polihexanide is a polymeric, preservative-free biguanide that has a dual mechanism of action which disrupts <i>Acanthamoeba</i> cell membranes and binds amoebal deoxyribonucleic acid (DNA) to block <i>Acanthamoeba</i> replication. This leads to cell lysis and inhibition of replication.²
Marketing authorisation/CE mark status	Polihexanide 0.8 mg/ml has MA from the European Medicines Agency (EMA) for the treatment of AK in adults and children from 12 years of age, with European Commission approval in August 2024.⁵ The Committee for Medicinal Products for Human Use (CHMP) granted a positive opinion in May 2024. The Committee for Orphan Medicinal Products (COMP) confirmed the orphan status of the product. An application to the Medicines and Healthcare products Regulatory Agency (MHRA) via the International Recognition Procedure (IRP) was submitted in December 2024, with MA approval granted in May 2025.⁶ Promising Innovative Medicine (PIM) status, Orphan Drug status and New Active Substance (NAS) status have been confirmed in the UK.
Indications and any restriction(s) as described in the SmPC	Polihexanide 0.8 mg/ml is indicated for the treatment of AK in adults and children from 12 years of age Polihexanide 0.8 mg/ml is contraindicated in the following cases: • Hypersensitivity to the active substance or to any excipients • In patients with urgent need of ocular surgery due to advanced AK
Method of administration and dosage	Polihexanide 0.8 mg/ml eye drops are administered as one drop in the affected eye according to the following regimen:⁶ 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 times a day at 4-hour intervals, until cure (i.e. corneal healing, absence of corneal inflammation or no evidence of infection) and for no longer than 12 months
Additional tests or investigations	No additional tests or investigations beyond those in the current clinical care pathway are required to identify people with AK eligible for treatment with polihexanide 0.8 mg/ml
List price and average cost of a course of treatment	The list price of polihexanide 0.8 mg/ml is £5,960.00 for 30 vials.

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Patient access scheme (if applicable)	A confidential simple discount Patient Access Scheme (PAS) would provide polihexanide 0.8 mg/ml at a price of [REDACTED] for 30 vials. This represents a [REDACTED] discount from the list price.

Abbreviations: AK: *Acanthamoeba* keratitis; CHMP: Committee for Medicinal Products for Human Use; COMP: Committee for Orphan Medicinal Products; DNA: deoxyribonucleic acid; EMA: European Medicines Agency; IRP: International Recognition Procedure; MHRA: Medicines and Healthcare products Regulatory Agency; NAS: New Active Substance; PAS: Patient Access Scheme; PIM: Promising Innovative Medicine

Source: Dart et al. 2024;² European Medicines Agency (EPAR Report);⁵ Akantior SmPC.⁶

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

Summary of the health condition

- AK is an extremely painful and devastating disease caused by *Acanthamoeba* infection of the cornea, with the potential for irreversible vision loss if not adequately treated. AK is most commonly acquired through contact lens misuse, however corneal injury is also a risk factor for developing the infection.⁷
- AK is a very rare disease, with an estimated incidence of <0.2 cases per 50,000 per year in the UK.⁸
- *Acanthamoeba* organisms can exist in two life-cycle stages, an active motile trophozoite and a resilient dormant cyst,⁹ which makes AK difficult to target.
- AK symptoms include redness, swelling, blurred vision, tearing and photophobia. Additionally, given that the cornea is one of the most densely innervated tissues, the infection is often characterised by severe ocular pain. These symptoms have a significant impact on health-related quality of life (HRQoL), causing sleep disturbances, social isolation and difficulties with carrying out daily activities.⁷
- Rapid diagnosis and treatment initiation of AK is crucial, as delayed treatment is associated with a poorer prognosis; research shows significantly worse outcomes for patients receiving treatment >30 days post-diagnosis versus <30 days post-diagnosis.¹⁰

Summary of the clinical care pathway and limitations of current clinical management

- There were no approved therapeutic treatments prior to polihexanide 0.8 mg/ml, or a definitive standard of care available in England and Wales for patients with AK. There are also no clear preferred or “best practice” treatments in clinical practice.
- Patients currently receive heterogenous care and a mixture of off-label and unlicensed anti-amoebic agents such as biguanides and diamidines, which are applied in dosing regimens that differ between prescribing ophthalmologists on the basis of their experience. In off-label applications, such as the use of propamidine, more intense regimens are used than recommended in treatment summary of product characteristics (SmPCs), leading to safety risks.¹¹ In addition to anti-amoebic therapies (AATs), medications for pain relief may be given, due to the intense pain associated with AK. Topical corticosteroids and antibiotics may also be given, to limit severe inflammation, and to treat secondary bacterial infection, respectively.¹¹
- Currently available biguanide therapies require compounding for individual cases and the short shelf-life of these compositions results in significant delays in treatment initiation for patients and therefore poorer outcomes.¹⁰ As biguanides are unlicensed for AK, they often

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do not meet good manufacturing practice (GMP) standards when compounded and there is often a lack of pharmacovigilance surrounding their use.¹²

- Currently available pharmacological options are also associated with a heavy administration burden, with people with AK required to administer drops every 20–30 minutes throughout the day and night in the intensive period of treatment, impacting the ability to sleep.¹³
- When pharmacological approaches fail to clear the *Acanthamoeba* infection, patients may have to undergo one or more surgical interventions. Therapeutic surgeries, such as keratoplasty, which can be used to clear the infection are associated with frequent complications in the years that follow, including development of glaucoma, cataract and a risk of graft rejection.¹¹ Once AK is cured, patients with severe vision impairment may undergo optical surgery to improve their visual acuity. However, half of these patients experience no improvement or even a worsening in their vision.¹¹
- There is consequently an urgent unmet need for an effective, safe, licensed treatment for people with AK, that is readily available without the need for compounding.

Positioning of polyhexanide 0.8 mg/ml

- Polyhexanide 0.8 mg/ml is a preservative-free ophthalmic product containing polyhexanide (a biguanide) specifically developed to treat AK. It is highly effective at eradicating *Acanthamoeba* in the active trophozoite form and, crucially, in the dormant cyst form. It acts through a dual mechanism of action that disrupts *Acanthamoeba* cell membranes and binds DNA to block *Acanthamoeba* replication.
- Polyhexanide 0.8 mg/ml is anticipated to be positioned as the first licensed, targeted treatment for AK specifically. Polyhexanide 0.8 mg/ml will address the clear unmet need for a readily available, licensed treatment of people with AK, aged 12 years and over.

1.3.1 Overview of AK

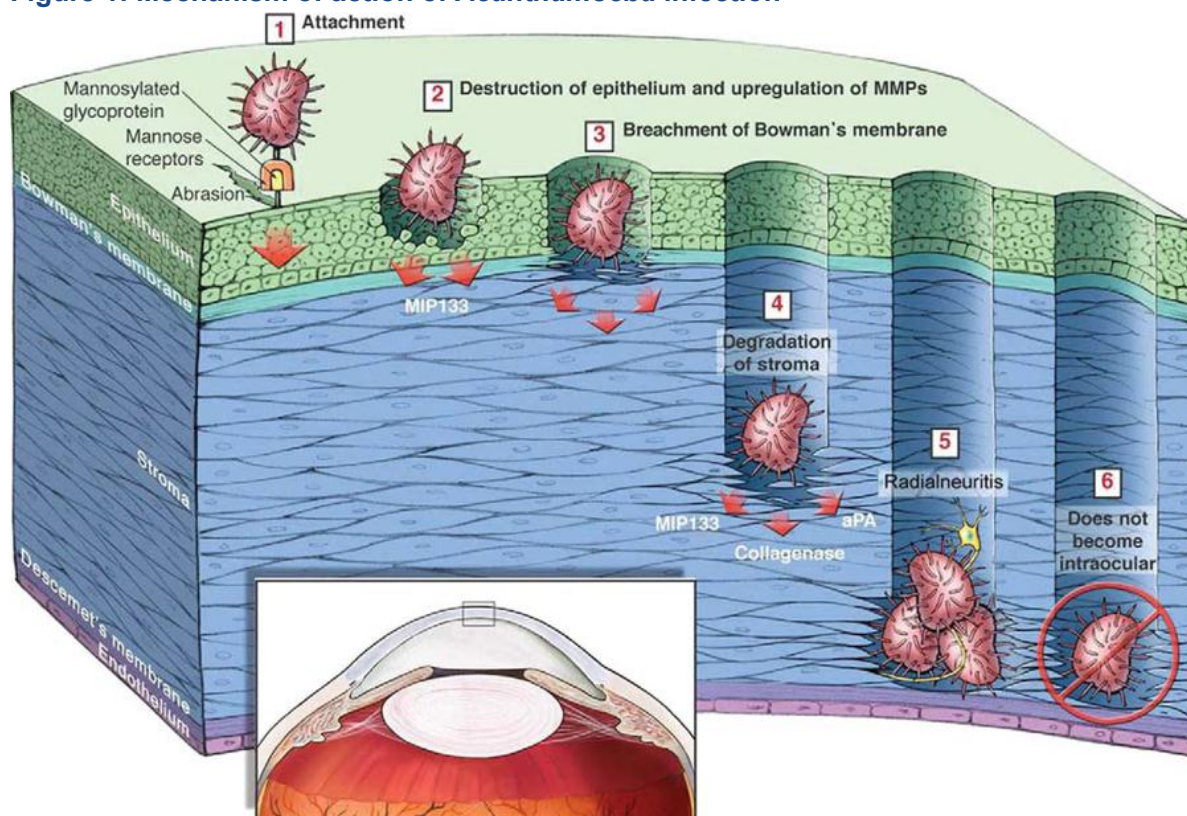
AK is a very rare, devastating, sight-threatening disease which occurs when *Acanthamoeba* adheres to the corneal surface and subsequently infiltrates the deeper layers of the cornea.^{7, 14} This process can lead to symptoms such as eye redness, swelling, ocular pain, blurred vision, tearing and photophobia (light sensitivity).^{14, 15} Additionally, given that the cornea is one of the most densely innervated tissues,¹⁶ this infection often manifests in severe neuropathic ocular pain. Most cases of AK are unilateral (affecting one eye), while around 4–11% of cases can be bilateral (affecting both eyes).^{16, 17} Moreover, AK can result in permanent vision impairment which affects around a third of patients with AK.⁹

Disease pathophysiology and risk factors for AK

AK occurs when *Acanthamoeba* adheres to the corneal surface through mannose-binding protein and lamin-binding protein interactions.¹⁸ The adhesion process triggers phagocytosis (an immune response involving white blood cells), releasing enzymes and toxins, stimulating corneal epithelial destruction, apoptosis and invasion of the stroma (the thickest layer of the cornea).¹⁸ Once stromal degradation has occurred, the pathogen can penetrate the cornea, causing corneal damage. *Acanthamoeba* proteases may also damage the corneal nerves, causing severe neuropathic pain.¹⁸

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Figure 1: Mechanism of action of *Acanthamoeba* infection



Abbreviations: kDa: kilodaltons; MIP133: mannose-induced 133 kDa protease; MMPs: matrix metalloproteases.

Source: Clarke et al. 2006;¹⁹ Niederkorn et al. 2021.²⁰

Acanthamoeba can exist in two life-cycle stages, an active motile trophozoite and a resilient dormant cyst.⁹ During the trophozoite stage, the amoebas are active and mobile, multiplying very rapidly, feeding on bacteria or other small organisms in their environment and damaging corneal cells, including the nerves, through their metabolism. This is when patients might experience frequent pain, light sensitivity and a deterioration in their vision.¹⁷ During the dormant cyst stage, the amoebas are passive, characterised by a very low metabolic rate but high resistance to adverse environments. The cycling between these two stages makes AK difficult to fully eradicate, leading to potential relapse in patients which can occur years after treatment.^{17, 21}

The risk factors for developing AK include eye trauma, poor contact lens hygiene, the latter accounting for 87% of cases and includes overnight wear, prolonged use and lens use during activities like swimming and showering.^{8, 18, 22}

1.3.2 Symptoms of AK

AK is characterised by a prolonged and often painful disease course, and disease progression can be classified into different stages (Figure 2).⁴ In the early stages, the infection is limited to the corneal epithelium (known as Stage 1 AK).⁴ At this stage, patients report non-specific symptoms, such as dry eyes, foreign body sensation, photophobia, blurred vision, tearing, moderate pain and eye redness.^{21, 23, 24} Patients can also experience micro-erosions in the corneal surface and the accumulation of inflammatory cells.^{21, 23, 24}

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In Stage 2 AK, the infection spreads, causing one or more epithelial defects and infiltrating the perineural (area surrounding the corneal nerves) or the stroma, causing severe ocular pain.^{4, 25, 26} Given that the cornea is one of the most densely innervated tissues, the infection often manifests in severe neuropathic ocular pain.²⁷ Stage 3 AK is characterised by one or more features of Stage 2 disease and inflammation in the cornea (corneal ring infiltrate) which results from deep stromal involvement.⁴ Additionally, the formation of open sores on the cornea (ulceration) can occur. If untreated or therapy-resistant, AK progresses further, potentially leading to corneal perforation (holes in the cornea) or extracorneal extension (infection spreading beyond the cornea into adjacent eye tissues) causing severe scleritis (inflammation of the white outer layer of the eye).²⁸ These symptoms can cause long-term consequences for people with AK, resulting in vision loss, which affects around a third of patients with AK,⁹ potential blindness which affects around a quarter of patients,²⁹ and the need for surgical interventions such as keratoplasty or enucleation (Section 1.3.5).¹⁵ Therefore, AK can have significant negative impacts on the HRQoL of people with AK, with people experiencing persistent pain, sensitivity to light and vision loss that requires individuals to significantly alter multiple aspects of daily life, including employment, education, driving, personal care and social interactions (Section 1.3.3). Rapid treatment of AK is crucial at diagnosis, as delayed treatment is associated with a poorer prognosis;³⁰ research by Bonini et al. shows significantly worse outcomes for patients receiving treatment >30 days post-diagnosis versus <30 days post-diagnosis.¹⁰ Prompt intervention is crucial to reducing the extent of corneal damage and minimising vision loss, minimising the need for invasive surgical procedures and reducing the impact on HRQoL.

Figure 2: Stages of AK infection



Footnotes: Images of participants in the ODAK trial at baseline, each image represents a participant at a different stage of AK infection: A) Stage 1 – epitheliopathy; B) Stage 2 – perineural; C) Stage 2 – stromal infiltration; D) Stage 3 – ring abscess outcomes

Source: Dart et al. 2024 (Figure S4).⁴

Several outcomes are regularly assessed to monitor clearance of the infection and treatment efficacy and downstream sequelae of the infection, such as vision loss and HRQoL impacts.^{29, 31} In AK, achieving a cure is the primary treatment goal for patients, as cure of the infection is crucial for preventing long-term complications, preserving vision and relieving the symptom burden. Definitions of clinical resolution/cure can vary in the literature but the most stringent definition identified in the literature describes elimination of *Acanthamoeba*, evidenced by an healed corneal epithelium and no signs of ocular inflammation, after one month off of any therapy (anti-amoebic or anti-inflammatory).³² This definition is used in a large-scale observational study by Papa et al. (2020) of 227 patients with AK.²⁹ As many patients are treated for several months with a combination of pharmacological and surgical interventions (Section 1.3.5), reducing the time to reach a cure is essential for improving patient outcomes and is another important metric of treatment success, with current AATs resulting in a median time to cure of 5 months,²⁹ with >50% failing a cure at 12 months.^{2, 33} A shorter time-to-cure minimises the risk of disease progression, reducing the likelihood of severe complications such as corneal scarring or the need for surgical interventions.^{4, 7, 13} Additionally, as discussed in Section 1.3.6, persistent AK

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infections often require surgical interventions that are associated with high levels of patient burden and may not lead to an improvement in visual acuity. This highlights the importance of achieving a medical cure in reducing the reliance on therapeutic surgery and its potential for suboptimal outcomes.^{11, 34}

To assess the impact of AK and potential treatments on vision, best-corrected visual acuity (BCVA) is commonly used in research studies and clinical settings as a measure of visual acuity in patients with AK. BCVA provides insights into the effect of the disease and treatments on overall visual function and allows for a consistent comparison between subjects. BCVA can be measured in various ways including using the logarithm of the minimum angle of resolution (LogMAR) or the Snellen chart, with results presented as BCVA ranges measured in Snellen feet (e.g. 20/40) or Snellen scale (0.5).³⁵ The Snellen chart consists of rows of letters decreasing in size. Each line on a Snellen chart corresponds to a specific visual acuity measurement, generally expressed as a fraction (e.g., 20/20). The numerator indicates the distance (in feet) from the chart (the distance at which the test subject can read) and the denominator indicates the distance at which a person with normal eyesight can read the same line. Whilst the Snellen chart has traditionally been used to measure visual acuity, LogMAR has been introduced more recently as a more precise and reliable measure.³⁶ The LogMAR chart is a logarithmic scale with characters sized logarithmically. LogMAR and Snellen measurements can be converted, with 20/20 on the Snellen scale corresponding to 0.00 LogMAR. An individual reading all letters on a specific line correctly will score the full 0.1 log unit on the LogMAR scale.

1.3.3 Burden of AK

Burden of AK symptoms on patient HRQoL

AK has significant physiological and functional impacts on patients, due to increasing worsening of symptoms which significantly diminishes patient HRQoL.¹³ After onset, pain and discomfort such as photosensitivity progressively increase to almost unbearable intensity.¹³ Alongside this, significant redness and swelling are common and people with AK may struggle to keep their eyes open which can cause significant discomfort. Some people with AK also develop deformation of the eyeball and can experience frequent, intense and constant tearing. These symptoms result in loss of the sense of depth and a reduced field of vision.¹³ Additionally, severe neuropathic pain caused by AK is persistent and significantly affects patients' HRQoL, causing sleep disturbances and leaving them feeling isolated.^{7, 15} AK significantly impacts patients' light sensitivity, forcing them to remain in the dark for long periods, making it difficult for them to carry out normal daily activities.⁷

Vision impairment, most commonly measured by visual acuity (e.g. using the BCVA test, as described in Section 1.3.2), has a profound impact on quality of life, affecting daily activities, social interactions and work capabilities. In daily life, individuals may struggle with tasks such as reading, navigating, and managing personal care, often requiring assistance or adaptive technologies to maintain independence. Socially, vision loss can lead to isolation and reduced participation in activities, as individuals may feel disconnected or unable to engage fully in social settings. Their work environment is also affected, with challenges in performing job duties, potentially leading to reduced employment opportunities or the need for workplace accommodations.¹³ This results in a significant burden on HRQoL for people with AK and their families, with one person with AK commenting that *"AK took my vision, my profession, my*

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hobbies, my familiar appearance, my energy and gave me a daily routine with medication, side effects, eye appointments full of anxiety and lost hopes.”⁷

The impact of AK on patients' HRQoL constitutes both a physical and mental burden, with patients reporting social anxiety and depression as a result of the constant pain, sleep disturbances and isolation. In a study involving patients, clinicians, researchers, industry and regulators aiming to create greater awareness for AK, one person with AK noted that *“AK is a living nightmare in excruciating pain, light sensitivity, isolated from the world, depressed and afraid of the future.”* *“Some days you want to give up. Or pull your eye out.”⁷* Even though AK is not life-threatening, depression and other psychological impacts of the disease have resulted in some patients considering suicide.¹³

People with AK also experience anxiety, frustration and anger due to the uncertainties associated with delayed diagnosis, complex treatment regimens, treatment failures and the potential for vision loss.^{7, 15} One person with AK explained: *“I had four corneal transplants. As I am still very young, my body rejects all the transplants and when I was 20 years old, I had to start taking steroids alongside my regular medication.”⁷* However, steroids also cause side effects like glaucoma which can also cause vision loss, adding to the physical burden.⁷ The emotional burden of current treatments is significant, as illustrated by another person with AK who stated *“Through all the traumatic surgeries at a relatively young age, PTSD came fairly soon. It grew from fears of never leaving the cycle of surgery and doctor appointments and manifested in nightmares.”⁷*

Isolation and loneliness further compound these issues, as patients often remain at home due to pain and photophobia, which discourages social interactions.² The reduced autonomy in daily and social activities also generates intense depression. The stigma attached to their condition leads to shame and a distorted self-image, with patients struggling to feel "normal." In a Delphi panel with 10 ophthalmologists conducted by SIFI in 2023 (see Appendix K for more information), it was estimated that 30.6% of patients with poor vision and 61.5% of patients severe vision loss experience anxiety or depression.¹¹

There is strong quantitative evidence that the associated symptom burden of AK results in a significantly reduced HRQoL for patients. Notably, people with AK within the Phase 3 Orphan Drug for *Acanthamoeba* Keratitis (ODAK) trial had an average baseline utility of [REDACTED], which is lower than the general population in the UK.^{37, 38} This constitutes a severe impact on HRQoL for people with AK, which aligns with the challenges highlighted in the Global Alliance Against *Acanthamoeba* Keratitis white paper (published October 2024), including the significant psychological challenges faced by patients (depression, anxiety, social isolation and post-traumatic stress disorder [PTSD]) and the side effects of current therapeutic approaches.⁷ This is comparable to other rare diseases that have been assessed by NICE through the HST route, including X-linked hypophosphataemia (mean baseline health utility: 0.648; HST8),³⁹ and hereditary transthyretin amyloidosis (baseline EQ-5D score 0.6 in both arms; HST10).⁴⁰ Additionally, the effects of AK on patients' HRQoL have been formally compared in a recent case control study using the vision-related quality of life questionnaire (VRQOL) showing a reduction of over 50% in reading, mobility and emotional domains.⁴¹ A retrospective, observational study of patients with AK from 1994–2019 has shown that quality of life measures remain reduced after 11.7 ± 4.7 years, emphasising the long-term impact of AK.¹⁰ Overall, AK imposes a multi-faceted burden, profoundly affecting the lives of those afflicted.²

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AK also imposes a significant burden on caregivers due to the complex, ongoing care requirements for those affected. Patients often experience severe pain, vision impairment, and light sensitivity, requiring regular assistance for frequent ophthalmological visits and daily activities including eating, personal care and household management.¹³ Caregivers may be required to help manage frequent medication schedules and provide emotional support to individuals with AK. Additionally, the uncertainty surrounding the progression of AK and potential for permanent vision loss of their family members can create psychological stress for caregivers, affecting their HRQoL.²

Impact on healthcare resource use (HCRU)

AK is associated with a high HCRU burden, due to the onerous and intense treatment regimens associated with current therapeutic approaches. Following treatment initiation, people with AK require frequent healthcare appointments every 2–3 days, which only decrease based on the response to treatment.¹³ The Delphi panel described above estimated that 86.6% of people with AK on current therapeutic approaches will require an average of 19.0 ophthalmologist or optometrist visits per year.¹¹ A combination of nurse (24.2% requiring 7.2 visits per year) and psychiatric visits (9.9% requiring 1.1 visits per year) may also be required.¹¹ Disease monitoring appointments also cause burden for the healthcare system, with intraocular pressure check (16.1 times per year) and ophthalmoscopy (9.6 times per year) required most frequently.¹¹ Additionally, some people with AK will require hospitalisation during the initial intensive therapeutic phase, with the Delphi panel estimating that 26.6% of patients require hospitalisation during the intensive phase for a mean duration of 4.2 days.¹¹ This cycle of frequent healthcare visits, hospitalisations and failed treatments add significantly to the overall burden faced by both patients and healthcare systems, emphasising the need for effective treatment options.¹¹

1.3.4 Epidemiology

AK is a very rare disease, with a study by Jasim et al. 2024 estimating an incidence of 0.1175 cases per 50,000 people per year, based on population data in the UK.⁸ This is aligned with the two-round Delphi panel (described above) in which a mean incidence of AK in the UK was estimated at 0.195 cases per 50,000 people per year by expert clinicians.¹¹

1.3.5 Clinical Pathway of Care

Diagnosis

AK is diagnosed in UK clinical practice through a combination of corneal swabs and corneal scans to confirm the presence of clinical features associated with AK.^{42, 43}

In vivo confocal microscopy is used to scan the cornea and assess for characteristic features indicative of AK within the corneal layers such as double-walled cysts or active trophozoites.^{42, 44} Additionally, a standard slit lamp microscope can also be used to identify signs of inflammation in the cornea as well as specific clinical findings consistent with AK such as epithelial lesions.⁴⁵

These clinical examinations are sometimes followed by a corneal scrape in which cells are collected from the surface of the cornea and analysed further using techniques such as microbiological culture, staining or polymerase chain reaction (PCR) to identify *Acanthamoeba* in the corneal samples.⁴⁵

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Pharmacological approaches

As described in Section 1.3.2, clinical resolution or cure is considered the principal objective in the treatment of AK, with achievement of a rapid medical cure considered the most important outcome for both patients and clinicians.^{4, 7, 13}

There were no approved therapeutic treatments available in England and Wales for patients with AK before polihexanide 0.8 mg/ml, with no standard treatment pathway for AK.⁴⁶ In the absence of products authorised in AK, current therapeutic approaches consist of unstandardised prescription of biguanides (chlorhexidine, polihexanide 0.2 mg/ml and polihexanide 0.6 mg/ml [as a compounded formulation made to order]) and diamidines (propamidine and hexamidine), which can be used as monotherapies or in combination.²⁸ Biguanides act by disrupting the integrity of the cell membranes of *Acanthamoeba*, resulting in cell lysis and inhibition of replication.⁴⁷ These are used in combination with diamidines in an attempt to further disrupt cell membrane structure and inhibit DNA synthesis within *Acanthamoeba* cells, yet >50% fail a cure at 12 months with current AATs.^{29, 48}

Broad treatment guidance is available from the Royal College of Ophthalmologists and through NHS trust websites,^{14, 21, 30, 49} which typically recommend intensive (day and night) topical medical treatment with either a biguanide or a diamidine or a combination of the two. The neuropathic pain experienced by patients combined with intensive treatment regimens which continue throughout the night result in negative impacts on sleep, which significantly impair HRQoL.^{7, 15} In addition to biguanides and diamidines, symptomatic treatments such as pain relief and topical corticosteroids are often used to control the pain caused by AK inflammation.^{7, 30} Additionally, topical antibiotics may also be administered, where necessary, to treat secondary bacterial infections.³⁰

However, there is no clear guidance on treatment regimens and which combination of treatments to use for patients with AK. As a result, prescribing ophthalmologists use treatment protocols that often differ widely, being individualised for each patient, resulting in patients experiencing heterogeneous care and clinical outcomes across the UK, with chosen treatment frequencies varying in intensity and length across the patient population.

Data from the Delphi panel support the lack of standardised treatment pathway for patients with AK, with experts reporting the use of nine different combinations of off-label and unlicensed AATs including biguanides and diamidines either as monotherapies or in combination. A summary of the estimated treatment distribution in the UK setting advanced by the expert panel is presented in Table 3. For these estimates, diamidines were grouped given that they are considered to have similar levels of efficacy.

Table 3: Distribution of current therapeutic approaches for patients with AK in UK clinical practice

AAT	Mean (%) (90% CI)
Polihexanide 0.2 mg/ml + diamidine	52.3 (43.9–60.8)
Polihexanide 0.2 mg/ml monotherapy	14.5 (11.2–17.7)
Chlorhexidine (0.2 mg/ml)+ diamidine	13.7 (10.7–16.7)
Polihexanide 0.6 mg/ml monotherapy	8.5 (5.1–11.9)
Polihexanide 0.6 mg/ml + diamidine	6.5 (4.4–8.5)

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AAT	Mean (%) (90% CI)
Diamidine monotherapy	1.9 (1.1–2.7)
Chlorhexidine monotherapy (0.2 mg/ml)	1.4 (0.7–2.2)
Polihexanide 0.2 mg/ml + chlorhexidine + diamidine	0.9 (0.5–1.2)
Polihexanide 0.2 mg/ml + chlorhexidine	0.3 (0.2–0.4)

Abbreviations: AAT: anti-amoebic therapy; AK: Acanthamoeba keratitis; CI: confidence interval; UK: United Kingdom.

Source: SIFI Delphi Panel. 2023 (Table 4).¹¹

The lack of standardised care in UK clinical practice results in unsatisfactory outcomes for patients with AK (see Section 1.3.6), with varying improvements and levels of visual acuity achieved following treatment.²⁹ Failure of these therapeutic approaches often results in treatment switching and the use of surgical interventions.

Therapeutic surgery

When pharmacological approaches fail to clear the *Acanthamoeba* infection, patients may have to resort to surgical interventions. Therapeutic keratoplasties, including penetrating keratoplasty, in which the damaged cornea is removed and replaced with a donor corneal transplant are conducted in the event of corneal perforation, or as a measure of last resort for either non-healing epithelial defects or eradicating the *Acanthamoeba* organism.^{34, 50} In some cases, deep lamellar keratoplasty (DALK) is also conducted and involves replacing the diseased stroma with the aim of removing residual *Acanthamoeba* infection. In severe cases of AK, patients may require surgery to remove parts of the eyeball including, enucleation (removal of the entire eyeball, leaving behind the lining of the eyelids and eye muscles) or evisceration (removal of the contents of the eye, leaving the sclera and eye muscles intact).¹¹ Using data from the Delphi panel, it was reported that 21.5% of patients who failed to achieve resolution of their infection with prior medical therapy (including those who switched to another AAT after 12 months) underwent surgery within 12 months.¹¹ It should be noted that patients may also experience graft rejection following therapeutic keratoplasty, which can lead to visual impairment and graft failure, often necessitating follow-up surgeries such as re-grafts.⁵¹ Graft rejection occurs when the immune system identifies the graft as foreign, resulting in blurred vision, discomfort and pain, affecting patient HRQoL and prolonging recovery time.⁵² To reduce the risk of graft rejection and recurrence of AK infection following therapeutic surgery, patients may be prescribed systemic immunosuppressive therapies, most commonly mycophenolate and steroids, and adjuvant systemic therapies such as prednisolone.¹¹

Optical surgery

Once the infection is presumed to have been eradicated and inflammation is no longer present, other surgeries (such as keratoplasty, DALK, cataract surgery) can be conducted for optical reasons to treat residual corneal scarring and restore vision or correct astigmatism.³⁴ Expert consensus from the Delphi panel suggested a mean of 41.9% (90% CI: 36.9–47.0) cured AK patients with poor vision, and a mean of 46.0% (90% CI: 40.0–52.0) cured AK patients with severe vision loss (according to BCVA), undergo optical surgery. However, improvement of visual outcomes is not guaranteed, with 23% of people with AK experiencing worsening in BCVA category or eye functionality loss and 27.3% remaining in the same BCVA category after optical surgery.¹¹ Similarly to therapeutic surgeries, patients undergoing optical surgeries may also experience graft rejection and graft failure.¹¹

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1.3.6 Limitations of current clinical management

As discussed in Section 1.3.2, rapid treatment of AK is crucial at diagnosis, with delayed treatment onset associated with poorer diagnosis. Specifically, a study by Bonini et al. found that patients treated for AK within 30 days of symptom onset experienced significantly shorter healing times ($p < 0.01$) as well as a better HRQoL compared with those treated after 30 days.¹⁰ Despite this, as is common with rare diseases, awareness of AK in non-specialists is low which often leads to initial misdiagnosis, with over 50% of AK cases firstly misdiagnosed as the viral infection Herpes Simplex keratitis (HSK).³⁰ The resulting treatment delays have a significant impact on the prognosis for patients, with every day of delay increasing the likelihood of a poor and unsatisfactory outcome for patients.^{10, 53} It is therefore crucial that patients are treated rapidly after diagnosis. Despite this, current clinical management of AK is associated with a number of delays. In the absence of licensed products, biguanide therapies must be compounded and are not always available at specialist centres. Given the short shelf life of these products, compounding is frequently initiated only upon request, resulting in a lack of availability of biguanide therapeutic options at the point of diagnosis, leading to delays in treatment.⁵⁴

The current reliance of ophthalmologists on off-label and unlicensed therapeutic approaches puts healthcare practitioners in the untenable position of having no option but to prescribe treatments that have not undergone a safety and efficacy assessment. For instance, current off-label therapeutic approaches such as propamidine have been studied and tested for other diseases, but crucially not AK, with safety and efficacy proven in different conditions, using different treatment regimens. The SmPC of Brolene® (whose active ingredient is propamidine isethionate), states that eye drops should be administered once or twice up to four times daily for the treatment of minor eye infections such as conjunctivitis and blepharitis.⁵⁵ This treatment regimen is much less aggressive than typical regimens for AK, and the efficacy and safety of using Brolene® as part of more aggressive treatment regimens has not been sufficiently studied to be licensed for AK. Furthermore, Brolene® contains benzalkonium chloride which is associated with corneal toxicity, therefore use of this treatment as part of a more frequent dosing regimen may cause further corneal damage.⁵⁵ Concerns also extend to biguanides, as during the compounding process, GMP is not always satisfied, and treatments are not used according to a standardised protocol, and there is often a lack of pharmacovigilance associated with their use.^{5, 33, 56}

Additionally, current therapeutic approaches are associated with a heavy administration burden, with patients required to administer drops at regular intervals throughout the day and night. In the initial phase of treatment, patient may be required to administer drops every 20–30 minutes during the nighttime, causing sleep deprivation which further impacts a patients' ability to perform normal daily activities.¹³ In addition, both therapeutic and optical surgeries carry significant risks and complications, which can include infection, graft rejection and consequently the need for follow-up procedures. These surgeries add considerable emotional and physical stress, further impacting HRQoL for individuals with AK,¹¹ therefore avoidance of surgical treatment through effective pharmacological treatment is an important outcome for patients.

The current lack of standard of care in AK leads to unsatisfactory treatment outcomes. Individuals with AK rely on compounded, unlicensed treatments which are often not available at the point of diagnosis, leading to delays in treatment that significantly affect their prognosis. Moreover, these treatments lack safety and efficacy assessments and do not meet GMP standards, leading to suboptimal outcomes. Consequently, patients often fail to avoid the need Company evidence submission template for polihexanide eye drops for treating acanthamoeba keratitis in people 12 years and over [ID6497]

for surgical intervention, which is associated with high levels of anxiety and burden for patients. There is therefore a clear unmet need in the AK patient population for a licensed, effective treatment that can be accessed rapidly by patients diagnosed with AK.

1.3.7 Anticipated positioning of polihexanide 0.8 mg/ml

AK is a very rare disease caused by *Acanthamoeba* infection of the cornea. Polihexanide 0.8 mg/ml is a preservative-free eye drops solution containing polihexanide, a polymeric biguanide that is highly effective at eradicating *Acanthamoeba* both in the active trophozoite form and the dormant cyst form. Polihexanide has a dual mechanism of action that disrupts *Acanthamoeba* cell membranes and binds to DNA to block *Acanthamoeba* replication, leading to cell lysis and inhibition of replication.² Polihexanide 0.8 mg/ml is the first licensed monotherapy treatment for people with AK aged 12 years and older.

In recognition of the high unmet need in AK and the potential of polihexanide 0.8 mg/ml as the first monotherapy for AK, to offer significant additional benefit, polihexanide 0.8 mg/ml has been awarded orphan drug designations by the EMA (polihexanide 0.8 mg/ml was approved in Europe by the EMA in August 2024)⁴⁷ and the Food and Drug Administration (FDA).⁵⁷ The innovative nature of polihexanide 0.8 mg/ml is also highlighted by its PIM designation from the MHRA in 2025 and its status as a NAS.

As described in Section 1.3.5, there were no approved therapeutic treatments available in England and Wales for patients with AK before polihexanide 0.8 mg/ml, with no standard treatment pathway.⁴⁶ It is therefore anticipated that polihexanide 0.8 mg/ml will displace the off-label and unlicensed therapeutic approaches currently used in England and Wales for the treatment of AK. Polihexanide 0.8 mg/ml meets GMP quality standards and is a stable treatment, removing the need for compounding of biguanide treatment on request as polihexanide 0.8 mg/ml could be kept in stock by treatment centres. This would allow centres to treat AK more rapidly and consistently which is crucial given that delayed treatment is associated with poorer prognosis and clinical outcome and will also reduce errors that are commonly associated with compounding, including contamination and concentration errors.⁵⁸ Polihexanide 0.8 mg/ml also offers a less burdensome dosing regimen, requiring the administration of eyedrops every hour in the daytime only in the initial treatment stage.¹³ It is therefore expected that polihexanide 0.8 mg/ml will reduce the disruption to sleep and treatment burden experienced by patients. An approval of polihexanide 0.8 mg/ml by NICE would represent an important step in formalising treatment for AK, providing patients with faster access to a long-overdue effective treatment and giving people an equal chance for cure across England and Wales.

1.4 Equality considerations

SIFI supports access to polihexanide 0.8 mg/ml to all people with AK within its marketing authorisation, regardless of their age, disease severity and socioeconomic background.

The care of people with AK in the UK is currently mainly provided by specialist centres, such as the Moorfields Eye Hospital, London.²⁹ SIFI are aware of patients who are required to travel long distances at considerable cost, in order to access specialist care. Variable access to treatment centres is therefore a potential driver of health inequalities in AK, particularly given that rapid treatment is crucial to improve eventual prognosis.⁵³

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As discussed in Section 1.3.5, there were no approved treatments available in England and Wales for patients with AK before polyhexanide 0.8 mg/ml, with no standard treatment pathway and no standard of care.⁴⁶ Therefore, patients with AK receive a heterogeneous combination of off-label and unlicensed (compounded) anti-amoebic agents including biguanides and diamidines as initial therapies within clinical practice.^{11, 13} The current reliance of ophthalmologists on off-label and unlicensed therapeutic approaches puts healthcare practitioners in the untenable position of having no option but to prescribe therapeutic approaches that are not supported by regulatory approval or aligned with GMP standards and are associated with a lack of pharmacovigilance.^{5, 33, 56} Consequently, dosing regimens differ among prescribing ophthalmologists, leading to increased variability in patient care.¹¹ This inequality of care between centres and treating clinicians leads to a range of treatment delays and poorer quality product, leading to varying prognosis for patients depending on the centre/clinician they visit.^{10, 53}

Equality of access is a key consideration for SIFI and we are committed to supporting the availability of polyhexanide 0.8 mg/ml to all eligible patients in England and Wales. While the NICE evaluation will follow the Single Technology Appraisal (STA) route, NICE are asked to apply flexibility in the STA process for polyhexanide 0.8 mg/ml for AK to enable timely and equitable access for people with a rare disease of this nature, when compared to treatments being assessed through the STA process for conditions with a much higher prevalence.

2 Clinical effectiveness

Clinical evidence base

The efficacy, safety and tolerability of polihexanide 0.8 mg/ml was investigated in the Orphan Drug for *Acanthamoeba* Keratitis (ODAK) trial, a randomised, double-masked, active-controlled, multicentre, parallel Phase 3 study. The trial compared polihexanide 0.8 mg/ml with placebo with a combination of polihexanide 0.2 mg/ml and propamidine 1 mg/ml as an active comparator arm in patients with AK. Inclusion of an active comparator arm in the ODAK trial was specifically requested by the EMA for ethical reasons, due to concerns around the impact of not providing patients with active treatment.

However, the effectiveness of the active comparator arm in the ODAK trial is not reflective of therapeutic approaches used in real-world practice and the results for this trial arm are not likely to be replicable in the real-world clinical setting:

- Patients in UK clinical practice experience significant delays caused by the need to compound unlicensed polihexanide 0.2 mg/ml and chlorhexidine at specified concentrations, which significantly impacts treatment outcomes.^{29, 54} Patients in the active comparator arm in the ODAK trial did not experience these delays and are therefore likely to have benefitted from greatly improved treatment outcomes compared with those typically seen and reported in routine clinical practice.

Furthermore, the ODAK trial used a detailed and standardised treatment protocol which patients were required to adhere to.⁴ This is in contrast to the current real-world clinical setting, where the active comparator treatment regimen is determined by physician discretion and judgement, and therefore is heterogenous between patients, leading to varying clinical outcomes. Dart et al. conclude that the availability of a standardised treatment protocol may have accounted for significant improvement seen in the ODAK trial compared with previous retrospective studies of AATs.^{29, 46}

- In contrast, the polihexanide 0.8 mg/ml arm of the ODAK trial is expected to be significantly more reflective of performance of the intervention in clinical practice as it will be a licensed and readily available (at GMP standards) product with a standardised treatment protocol. As a result of the factors discussed above, the efficacy of the active comparator arm is likely to have been overestimated in the ODAK trial and these data are therefore unsuitable for comparison with polihexanide 0.8 mg/ml.

Therefore, in line with the approach approved by the EMA as part of the European marketing authorisation process, alternative efficacy data reflective of a pooled AAT comparator, in line with NICE's decision problem, were sourced to explore the comparative effectiveness of polihexanide 0.8 mg/ml. An indirect treatment comparison (ITC) was conducted to better reflect the true differences in treatment effect between polihexanide 0.8 mg/ml and currently available therapeutic approaches.

Papa et al. (2020) was a retrospective, multinational, observational, cohort study of 227 patients with AK.²⁹ This study was selected for use in the ITC as it was identified as the only available study providing efficacy data reflective of the proposed 'current practice' pooled AAT comparator in real-world UK practice; the appropriateness of the comparative data from this study, in terms of therapeutic approaches included, was confirmed by responses in the 2023 Delphi panel of 10 UK ophthalmologists.¹¹ Additionally, the primary endpoint definition matched that of the ODAK

trial, with medical cure rate (MCR) at 12 months measured as the primary endpoint in both instances. The clinical efficacy of polihexanide 0.8 mg/ml (from ODAK) was therefore compared with this pooled AAT comparator via an ITC (results from the ODAK trial are presented in Appendix J for completeness).

Clinical effectiveness

- Polihexanide 0.8 mg/ml had a statistically significantly higher MCR without surgery compared with the pooled AAT comparator from Papa et al. before weighting (RR: [REDACTED] [95% CI: [REDACTED], [REDACTED]]) and in PSA analyses after adjustment (RR: [REDACTED] [95% CI: [REDACTED], [REDACTED]]).³³
- Improvements compared with baseline were also observed across a range of secondary endpoints for patients treated with polihexanide 0.8 mg/ml in the ODAK trial. These included improvements in visual acuity and corneal abnormality, with the rates of surgery and adjunctive therapy remaining low.
- The results support the role of polihexanide 0.8 mg/ml in addressing the significant unmet need for standardised, readily available treatments that can improve medical cure rates and a broad range of other clinically and patient-relevant endpoints in AK.

Adverse reactions

In the ODAK trial, polihexanide 0.8 mg/ml demonstrated an acceptable safety profile in patients with AK, with most treatment-emergent adverse events (TEAEs) being mild to moderate in severity and consistent with those seen in real-world clinical practice for AK. Additionally, few serious adverse events (SAEs) were observed and no deaths were reported in the ODAK trial.⁵

- Polihexanide 0.8 mg/ml is therefore considered to be well-tolerated, which aligns with the EMA's overview of polihexanide 0.8 mg/ml in their European public assessment report (EPAR).⁵

In summary, the ITC approach approved by the EMA, comparing polihexanide 0.8 mg/ml with a pooled AAT comparator reflective of the therapeutic approaches used in UK clinical practice, demonstrated a significantly improved MCR without surgery in patients with AK. Results from the ODAK trial and compassionate use programmes (CUPs) further support the effectiveness and acceptable safety profile of polihexanide 0.8 mg/ml.

Suitability of the evidence base

The efficacy, safety and tolerability of polihexanide 0.8 mg/ml was investigated in the Orphan Drug for *Acanthamoeba* Keratitis (ODAK) trial: a randomised, double-masked, active-controlled, multicentre, parallel Phase 3 study. This trial compared polihexanide 0.8 mg/ml with placebo to polihexanide 0.2 mg/ml with propamidine 1 mg/ml (active comparator arm).

However, the active comparator arm is not reflective of the effectiveness of therapeutic options in real-world practice and was included in the ODAK trial in response to a request from the EMA to use an active comparator arm for ethical reasons, despite its effectiveness having never previously been demonstrated in a clinical trial, as explained below:

Patients with AK in UK clinical practice experience significant delays in receiving treatment, which negatively impacts outcomes. It is well established that rapid treatment of AK is crucial to improve prognosis and QoL outcomes;¹⁰ however, UK-based ophthalmologists estimated an average wait

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time of 17.7 days in real-world clinical practice between diagnosis of AK and treatment initiation.¹¹ These delays may be caused by reported shortages of stock, and the need to compound unlicensed AATs (polihexanide 0.2 mg/ml, polihexanide 0.6 mg/ml and chlorhexidine) at specified concentrations (GMP regulations are typically not satisfied during this process).^{29, 54} Moreover, availability of existing AATs is not consistent between centres, which leads to inequality in access to current therapeutic approaches in the UK. In contrast to delays in real-world practice reported by UK ophthalmologists, the median time between diagnosis and treatment in the ODAK active comparator arm was only 4 days.⁴ Thus, patients in the ODAK active comparator arm are likely to have benefitted from greatly improved treatment outcomes compared with those typically seen and reported in routine clinical practice. Whilst similarly short delays in treatment initiation were observed in the intervention arm of the ODAK trial, this is expected to reflect real-world practice with polihexanide 0.8 mg/ml as, if licensed in the UK, it would not require compounding and would be available at the point of diagnosis

- As noted in Dart et al. (2020), the ODAK active comparator arm used a detailed and standardised treatment protocol which patients were required to adhere to.⁴ This is in contrast to the current real-world clinical setting, where the lack of AK-specific summary of product characteristics (SmPCs) associated with unlicensed (compounded) and off-label eye drops means that treatment regimens are determined by physician discretion and previous experience, which is often limited due to the rare nature of AK. This leads to heterogeneity in the care received by patients and therefore varying clinical outcomes. Dart et al. (2020) confirmed that the standardised treatment protocol in the ODAK trial may have contributed to the significant improvement in the active comparator arm compared with previous retrospective studies of AATs, in addition to the other factors discussed above.^{29, 46} This further undermines the generalisability of the ODAK trial as a source of evidence for the efficacy of AATs in current clinical practice, given that the active comparator arm likely demonstrated artificially improved efficacy compared to if the same treatment were used in a real-world setting.

In contrast, the polihexanide 0.8 mg/ml arm is not subject to the significant issues described above which impact generalisability of the active comparator arm in the ODAK trial. Unlike current AATs (including polihexanide 0.2 mg/ml with propamidine 1 mg/ml), polihexanide 0.8 mg/ml would be a licensed treatment to be used as a monotherapy, manufactured to GMP standards and guided by a SmPC and a standardised protocol. Therefore, the context surrounding the use of polihexanide 0.8 mg/ml in real-world practice would be more similar to the ODAK trial setting (acknowledging that use of an intervention in a clinical trial setting will never be exactly the same as in real-world practice). This is supported by results to date from an ongoing CUP across 15 European countries (treating more than 250 patients), showing that polihexanide 0.8 mg/ml is an efficacious treatment for AK in the real-world setting (see Section 2.12 for further details).^{59, 60} As a result, the ODAK trial is a robust source of evidence for understanding the likely effectiveness of polihexanide 0.8 mg/ml in real-world practice, but is likely to underestimate comparative effectiveness of polihexanide 0.8 mg/ml compared with polihexanide 0.2 mg/ml with propamidine 1 mg/ml. In line with the above, the medical cure rate in the active comparator arm was higher than expected (88.52%; CI: 77.78–95.26%) when compared with data from other retrospective studies in which the cure rate in patients without surgery was approximately 60%.^{29, 46, 61}

Considering this, the efficacy observed in the active comparator arm of the ODAK trial is unlikely to reflect current UK clinical practice and therefore, the ODAK trial is considered as a pseudo single-arm trial within this submission. The clinical effectiveness results for the polihexanide 0.8 mg/ml treatment arm are presented in Section 2.6, with the relative comparisons to the active comparator arm presented in Appendix J, for completeness.

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In line with the approach approved by the EMA as part of the EMA marketing authorisation process, alternative sources of comparative efficacy were sought as part of a systematic literature review (SLR) (Section 2.1 and Appendix B). Papa et al. (2020), a retrospective, multinational, observational study, was identified as the only available study providing efficacy data reflective of the proposed 'current practice' pooled AAT comparator in real-world UK practice, using a definition of cure matching that used in the ODAK trial (see Section 2.10).^{4, 29} The clinical efficacy of polihexanide 0.8 mg/ml (from ODAK) was therefore compared with this pooled AAT comparator via an ITC. The generalisability of the composition of the pooled AAT comparator used in the ITC to real world clinical practice was confirmed by UK ophthalmologists in a SIFI-conducted Delphi panel, when asked about the distribution of current therapeutic approaches used.¹¹ The ITC is described in detail in Section 2.10 and the Delphi panel methodology is described in Appendix K.

2.1 Identification and selection of relevant studies

A clinical SLR was conducted on 25th and 26th July 2022, and subsequently updated on 24th March 2025, to identify relevant evidence on the clinical efficacy and safety outcomes of therapeutic approaches used for AK. The SLR and update were conducted from a global perspective and therefore comparator therapies beyond those relevant to the decision problem of this appraisal were eligible for inclusion. The SLR was designed to capture data specifically in patients with a confirmed diagnosis of AK, who were treated with an ophthalmic eye drop medication or oral miltefosine in any concentration or combination. The SLR was conducted according to a pre-specified protocol and performed in accordance with established guidelines (i.e., Preferred Reporting Items for Systematic Reviews and Meta-analyses [PRISMA] and the Cochrane Handbook for Systematic Reviews of Interventions).^{62, 63}

A total of 2,250 studies were identified from electronic databases and supplementary internet searches. Of these, 48 eligible studies were included in the SLR, comprising data for 2,422 patients. Full details of the SLR search strategy, study selection process and results are presented in Appendix B.

2.2 List of relevant clinical effectiveness evidence

Of the 48 studies considered for full extraction, only the ODAK trial programme provided evidence for the clinical efficacy and safety of polihexanide 0.8 mg/ml in the patient population of interest for this appraisal (patients with AK aged 12 years and over) in the form of a randomised controlled trial (RCT). As a result, evidence derived from the polihexanide 0.8 mg/ml treatment arm of the Phase 3 ODAK trial has been used to address the decision problem in this submission. The ODAK trial was used to support the marketing authorisation for polihexanide 0.8 mg/ml in the indication of relevance to this submission, with both the EMA and MHRA approving polihexanide 0.8 mg/ml based on ODAK being regarded as a single-arm trial.

As discussed above, the ODAK trial is considered as a pseudo single-arm trial within this submission. The SLR and feasibility assessment described in Section 2.1 and Appendix B identified Papa et al. (2020), a retrospective, multinational, observational study, as the only available study providing efficacy data reflective of the proposed 'current practice' AAT comparator in real-world UK practice, with a definition of clinical resolution which fully aligned with the ODAK trial.²⁹ An ITC was therefore conducted using the Papa et al. study to demonstrate the key comparative efficacy data between polihexanide 0.8 mg/ml and the Company evidence submission template for polihexanide eye drops for treating *acanthamoeba* keratitis in people 12 years and over [ID6497]

proposed 'current practice' AAT comparator used in real-world UK practice for this submission. The methodology and results of the ITC are described in detail in Section 2.10. The clinical effectiveness results for the polihexanide 0.8 mg/ml treatment arm in the ODAK trial are presented in Section 2.6, with the relative comparisons to the active comparator arm presented in Appendix J, for completeness.

The ODAK trial was a randomised, assessor-masked, active-controlled, Phase 3 study to evaluate the efficacy, safety and tolerability of polihexanide 0.8 mg/ml in comparison with polihexanide 0.2 mg/ml with propamidine 1 mg/ml in patients with AK. An overview of the ODAK trial is presented in Table 4 and the methodology and results are presented below.

Table 4: Clinical effectiveness evidence

Study	ODAK (NCT03274895)⁶⁴
Study design	A randomised, assessor-masked, active-controlled, Phase 3 study to evaluate the efficacy, safety and tolerability of polihexanide 0.8 mg/ml in comparison with polihexanide 0.2 mg/ml with propamidine 1 mg/ml in patients with AK
Population	Patients aged 12 years or older with AK
Intervention(s)	Polihexanide 0.8 mg/ml (with placebo) (n=66)
Comparator(s)	Polihexanide 0.2 mg/ml with propamidine 1 mg/ml (n=61)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	NA
Reported outcomes specified in the decision problem^a	Measures of disease severity: • Medical cure rate (MCR) within 12 months from randomisation • Time-to-cure • Best-corrected visual acuity (BCVA) Reduction of symptoms: • Corneal scarring • Ulceration severity • Anterior chamber inflammation Safety outcomes: • AEs Patient-reported outcomes: • EQ-5D • VFQ-25
All other reported outcomes^a	• Use of alternative treatment and surgery

Footnote: ^aEndpoints in **bold** are those used to inform the cost-effectiveness model.

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Abbreviations: AE: adverse event; AK: Acanthamoeba keratitis; BCVA: best-corrected visual acuity; MCR: medical cure rate; N/A: not applicable; ODAK: Orphan Drug for Acanthamoeba Keratitis; VFQ: Visual Function Questionnaire.

Source: Dart et al. 2024.⁴

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Trial design

The ODAK trial was a randomised, double-masked, active-controlled, multicentre, parallel Phase 3 study to evaluate the efficacy, safety and tolerability of polihexanide 0.8 mg/ml (0.08%) ophthalmic solution with placebo compared with polihexanide 0.2 mg/ml (0.02%) with propamidine 1 mg/ml (0.1%) combination therapy in patients with AK. A Phase 1 trial was conducted to evaluate the safety and tolerability of polihexanide 0.4 mg/ml, 0.6 mg/ml and 0.8 mg/ml concentrations in healthy volunteers.⁵⁶ A Phase 2 trial was not carried out as, in lieu of a Phase 2 study, SIFI were advised in a scientific advice meeting with the EMA to conduct a robust assessment of current treatment practices in AK. Accordingly, SIFI conducted a retrospective study ("038/SI Study") that evaluated therapeutic approaches and outcomes in two specialist centres (San Raffaele Hospital, Milan and Moorfields Hospital, London; N=100 patients with AK).⁶⁵ This study informed the choice of comparator and statistical analysis plan of the subsequent Phase 3 ODAK trial, the methodology and results of which are presented below.

For the Phase 3 trial, patients who met eligibility screening criteria were randomised in a 1:1 ratio to one of the following treatment arms (see Figure 3):

- Polihexanide 0.8 mg/ml with placebo (n=69; hereafter referred to as polihexanide 0.8 mg/ml)
- Polihexanide 0.2 mg/ml with propamidine 1 mg/ml (n=65)

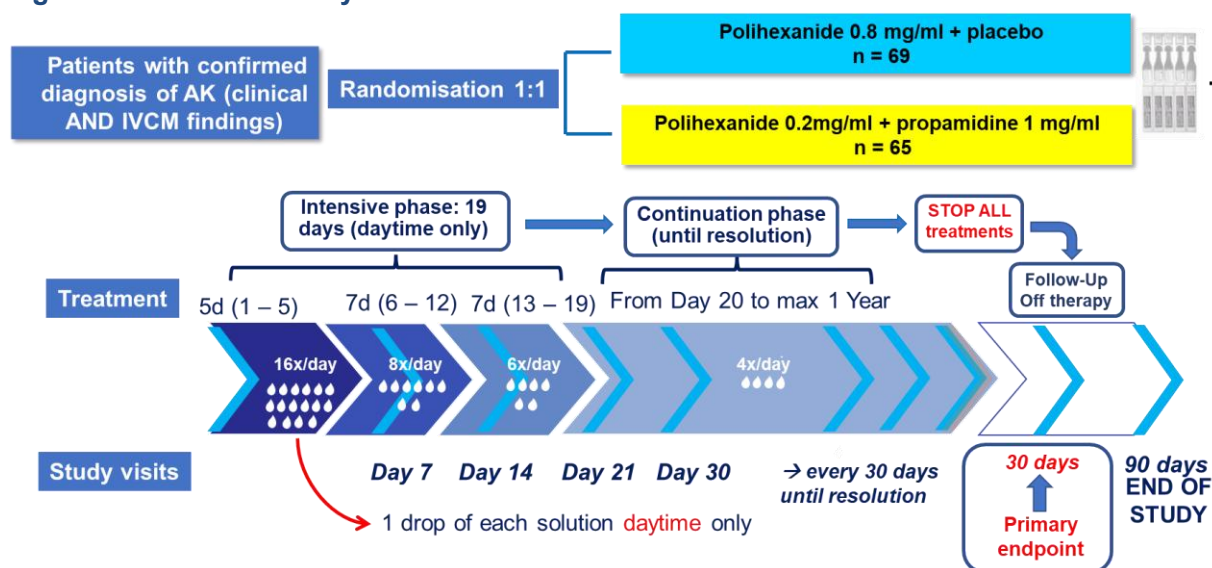
All patients with clinical signs consistent with AK (Table 5) and positive confocal microscopy findings consistent with AK were eligible for randomisation in the trial. For both treatment arms, the first application of the study medication was conducted at the research centre with subsequent dosing self-administered at home. Patients received multiple self-administered doses of polihexanide 0.8 mg/ml or polihexanide 0.2 mg/ml with propamidine 1 mg/ml in the affected eye according to the dosing schedule presented in Section 2.3.2.

For patients with bilateral AK, only one eye was treated with the study treatment, typically the right eye, unless infection severity differed, in which case the worse eye was treated. The other eye received the treatment used by clinicians at the participating centre at that time.

Patients were treated for a maximum of 12 months after randomisation with patients meeting the criteria for medical cure (the primary endpoint) at or before 12 months followed up for 90 days before completing the study. Follow-up visits occurred on Days 7, 14, 21 and 30 and every 30 days thereafter until resolution or treatment failure (Figure 3). Patients whose disease had not resolved after 12 months were deemed to have failed treatment. However, they were permitted to continue receiving polihexanide 0.8 mg/ml, provided that they remained in the trial for follow-up safety evaluations.⁴

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Figure 3. ODAK trial study schematic



Abbreviations: AK: *Acanthamoeba* keratitis; IVCN: in vivo confocal microscopy.

Source: SIFI ODAK CSR 2022.²

2.3.2 ODAK trial methodology

A summary of the methodology of the ODAK trial is presented in Table 5 below.

Table 5: Summary of the methodology of the ODAK trial

Trial name	ODAK (NCT03274895)⁶⁴
Location	International: six sites in three countries: UK, Italy and Poland
Trial design	A randomised, assessor-masked, active-controlled, Phase 3 study
Trial duration	Patients were treated for a maximum of 12-months after randomisation, with those meeting the criteria for medical cure (the primary endpoint) at or before 12 months followed up for 90 days before completing the study.
Eligibility criteria for patients	Key inclusion criteria - Male or female patients of any race ≥ 12 years of age - Clinical findings consistent with AK: - Epithelial lesions (epithelial punctate keratopathy, epithelial infiltrates, epithelial defects, dendritiform epithelial ulcers) - Extracorneal lesions (limbitis and diffuse or nodular anterior scleral inflammation) - Stromal lesions (perineural infiltrates, anterior stromal infiltrates, disciform corneal swelling, stromal ulceration, ring abscess) - Anterior chamber lesions (keratic precipitates, hypopyon) - Late findings (fixed dilated pupil, mature cataract) - Confocal microscopy findings consistent with AK (performed within 7 days prior to study entry or as part of screening procedures) - Confocal microscopy findings included: cysts are round or ovoid, may show a double wall and are 15-30 μm in size

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Trial name	ODAK (NCT03274895)⁶⁴
	• Permitted previous treatments: ○ Antibiotics ○ Antiviral drugs ○ Anti-inflammatory drugs Key exclusion criteria • Patient with documented history and/or clinical signs of concomitant presence of an ocular infection caused by viruses (herpes simplex virus [HSV]) or fungi) • Patient treated with drugs having effects on <i>Acanthamoeba</i> cysts prior to study entry, including biguanides (polihexanide, chlorhexidine) and diamidines (propamidine, hexamidine) • Patients requiring systemic immunosuppression for <i>Acanthamoeba</i> associated scleritis • Patients requiring urgent surgical intervention for advanced AK in either eye (e.g., for advanced corneal thinning/melting etc.) • Patient with known or suspected allergy to biguanides, diamidines or intolerance to any other ingredient of the investigational treatments • Patient affected by immunodeficiency diseases or taking systemic immunosuppressive therapy The full list of inclusion and exclusion criteria are presented in the ODAK trial protocol.⁴
Intervention	After confirmation of the eligibility criteria, patients were randomised 1:1 to receive up to 12 months of treatment with: • Polihexanide 0.8 mg/ml with placebo or • Polihexanide 0.2 mg/ml with propamidine 1 mg/ml
Method of study drug administration	Treatment throughout the study will be given using one drop of each ophthalmic solution in the affected eye at different frequencies during the daytime only. Placebo drops were used within the polihexanide 0.8 mg/ml arm to mimic propamidine within the active comparator arm. For both treatment arms, dosing of the solutions was administered according to the following regimen: • Day 0–5: 1-hourly drops (16 drops in a day) for 5 days • Day 6–12: 2-hourly drops (8 drops in a day) for 7 days • Day 13–19: 3-hourly drops (6 drops in a day) for 7 days • Day 20 onwards: 4 drops in a day until resolution (maximum 12 months)
Permitted and disallowed concomitant medication	• Antibiotics: Topical moxifloxacin was permitted for the treatment of intercurrent bacterial infections (unless culture and sensitivity, or clinical progress demands a change). Topical moxifloxacin was not permitted for use as a prophylactic antibiotic in patients with corneal ulcers. • Antiviral drugs and antifungal drugs: The use of these drugs was not allowed during the study. If patients were using antiviral or antifungal drugs at study entry, they were discontinued. • Anti-inflammatory drugs: For patients who were on steroids at study entry (already using topical steroids for e.g. mistaken diagnosis of HSV keratitis or as adjunctive treatment for bacterial keratitis), there were the following options:

Trial name	ODAK (NCT03274895)⁶⁴
	○ Steroids were stopped, maintained or the dose was reduced (at the investigator's discretion) Unpreserved Dexamethasone (0.1% or 0.15%) was the only topical steroid permitted for use in this trial. Patients using any other topical steroids on trial entry were changed to this at the appropriate frequency. ○ Patients who were using topical NSAIDs and ciclosporin at study entry had these discontinued after randomisation: ○ Patients who were using no topical steroids at study entry could have these started together with oral NSAIDs (recommended diclofenac, 75 mg to 150 mg daily, divided into two or three doses) during the study.
Primary analysis population	Full analysis set: all patients who have been randomised and for whom the primary efficacy variable is assessed will be included in the full analysis set. The full analysis set is used in all efficacy analyses (see Section 2.4.1).
Primary outcomes	MCR at 12 months from randomisation, defined as the percentage of patients cured 30 days after discontinuing all study therapies, within 12 months of randomisation. Within this, cure was defined as clinical evidence of elimination of <i>Acanthamoeba</i> , including an intact corneal epithelium with no clinical signs or symptoms of ocular inflammation after discontinuing AAT and anti-inflammatory treatment for 30 days (confirmed at the end-of-study visit 90 days after treatment discontinuation) as determined by clinical examination.
Secondary and exploratory outcomes	Secondary outcomes: • Time-to-cure, defined as the time needed to reach clinical resolution for all participants defined as cured or not cured at the 30-day follow-up visit (checked at 90 days) either after discontinuation of the study drug or within 12 months of starting AAT, whichever came first • Best-corrected visual acuity (BCVA) measured by Snellen feet • Corneal scarring as identified by slit lamp examination using a 2-grade scoring procedure i.e. present or absent • Ulceration severity as identified by slit lamp examination using a 2-grade scoring procedure i.e. present or absent • Anterior chamber inflammation as identified by ophthalmoscopy • Use of alternative treatment and surgery ○ Adjunctive therapy was defined as new use after baseline or any increase of at least one of the following medications: topical steroid (dexamethasone, prednisolone, fluorometholone, loteprednol) or oral non-steroidal anti-inflammatory drugs (NSAIDs) (diclofenac, ibuprofen, flurbiprofen, naproxen) ○ Surgical interventions included amniotic membrane transplants, superficial keratectomy, application of cyanoacrylate glue, therapeutic penetrating, lamellar keratoplasty, cataract surgery, evisceration or enucleation Safety outcomes: • Treatment exposure • AEs

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Trial name	ODAK (NCT03274895) ⁶⁴
	Patient-reported outcomes: • EQ-5D-5L ○ EQ-5D-5L is a five-item questionnaire that assesses five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. ○ EQ-5D-5L visual analogue scale (VAS) measures patients' self-rated health on a vertical VAS scale scored between 0–100 where 0 represents 'the worst health you can imagine' and 100 represents the 'best health possible'.⁶⁶ • VFQ-25 ○ The VFQ-25 is a patient survey that aims to measure the dimensions of self-reported vision-targeted health status that are most important for patients who have chronic eye disease.⁶⁷ ○ The VFQ-25 consists of a core set of 25 vision-targeted questions covering 11 vision-related constructs, along with an additional single-item general health rating question.⁶⁷ ○ Each item is converted to a 0–100 scale, with a higher score representing better functioning.⁶⁷

Abbreviations: AAT: anti-amoebic therapy; AE: adverse event; AK: Acanthamoeba keratitis; BCVA: best-corrected visual acuity; HSV: herpes simplex virus; MCR: medical cure rate; N/A: not applicable; NSAID: non-steroidal anti-inflammatory drug; ODAK: Orphan Drug for Acanthamoeba Keratitis; UK: United Kingdom; VAS: visual analogue scale; VFQ: Visual Function Questionnaire.

Source: SIFI ODAK CSR 2022.²

2.3.3 ODAK baseline characteristics

Baseline demographics and clinical characteristics for the full analysis set (n=127; see Table 7 for definitions of the analysis populations) of patients with AK included in the ODAK trial are presented in Table 6. Baseline was defined as the last valid evaluation prior to the first dose of study medication. The overall demographic characteristics were well balanced across the two treatment arms. The median age of the polihexanide 0.8 mg/ml arm and the polihexanide 0.2 mg/ml with propamidine 1 mg/ml was 35.2 years and 38.3 years, respectively.

In the full analysis set (n=127), disease stage at baseline was broadly balanced between the treatment arms; the polihexanide 0.8 mg/ml comprised of 16.7% patients with Stage III disease compared to 11.5% in the polihexanide 0.2 mg/ml with propamidine 1 mg/ml arm. A total of 64 participants were recruited from centres in the UK (Moorfields Hospital, Manchester Eye Hospital, University Hospital Southampton), ensuring that the ODAK trial cohort was generalisable to real-world clinical practice in the UK.

Table 6: Baseline demographics and clinical characteristics in the full analysis set (n=127)

Characteristics	Polihexanide 0.8 mg/ml (n=66)	Polihexanide 0.2 mg/ml with propamidine 1 mg/ml (n=61)
Age, years		
Mean (SD)	35.2 (13.2)	38.3 (14.4)
Median (IQR)	33.5 (25.0–44.0)	37.0 (26.0–49.0)
Minimum–maximum	15–73	17–71
15–35 n (%)	36 (54.6)	28 (45.9)
36–73 n (%)	30 (45.5)	33 (54.1)
Sex, n (%)		
Female	39 (59.1)	35 (57.4)
Male	27 (40.9)	26 (42.6)
BCVA (in metres) before AK, 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)
Unknown	5	8
Study centre, n (%)		
Moorfields Eye Hospital, United Kingdom	28 (42.4)	30 (49.2)
Manchester Eye Hospital, United Kingdom	1 (1.5)	1 (1.6)
University Hospital Southampton, United Kingdom	1 (1.5)	3 (4.9)
Ospedale San Raffaele, Milano, Italy	23 (34.8)	17 (27.9)
Ospedale SS Giovanni e Paolo, Venice, Italy	9 (13.6)	5 (8.2)
Medical University of Silesia, Katowice, Poland	4 (6.1)	5 (8.2)
Risk factors for keratitis CL wear, n (%)		
No	2 (3.0)	3 (4.9)
Yes	64 (97.0)	58 (95.1)
Ocular trauma, n (%)		
No	63 (95.4)	59 (96.7)
Yes	3 (4.6)	2 (3.3)
Time from onset of symptoms, days		
Mean (SD)	33.5 (39.2)	36.9 (55.0)
Median (IQR)	19 (8–42)	20 (8–37)
Days from onset of symptoms, grouped, n (%)		
≤ 41	49 (74.2)	47 (77.0)
> 41	17 (25.8)	14 (23.0)

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Characteristics	Polihexanide 0.8 mg/ml (n=66)	Polihexanide 0.2 mg/ml with propamidine 1 mg/ml (n=61)
Time from first treatment for keratitis, days		
Mean (SD)	12.0 (22.2)	13.5 (22.3)
Median (IQR)	4 (0–17)	4 (0–20)
Antibiotics for keratitis before baseline, n (%)		
No	10 (15.2)	11 (18.0)
Yes	56 (84.8)	50 (82.0)
Antivirals for keratitis before baseline, n (%)		
No	48 (72.7)	42 (68.9)
Yes	18 (27.3)	19 (31.1)
Antifungals for keratitis before baseline, n (%)		
No	65 (98.5)	61 (100)
Yes	1 (1.5)	0
Corticosteroids before baseline (any cause), n (%)		
No	35 (53.0)	41 (67.2)
Yes	31 (47.0)	20 (32.8)
Disease stage at baseline, n (%)		
I	14 (21.2)	8 (13.1)
II	41 (62.1)	46 (75.4)
III	11 (16.7)	7 (11.5)
Severe inflammatory disease: scleritis or hypopyon	0	0
Bilateral disease, n (%)		
Absent	55 (83.3)	57 (93.4)
Present	10 (15.2)	4 (6.6)
Unknown	1 (1.5)	0

Abbreviations: AK: Acanthamoeba keratitis; BCVA: best-corrected visual acuity; CL: contact lens; IQR: interquartile range; SD: standard deviation.

Source: Dart et al. 2024 (Table 1, Page 6).⁴

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

The study populations and statistical analysis methods used in the ODAK trial are summarised in Sections 2.4.1 and 2.4.2, respectively. The participant flow (CONSORT) diagram for the ODAK trial is presented in Appendix B.2.

2.4.1 Study populations

Study population definitions and patient numbers are summarised in Table 7.

Table 7: Trial populations of the ODAK trial

Analysis population	Definition
All randomised (N=135)	All eligible patients who were randomised to receive study treatment, either arm
Efficacy results	
Full analysis set (n=127)	All randomised patients for whom the primary efficacy variable had been assessed. This population was used in all efficacy analyses
Per-protocol (n=119)	A subset of patients from the full analysis population, for whom no major protocol deviation was deemed to impact the primary efficacy analysis was reported or identified. This population was used in the analysis of the primary efficacy endpoint only
Safety results	
Safety (n=134)	All randomised patients who had received at least one dose of the study drug. This population was used in all safety analyses

Source: SIFI ODAK SAP⁶⁸ and SIFI ODAK CSR.²

2.4.2 Analyses conducted in the ODAK trial

The methods for endpoint assessment in each analysis set of the ODAK trial are presented in Table 8.

Table 8: Overview of analyses conducted in the ODAK trial

	Full analysis set	Per-protocol
Primary endpoint	MCR at 12 months after baseline, assessed at each visit up to Day 365 - Defined as the percentage of patients cured 30 days after discontinuing all study therapies, within 12 months of randomisation. Cure was defined as: - No corneal inflammation (including subepithelial infiltrates, stromal infiltrates and oedema) that requires treatment, with a healed corneal epithelium and minimal punctate staining - No or mild conjunctival inflammation (including bulbar injections, bulbar oedema, tarsal hyperaemia): mild conjunctival inflammation is acceptable if related to other concurrent conditions such as blepharitis - No limbitis, scleritis or anterior chamber inflammation - No relapse within 30 days of discontinuing all topical and systemic therapy given for AK - For a MCR classification, there should be no	The per-protocol set was used for supportive sensitivity analysis of the primary efficacy variable only (MCR at 12 months)

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	Full analysis set	Per-protocol
	relapses within 90 days of the end-of-treatment and within 11 months of randomisation; discontinued participants were regarded as not cured Analysis of the primary endpoint was designed to test for superiority and, if this was not met, additional conditions were specified to meet the requirements of a non-inferiority study, making it feasible to test for non-inferiority using the results from the superiority analysis, without a separate analysis. The 90% confidence interval (CI) for the difference between the treatments obtained from the superiority analysis defined the bounds for conclusions on non-inferiority i.e. the value of the lower end of the CI relative to the pre-defined 0.20 non-inferiority margin (Δ)^a	
Secondary endpoints	Time-to-cure was subject to formal statistical testing; other secondary efficacy variables were exploratory and no control for multiplicity was conducted – results from these endpoints are therefore considered descriptive. Time-to-cure - The date that clinical resolution was achieved (primary endpoint, see definition above) was used to calculate the number of days from randomisation to cure - Time-to-cure was analysed using Cox proportional hazard regression and Kaplan-Meier survival plots. If the proportional hazard assumption was not fulfilled, a log-rank test was performed. Patients who discontinued the study without being classified as cured were censored at the last observation when cure status was assessed BCVA - BCVA was presented and analysed using the LogMAR notation (change from baseline); see Section 1.3.2 for a description of this notation and its relation to the BCVA Snellen scale) <i>Corneal scarring by slit-lamp examination</i> - Corneal scarring (assessed as present or absent) at end of treatment was analysed with logistic regression using treatment arm and corneal scarring at baseline as covariates <i>Ulceration severity by slit-lamp examination</i> - Ulceration severity (assessed as present or absent) was analysed with logistic regression using treatment arm and ulceration severity at baseline as covariates <i>Anterior chamber inflammation by ophthalmoscopy</i>	N/A: The per-protocol population was used in the analysis of the primary efficacy endpoint only

	Full analysis set	Per-protocol
	- Anterior chamber inflammation was assessed using a 4-grade scoring procedure (0 = none; 1 = mild; 2 = moderate; 3 = severe, based on the severity of the Tyndall effect observed). The grade scores were analysed using an ordinal logistic regression approach with treatment and the baseline anterior chamber inflammation as covariates EQ-5D-5L and EQ-5D-VAS - The EQ-5D was summarised for each dimension. A repeated measures ANCOVA for each dimension was conducted using treatment and the baseline value as predictors - The EQ-5D VAS score was recorded at all visits, including baseline. Integer values range from 0 to 100. A repeated measures ANCOVA was used to compare potential differences in trends over the treatment period using treatment and the baseline VAS value as covariates VFQ-25 - Averaging the means for each VFQ-25 subscale for each patient, excluding the General health score, provides a composite score for each patient, which was then used to calculate the composite score for each treatment arm	

Footnote: ^aFurther detail and rationale for the selection of the non-inferiority margin is described in Appendix J.1.1.

Abbreviations: BCVA: best-corrected visual acuity; CI: confidence interval; LogMAR: Logarithm of the Minimum Angle of Resolution; MCR: medical cure rate; N/A: not applicable; VAS: visual analogue scale; VFQ: Visual Function Questionnaire.

Source: SIFI ODAK SAP⁶⁸ and SIFI ODAK CSR.²

Statistical analyses

All results are presented for each visit by treatment arm and in total, unless stated otherwise. Continuous data are summarised using descriptive statistics, and the following parameters were reported: number of patients with evaluable observations and missing observations, arithmetic mean and change from baseline with standard deviations, median, first and third quartiles, minimum and maximum. Categorical data were presented using absolute frequency and percentage. Unless stated otherwise, the denominator for percentage calculations was the total number of patients in the applicable analysis set, including patients with missing data.

The amount of missing data was considered negligible and too little to allow recognition of a missingness pattern. As such, data presented for all outcomes are as observed. A sensitivity analysis of the primary endpoint using the per-protocol population (as opposed to the FAS) was conducted to explore the effect of missing data on the primary outcome.

Significance tests were two-sided and performed at the 5% significance level, unless stated otherwise. When reporting the results of significance tests, p-values were presented. All

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confidence intervals (CIs) presented were two-sided with a nominal confidence level of 95%, unless stated otherwise.

Sample size determination

A total of 135 patients affected by AK were randomised 1:1 to receive either polihexanide 0.8 mg/ml or polihexanide 0.2 mg/ml with propamidine 1 mg/ml combination therapy.

From the results of a previous observational, retrospective study (038SI Study; see Section 2.3.1), a MCR of 67% for the combination therapy of polihexanide 0.2 mg/ml with propamidine 1 mg/ml was expected.⁶⁸ This figure is in the range of cure rates described in the literature.^{29, 46, 61} If the true difference in MCR is ≥ 0.20 (Δ) in favour of polihexanide 0.8 mg/ml, a total sample size of 116 patients (allowing for 10% loss to follow-up) was expected to give the study at least 80% power to detect superiority, with a 2-sided alpha = 0.10 (or equivalently 1-sided alpha = 0.05). The sample size was adjusted to 130 patients, to allow for a 10% loss to follow-up (i.e. 116 evaluable patients).

Protocol deviations

Major protocol deviations were defined as deviations that could affect the scientific integrity of the study i.e. did not comply with the allocated treatment and/or did not attend the two follow-up visits.

A total of eight patients (four patients in each treatment arm) reported major protocol deviations in the ODAK trial and were not included in the per-protocol analysis set. Specifically, within the polihexanide 0.8 mg/ml treatment arm one patient received a disallowed medication (self-prescribed over-the-counter propamidine) before randomisation, one patient did not undergo repeated culture analysis before restarting a course of intensive treatment, and two patients did not comply with treatment. Within the active comparator arm, one patient received a disallowed medication (self-prescribed over-the-counter propamidine) before randomisation, one patient was prescribed an antiviral after trial drug discontinuation, but before the end of the study visit, and two patients did not comply with treatment.

2.5 *Critical appraisal of the relevant clinical effectiveness evidence*

Quality assessment of the ODAK trial was performed using the Quality Assessment of Controlled Intervention Studies tool.⁶⁹ The domains included within this tool align with the criteria for assessment of risk of bias in RCTs, as recommended by the University of York's Centre for Reviews and Dissemination (CRD).⁷⁰ Randomisation and blinding were adequate, with an intention-to-treat (ITT) analysis included. As a result, the ODAK trial, which provides the source of the clinical efficacy of polihexanide 0.8 mg/ml, is of good quality and low risk of bias (Table 9).

Table 9: Critical appraisal and quality assessment of the pivotal ODAK trial

Question	Description
Was the study described as randomised, a randomised trial, a randomised clinical trial, or an RCT?	Yes

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Question	Description
Was the method of randomisation adequate (i.e., use of randomly generated assignment)?	Yes
Was the treatment allocation concealed (so that assignments could not be predicted)?	Yes
Were study participants and providers blinded to treatment group assignment?	Yes
Were the people assessing the outcomes blinded to the participants' group assignments?	Yes
Were the groups similar at baseline on important characteristics that could affect outcomes (e.g. demographics, risk factors, co-morbid conditions)?	Yes
Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	Yes
Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	Yes
Was there high adherence to the intervention protocols for each treatment group?	Yes
Were other interventions avoided or similar in the groups (e.g. similar background treatments)?	Yes
Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Yes
Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	Yes
Were outcomes reported or subgroups analysed prespecified (i.e. identified before analyses were conducted)?	Yes
Were all randomised participants analysed in the group to which they were originally assigned, i.e. did they use an intention-to-treat analysis?	Yes
Overall quality	Good

Abbreviations: ODAK: Orphan Drug for Acanthamoeba Keratitis.

Source: SIFI. Data on File. Clinical SLR Report, 2025.⁷¹

Additionally, as discussed previously in Section 2, due to concerns regarding the representativeness of the active comparator arm in the ODAK trial to real-world UK clinical practice, comparator efficacy data were derived from an ITC using clinical resolution data from Papa et al. 2020.²⁹ This source was used to better reflect the proposed 'current practice' pooled AAT comparator within real-world UK practice. A quality assessment of the Papa et al. (2020) study was performed using the Quality Assessment Tool for Case Series Studies.⁶⁹ As summarised in Table 10, the Papa et al. study, which provides the key source of clinical effectiveness of polyhexanide 0.8 mg/ml versus the pooled AAT comparator in the ITC (see Section 2.10), is of good quality and low risk of bias.

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Table 10: Critical appraisal and quality assessment of the Papa et al. study

Question	Description
Was the study question or objective clearly stated?	Yes
Was the study population clearly and fully described, including a case definition?	Yes
Were the cases consecutive?	Yes
Were the subjects comparable?	Yes
Was the intervention clearly described?	Yes
Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes
Was the length of follow-up adequate?	Yes
Were the statistical methods well-described?	Yes
Were the results well-described?	Yes
Overall quality	Good

Source: SIFI. Data on File. Clinical SLR Report, 2025.⁷¹

2.6 *Clinical effectiveness results of the relevant studies*

Efficacy results from the ODAK trial in this submission are presented from the full analysis set, consisting of 66 patients in the polihexanide 0.8 mg/ml treatment arm.

As discussed previously, the active comparator arm within the ODAK trial is not representative of UK clinical practice and as such the ODAK trial is considered as a pseudo-single arm trial within this submission. Results of an indirect treatment comparison of polihexanide 0.8 mg/ml and a proposed 'current practice' pooled AAT comparator in real-world UK practice forms the main source of comparative evidence for this submission (see Section 2.10). Based on the limitations of the active comparator arm of ODAK, data are presented for the polihexanide 0.8 mg/ml treatment arm only within this section, with comparative data and associated comparative analyses presented in Appendix J for completeness.

2.6.1 **Primary endpoint: MCR at 12 months**

MCR at 12 months, which was the primary endpoint of the ODAK trial, was defined as the rate patients were cured without the need for surgery or a change of AAT, and independent of visual acuity, within 12 months of randomisation. Within this, cure was defined as clinical evidence of elimination of *Acanthamoeba*, including an intact corneal epithelium with no clinical signs or symptoms of ocular inflammation after discontinuing AAT and anti-inflammatory treatment for 30 days (confirmed at the end-of-study visit 90 days after treatment discontinuation) as determined by clinical examination.

MCR was selected as the primary endpoint for the ODAK trial as it represents a highly important outcome measure for both patients and clinicians. As discussed in Section 1.3.2, achieving a cure and avoiding prolonged damage to the eye associated with long AK exposure is a key treatment priority for patients.

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Polihexanide 0.8 mg/ml resulted in a MCR of 84.85% at 12 months (Table 11). The MCR results for both the polihexanide 0.8 mg/ml treatment arm and the active comparator arm are presented in Appendix J.1.2, alongside the results of the comparative non-inferiority analysis.

Table 11: Summary of adjusted 12-month MCR (full analysis set)

12-month MCR	Polihexanide 0.8 mg/ml (n=66)
Resolved (%)	84.85
Not resolved (%)	15.2
Ratio of resolved versus not resolved (95% CI)	5.60 (2.86, 10.98)

Abbreviations: CI: confidence interval; MCR: medical cure rate.

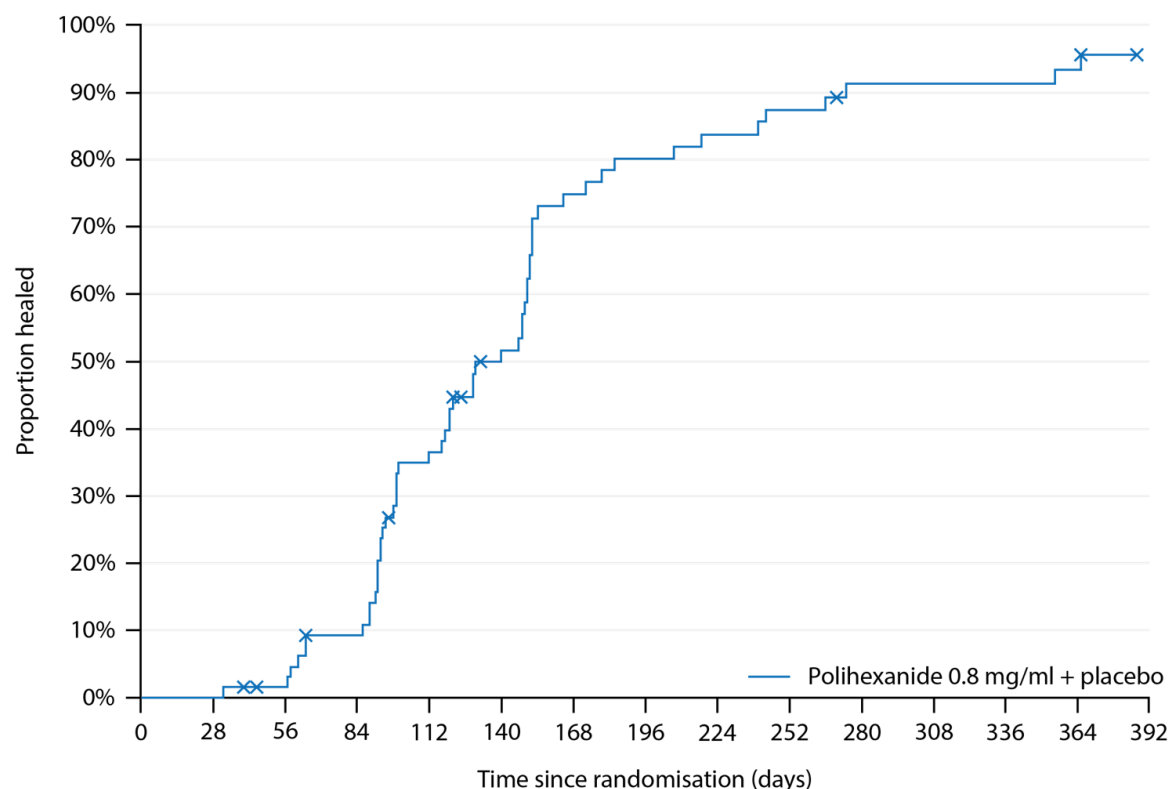
Source: SIFI ODAK CSR (Table 11.6);² Akantior EMA EPAR (Table 19).⁵

2.6.2 Secondary endpoint: Time-to-cure

Within this analysis, time-to-cure was defined as the time needed to reach clinical resolution for all participants defined as cured or not cured at the 30-day follow-up visit (checked at 90 days) either after discontinuation of the study drug or within 12 months of starting AAT, whichever came first.² The median time-to-cure for the polihexanide 0.8 mg/ml treatment arm was 140 days (n=66), with an associated Kaplan-Meier (KM) plot for the time-to-cure data presented in Figure 4.

The time-to-cure results for both the polihexanide 0.8 mg/ml treatment arm and active comparator arm, alongside an associated comparative analysis, are presented in Appendix J.1.3.

Figure 4: KM plot of time-to-cure analysis (full analysis set)



Abbreviations: KM: Kaplan-Meier.

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Source: SIFI ODAK CSR (Figure 1).²

2.6.3 Secondary endpoint: BCVA

BCVA, measured using the LogMAR notation, at baseline and the end-of-study visit for patients in the polihexanide 0.8 mg/ml treatment arm is presented in Table 12. Results for the active comparator arm, alongside an associated comparative analysis, are presented in Appendix J.1.4.

Table 12: BCVA through LogMAR score (full analysis set)

BCVA (LogMAR)	Polihexanide 0.8 mg/ml (n=64)
Baseline ^a	
n	58
Mean (SD)	0.473 (0.430)
End-of-study visit	
n	56
Mean (SD)	0.188 (0.399)
Change from baseline to end-of-study visit	
n	53
Mean (SD)	-0.293 (0.469)
p-value ^b	<0.0001

Footnote: ^aBaseline is defined as the last valid evaluation prior to the first dose of study medication; ^bThe p-values are based on paired t-tests where the baseline value is compared to the value at end-of-study.

Abbreviations: BCVA: best-corrected visual acuity; LogMAR: Logarithm of the Minimum Angle of Resolution; SD: standard deviation.

Source: SIFI ODAK CSR (Table 14.2.3.2).²

2.6.4 Secondary endpoint: Corneal scarring

As described in Section 1.3.6, after the medical treatment, patients with AK may have a residual leucoma (corneal scarring), therefore, a summary of the corneal scarring data for the polihexanide 0.8 mg/ml treatment arm is presented in Table 13. At the end-of-study visit, 50% of patients in the polihexanide 0.8 mg/ml arm presented with corneal scarring.

A summary of corneal scarring data at baseline and the end-of-study visit is presented for both treatment arms in Appendix J.1.5, alongside the associated comparative analysis.

Table 13: Summary of corneal scarring (full analysis set)

Corneal scarring	Polihexanide 0.8 mg/ml (n=66)
Baseline, n (%)	
Absent	66 (100.0)
Present	0
Missing	0
End-of-study visit, n (%)	
Absent	31 (47.0)
Present	33 (50.0)

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Corneal scarring	Polihexanide 0.8 mg/ml (n=66)
Missing	2 (3.0)
McNemar's test p-value for difference from baseline	<0.0001
Shift from baseline to end-of-study visit, n (%)	
Absent to Absent	31 (47.0)
Absent to Present	33 (50.0)
Present to Absent	0
Present to Present	0
Missing at any of these visits	2 (3.0)

Footnote: Baseline is defined as the last valid evaluation prior to the first dose of study medication.

Source: SIFI ODAK CSR 2022 (Table 14.2.4.10).²

2.6.5 Secondary endpoint: Ulceration severity

Within the full analysis set, there was an improvement ($p=0.001$) in the condition/status of corneal ulceration from baseline to the end-of-study visit within the polihexanide 0.8 mg/ml treatment arm, with summary data presented in Table 14. Corneal ulceration data for the active comparator arm are presented in Appendix J.1.6, alongside the associated comparative analysis.

Table 14: Summary of corneal ulceration (full analysis set)

Corneal ulceration	Polihexanide 0.8 mg/ml (n=66)
Baseline, n (%)	
Absent	48 (72.7)
Present	18 (27.3)
Missing	0
End-of-study visit, n (%)	
Absent	60 (90.9)
Present	4 (6.1)
Missing	2 (3.0)
McNemar's test p-value for difference from baseline	0.001
Shift from baseline to end-of-study visit, n (%)	
Absent to Absent	44 (66.7)
Absent to Present	2 (3.0)
Present to Absent	16 (24.2)
Present to Present	2 (3.0)
Missing at any of these visits	2 (3.0)

Footnote: Baseline is defined as the last valid evaluation prior to the first dose of study medication.

Source: SIFI ODAK CSR 2022 (Table 14.2.4.4).²

2.6.6 Secondary endpoint: Anterior chamber inflammation

There was an improvement ($p < 0.05$) in the condition/status change in anterior chamber inflammation grade from baseline to the end-of-study visit within the polihexanide 0.8 mg/ml treatment arm, with 74.2% of patients with no anterior chamber inflammation at baseline also having no inflammation at the end-of-study visit.

Data summarising anterior chamber inflammation for the polihexanide 0.8 mg/ml treatment arm are presented in Table 15. Anterior chamber inflammation data for the active comparator arm are presented in Appendix J.1.7, alongside the associated comparative analysis.

Table 15: Summary of anterior chamber inflammation (full analysis set)

Anterior chamber inflammation	Polihexanide 0.8 mg/ml (n=66)
Baseline, n (%)	
None	52 (78.8)
Mild	11 (16.7)
Moderate	1 (1.5)
Severe	1 (1.5)
Missing	1 (1.5)
End-of-study visit, n (%)	
None	62 (93.9)
Mild	1 (1.5)
Moderate	0
Severe	1 (1.5)
Missing	2 (3.0)
Paired T-test p-value for change from baseline within treatment arm	0.0221
Shift from baseline to end-of-study visit, n (%)	
None to None	49 (74.2)
None to Mild	1 (1.5)
None to Moderate	0
None to Severe	0
Mild to None	10 (15.2)
Mild to Mild	0
Mild to Moderate	0
Mild to Severe	1 (1.5)
Moderate to None	1 (1.5)
Moderate to Mild	0
Moderate to Moderate	0
Severe to None	1 (1.5)
Severe to Mild	0
Severe to Moderate	0
Missing at any of these visits	3 (4.5)

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Footnote: Baseline is defined as the last valid evaluation prior to the first dose of study medication. P-values are based on paired t-tests where the baseline value is compared to the value at end-of-study.

Source: SIFI ODAK CSR 2022 (Table 14.2.4.4.2).²

2.6.7 Use of alternative treatment and surgery

Overall, rates of surgery and adjunctive therapy were low for the polihexanide 0.8 mg/ml treatment arm during the ODAK trial. Only two (n=2/69; 2.9%) participants (both in the polihexanide 0.8 mg/ml arm) required surgery (corneal transplantation), with one instance being assessed as possibly related the study treatment. A summary of the proportion of patients requiring adjunctive therapy in the polihexanide 0.8 mg/ml treatment arm is presented in Table 16. Surgical treatment and adjunctive therapy data for the active comparator arm are presented in Appendix J.1.8.

Table 16: Rate of patients with adjunctive therapy (full analysis set)

Rate of adjunctive therapy, n (%)	0.8 mg/ml polihexanide (n=66)
Rate of patients with adjunctive therapy	30 (45.5)
Rate of patients with adjunctive therapy and using steroids after randomisation	11 (16.7)

Footnote: Adjunctive therapy was defined as new use after baseline or any increase of at least one of the following medications: topical steroid (dexamethasone, prednisolone, fluorometholone, loteprednol), oral NSAIDs (diclofenac, ibuprofen, flurbiprofen, naproxen).

Abbreviations: NSAID: Non-Steroidal Anti-Inflammatory Drug.

Source: SIFI ODAK CSR 2022 (Table 14.3.2.1).²

2.6.8 Health-related quality of life outcomes

EQ-5D-5L

There was a significant improvement ($p < 0.0001$) in EQ-5D-5L VAS score from baseline to the end-of-study visit observed in patients treated with polihexanide 0.8 mg/ml.

Change from baseline (CfB) in EQ-5D-5L VAS scores for patients treated with polihexanide 0.8 mg/ml are presented in Table 17. The EQ-5D-5L VAS scores for the active comparator arm are presented in Appendix J.1.9, alongside the associated comparative analysis.

Table 17: Analysis of EQ-5D-5L VAS score (full analysis set)

EQ-5D-5L VAS score	Polihexanide 0.8 mg/ml (n=65)
Baseline	
Number assessed/number missing	64/1
Mean (SD)	69.8 (19.5)
Median	73.0
Q1–Q3	57.5–85.0
Min, Max	10, 100
End-of-study visit	
Number assessed/number missing	61/4

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EQ-5D-5L VAS score	Polihexanide 0.8 mg/ml (n=65)
Mean (SD)	88.3 (13.4)
Median	95.0
Q1–Q3	80.0–99.0
Min, Max	40, 100
Change from baseline to end-of-study visit	
Number assessed/number missing	60/5
Mean (SD)	17.9 (19.6)
Median	14.5
Q1–Q3	5.0–28.0
Min, Max	-20, 65
p-value	<0.0001

Footnote: Baseline is defined as the last valid evaluation prior to the first dose of study medication. P-values are based on paired t-tests where the baseline value is compared to the value at end-of-study.

Abbreviations: SD: standard deviations; VAS: visual analogue scale.

Source: SIFI ODAK CSR 2022 (Table 14.2.5.2).²

VFQ-25

The mean change in VFQ-25 composite score from baseline to end-of-study visit was statistically significant ($p < 0.0001$) within the polihexanide 0.8 mg/ml treatment arm (Table 18). The VFQ-25 composite scores for the active comparator arm of ODAK are presented in Appendix J.1.9, alongside the associated comparative analysis.

Table 18: Analysis of VFQ-25 composite scores (full analysis set)

VFQ-25 composite score	Polihexanide 0.8 mg/ml (n=65)
Baseline	
Number assessed/number missing	65/1
Mean (SD)	64.9 (22.3)
Median	63.3
Q1–Q3	48.7–84.8
Min, Max	15, 97
End-of-study visit	
Number assessed/number missing	60/5
Mean (SD)	88.1 (15.6)
Median	93.7
Q1–Q3	83.7–97.8
Min, Max	22, 100
Change from baseline to end-of-study visit	
Number assessed/number missing	60/5
Mean (SD)	23.5 (19.4)
Median	22.1
Q1–Q3	7.9–37.3

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VFQ-25 composite score	Polihexanide 0.8 mg/ml (n=65)
Min, Max	-10, 70
p-value	<0.0001

Footnote: Baseline is defined as the last valid evaluation prior to the first dose of study medication. The p-values are based on paired t-tests where the baseline value is compared to the value at end-of-study.

Abbreviations: SD: standard deviations; VFQ: visual functioning questionnaire.

Source: SIFI ODAK CSR 2022 (Table 14.2.6.1).²

2.7 *Subsequent treatments used in the relevant studies*

As outlined in Section 2.6.7, two patients in the polihexanide 0.8 mg/ml treatment arm required surgery (corneal transplantation) in the ODAK trial.

Overall, as presented in Section 1.3.5, there are currently no reimbursed therapeutic treatments or a definitive standard of care available in the UK for patients with AK, with patients receiving heterogeneous care and a mixture of off-label and unlicensed therapeutic approaches.¹¹ As a result, there are no guidelines on second or third line treatment for patients with AK. Data on subsequent usage of AATs was not collected within the ODAK trial.

2.8 *Subgroup analysis*

There are no subgroups that are clinically relevant and for which polihexanide 0.8 mg/ml is expected to be more clinically or cost-effective. Furthermore, considering the overall size of the disease population in AK (with an estimated incidence of <0.2 cases per 50,000 per year in the UK, see Section 1.3.4),⁸ it is not considered appropriate to further reduce this population size by considering subgroups in terms of clinical outcomes or cost effectiveness. In line with its marketing authorisation, polihexanide 0.8 mg/ml is intended to offer a treatment option for the broad population of eligible people with AK, for whom there is a clear unmet need for effective, licensed and readily available treatments.

2.9 *Meta-analysis*

As outlined in Section 2.2, the ODAK trial was the only RCT identified evaluating the efficacy and safety of polihexanide 0.8 mg/ml, for the treatment of AK in adults and children from 12 years of age. Therefore, no meta-analysis was performed.

2.10 *Indirect and mixed treatment comparisons*

As discussed previously in Section 2, comparative efficacy results from the ODAK trial are not suitable for the appraisal of polihexanide 0.8 mg/ml as the active comparator arm in the ODAK trial is associated with significant issues in terms of representative of expected outcomes in real-world UK clinical practice, over and beyond usual considerations relating to generalisability of results from a trial setting to clinical practice. In UK clinical practice, in most centres, there is a lack of readily available licensed therapeutic approaches, leading to delays in treatment and poorer patient outcomes.^{9, 15} In addition, there are a lack of standardised treatment protocols in UK clinical practice.¹¹ The active comparator arm is therefore not reflective of the effectiveness of therapeutic options in real-world practice and was included in the ODAK trial for ethical reasons, despite its effectiveness having never previously been demonstrated in a clinical trial. In contrast,

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the polihexanide 0.8 mg/ml arm of the ODAK trial is expected to be significantly more reflective of performance in clinical practice as it will be a licensed and ready to use pharmaceutical product, guided by a SmPC and a standardised protocol, and manufactured to GMP standard. Therefore, the context surrounding the use of polihexanide 0.8 mg/ml in real-world practice would be more similar to the ODAK trial setting (as described at the top of Section 2).

In line with the approach approved by the EMA as part of the EMA marketing authorisation process, alternative sources of comparative efficacy were sought to be compared with polihexanide 0.8 mg/ml (from ODAK) using an indirect treatment comparison (ITC), to better reflect true differences in treatment effect between polihexanide 0.8 mg/ml and currently available therapeutic approaches.

2.10.1 Identification of comparator data and feasibility assessment

To inform the ITC, a clinical SLR was conducted to identify relevant studies that reported clinical outcome data for people with AK, as described in Section 2.1 and Appendix B. In the SLR update searches conducted on 24th March 2025, no further studies relevant to the ITC were identified (see Appendix B.1.6 for rationale). The SLR included studies with ≥ 5 patients with AK. The intervention of interest was any AAT administered as eye-drops or orally in any concentration or combination and the main outcome of interest was clinical resolution, in line with the ODAK trial. The SLR identified 48 eligible studies, comprising data for 2,422 patients.

Feasibility assessment

A feasibility assessment was conducted and used to ascertain whether any of the 48 studies identified in the original 2022 SLR and the 2025 SLR update used outcome definitions that were sufficiently aligned with those used in the pivotal ODAK trial to allow evidence synthesis, given that heterogeneity between outcome definitions cannot be accounted for within an ITC analysis.⁷² The primary endpoint of MCR from the ODAK trial was the most relevant for the assessment of comparative effectiveness, given that cure is the primary treatment goal in AK and hence outcome definitions for the MCR outcome were assessed across SLR-identified studies in order to assess feasibility of comparison.

In the SLR, 28/48 studies reported MCR; a summary of the 28 studies and the endpoint definitions is provided in Appendix B.1.6. Only one retrospective study, which considered AATs included in the pooled AAT comparator, used a definition of clinical resolution which fully aligned (regarding timepoint and specific criteria) with the ODAK trial (see Table 5 for full definition) which was the most stringent definition of clinical cure (clinical evidence of elimination of *Acanthamoeba*, including an intact corneal epithelium with no clinical signs or symptoms of ocular inflammation after discontinuing AAT and anti-inflammatory treatment for 30 days); this study was therefore selected for the ITC analysis.²⁹ Discontinuations from AAT were considered as treatment 'failure' in the ODAK trial but not in Papa et al. (2020), therefore data from the Papa et al. study which used the same definition as the ODAK trial were acquired from the authors in order to align definitions (see Appendix B.1.2 for further details).

2.10.2 Sources included in the ITC

Design of evidence sources

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A summary of the key characteristics of the data sources used in the ITC is summarised in Table 19.

Table 19: Evidence sources used in the ITC

Data source	Country	Design	Period (years)	Data available
ODAK	Multi-centre	RCT	2017–2021	IPD
Papa et al. 2020	UK and Italy	RWE	1991–2012 ^a	IPD

Footnote: ^a16% (n=38) of participants were diagnosed between 1991–2000 and 83% (n=189) were diagnosed between 2001–2012.

Abbreviations: IPD: individual patient data; RCT: randomised controlled trial; RWE: real-world evidence.

Source: Dart et al. 2024;⁴ Papa et al. 2020.²⁹

Data for polihexanide 0.8 mg/ml were available from the pivotal ODAK trial; a multi-centre, randomised, assessor-masked, active-controlled, Phase 3 study.⁴ The methodology and results for this trial are presented in Section 2.3 and Section 2.6, respectively.

In the absence of appropriate head-to-head evidence (see Section 2.1), the Papa et al. (2020) study was used as a source of evidence for the clinical effectiveness for the pooled AAT comparator.²⁹ This was a retrospective, multi-national, observational study to estimate the efficacy of AATs in people with AK. The Papa et al. (2020) study was selected for use in the ITC as the specific primary endpoint definition matched that of the ODAK trial (see Table 5 in Section 2.3.2), with MCR at 12 months measured as the primary endpoint in both instances, with both studies requiring multiple clinical criteria be met for a classification of resolution.

Full details of the Papa et al. (2020) study methodology are available from the publication (provided as part of the submission reference pack). An overview of the key methodology is presented below.

Summary of Papa et al. 2020

Papa et al. (2020) was a retrospective cohort study of 227 patients who developed AK between 25th July 1991 and 10th August 2012. The study included 177 patients treated for AK at Moorfields Eye Hospital (London, UK) with retrievable medical records. The primary outcome of this study was to determine the MCR (without surgery) of different AATs at 12 months in patients with AK.

Patients with a diagnosis of AK, for whom the primary and secondary outcome measures could be ascertained from complete data, were included in the analysis. Patients with concurrent bacterial keratitis were included, as well as those developing bacterial keratitis as a complication of AK. Patients with a diagnosis of other causes of chronic microbial keratitis, including fungal and herpes keratitis, were excluded.

All patients were treated with topical AAT, which included biguanides (polihexanide 0.2 mg/ml and chlorhexidine 0.2 mg/ml) and diamidines (either propamidine 1 mg/ml or hexamidine 1 mg/ml) either as monotherapy or in combination. To reflect the heterogeneity of treatment classes and regimens received by patients, Papa et al. (2020) presented pooled results for all of the AAT combinations listed above and reported the overall MCR at 12 months, proportion of poor outcomes (defined as Snellen visual acuity ≤6/24 and/or surgery) and time-to-cure.

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Comparison of trial and patient baseline characteristics of sources included in the ITC

In addition to alignment in the endpoint definitions used in the ODAK trial and Papa et al. (2020), both studies were well aligned in terms of inclusion and exclusion criteria and study locations. A comparison of the key methodology of both studies is presented in Table 20 (a more detailed summary of the methodology of the ODAK trial is in Table 5 of Section 2.3.2). The distribution of therapeutic approaches used in Papa et al. (2020; shown in Table 31 of in Section 3.2.3) was similar to that reported in current UK clinical practice by ophthalmologists in a 2023 Delphi panel (reported in Table 3), confirming that Papa et al. (2020) is an appropriate source of comparative data, reflecting real-world clinical practice.

Table 20: Overview of the Papa et al. (2020) and Dart et al. (2023) studies included in the ITC

Study author, year	Papa et al, 2020 ²⁹	Dart et al., 2023 (ODAK) ⁴
Location	UK and Italy: • Moorfields Eye Hospital (London, UK) • San Raffaele Hospital (Milan, Italy)	UK, Italy and Poland: • Moorfields Eye Hospital (London, UK) • Manchester Eye Hospital (Manchester, UK) • University Hospital Southampton (Southampton, UK) • San Raffaele Hospital (Milan, Italy) • SS Giovanni e Paolo Hospital (Venice, Italy) • Medical University of Silesia (Katowice, Poland)
Study design	A retrospective cohort study	A prospective randomised controlled trial
Treatments	• The distribution of therapeutic approaches in the Papa et al. (2020) study is presented in Table 31 in Section 3.2.3 • The primary and secondary outcomes for the therapeutic approaches were pooled	• Polihexanide 0.8 mg/ml with placebo • Polihexanide 0.2 mg/ml and propamidine 1 mg/ml
Sample size	N=227 patients	N=135 patients
Eligibility criteria for patients	Inclusion criteria • Patients developing AK between 25th July 1991 and 10th August 2012, and with retrievable medical records • Patients with a diagnosis of AK, for whom the primary and secondary outcome measures could be ascertained from complete data • Patients with concurrent	Inclusion criteria • Patients aged ≥12 years of age with a diagnosis of AK • Participants with AK using the following previous treatments for keratitis (mis)diagnoses were also eligible: ○ Antibiotics for a presumed or proven ocular bacterial infection at baseline

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	bacterial keratitis, as well as those developing bacterial keratitis as a complication of AK Exclusion criteria Patients with a diagnosis of other causes of chronic microbial keratitis, including fungal and herpes keratitis	- Antiviral and antifungal drugs given for a misdiagnosis and discontinued at baseline - Anti-inflammatory drugs, including those using topical steroids, oral nonsteroidal anti-inflammatory drugs, or both before baseline Exclusion criteria - Patients with a document history or clinical signs of concomitant keratitis or both, caused by fungi or herpes simplex virus - Treatment before baseline with anti-amoebic agents - Participants using systemic IST - Participants requiring urgent surgical intervention for AK
Outcomes	Primary outcome - MCR at 12 months without surgery Secondary outcomes - Proportion of patients with poor outcomes (defined as Snellen visual acuity $\leq 6/24$ and/or surgery) - Median time-to-cure The analyses of the primary and secondary outcomes included both an unadjusted and adjusted analysis to account for baseline risk factors including age, year of diagnosis, severity of disease at baseline (presence of hypopyon and/or scleritis and /or Stage 3 disease) and corticosteroid use prior to the start of AAT.	Primary outcome - MCR at 12 months without surgery Secondary outcomes - Time-to-cure - BCVA (LogMAR notation) - Corneal scarring - Ulceration severity - Use of alternative treatment and surgery - EQ-5D-5L - VFQ-25
Key results	- Pooled AAT MCR: 60.79% (95% CI: 54.11–67.19) - Pooled AAT poor outcomes: 49.34% of patients (95% CI: 42.66–56.03) - Pooled AAT median time-to-cure: 5.00 months It should be noted that these data reported in the Papa et al. (2020) publication do not consider baseline AAT discontinuation as failure. The MCR included in the ITC was estimated from individual patient data provided by the author with discontinuation of baseline AAT	- Polihexanide 0.8 mg/ml MCR: 84.85% - Polihexanide 0.8 mg/ml median time-to-cure: 140 days Results for other secondary outcomes are described in detail in Section 2.6.

	considered as failure in line with the definition for MCR in the ODAK trial (see Section 2.10.1 and Appendix B.1.2 and B.1.6)	

Abbreviations: AAT: anti-amoebic therapy; AK: Acanthamoeba keratitis; CI: confidence interval; ITC: indirect treatment comparison; UK: United Kingdom.

Source: Papa et al. 2020;²⁹ Dart et al. 2023;⁴ SIFI ODAK CSR.²

The baseline characteristics of the ODAK trial and Papa et al. (2020) study populations were broadly aligned, as reported in Table 21, with only minor imbalances in the proportion of patients at AK disease Stage 3, treatment delay and prior use of topical antivirals. Taken together, the study and patient baseline characteristics of studies included in the ITC were considered to be sufficiently similar that an assessment of comparative treatment effectiveness based on these studies was feasible. Further methodological considerations, taken to ensure a robust comparison was generated, are described in Section 2.10.3.

Table 21: Comparison of baseline characteristics in the ODAK trial and Papa et al. 2020 study

Baseline characteristic	Polihexanide 0.8 mg/ml (ODAK, FAS)	Pooled AAT (Papa et al. 2020)
Number of patients	66	227
Age, years		
Mean (SD)	35.2 (13.2)	35.7 (13.8)
Median (min, max)	33.5 (15.0, 73.0)	33.0 (13.0, 76.0)
Male, %	40.9	44.1
AK disease Stage 3, %	16.7	27.3
Treatment delay,^a days		
Mean (SD)	33.5 (39.2)	44.9 (48.4)
Median (min, max)	19.0 (1.0, 177.0)	30.0 (0.0, 330.0)
Prior use of corticosteroids, n (%)	47.0	44.5
Prior use of topical antivirals, n (%)	25.8	44.9

Footnote: ^aTime from symptoms onset to treatment initiation.

Abbreviations: AAT: anti-amoebic therapy; AK: Acanthamoeba keratitis; FAS: full analysis set; ITC: indirect treatment comparison; SD: standard deviation.

Source: Papa et al. 2020;²⁹ Dart et al. 2023.⁴

2.10.3 Methodology of the indirect treatment comparison

Patient populations included in the analysis

Individual patient data (IPD) available for all patients in the polihexanide 0.8 mg/ml arm of the ODAK trial (N=66) were used in the ITC. IPD from the whole study population in the Papa et al. (2020) study were included (N=227), regardless of whether baseline treatment was received i.e. the pooled AAT group. A majority of the study participants from Papa et al. (2020) were treated in the UK (n=177/277; 64%), in some of the same centres as the ODAK trial of polihexanide 0.8 mg/ml, making it a representative assessment of real-world clinical practice.

Statistical methods

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As IPD were available for both the ODAK trial and the Papa et al. (2020) study, analyses were conducted using propensity scoring analysis (PSA) with overlap weighting (OW). This approach estimates the relevant treatment effect by employing weighted regression techniques to address potential selection bias linked to treatment-related factors, even when substantial differences exist between patient cohorts.⁷³ The OW accounts for selection assignment differences between treatment and control groups.³³

PSA is a recognised technique used to control for selection biases when combining multiple sources of non-randomised evidence. Propensity scores are used as weights to account for differences between populations of different studies; PSA methods therefore aim to mimic an experimental study using data arising from multiple sources. The OW approach uses the propensity score function which assigns more weight to individuals in one study whose measured covariate values best match those of patients in the other study.

Within the PSA, weighted regression methods were used with the treatment group as the binary outcomes and adjustment for key effect modifiers or prognostic factors of AK as covariates (identified as potential confounding variables, see below) to attempt to balance study populations before estimation of the treatment effect. This ITC methodology is considered more methodologically robust compared to a naïve comparison and is recommended when there are observed imbalances between studies. The overlap weight was calculated as 1 minus the propensity score for the corresponding treatment (i.e. polihexanide 0.8 mg/ml or combined AATs). IPD were reweighted to balance study populations by adjusting for observed cross-study differences. The overlap weights were normalised to account for the study sample size by adapting the sum of the weights by study to represent the sample size by study. The calculated estimate was based on the average treatment effect. Clinical resolution was assessed using logistic regression methods to estimate the absolute difference in MCR and corresponding 95% CIs between treatments.

The methodology of the ITC presented aligns with the NICE Decision Support Unit (DSU) guidance (Technical support document [TSD] 17) on statistical approaches for conducting an ITC where IPD are available for all studies in the comparison.⁷⁴

PSA covariate selection

Clinical feedback was sought to identify which factors were considered to be potential prognostic factors and/or treatment effect modifiers. Six factors were identified for inclusion in the population-adjusted analyses: age, gender, AK disease stage, prior use of corticosteroids, prior use of antivirals and delay in starting treatment. However, these covariates were not reported consistently in both studies, therefore, adjustment for cross-trial differences was limited to those factors which were available in each data source. Patients with missing covariate or outcome data were excluded from the analysis, except for treatment delay and age. Missing treatment delay data were imputed with the median value and missing age data were imputed with the mean value. The results of the analyses were then re-adjusted to the original sample size to represent the results on the original cohort sizes.

Outcome selection and definitions

The outcome of interest was MCR within 12 months of starting treatment. To measure the treatment effect, both the absolute difference and the relative risk (RR) of achieving MCR were

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estimated, each accompanied by a 95% CI. The absolute difference in MCR was estimated using logistic regression methods. To estimate the RR of achieving MCR, a generalised linear model with a binary distribution and a log link function was used.

2.10.4 Results of the indirect treatment comparisons

Baseline characteristics

The unadjusted and adjusted baseline characteristics for the ODAK trial population and the Papa et al. (2020) population are summarised in Table 22 (adjustment based on the following covariates considered to be prognostic factors: age, gender, AK disease stage, prior use of corticosteroids, prior use of antivirals and time to treatment delay). Differences among populations were observed; since stage of disease at baseline, as well as treatment delay and prior use of steroids and antivirals, are risk factors for poor prognosis for patients with AK, these characteristics were adjusted for.⁹ As presented in Table 22, the adjustment aligned the populations analysed within the ITC and the effective sample size of both studies were only minimally reduced upon adjustment.

Table 22: Comparison of unadjusted and adjusted baseline characteristics for patient populations in the ITC

Baseline characteristic	Polihexanide 0.8 mg/ml (ODAK)		Pooled AAT (Papa et al. 2020)	
Weighting	Unadjusted	Adjusted	Unadjusted	Adjusted
Number of patients	66	64.8 ^a	227	174 ^a
Age, years				
Mean (SD)	35.2 (13.2)	34.9 (13.0)	35.7 (13.8)	34.9 (14.1)
Median (min, max)	33.5 (15.0, 73.0)	33.0 (15.0, 73.0)	33.0 (13.0, 76.0)	32.0 (13.0, 76.0)
Male, %	40.9	40.6	44.1	40.6
AK disease Stage 3, %	16.7	18.8	27.3	18.8
Treatment delay,^b days				
Mean (SD)	33.5 (39.2)	35.6 (41.3)	44.9 (48.4)	35.6 (36.7)
Median (min, max)	19.0 (1.0, 177.0)	21.0 (1.0, 177.0)	30.0 (0.0, 330.0)	28.0 (0.0, 257.0)
Prior use of corticosteroids, n (%)	47.0	45.2	44.5	45.2
Prior use of topical antivirals, n (%)	25.8	30.0	44.9	30.0

Footnote: Characteristics in bold were used for adjustment. ^aEffective sample size is estimated from adjusted data;

^bTime from symptoms onset to treatment initiation.

Abbreviations: AAT: anti-amoebic therapy; AK: Acanthamoeba keratitis; ITC: indirect treatment comparison; SD: standard deviation.

Source: SIFI ITC Report May 2025 (Table 4);³³ SIFI Data on File. Draft ITC manuscript.¹²

ITC outcome: MCR

Polihexanide 0.8 mg/ml had a statistically significantly higher MCR without surgery compared with pooled AAT before weighting (RR: ■■■ [95% CI: ■■■, ■■■]) and in PSA analyses after adjustment (RR: ■■■ [95% CI: ■■■, ■■■]). A summary of the results is presented in Table 23.

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Table 23: PSA with OW comparison of MCR for polihexanide 0.8 mg/ml (ODAK trial) with pooled AAT (Papa et al. 2020)

	Polihexanide 0.8 mg/ml (ODAK)		Pooled AAT (Papa et al. 2020)	
Weighting	Unadjusted	Adjusted	Unadjusted	Adjusted
Number of patients	66	64.8 ^a	227	174 ^a
MCR without surgery				
N responders (95% CI ^b)	56 (73.9, 92.5)	55.9 (76.1, 93.4)	99 ^c (37.1, 50.3)	109.7 (41.8, 54.8)
% responders	84.8%	84.7%	43.6%	48.3%
Absolute % difference (95% CI) versus comparator	41.2^d (28.8, 51.2)	36.4^d (24.9, 47.9)	Reference	Reference
RR (95% CI) versus comparator			Reference	Reference

Footnote: ^aEffective sample size is estimated from adjusted data. ^b95% CI is based on binomial proportion. ^cThis value was provided by the author and it is not directly available in the publication. ^dBold denotes statistical significance at 5% level.

Abbreviations: AAT: anti-amoebic therapy; CI: confidence interval; RR: relative risk; OW: overlap weighting; PSA: propensity scoring analysis.

Source: SIFI ITC Report May 2025 (Table 4);³³ SIFI Data on File. Draft ITC manuscript.¹²

2.10.5 Strengths and limitations of the indirect treatment comparison

The results of the ITC are supportive of superior efficacy of polihexanide 0.8 mg/ml over current therapeutic approaches for AK, with polihexanide 0.8 mg/ml resulting in a significantly higher MCR compared with the pooled AAT comparator.

As the comparative effect obtained from the ODAK trial is not representative of real-world practice (see beginning of Section 2 for detailed rationale), an ITC was conducted to compare polihexanide 0.8 mg/ml with current therapeutic approaches used in clinical practice for treating AK, in line with the approach approved by the EMA as part of the EMA marketing authorisation process. The most appropriate comparative data were selected through a SLR and feasibility assessment, with the retrospective Papa et al. (2020) study identified as the most appropriate source, given that the endpoint definitions fully aligned with the primary endpoint in the ODAK trial.¹² In addition, the study comprised outcome data from N=277 patients with AK, which is a large cohort considering the incidence of AK is <0.2 cases per 50,000.⁸ A majority of the study participants were also treated in the UK (n=177/277; 64%), in some of the same centres as the ODAK trial of polihexanide 0.8 mg/ml. The study and patient baseline characteristics of the Papa et al. (2020) study and ODAK trials were broadly aligned and sufficiently similar to enable an assessment of comparative treatment effectiveness. The Papa et al. (2020) study also provided outcome data for several of the AATs currently used in the UK, rather than the single active comparator used in the ODAK trial, making it a more representative assessment of the real-world treatment effectiveness expected in clinical practice.

IPD availability from all studies in an ITC analysis is considered the gold standard and is preferred whenever possible.⁷⁵ This is because IPD enables analyses with greater statistical power, requires fewer assumptions and allows underlying assumptions to be tested.³³ Historically, naïve comparisons have been performed, whereby the efficacy of one treatment arm

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from one study is directly compared with the efficacy of another treatment arm of a different study.³³ However, this approach is considered to lack robustness due to potentially confounding differences between study populations.³³

The availability of IPD from both the ODAK trial and the Papa et al. (2020) retrospective study permitted a population-adjusted ITC method to be employed (PSA approach) to balance the study populations through weighting before estimation of the treatment effect. The PSA approach is an improvement to a naïve approach which is considered to provide biased estimates of the treatment effect and is generally not recommended.³³ In alignment with the NICE DSU TSD 18, effect modifiers and prognostic variables to be included for adjustment were carefully considered.⁷⁵

ITC approaches are generally considered less robust for estimating treatment effectiveness than comparative data from RCTs. However, there are considerable limitations associated with the active comparator arm of the ODAK trial that mean this study should not be viewed as an RCT and should instead be viewed as a pseudo-single-arm study in the context of the evidence for this appraisal. Therefore, a highly appropriate source of indirect comparative data was sourced from the literature. Additional limitations of the ITC included the different time periods of the two studies that were compared, although this is anticipated to have limited impact of the ITC conclusions, since clinical practice has not changed significantly from the point at which data were collected in Papa et al.¹²

Despite the limitations acknowledged above, the ITC made use of the most robust clinical data available for polihexanide 0.8 mg/ml and current therapeutic approaches for AK i.e. pooled AATs. The methodology of the ITC was robust and developed in line with NICE guidance; the comparative results of the ITC are therefore the most appropriate data for decision-making within this appraisal, as the evidence from Papa et al. (2020) are more reflective of current UK clinical practice than the active comparator arm presented in the ODAK trial.

2.11 Adverse reactions

The safety and tolerability of polihexanide 0.8 mg/ml was investigated in the ODAK trial programme. Treatment compliance is reported for the FAS, while all other safety outcomes are presented for all randomised patients i.e. the safety analysis set (Table 7).

Polihexanide 0.8 mg/ml was generally well-tolerated across a median (range) duration of exposure of 120.0 days (10.0–387.0). Treatment compliance was high in the polihexanide 0.8 mg/ml arm (93.9%; n=62/66 FAS) and the active comparator arm (95.1%; n=58/61 FAS).² There was no clinically meaningful difference in safety outcomes between the 0.8 mg/ml polihexanide and active comparator arm observed. Both treatment regimens were found to be safe and well-tolerated in subjects. Full safety results for ODAK can be found within the ODAK CSR.²

2.11.1 Summary of adverse events

For the overall trial cohort (both treatment arms), a total of 152 AEs were reported in 60 participants (44.8%). Overall, the proportion of participants with ≥1 AE was similar in the 0.8 mg/ml polihexanide (31/69; 44.9%) and active comparator (29/65; 44.6%) treatment groups. According to analysis specified in the ODAK protocol and results in the CSR, there were no SAEs (defined as AEs resulting in death, in-patient hospitalisation, persistent disability or life-

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threatening AEs) or AEs leading to dose reduction of the study treatment reported in the study (based on coding using the MedDRA® [Medical Dictionary for Regulatory Activities] version 20.0–24.0). However, during engagement with the EMA and as reflected in the EPAR report for polihexanide 0.8 mg/ml, AEs were re-evaluated for seriousness according to CIOMS (Council for International Organisations of Medical Sciences) criteria, leading to the further recategorisation of four severe AEs to serious AEs (corneal perforation [1 case in the 0.8 mg/mL polihexanide arm, 1 case in the combination therapy arm], corneal transplant [1 case in the 0.8 mg/ml polihexanide arm], and visual impairment [1 case in the 0.8 mg/mL polihexanide arm]).⁵ Clinical laboratory assessments (haematology, biochemistry and urinalysis) found no clinically relevant changes between baseline and end of study or between treatment arms.² Safety outcomes for the polihexanide 0.8 mg/ml arm (n=69) of the ODAK trial are presented below with results for the active comparator arm (n=65) presented in Appendix D.1.1.

A total of 83 AEs were reported in 31 of 69 (44.9%) patients in the 0.8 mg/ml polihexanide arm. The majority of AEs reported during the study were mild or moderate in severity. Overall, 4 patients out of 69 (5.8%) had 7 severe AEs in the study treatment arm (defined as medically significant but not immediately life-threatening). No AEs were deemed to be related to the study drug by the investigator. An overview of AEs for the polihexanide 0.8 mg/ml arm is presented in Table 24.

Table 24. Adverse events reported in the ODAK trial (safety analysis set)

Adverse event, n (%), #	0.8 mg/ml polihexanide (n=69)
≥1 AE	31 (44.9), 83
≥1 SAE ^a	0 (0.0), 0
Any AE leading to death	0 (0.0), 0
AEs by severity	
Mild	24 (34.8), 46
Moderate	12 (17.4), 30
Severe	4 (5.8), 7
AEs by causality	
Not related	11 (15.9), 17
Unlikely related	10 (14.5), 13
Possibly related	13 (18.8), 35
Probably related	8 (11.6), 18
Related	0 (0.0), 0
AEs by action taken with study treatment	
Dose increased	5 (7.2), 7
Dose not changed	24 (34.8), 48
Dose reduced	0 (0.0), 0
Drug interrupted	11 (15.9), 16
Not applicable	6 (8.7), 12

Footnotes: Percentages are based on the number of patients within each treatment arm, n is the number of participants, # is the number of events. AEs were coded using MedDRA® (Medical Dictionary for Regulatory Activities) version 20.0–24.0. ^aThere were no SAEs according to the coding of AEs using MedDRA as defined in the ODAK SAP, however following EMA feedback on the EPAR, severe AEs were re-evaluated for seriousness, leading to the identification of three SAEs in two patients.

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Abbreviations: AE: adverse event; EMA: European Medicines Agency; EPAR: European Public Assessment Report; SAE: serious adverse event; SAP: statistical analysis plan.

Sources: ODAK Phase 3 CSR: Table 12.2.²

Incidence of common AEs

The most common AEs (incidence >5% of participants) by system organ class (SOC) were: eye disorders, infections and infestations and general disorders and administration site conditions. The most common AEs by preferred term (PT) were eye pain, ocular hyperaemia and lacrimation increased. A summary of AEs with an incidence >5% in the 0.8 mg/ml polihexanide arm by SOC and PT is presented in Table 25.

Table 25. Most commonly reported AEs (>5% of participants; safety analysis set)

Adverse event, n (%), #	0.8 mg/ml polihexanide (n=69)
Any AE	31 (44.9), 83
Eye disorders	23 (33.3), 60
<i>Eye pain</i>	9 (13.0), 11
<i>Ocular hyperaemia</i>	8 (11.6), 9
<i>Lacrimation increased</i>	6 (8.7), 6
Infections and infestations	9 (13.0), 9
General disorders and administration site conditions	4 (5.8), 5

Footnotes: Frequency cut-off is set to 5%. PTs are shown in *italics*. Percentages are based on the number of patients within each treatment arm, n is the number of participants, # is the number of events. AEs were coded using MedDRA® (Medical Dictionary for Regulatory Activities) version 20.0–24.0.

Abbreviations: AE: adverse event; PT: preferred term.

Sources: ODAK Phase 3 CSR: Table 12.3 and 12.4.²

Incidence of common AEs by severity

In the 0.8 mg/ml polihexanide treatment arm, the majority of participants experienced at least one mild or moderate AE: 24 out of 69 participants (34.8%) experienced mild AEs, 12 participants (17.4%) experienced at least one moderate AE and 4 participants (5.8%) experienced at least one severe AE. The most common AEs of any severity (reported in >5% of participants) are presented in Table 26.

Table 26. Most commonly reported AEs by severity (>5% of participants; safety analysis set)

Adverse event, n (%), #	0.8 mg/ml polihexanide (N=69)		
	Mild	Moderate	Severe
Any AE	24 (34.8), 46	12 (17.4), 30	4 (5.8), 7
Eye disorders	16 (23.2), 30	12 (17.4), 27	2 (2.9), 3
<i>Eye pain</i>	6 (8.7), 6	3 (4.3), 4	1 (1.4), 1
<i>Ocular hyperaemia</i>	4 (5.8), 4	5 (7.2), 5	0 (0.0), 0
<i>Lacrimation increased</i>	4 (5.8), 4	2 (2.9), 2	0 (0.0), 0
Infections and infestations	7 (10.1), 7	1 (1.4), 1	1 (1.4), 1

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Adverse event, n (%), #	0.8 mg/ml polihexanide (N=69)		
	Mild	Moderate	Severe
General disorders and administration site conditions	2 (2.9), 2	1 (1.4), 1	1 (1.4), 2

Footnotes: Frequency cut-off is set to 5%. PTs are shown in *italics*. Percentages are based on the number of patients within each treatment arm, n is the number of participants, # is the number of events. AEs were coded using MedDRA® (Medical Dictionary for Regulatory Activities) version 20.0-24.0.

Abbreviations: AE: adverse event; PT: preferred term.

Sources: ODAK Phase 3 CSR: Table 14.3.3.4.²

2.11.2 Study discontinuation

Overall, 11 participants (15.9%) in the 0.8 mg/ml polihexanide arm discontinued from the study treatment. Of these, 7 participants (63.6%) discontinued due to AEs. A summary of reasons for study discontinuation is in Table 27. Results for the active comparator arm (n=65) are presented in Appendix D.1.2.

Table 27. Reasons for study discontinuations (safety analysis set)

Discontinuations, n (%)	0.8 mg/ml polihexanide (n=69)
Prematurely discontinued study ^a	11 (15.9)
Primary reason for discontinuation ^b	
Adverse event	7 (63.6)
Lost to follow-up	1 (9.1)
Ocular intolerance	1 (9.1)
Other	2 (18.2)

Footnotes: ^aPercentages are based on the number of patients within each treatment arm, n is the number of participants; ^bPercentages are based on the number of prematurely discontinued patients within each treatment arm.

Sources: ODAK Phase 3 CSR: Table 14.1.1.3.²

2.12 Ongoing studies

SIFI is committed to confirming the clinical benefit of polihexanide 0.8 mg/ml. The ODAK trial has completed and a CUP has been conducted across European countries, including the UK, with the aim of supporting patients to access a proven and effective therapy.^{59, 60} A full dataset from the CUP is only available for a small number of cases currently and therefore has not been described in detail here.⁵ Evidence from this programme to date confirms findings from the ODAK trial that polihexanide 0.8 mg/ml is a safe and efficacious treatment and offers the potential of lasting cure for people with AK. Future publications from the CUP will offer a real-world perspective on the AK patient population experiencing the greatest unmet need on current practice, for whom their healthcare provider believed polihexanide 0.8 mg/ml would offer benefit.

2.13 Interpretation of clinical effectiveness and safety evidence

2.13.1 Clinical efficacy of polihexanide 0.8 mg/ml

Results from the ITC were supportive of superior efficacy of polihexanide 0.8 mg/ml over current therapeutic approaches for AK, with polihexanide 0.8 mg/ml resulting in a significantly higher MCR compared with the pooled AAT comparator. Use of the ITC as the primary source of comparative evidence for this appraisal (as opposed to the ODAK trial in which the active comparator arm was not reflective of real-world practice) allowed the real-world comparative efficacy of polihexanide 0.8 mg/ml versus current AATs to be fully captured, and therefore was able to robustly inform comparative efficacy estimates (as described at the beginning of Section 2).

Results of the ITC were supported by outcomes from the polihexanide 0.8 mg/ml arm in the ODAK trial, which was demonstrated to be an effective treatment for patients with AK. The MCR for polihexanide 0.8 mg/ml of 84.85% achieved in the ODAK trial is one of the highest reported since 2000 and is higher than those reported in comparable studies.^{29, 46, 76} Improvements compared with baseline were also observed across a range of secondary endpoints including visual acuity and corneal abnormality, and rates of surgery use and adjunctive therapy remained low. While corneal scarring did increase from baseline to end-of-study visit for patients receiving polihexanide 0.8 mg/ml, as expected with administration of eyedrops,⁷⁷ this was comparable to the results for the active comparator arm (see Appendix J.1.5). Although the active comparator arm in the ODAK trial is not considered a suitable comparator, a comparison of the therapeutic approaches is appropriate in this instance given that corneal scarring is related to the administration of eye drops in general, rather than the treatment class. The results support the role of polihexanide 0.8 mg/ml in addressing the significant unmet need for effective, safe and standardised treatments that are readily available and can improve medical cure rates and a broad range of other clinically and patient-relevant endpoints in AK.

While the trial did not demonstrate superiority of polihexanide 0.8 mg/ml over the comparator, non-inferiority of polihexanide 0.8 mg/ml versus the active comparator arm was demonstrated (see Appendix J.1.2) despite the fact that the efficacy of the comparator was likely to have been higher than would be observed in a real-world setting.

The ITC and ODAK trial results are further supported by recent evidence published from CUPs (see Section 2.12) in Europe, in which real-world treatment with polihexanide 0.8 mg/ml led to a MCR without surgery of 91.7% (n=11/12 eyes) in one study (Franch et al, 2024), and complete cure in another two cases with no recurrence of infection after seven months (Di Zazzo et al, 2024).^{59, 60} This RWE supports the generalisability of the effectiveness of polihexanide 0.8 mg/ml, demonstrated in the ITC, to current clinical practice.

2.13.2 Safety evidence for polihexanide 0.8 mg/ml

The safety of polihexanide 0.8 mg/ml was investigated in the Phase 3 ODAK trial. The overall polihexanide 0.8 mg/ml exposure across the ODAK trial allows for an adequate assessment of safety in the context of this orphan disease, with around 120 days of exposure at the end of the study.

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In the ODAK trial, polihexanide 0.8 mg/ml demonstrated an acceptable safety profile patients with AK, with most TEAEs reported being consistent with those observed in AK in real-world clinical practice. TEAEs were generally mild to moderate in severity and none were deemed related to the study drug. No SAEs were observed (according to the analysis specified in the ODAK protocol and as reported in the CSR) and no deaths were reported.⁵ Polihexanide 0.8 mg/ml is therefore considered to be well-tolerated, with an acceptable safety profile, which aligns with the EMA's overview of polihexanide 0.8 mg/ml in their EPAR report.⁵

2.13.3 Strengths and limitations of the clinical evidence base

Strengths

- The Papa et al. (2020) study, used as the primary source of comparative data in this appraisal, has several key strengths. Firstly, the study comprised outcome data from N=277 participants with AK, which is a large cohort considering the incidence of AK is <0.2 cases per 50,000.⁸ A majority of the study participants were also treated in the UK (n=177/277; 64%), in many of the same centres as the ODAK trial of polihexanide 0.8 mg/ml. The study and patient baseline characteristics of the Papa et al. (2020) study and ODAK trials were broadly aligned and sufficiently similar to enable an assessment of comparative treatment effectiveness. The Papa et al. (2020) study also provided outcome data for several of the AATs currently used in the UK, rather than the single active comparator used in the ODAK trial, making it a more representative assessment of the real-world treatment effectiveness expected in clinical practice. Finally, the outcome definitions of the primary endpoint were identical in Papa et al. (2020) and the ODAK trial, making a robust ITC feasible.
- The ITC presented in Section 2.10, which forms the primary source of comparative evidence for polihexanide 0.8 mg/ml, used an SLR and feasibility assessment to source the most appropriate comparative evidence, that reflects the real-world use of current AATs. As IPD were available for both the polihexanide 0.8 mg/ml treatment arm from ODAK and from Papa et al. (2020), a population-adjusted ITC method could be used, to balance the study populations through weighting before estimating the treatment effect (PSA approach). With this methodology, potential prognostic factors and/or treatment effect modifiers identified through clinical expert opinion were adjusted for when estimating treatment effectiveness. This methodology is more robust than a naïve comparison and aligns with NICE's guidance (TSD 17) on statistical approaches for conducting an ITC where IPD are available.⁷⁴
- Despite the limitations associated with the active comparator arm of the ODAK study discussed previously, the ODAK trial itself was a randomised, active-controlled, double-blind multicentre international study. Given that these real-world limitations did not apply to the polihexanide 0.8 mg/ml treatment arm, this study provides robust evidence for the efficacy of polihexanide 0.8 mg/ml. The MCR reported for polihexanide 0.8 mg/ml of 84.85% was one of the highest reported to date, demonstrating its clear value in the treatment of AK.^{29, 46, 76}

The relevance of the evidence base to the NICE final scope is further supported by the following:

- **Population:** All of the patients included in the ITC (from Papa et al. [2020] and the ODAK trial) had a diagnosis of AK and patients in the ODAK trial were ≥12 years of age, in line with the decision problem
- **Comparators:** Polihexanide 0.8 mg/ml was compared with pooled AAT, which best reflects the lack of standardised care and therefore heterogeneity in the care received by patients in

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the UK; the appropriateness of the comparative data from this study was in terms of therapeutic approaches included was confirmed by responses in the 2023 Delphi panel of 10 UK ophthalmologists.¹¹ Use of the Papa et al. (2020) study as a source of comparative data in the ITC enabled the effectiveness of polihexanide 0.8 mg/ml and the therapeutic approaches listed in the NICE scope to be captured.

- **Outcomes:** Across the ODAK trial and the ITC, MCR was used as the primary endpoint, which represents a clinically- and patient-relevant endpoint, as the primary goal of AK treatment is eradication of *Acanthamoeba* to avoid further damage to the eye. The ODAK trial also explored a range of other clinical outcomes including visual acuity, HRQoL and rate of use of surgery, providing a comprehensive assessment of the clinical value of polihexanide 0.8 mg/ml

Limitations

- As discussed previously, the active comparator arm of the ODAK trial was not reflective of real-world UK clinical practice, with higher-than-expected treatment efficacy observed in the active comparator arm, likely due to standardisation of treatment timing, compounding and protocols in the trial. Efficacy gains that would be expected in a real-world setting versus the comparator were therefore limited for polihexanide 0.8 mg/ml. The polihexanide 0.8 mg/ml arm is not subject to the same issues of generalisability of the active comparator arm, as unlike current AATs, it would represent a licensed treatment, guided by a SmPC and a standardised protocol that would meet regulatory standard. For this reason, the ODAK trial is presented as a pseudo single-arm study for this appraisal, with comparative evidence sourced from the literature, in line with the approach approved by the EMA as part of marketing authorisation.
- The Papa et al. (2020) study was conducted between 1991–2012, which may be considered outdated. Nevertheless, the long study duration of Papa et al. (2020) carries the significant advantage of being able to include a relatively high number of patients (N=277), despite the very rare nature of AK, making the comparative cohort more robust than for instance, a short-term study with a smaller cohort. Further, 83% of participants in the study were diagnosed after 2001.¹²

2.13.4 Conclusion

Results of the ITC, using retrospective, observational IPD from the largest study of clinical outcomes in AK patients to date, was supportive of superior efficacy of polihexanide 0.8 mg/ml over current therapeutic approaches for AK in the primary endpoint of MCR. The ITC results are supported by outcomes in the ODAK trial, in which an MCR of greater than 84% was observed for polihexanide 0.8 mg/ml, alongside improvements across a range of other clinically-relevant outcomes.^{29, 46, 76} Polihexanide 0.8 mg/ml was also demonstrated to have an acceptable safety profile and was well-tolerated, with TEAEs in the ODAK trial mostly being mild or moderate. The evidence presented therefore highlights that polihexanide 0.8 mg/ml would provide a safe and efficacious treatment for people with AK.

Given the current lack of standardised treatments, there is an urgent unmet need for a licensed, readily available treatment which is produced to GMP quality standards and provided using a standardised protocol. Polihexanide 0.8 mg/ml monotherapy is the first licensed treatment approved specifically for AK and this will allow rapid access to a proven efficacious treatment at the point of diagnosis.

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3 Cost effectiveness

Model approach and structure

- No prior cost-effectiveness analyses or previous NICE evaluations have been conducted in AK. Accordingly, a *de novo* cost-effectiveness model (CEM) was developed for this submission to evaluate the cost-effectiveness of polihexanide 0.8 mg/ml compared with a pooled AAT comparator in people with AK.
- A *de novo* decision tree combined with a semi-Markov model with time-dependent transitions was developed. The decision tree segment of the model was used to model the first 12 months of AK infection, due to its ability to accommodate a wide variety of treatment decisions and outcomes during first year of AK treatment.
- During the decision tree segment of the model, patients can achieve a medical cure, switch to an alternative AAT or undergo therapeutic surgery within the first 12 months of AK infection.
- Upon exit from the decision tree at the end of Year 1, patients transition into a semi-Markov model, which was used to capture longer-term outcomes and costs associated with AK and its treatment. Patients are stratified into health states according to the final health state achieved in the decision tree, e.g. whether their AK infection remains unresolved, their visual acuity following AK resolution, and whether they have lost functionality in the affected eye.

Model inputs

- Cure is considered the primary goal of treatment and the most important measure for patients and clinicians and therefore MCR was used as the key efficacy input in the model. MCR data for polihexanide 0.8 mg/ml were informed by the primary endpoint of the ODAK trial at 12 months, whilst MCR data for the pooled AAT comparator were informed by the ITC analysis which assessed the comparative efficacy of polihexanide 0.8 mg/ml versus the pooled AAT comparator.
- Other model inputs included those relating to therapeutic and optical surgeries (and associated graft failure), BCVA outcomes associated with events in the model and infection recurrence. These outcomes are dependent on modelled patients achieving or not achieving medical cure within the first 12 months of treatment. Clinical model inputs were primarily sourced from the polihexanide 0.8 mg/ml treatment arm of the ODAK trial, the retrospective Papa et al. 2020 study and results from a SIFI-conducted UK Delphi panel.^{4, 11, 29}
- AK is generally not a life-threatening disease; however, previous studies identified an association between visual impairment and mortality.⁷⁸ The analysis therefore considers a higher mortality than the general population for poor vision, severe vision loss and loss of eye functionality.
- Adverse events were not included in the model as they occurred at a similar frequency in both treatment arms of the ODAK study (44.9% in the polihexanide 0.8 mg/ml arm and 44.6% in the active comparator arm).
- Health-state utility values (HSUVs) were assigned to patients in each of the health states in the CEM: AK infection, cured with poor vision, cured with severe vision loss and loss of eye functionality. HSUVs were derived from EQ-5D-5L data from the ODAK trial and cross-walked to EQ-5D-3L using the method reported by Hernández Alava et al. (2017).^{79, 80}

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- The model considers utility decrements associated with long-term complications of AK such as lacrimation, photophobia, pain, depression and anxiety. These utility decrements were derived from published literature, with the prevalence of each complication (by health state) obtained from the UK Delphi Panel.^{81, 82}
- One-off disutilities associated with intensive treatment, therapeutic surgery, graft rejection and optical surgery were also included. Caregiver disutilities were also included and were sourced from NICE HST11 of a proxy ophthalmological disease.⁸³
- Costs included in the model comprised drug acquisition costs, hospitalisation costs, surgery (therapeutic and optical) costs and healthcare resource use (HCRU) costs.
- In line with the NICE reference case,⁸⁰ the analysis was conducted from the perspective of the NHS and PSS over a lifetime time horizon, which reflects the lifelong nature of visual impairment caused by AK infection. A longer-term horizon was also used to ensure potential recurrence of AK infection was captured.

Cost-effectiveness model results

- Over a lifetime horizon in the base case of the model, polihexanide 0.8 mg/ml (with the proposed PAS discount) was associated with +2.56 incremental QALYs at an incremental cost of £█████ versus the pooled AAT comparator (deterministic). The resulting ICER was £█████ per QALY gained.
- As such, considering the cost-effectiveness threshold of £20,000–£30,000 per QALY polihexanide 0.8 mg/ml represents a cost-effective treatment use of NHS resources versus the pooled AAT comparator for patients with AK.
- The majority of scenario analyses, which explored key modelling assumptions and approaches, resulted in polihexanide 0.8 mg/ml remaining a cost-effective use of NHS resources, demonstrating the robustness of the economic model results.
- Probabilistic sensitivity analysis (PSA) was conducted to assess the impact of uncertainty around parameter values on the results of the base-case model. In the PSA based on 1,000 simulations, the mean PSA results were similar to the base case results.
- Deterministic sensitivity analyses (DSA) were also conducted and demonstrated that the parameters with the greatest influence on the base-case ICER were the discount rate applied for the outcomes, the RR for the 12-month MCR for polihexanide 0.8 mg/ml versus the pooled AAT comparator (ODAK trial versus Papa et al. 2020) and treatment duration.

3.1 Published cost-effectiveness studies

A *de novo* economic SLR was conducted on 25th July 2022 and subsequently updated on 14th April 2025. The objective of this SLR was to identify economic evaluations, utility studies and cost and healthcare resource use (HCRU) studies associated with treatment options for patients with AK or microbial keratitis (MK).⁸⁴ The SLR and its update were conducted from a global perspective and therefore comparator therapies beyond those relevant to the decision problem of this appraisal were eligible for inclusion. The population of people with AK or MK explored in the economic SLR was broader than the scope of the decision problem, to ensure no relevant economic evidence was missed. Of the records identified as part of the economic SLR, no previous economic evaluations or cost effectiveness studies were identified in AK.

Full details of the cost-effectiveness SLR methods and results, including search terms and eligibility criteria, can be found in Appendix E.

3.2 Economic analysis

Given the absence of published economic evaluations and relevant CEMs in AK, a *de novo* CEM was developed for the purpose of this submission. The CEM was built in Microsoft Excel® and was designed in close coordination with health economic modelling experts and expert clinicians.

The objective of the CEM was to evaluate the cost-effectiveness of polihexanide 0.8 mg/ml versus a pooled AAT comparator, in line with the comparative effectiveness evidence presented in Section 2.10 and the decision problem presented in Section 1.1.

The model was developed from the perspective of the National Health Service (NHS) and Personal Social Services (PSS) in the UK and include direct medical costs over a lifetime horizon, in alignment with the NICE reference case.³ Sections 3.2.1, 3.2.2 and 3.2.3, present details on the patient population, the model structure and the included interventions and comparators, respectively.

3.2.1 Patient population

The patient population considered in this CEM was people with AK aged 12 and over. This population aligns with the full anticipated marketing authorisation for polihexanide 0.8 mg/ml in this indication, and the population detailed in the NICE final scope.

3.2.2 Model structure

Choice of model and rationale

There are no previously published models in AK and NICE have not previously assessed a treatment for AK. Accordingly, a *de novo* decision tree combined with a semi-Markov model with time-dependent transitions was built in Microsoft Excel® to assess the cost-effectiveness of polihexanide 0.8 mg/ml in the treatment of AK.

In the context of AK, achieving a rapid cure is crucial, particularly within the first year. As described in Section 1.3.5, people with AK can receive a range of different therapeutic approaches, reflecting a lack of standardised care. As a result, outcomes may vary widely in line with the heterogeneity of care received, which can also lead to frequent changes in therapeutic approach. As a result, the first year following treatment initiation represents a period in which patients undergo an intensive treatment phase whilst also experiencing multiple, often sequential, outcomes including resolution of infection, changes in visual acuity, treatment switching and therapeutic surgery. A decision tree model was therefore chosen for this initial 12-month period due to its ability capture the wide variety of treatment decisions and time-sensitive clinical events with sufficient granularity. The structure provides the flexibility to accommodate the complex sequencing of clinical outcomes within a fixed time horizon and reflects the compressed timeframe in which important and varied health events occur, which would be less efficiently modelled using a standard Markov process with fixed cycle transitions. The decision tree also allows the initial intensive treatment phase to be effectively captured within the model, therefore more accurately reflecting the impact of AK infection on patients. The decision tree

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allows estimation of the proportion of the patient cohort that remain infected with AK (and therefore are assumed to await therapeutic surgery), whilst also capturing the visual acuity of patients who experience resolution of AK infection within the first year.

Once the infection resolves via AAT and/or therapeutic surgery, patients remain in the same health state until longer-term events occur, such as optical surgery, graft failure and associated visual outcomes. For these longer-term outcomes, a decision tree is inadequate due to its complexity in long-term scenarios. Therefore, a semi-Markov model was employed in order to capture long-term aspects of the AK treatment pathway.

Model structure

The CEM uses a decision-tree and semi-Markov approach to track the development of the modelled cohort through the health states and measure the costs and health outcomes from initiation of treatment until the end of the time horizon. An outline of the two substructures is presented below.

Decision tree

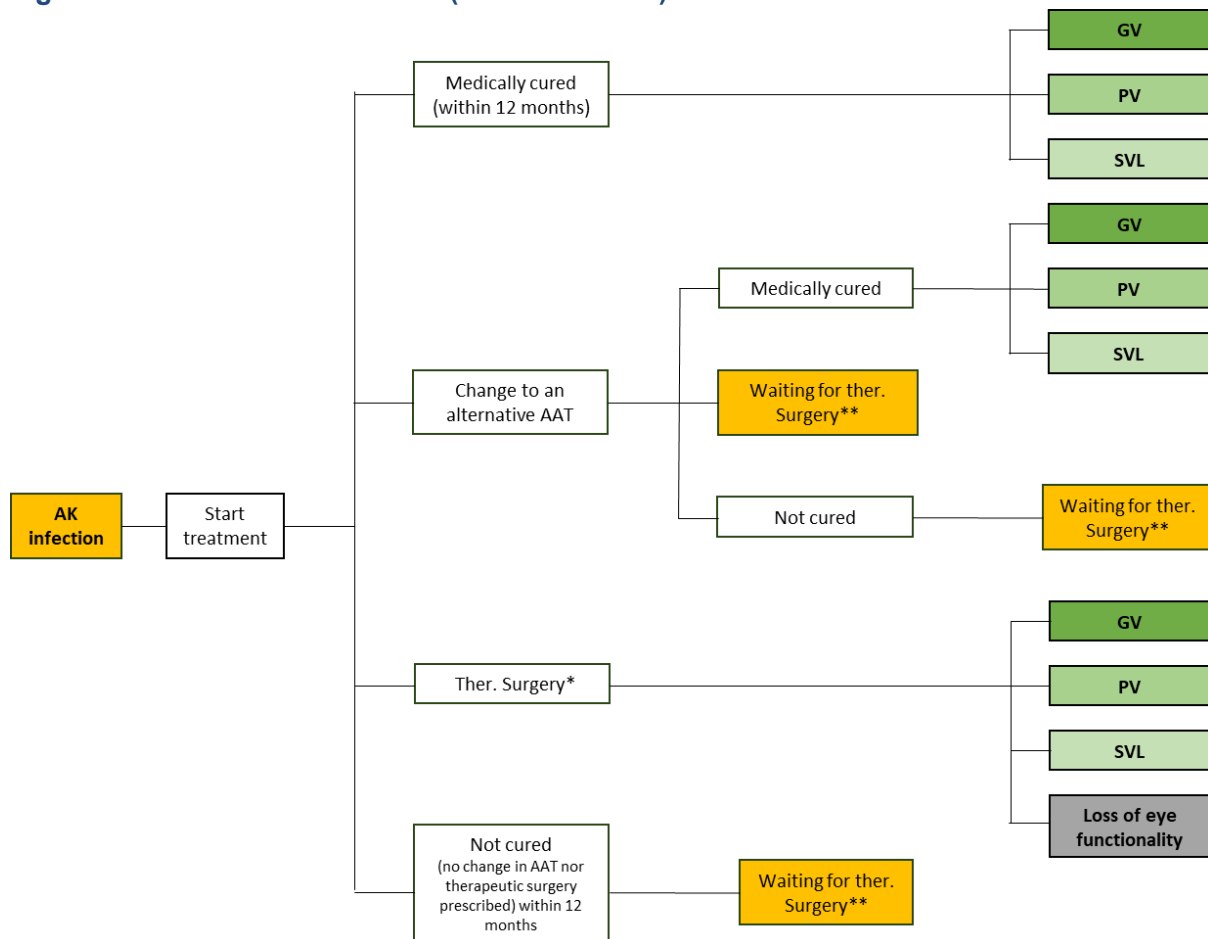
Upon entry into the decision tree segment of the model, all patients are alive and assigned to receive treatment with either polihexanide 0.8 mg/ml or the pooled AAT comparator (Figure 5). Within the CEM, the entire cohort enters the model at the AK infection node of the decision-tree (i.e. with active AK infection) and can follow any of the following different pathways within the first 12 months of AK infection:

- **Achieve a medical resolution of AK infection within 12 months on initial AAT:** the cohort can achieve a medical cure with the initial treatment with good vision, poor vision, or severe vision loss (defined in Table 28).
- **Change in AAT** (treatment switch to alternative AAT): a proportion of the cohort who do not achieve a medical cure with initial treatment may switch AAT. Under treatment with the new AAT, patients can then either achieve a medical cure of AK infection (aligning to pathway above), undergo therapeutic surgery or fail to achieve AK resolution by the end of Year 1 ('not cured'), in which case they are assumed to be awaiting therapeutic surgery.
- **Therapeutic surgery:** a proportion of patients who are unresponsive to medical treatment will undergo therapeutic surgery. The model assumes that patients must wait to receive therapeutic surgery:
 - If the duration of initial therapy plus the waiting time for the therapeutic surgery is less than one year, then the cohort is assumed to undergo therapeutic surgery within the first year and the proportion of the cohort in each of the BCVA levels and who experience loss of eye functionality after surgery are estimated using the decision tree.
 - Similarly, for patients who switch therapies within the first year, if the duration of initial treatment plus the duration of treatment with alternative AAT plus the waiting time for the therapeutic surgery is less than one year, the cohort will undergo therapeutic surgery within the first year, modelled as part of the decision tree.

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- If the duration of initial therapy plus the waiting time for the therapeutic surgery is over one year, patients enter the sub health state for 'waiting for therapeutic surgery' in the semi-Markov model (Figure 6).
- **Not cured at end of Year 1:** a proportion of the cohort are assumed not to achieve a resolution of the AK infection during the first year, with no change in AAT nor therapeutic surgery prescribed during this time; this cohort are assumed to be awaiting therapeutic surgery.

Figure 5: Decision tree structure (first 12 months)



Footnote: *Depending on the waiting time and treatment duration of initial treatment, patients may undergo therapeutic surgery within the first year (captured in the decision tree subsection of the model), or between Year 1 and Year 2 (captured in the semi-Markov subsection of the model). **Depending on the waiting time, treatment duration of initial treatment and alternative AAT, patients may undergo therapeutic surgery within the first year (captured in the decision tree subsection of the model), or between Year 1 and Year 2 (captured in the semi-Markov subsection of the model). The model assumes that all patients that did not achieve medical resolution within two years undergo therapeutic surgery and enter the sub health state for 'waiting for therapeutic surgery' in the semi-Markov model. If therapeutic surgery is received before the end of Year 1, patients will start the semi-Markov model in one of the green health states stratified by visual acuity, whereas if therapeutic surgery is received between Year 1 and Year 2, patients will start the semi-Markov model in the sub health state for 'waiting for therapeutic surgery' in the AK infection state.

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

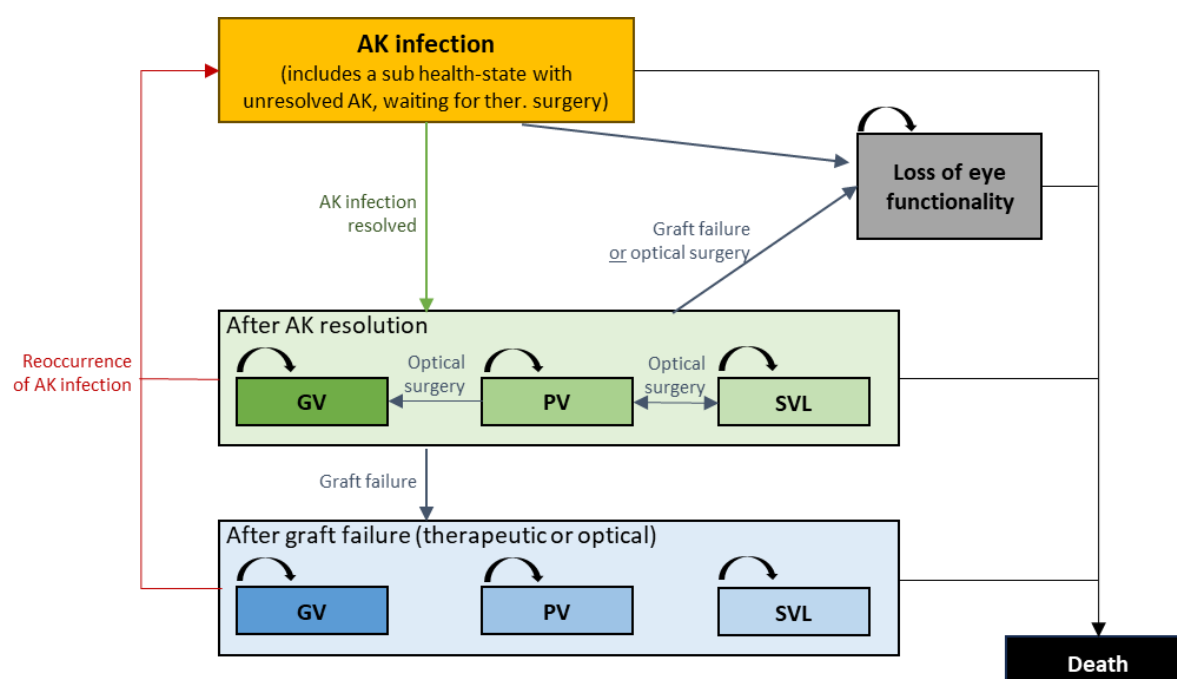
Semi-Markov

Upon exit from the decision tree at the end of Year 1, patients are stratified into health states based on whether their AK infection remains unresolved, their visual acuity following AK resolution, and whether they have lost functionality in the affected eye (Figure 6). The model assumes that all patients that did not achieve medical resolution within two years undergo therapeutic surgery and enter the sub health state for 'waiting for therapeutic surgery' under 'AK infection' (Figure 6).

After a patient achieves resolution of the infection (either through successful treatment with AAT or therapeutic surgery), patients may remain in the same health state until one of the following events occurs:

- **Optical surgery** (see Section 3.3.3): A proportion of the cohort with poor vision or severe vision loss may undergo optical surgery. The cohort is assumed to wait for the optical surgery for a defined time (up to three years). Following the optical surgery, the cohort may improve, worsen, or maintain the same BCVA, or lose their eye functionality altogether. It is assumed that patients with good vision after AK resolution would not require optical surgery.
- **Graft failure** (see Section 3.3.3): The cohort may experience graft failure up to three years after receipt of surgery (therapeutic or optical keratoplasties). The number of patients at risk from Year 3 onwards was relatively small and therefore this conservative assumption was used to avoid unnecessary complexity in the model. Following the graft failure, patients are distributed in health states according to their BCVA or loss of eye functionality. Graft failure is assumed to only take place within the semi-Markov model. Graft failure rates are not considered within the 12-month decision tree model, since therapeutic surgery is likely to be performed towards the end of Year 1 (following time taken for patients to receive initial AAT, to switch AAT if they do not achieve a cure, and the waiting time for surgery) and therefore is only reflected in Year 2.
- **Recurrence of AK infection** (see Section 3.3.3): A probability per cycle of reoccurrence of AK infection is applied to the proportion of the cohort in the cured health states (good vision, poor vision, or severe vision loss) after AK resolution, up to Year 15 of the time horizon. This was validated by a UK clinician, who agreed that 15 years appropriately represents the latest possible timepoint that AK may reoccur after an initial cure. The cohort that experiences a recurrence of AK infection will re-enter the AK infection node of the decision-tree.
- **Death** (see Section 3.3.4): The cohort could transition to death from any alive health state, with probabilities based on national statistics for the age-specific mortality rate in the population and values reported in the literature describing association between visual impairment and mortality.⁷⁸

Figure 6: Semi-Markov model structure



Footnote: Upon recurrence of AK infection patients will move back into the AK infection health state, which is modelled through the decision tree (Figure 5). Consequently, patients are assumed to re-enter the AK infection node of the decision tree upon recurrence.

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

Defining visual impairment

Costs and quality-of-life in individuals with AK are expected to vary depending on presence of AK infection and on the level of visual impairment after AK infection is resolved. After patients achieve a resolution of AK infection, they are distributed within the model according to their vision outcome defined by BCVA ranges. The definitions of visual impairment used in the CEM are presented in Table 28.

Table 28: Definitions of visual impairment in the model

Visual impairment	Definition
AK infection	Patients with AK infection (not resolved)
Good vision	Patients who achieved a resolution of the AK infection (with or without therapeutic surgery) with BCVA $\geq 20/40$ (logMAR ≤ 0.3)
Poor vision	Patients who achieved a resolution of the AK infection (with or without therapeutic surgery) with BCVA $\geq 20/200$ and $< 20/40$ (logMAR ≤ 1.00 and > 0.3)
Severe vision loss	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

Abbreviations: AK: Acanthamoeba keratitis; BCVA: best-corrected visual acuity; LogMAR: Logarithm of the Minimum Angle of Resolution.

The threshold 20/40 (i.e. 0.5 measured in Snellen scale with glasses or contact lenses, if necessary) is the required minimum BCVA for the driving licence in England.^{85, 86} Severe vision loss was defined as <20/200 (i.e. <0.05 measured in Snellen scale); this threshold is in line with the definition of severe vision loss in the Papa et al. (2020) study and the classification of severity of vision impairment defined by World Health Organisation (WHO).^{29, 87}

As discussed in Section 1.3.3, in addition to vision loss, patients may also experience long-term pain, lacrimation, photophobia, anxiety and depression, affecting HRQoL. Therefore, the model also captures detriments to quality of life associated with these long-term complications (see Section 3.3.3).

Summary of modelling framework

A summary of the key features of the economic analysis and their justifications are presented in Table 29. Of note, no previous evaluations have been conducted for treatments for people with AK.

Table 29: Features of the economic analysis

Factor	Current evaluation	
	Chosen value	Justification
Time horizon	Lifetime horizon (up to age 100)	In line with the NICE reference case and reflects the lifelong nature of visual impairment caused by AK infection. A longer-term horizon was also used to ensure potential recurrence of AK infection was captured⁸⁰
Severity modifier	NA	Despite the severity of the condition and large unmet need in people with AK, polihexanide 0.8 mg/ml does not meet the criteria for a severity modifier in this indication
Discount rates	3.5% per year for both costs and outcomes	In line with the NICE reference case⁸⁰
Cycle length	1 year, including half-cycle correction	- The cycle-length reflects the timespan of the ODAK trial for the primary endpoint - The cycle length was deemed appropriate to capture meaningful changes in clinical outcomes, given that events captured in the model (surgeries, recurrence) are unlikely to occur multiple times in a given year - A half-cycle correction was employed to adjust for the distribution of costs and benefits accrued throughout each cycle

Factor	Current evaluation	
	Chosen value	Justification
Perspective	NHS and personal social services	In line with the NICE reference case⁸⁰
Source of costs	- National Schedule of NHS Costs 2023/24⁸⁸ - PSSRU 2024⁸⁹ - NHS Payment Scheme⁹⁰ 2025/26 - BNF 2025⁹¹	In line with the NICE reference case⁸⁰
Source of utilities	EQ-5D-5L results collected in the ODAK trial, cross-walked to EQ-5D-3L using mapping as described by Hernández-Alava which is recommended by NICE guidance^{80, 92}	EQ-5D-5L data from the ODAK trial cross-walked to the EQ-5D-3L index values provide the most appropriate source of HRQoL data, aligning with NICE's preference.³ These are the most applicable utilities as they are derived directly from the patient population of interest (i.e., people with AK aged 12 years and over)
Source of disutilities	- Utility decrements associated with long-term complications of AK such as lacrimation, photophobia, pain, depression and anxiety were derived from published literature^{81, 82} - One-off disutilities associated with intensive treatment, therapeutic surgery, graft rejection and optical surgery were also included - Caregiver disutilities sourced from NICE HST11 of a proxy ophthalmological disease.⁸³	The long-term complications of AK, along with the substantial burden of surgery and its impact on caregivers, are unlikely to be fully captured within the 12-month ODAK trial period

Abbreviations: AK: Acanthamoeba keratitis; HRQoL: health-related quality of life; HST: highly specialised technology; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSSRU: Personal Social Services Research Unit.

3.2.3 Intervention technology and comparators

Intervention

The intervention considered in the CEM was polihexanide 0.8 mg/ml. The dosing for polihexanide 0.8 mg/ml included in the model is in line with the regimen included in the Phase 3 ODAK trial:⁴

- Day 0–5: 1-hourly drops (16 drops in a day) for 5 days
- Day 6–12: 2-hourly drops (8 drops in a day) for 7 days

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- Day 13–19: 3-hourly drops (6 drops in a day) for 7 days
- Day 20 onwards: 4 drops in a day until resolution (maximum 12 months)

Comparator

In the absence of an established standard of care or reimbursed treatments for AK in the UK (as discussed in Section 1.3.5), the CEM adopts a “current practice” comparator, represented by a group of AATs currently used in routine clinical management, referred to as the pooled AAT comparator. This approach reflects the highly heterogeneous nature of AK treatment in England and Wales, whereby patients with AK are treated with a diverse range of AATs, often in varying combinations and dosing regimens. The composition of therapeutic approaches and sequencing vary both within and between treatment centres across England and Wales.

Polihexanide 0.8 mg/ml is anticipated to be used as a first-line, first-in-class treatment for AK. It is therefore appropriate to compare its cost-effectiveness against the collective mix of current therapeutic approaches, rather than any single AAT, which it would plausibly replace in clinical practice. By pooling the AATs used in current UK practice into a single representative comparator arm, the model captures the real-world diversity of current care, offering a pragmatic and realistic basis for assessing the value of polihexanide 0.8 mg/ml. This approach avoids over-reliance on any one regimen and enhances the generalisability of the results to the NHS context. The resulting ICER, comparing polihexanide 0.8 mg/ml to the pooled AAT comparator, is therefore considered the most relevant and appropriate estimate of cost-effectiveness for decision-making in the current UK clinical landscape.

The distribution of therapeutic approaches within the pooled AAT comparator used in the base case is presented in Table 30. These represent the most frequently used therapeutic approaches in the UK, according to 10 expert clinicians consulted as part of a two-round Delphi panel, which systematically validated insights on the epidemiology of AK in the UK, local treatment patterns, pharmacological options, surgical options and HCRU. The full methodology for the Delphi panel is presented in Appendix K.

Table 30: Distribution of current therapeutic approaches for patients with AK in UK clinical practice (UK Delphi panel)

AAT in pooled AAT comparator	Mean (%) (90% CI)
Polihexanide 0.2 mg/ml + diamidine	52.3 (43.9–60.8)
Polihexanide 0.2 mg/ml monotherapy	14.5 (11.2–17.7)
Chlorhexidine 0.2 mg/ml + diamidine	13.7 (10.7–16.7)
Polihexanide 0.6 mg/ml monotherapy	8.5 (5.1–11.9)
Polihexanide 0.6 mg/ml + diamidine	6.5 (4.4–8.5)
Diamidine monotherapy	1.9 (1.1–2.7)
Chlorhexidine 0.2 mg/ml monotherapy	1.4 (0.7–2.2)
Polihexanide 0.2 mg/ml + chlorhexidine + diamidine	0.9 (0.5–1.2)
Polihexanide 0.2 mg/ml + chlorhexidine	0.3 (0.2–0.4)

Abbreviations: AAT: anti-amoebic therapy; AK: Acanthamoeba keratitis; CI: confidence interval; UK: United Kingdom.

Source: SIFI Delphi Panel 2023. (Table 4).¹¹

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Additionally, a scenario analysis was explored (see Section 3.11.3), in which the treatment distribution within the pooled AAT comparator was based on data from Papa et al. 2020; the study used as the source for the clinical effectiveness of the pooled AAT comparator in the ITC (Section 2.10). The treatment distribution from the Papa et al. study is presented in Table 31.

Table 31: Distribution of current therapeutic approaches for patients with AK based on data from Papa et al. 2020

AAT distribution in Papa et al. 2020	Proportion (%)
Polihexanide 0.2 mg/ml + Propamidine 1 mg/ml	48.90
Polihexanide 0.2 mg/ml monotherapy	19.38
Diamidine monotherapy	11.01
Diamidine + Chlorhexidine 0.2 mg/ml	9.25
Chlorhexidine 0.2 mg/ml monotherapy	6.17
Polihexanide 0.2 mg/ml + Chlorhexidine 0.2mg/ml	0.44
Polihexanide 0.2 mg/ml + Chlorhexidine 0.2 mg/ml + diamidine	0.88
Polihexanide 0.6 mg/ml monotherapy	1.32
Polihexanide 0.6 mg/ml + diamidine	2.64

Abbreviations: AAT: anti-amoebic therapy; AK: Acanthamoeba keratitis.

Source: Papa et al. 2020.²⁹

3.3 Clinical parameters and variables

3.3.1 Population characteristics

The target population comprises patients diagnosed with AK, in accordance with the expected indication for polihexanide 0.8 mg/ml and the pivotal trial population. Baseline data used in the model were obtained from the baseline characteristics of the total population in the ODAK trial (N=127) as presented in Table 32. As outlined in Table 21 in Section 2.10.2, the baseline characteristics of the ODAK trial were broadly aligned with the baseline characteristics reported in the retrospective Papa et al. 2020 study. Age and gender are included in the model in order to inform general mortality inputs, whilst body weight is included to estimate the cost of systemic immunosuppressive drugs. Mean body weight was calculated based on general population weight data from NHS Digital 2022 (84.2 kg and 70.2 kg for males and females, respectively) and the percentage of male patients within the ODAK trial.

Table 32: Baseline characteristics of modelled cohort

Baseline characteristic	Model Input	Source
Mean initial age (years)	36.70	Dart et al. 2024. ⁴
Male (%)	41.73	Dart et al. 2024. ⁴
Mean body weight (kg)	76.04	NHS Digital 2022. (Table 6, corrected value). ⁹³

Source: Dart et al. 2024 (Table 1);⁴ NHS Digital. 2022.⁹³

3.3.2 Clinical inputs for the first 12 months

As discussed in Section 3.2.2, a decision-tree approach was used to model the initial 12-month period following AK infection. The clinical inputs for this initial 12-month period are presented below.

3.3.2.1 MCR

As discussed in Section 1.3.2, cure is considered the most important measure for patients and clinicians and therefore MCR was used as the key efficacy input in the model. MCR was defined as the rate (proportion) of patients cured by each treatment without the need for surgery or a change of AAT, and independent of visual acuity, within 12 months of randomisation.

MCR data for polihexanide 0.8 mg/ml were informed by the primary endpoint of the ODAK trial (MCR at 12 months; see Section 2.6.1).

12-month MCR data for the pooled AAT comparator were informed by the ITC analysis which assessed the comparative effectiveness of the pooled comparator versus polihexanide 0.8 mg/ml (as described in Section 2.10). RRs were calculated for polihexanide 0.8 mg/ml versus the pooled AAT comparator, based on the number of patients cured within 12 months in the ODAK trial and Papa et al. study for polihexanide 0.8 mg/ml and the pooled comparator, respectively. The inverse of this value (RR for the pooled AAT comparator versus polihexanide 0.8 mg/ml) was then used to calculate the estimated 12-month MCR for the pooled AAT comparator (Table 33).

Table 33: 12-month MCR data for polihexanide 0.8 mg/ml and pooled AAT

Baseline characteristic	Model Input
Polihexanide 0.8 mg/ml	
12-month MCR (%)	84.85
Pooled AAT	
RR for 12-month MCR polihexanide 0.8 mg/ml versus pooled AAT (95% CI)	■ (■)
Estimated 12-month MCR (%)	■

Footnote: In line with the definitions presented in the ODAK trial and the retrospective Papa et al. study, cure was defined as elimination of *Acanthamoeba*, evidenced by an intact corneal epithelium and no signs of ocular inflammation after one month without anti-amoebic or anti-inflammatory treatments.

Abbreviations: AAT: anti-amoebic therapy; CI: confidence interval; MCR: medical cure rate; RR: relative risk.

Source: SIFI ODAK CSR 2022;² SIFI ITC Report May 2025.³³

Alternative treatment effectiveness inputs were explored in scenario analyses for polihexanide 0.8 mg/ml, by using available real-world data reflective of clinical practice, reported in Franch et al, 2024.⁶⁰ Franch et al. reported IPD data for 11 patients (12 affected eyes) treated with polihexanide 0.8 mg/ml in the real world.⁶⁰ Patient level data were reported for medical cure and key covariates, including treatment delay, disease stage, prior use of corticosteroids and prior use of antivirals. Age and proportion of males were reported as an average across the entire cohort.

Data from Franch et al were used in an ITC conducted using PSA with OW, in line with the method used in the base case. Two scenario analyses were explored; one scenario estimated the RR of MCR (as described above) for polihexanide 0.8 mg/ml versus the pooled AAT (from Company evidence submission template for polihexanide eye drops for treating acanthamoeba keratitis in people 12 years and over [ID6497]

Papa et al, 2020), with adjustment of the proportion of males and mean age. In this scenario, all covariates used in the base case ITC were therefore included in the weighting process. A second scenario estimated the RR using the Franch et al, 2024 study without an adjustment for age or sex. The resulting RRs of MCR, along with the 95% CI, used in these scenario analyses are presented in Table 34.

Table 34: 12-month MCR data for polihexanide 0.8 mg/ml (from Franch et al, 2024) and pooled AAT used in scenario analyses

Scenario	Model Input
RR for 12-month MCR polihexanide 0.8 mg/ml versus pooled AAT, imputing age and sex based on cohort average (95% CI)	■ (■)
RR for 12-month MCR polihexanide 0.8 mg/ml versus pooled AAT, not adjusting for age and sex (95% CI)	■

Abbreviations: AAT: anti-amoebic therapy; CI: confidence interval; MCR: medical cure rate; RR: relative risk.

Source: Franch et al, 2024;⁶⁰ SIFI ITC Report May 2025;³³ Papa et al. 2020.²⁹

3.3.2.2 Change to an alternative AAT

As discussed in Section 1.3.6, the heterogeneous treatment landscape for AK often results in the requirement for multiple pharmacological options, and poor outcomes can lead to therapeutic switching. Therefore, in the model, patients with an inadequate response to initial pharmacological therapy could change to an alternative AAT. This assumption was validated by two UK clinicians who agreed that patients in clinical practice would typically switch to an alternative AAT after failure of initial treatment. The proportion of patients switching to an alternative AAT is applied to the proportion of patients that did not achieve a cure within 12 months with the initial treatment (regardless of treatment type). It was assumed that patients could only change to an alternative AAT once, and that patients could only switch to AATs described in Table 30 in Section 3.2.3. This assumption was used to avoid additional complexity in the model, considering the heterogeneity of therapeutic approaches in AK and the numerous potential treatment combinations, and this approach was validated by two UK clinicians. The proportion of patients cured after switching to an alternative AAT within 12 months was assumed to be equivalent to the 12-month MCR for the pooled AAT comparator derived from the ITC analysis (Table 33), given that the 'alternative AATs' that patients can switch to as a second-line treatment are the same as those captured within the pooled AAT comparator in the model. The relevant model inputs for AAT switching within the first 12 months are presented in Table 35.

Table 35: AAT switching within the first 12 months

Inputs related to switching to an alternative AAT	Proportion of patients (%)	Source
Patients who do not achieve a cure with initial treatment who switch to an alternative pharmacological option within 12 months	23.40	UK Delphi Panel ¹¹
Patients who achieved a clinical resolution with the alternative pharmacological option within 12 months	■	Assumed the same as the 12-month MCR calculated for the pooled AAT comparator based on the ITC analysis (Table 33)

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Abbreviations: AAT: anti-amoebic therapy; ITC: indirect treatment comparison; MCR: medical cure rate; UK: United Kingdom.

Source: SIFI Delphi Panel 2023;¹¹ SIFI ITC Report May 2025.³³

In order to calculate the proportion of patients that switch treatment by treatment arm, the proportion of patients who were not cured by polihexanide 0.8 mg/ml or pooled AAT comparator was multiplied by the proportion of patients who switch to an alternative pharmacological option within 12 months (Table 35). The proportion of patients estimated to switch by treatment arm is presented in Table 36.

Table 36: Proportion of patients that switch treatment within the first 12 months by treatment arm

Treatment	Proportion of patients (%)
Polihexanide 0.8 mg/ml	3.55 ^a
Pooled AAT	■ ^b

Footnote: ^aCalculated by multiplying the proportion of patients who were not cured with polihexanide 0.8 mg/ml (100%–84.85%) by the proportion of patients who switch to an alternative pharmacological option within 12 months (23.40%). ^bCalculated by multiplying the proportion of patients who were not cured with pooled AAT (100%–■%) by the proportion of patients who switch to an alternative pharmacological option within 12 months (23.40%).

Abbreviations: AAT: anti-amoebic therapy.

3.3.2.3 Therapeutic surgery

As discussed in Section 1.3.5, when pharmacological approaches fail to clear the *Acanthamoeba* infection, patients may have to resort to surgical interventions. To account for this in the model, patients with AK unresponsive to pharmacological treatment (i.e. patients that did not achieve a medical resolution of the infection with the initial treatment nor following a change of AAT) can undergo a therapeutic surgery. The proportion of patients who undergo a therapeutic surgery was estimated based on the UK Delphi panel which reported that 21.50% of patients who failed to achieve resolution of their infection with prior pharmacological therapy (including those who switched to another AAT after 12 months) underwent surgery within 12 months.¹¹ The model inputs associated with therapeutic surgery are presented in Table 37.

As noted in Section 3.2.2, the model assumes that patients must wait to receive therapeutic surgery:

- If the duration of initial therapy plus the waiting time for the therapeutic surgery is less than one year, then the cohort is assumed to undergo therapeutic surgery within the first year and the proportion of the cohort in each of the BCVA levels and who experience loss of eye functionality after surgery are estimated using the decision tree.
- If the duration of initial therapy plus the waiting time for the therapeutic surgery is over one year, patients enter the sub health state for ‘waiting for therapeutic surgery’ in the semi-Markov model (Figure 6).

The mean waiting time for surgery was informed by the UK Delphi Panel (Table 37).

Table 37: Model inputs for therapeutic surgery within the first 12 months

Parameter	Model input	Source
AK patients not cured with pharmacological treatment that undergo therapeutic surgery (%)	21.50%	UK Delphi Panel ¹¹
Mean waiting time for surgery (days)	141.70	UK Delphi Panel ¹¹

Abbreviations: AK: Acanthamoeba keratitis; UK: United Kingdom.

Source: SIFI Delphi Panel 2023.¹¹

In order to calculate the proportion of patients that undergo therapeutic surgery in the first 12 months by treatment arm, the proportion of patients who had not been cured whilst receiving the treatment of interest (polihexanide 0.8 mg/ml or pooled AAT comparator) and had not switched treatments was multiplied by the proportion of patients that underwent therapeutic surgery (as presented in Table 37). The resultant proportion of patients that undergo therapeutic surgery within 12 months by treatment arm is presented in Table 38.

Table 38: Proportion of patients that undergo therapeutic surgery within the first 12 months by treatment arm

Treatment	Proportion of patients (%)
Polihexanide 0.8 mg/ml	2.50 ^a
Pooled AAT	█ ^b

Footnote: ^aCalculated by multiplying the proportion of patients who were not cured with polihexanide 0.8 mg/ml and had not switched treatment (100%–84.85%–3.55%) by the proportion of patients that underwent therapeutic surgery (21.50%). ^bCalculated by multiplying the proportion of patients who were not cured with pooled AAT and had not switched treatment (100%–█%–█%) by the proportion of patients that underwent therapeutic surgery (21.50%).

Abbreviations: AAT: anti-amoebic therapy.

The type and distribution of therapeutic surgeries included in the analysis were based on the SIFI-conducted UK Delphi panel and are summarised in Table 39. These figures are applied to both the polihexanide 0.8 mg/ml and pooled AAT comparator arms in the model.

Table 39: Type and distribution of therapeutic surgeries included in the model

Therapeutic surgery	Distribution (%)
Therapeutic keratoplasty	60.40
Enucleation	2.60
Deep lamellar keratoplasty	16.90
Evisceration	4.20
Other ^a	15.90

Footnote: ^aIncludes amniotic membrane, combined amniotic membrane and penetrating keratoplasty, and conjunctiva flap.

Source: SIFI Delphi Panel 2023 (Table 7).¹¹

3.3.2.4 BCVA

As outlined in Table 28 in Section 3.2.2, after patients achieve a resolution of AK infection, they are distributed in the model according to their vision outcomes defined by BCVA ranges: good vision, poor vision, severe vision loss and loss of eye functionality. The model allows for definition of a different distribution of the patients depending on whether patients were cured using a pharmacological treatment or if a therapeutic surgery was required.

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After clinical resolution of the infection with pharmacological treatment

The distribution of patients within each vision category following medical resolution of AK infection is presented in Table 40. There were no data available from the retrospective Papa et al. 2020 study or the UK Delphi panel to model this distribution for the pooled AAT comparator following medical resolution with pharmacological treatment. Therefore, the distributions for both interventions (polihexanide 0.8 mg/ml and the pooled AAT comparator) are based on the 12-month assessment data (end of study visit) for the polihexanide 0.8 mg/ml treatment arm in the ODAK trial (n=52).

Table 40: BCVA outcomes after clinical resolution of AK infection with pharmacological treatment within the first 12 months

BCVA	Distribution of patients (%)
Good vision	■
Poor vision	■
Severe vision loss	■

Footnote: Given the lack of available evidence, it was assumed that the visual acuity after changing to an alternative AAT was the same as after initial pharmacological treatment.

Abbreviations: AAT: anti-amoebic therapy; AK: Acanthamoeba keratitis; BCVA: best-corrected visual acuity.

Source: SIFI ODAK CSR 2022.²

After clinical resolution of the infection with therapeutic surgery

After therapeutic surgery (Section 3.3.2), in addition to changes in visual acuity described above, patients can also lose functionality of the eye. The distribution of patients in each vision category following each of the surgical interventions that can be undertaken is presented in Table 41. These figures are applied to both the polihexanide 0.8 mg/ml and pooled AAT comparator treatment arms in the model.

Table 41: BCVA outcomes after clinical resolution of the infection with therapeutic surgery within the first 12 months

BCVA	Distribution of patients (%)	Notes/Source
After therapeutic keratoplasty		
Good vision ^a	34.68	Robaei et al. 2015. ³⁴
Poor vision ^a	11.56	Robaei et al. 2015. ³⁴
Severe vision loss	35.56	Calculated as 1 minus the sum of the proportion with good vision, poor vision, and loss of eye functionality
Loss of eye functionality	18.20	UK Delphi panel ¹¹
After deep lamellar keratoplasty		
Good vision	34.68	Assumed to be the same as therapeutic keratoplasty
Poor vision	11.56	
Severe vision loss	35.56	
Loss of eye functionality	18.20	
After enucleation		

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BCVA	Distribution of patients (%)	Notes/Source
Good vision	0.00	Since an enucleation is surgical procedure in which the entire eyeball is removed while the surrounding eye muscles and tissues are preserved, it was assumed that all patients lose their eye functionality
Poor vision	0.00	
Severe vision loss	0.00	
Loss of eye functionality	100.00	
After evisceration		
Good vision	0.00%	Since an evisceration is surgical procedure in which the content of the eyeball is removed, while the outer shell of the eye is left intact, it was assumed that all patients lose their eye functionality
Poor vision	0.00%	
Severe vision loss	0.00%	
Loss of eye functionality	100.00%	
After other surgeries ^b		
Good vision	34.68	Assumed to be the same as therapeutic keratoplasty
Poor vision	11.56	
Severe vision loss	35.56	
Loss of eye functionality	18.20	

Footnote: ^aThe study by Robaei et al. is a UK study using medical records from patients diagnosed with AK at Moorfields Eye Hospital. The Snellen feet definitions for vision categories in this study broadly align with those included in the model: Grade 0 (good outcome: $\geq 20/30$ [logMAR ≤ 0.18]), Grade 2 (20/40–20/60 [logMAR 0.30–0.48]), Grade 3 (20/80–20/200 [logMAR 0.60–1.00]) and Grade 4 (poor outcome: $< 20/200$ [logMAR > 1.00]).

^bIncludes amniotic membrane, combined amniotic membrane and penetrating keratoplasty, and conjunctiva flap.
Abbreviations: BCVA: best-corrected visual acuity; LogMAR: Logarithm of the Minimum Angle of Resolution; UK: United Kingdom.

Sources: SIFI Delphi Panel 2023;¹¹ Robaei et al. 2015.³⁴

3.3.3 Clinical inputs beyond 12 months

As discussed in Section 3.2.2, a semi-Markov model was used to model the long-term outcomes for patients with AK after the first year. The clinical inputs for the long-term outcomes beyond 12 months are presented below.

3.3.3.1 Therapeutic surgery after Year 1

The model assumes that all patients that do not achieve medical resolution within two years undergo therapeutic surgery and enter the sub health state for ‘waiting for therapeutic surgery’ in the semi-Markov model (Figure 6 in Section 3.2.2). This assumption was validated with a UK clinician, who confirmed that a surgical intervention would remain the only option and that at such disease stage, with enucleation comprising the intervention mostly performed. When these patients eventually undergo therapeutic surgery, the same inputs presented in and 3.3.2.4 are applied.

3.3.3.2 Optical surgery

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As discussed in Section 1.3.5, optical surgeries are performed electively for visual rehabilitation of patients with AK, once the infection is presumed to have been eradicated.

Therefore, in the model, it was assumed that patients with poor vision or severe vision loss who achieved resolution of infection with or without therapeutic surgery would be eligible to undergo an optical surgery. Based on the UK Delphi panel, the percentage of patients undergoing optical surgery during their lifetime is 41.90% and 46.00% for patients with poor vision and severe vision loss, respectively. These proportions were applied as a one-off within the model to avoid complexity, as the use of 'tunnel states' within the model already accounts for the waiting times before optical surgery. Within the model, the mean waiting time for optical surgery is assumed to be 1 year, as validated by a UK clinician. It was assumed that patients who achieved a resolution of infection with good vision would not undergo optical surgery. The model inputs associated with optical surgery are presented in Table 42.

Table 42: Model inputs associated with optical surgery

Parameter	Model input	Source
Proportion of patients who achieve AK resolution with poor vision and undergo optical surgery (% [lifetime])	41.90	UK Delphi Panel ¹¹
Proportion of patients who achieve AK resolution with severe vision loss and undergo optical surgery (% [lifetime])	46.00	UK Delphi Panel ¹¹
Mean waiting time for surgery (days)	365.25	UK clinician

Abbreviations: AK: Acanthamoeba keratitis; UK: United Kingdom.

Source: SIFI Delphi Panel 2023.¹¹

The type and distribution of optical surgeries included in the analysis were based on the SIFI-conducted UK Delphi panel and are summarised in Table 43. These figures are applied to both the polihexanide 0.8 mg/ml and pooled AAT comparator arms in the model.

Table 43: Type and distribution of optical surgeries included in the model

Optical surgery	Distribution (%)
Optical keratoplasty	41.48
Evisceration	3.70
Cataract	43.70
DALK	5.78
Surgical correction for astigmatism	5.33

Abbreviations: DALK: deep anterior lamellar keratoplasty

Source: SIFI Delphi Panel 2023. (Table 14).¹¹

3.3.3.3 Graft failure

As discussed in Section 1.3.5, patients can experience graft failure after therapeutic or optical keratoplasty, which can lead to visual impairment and graft rejection. The probability of graft failure was assumed to be consistent across the polihexanide 0.8 mg/ml and pooled AAT comparator treatment arms in the model.

Data from a study by Veugen et al. 2023 was used to estimate the probability of graft failure within the model.⁵¹ This prospective Dutch registry study analysed graft survival after corneal

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transplantation for infectious keratitis, including AK, in the Netherlands. A total of 121 keratoplasties for AK were registered between 2007 and 2017. This study was used as it provides the most recent and comprehensive report of graft failure following corneal transplant, reporting specific probabilities for graft failure in AK.

Two KM curves were available from Veugen et al. 2023 one related to therapeutic keratoplasty and the other related to optical keratoplasty. Each of the KM curves was digitised and patient-level data were reconstructed via the Guyot method (based on the published number at risk). The number of patients at risk from Year 3 onwards was relatively small and therefore the probability of a graft failure was applied only up to 3 cycles (years) after surgery, as a conservative assumption. In the model, tunnel states were implemented to reflect the differing risk of graft failure in each of the three years following keratoplasty, as outlined in Table 44.

It was assumed that the therapeutic surgeries for which graft failure could occur included penetrating keratoplasty, deep anterior lamellar keratoplasty, and other surgeries (Table 39). It was also assumed that the optical surgeries for which graft failure could occur included optical keratoplasty, deep anterior lamellar keratoplasty and surgical correction (see Table 43). The yearly probabilities for graft failure up to Cycle 3 after therapeutic and optical keratoplasty are presented in Table 44. As outlined in Section 3.2.2, graft failure was not assumed to take place within the 12-month decision tree model, with the probability of graft failure accounted for within the long-term semi-Markov model.

Table 44: Yearly probability of graft failure after therapeutic and optical keratoplasty

Year	S(t) ^a	1-year probability
Therapeutic keratoplasty		
0	100%	—
1	64%	0.362
2	52%	0.179
3	43%	0.170
Optical keratoplasty		
0	100%	—
1	92%	0.082
2	85%	0.078
3	79%	0.071

Footnote: ^aReconstructed Kaplan-Meier data

Source: Veugen et al. 2023.⁵¹

3.3.3.4 BCVA

After undergoing an optical surgery

In the semi-Markov model, patients who achieved a clinical resolution of the infection and underwent optical surgery for visual rehabilitation (see Section 3.3.3.2) were distributed in health states stratified by the visual outcome following optical surgery. In the model, patients can either improve or worsen to the next BCVA range, remain in the same BCVA range or lose functionality of the eye following optical surgery. The distribution of patients by BCVA after optical surgery is presented in Table 45, and are based on the SIFI-conducted UK Delphi panel. These figures are

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applied to both the polihexanide 0.8 mg/ml and pooled AAT comparator treatment arms in the model.

Table 45: BCVA outcomes after optical surgery

BCVA	Distribution of patients (%)
Improved to the next BCVA range	49.70
Remain in the same BCVA range	27.30
Worsened to the next BCVA range	16.30
Loss of eye functionality	6.70

Abbreviations: BCVA: best-corrected visual acuity.

Source: SIFI Delphi Panel 2023.¹¹

After experiencing graft failure

The distribution of patients according to their BCVA after a graft failure (either due to an optical or therapeutic surgery) is presented in Table 46 and was based on data from the SIFI-conducted UK Delphi panel. These figures are applied to both the polihexanide 0.8 mg/ml and pooled AAT comparator treatment arms in the model.

Table 46: BCVA outcomes after graft failure

BCVA	Distribution of patients (%)
Good vision	8.46
Poor vision	2.82
Severe vision loss	8.68
Loss of eye functionality	80.03

Abbreviations: BCVA: best-corrected visual acuity.

Source: SIFI Delphi Panel 2023.¹¹

3.3.3.5 Recurrence of the infection

In the model, recurrence of AK infection is defined as an AK infection that occurs after achieving medical or surgical resolution of the infection and when patients are off treatment. As outlined in Section 3.2.2, patients that experience a recurrence of AK infection will re-enter the AK infection node of the decision tree. Therefore, all inputs associated with initial AK infection, as described above, are assumed to be the same for recurrent AK infection. It is assumed that patients who experience complete loss of eye functionality do not experience a recurrence of infection.

The probability of recurrence for the pooled AAT comparator was informed by the SIFI-conducted Delphi panel for Year 1 and Year 2 onwards.¹¹ Beyond Year 1, a lower probability of recurrence is applied in the model to reflect that if recurrence does not occur within the first months after stopping treatment, then the likelihood of a recurrence thereafter is smaller, as reflected in the Delphi panel. The probability of recurrence of AK infection is applied up to Year 15 of the time horizon. Recent published case studies have documented instances of recurrence at 15 months after initial AK resolution, with instances of 'late' recurrence documented after five years.^{94, 95} However, given the lack of robust data in AK, the probability of recurrence of AK infection in the

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model is applied up to 15 years as a conservative approach. This assumption was validated by a UK clinician, who agreed that 15 years appropriately represents the latest possible timepoint that AK may reoccur after an initial cure. The probability of recurrence of AK infection in the year following resolution (Year 1) and in the subsequent years (Year 2+) is presented in Table 47.

Table 47: Per-cycle probability of recurrence of AK infection

Treatment	Model input (%)
Year 1	
Polihexanide 0.8 mg/ml	■
Pooled AAT	11.5
Year 2+	
Polihexanide 0.8 mg/ml	■
Pooled AAT	3.0

Footnote: Probabilities for recurrence are only applied up to Year 15 of the time horizon.

Abbreviations: AAT: anti-amoebic therapy; AK: *Acanthamoeba* keratitis.

Source: SIFI ODAK CSR 2022;² SIFI Delphi Panel 2023.¹¹

3.3.3.6 Long-term complications associated with AK

As described in Section 1.3.3, after achieving AK resolution, patients may still experience long-term pain, lacrimation, photophobia, anxiety and depression. Research from a patient roundtable reports that patients may feel a gradual increase in pain over time accompanied by increasingly intense symptoms such as lacrimation and photophobia. Fear and uncertainty around treatment failures, the potential for losing eye function and the requirement for surgeries can lead to intense anxiety and depression into the long-term.¹³ Due to the 12-month duration of the ODAK trial, these long-term complications were insufficiently reflected in the data and so inputs sourced from the Delphi panel (shown in Table 48) were used to generate disutilities to capture the long-term impairment to HRQoL (see Section 3.4.4.1). These figures are applied to both the polihexanide 0.8 mg/ml and pooled AAT comparator treatment arms in the model.

Table 48: Proportion of patients with long-term complications

	Patients (%)	
	Intense and constant lacrimation/photophobia/pain	Depression/anxiety
Cured with good vision	19	10
Cured with poor vision	34	31
Cured with severe loss	33	55
Loss of eye functionality	32	62

Source: SIFI Delphi Panel 2023.¹¹

3.3.4 Mortality

AK is generally not a life-threatening disease; however, visual impairment is associated with an increased mortality risk and, as discussed in Section 1.3.3, depression and other psychological impacts of AK have resulted in some patients committing suicide. Mortality values associated with visual impairment were derived from a study by Christ et al. (2008) which analysed a pooled sample of 135,581 adults from the National Health Interview Survey to assess both direct and

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indirect effects of visual impairment on mortality risk.⁷⁸ This is in line with the approach taken in NICE TA799 and NICE TA824 for visual impairment in diabetic macular oedema.^{96, 97} In the model, these values were applied to individuals cured with PV, cured with SVL and loss of eye functionality health states, as presented in Table 49. A scenario analysis explored a conservative approach to mortality risk by applying the general population mortality to the PV, SVL and loss of eye functionality health states.

Table 49: Mortality rates

	HR versus general population (95% CI)
Cured with PV	1.23 (1.16, 1.31)
Cured with SVL	1.54 (1.28, 1.86)
Loss of eye functionality	

Abbreviations: CI: confidence interval; HR: hazard ratio; PV: poor vision; SVL: severe vision loss.

Source: NICE TA799.⁹⁶

3.3.5 Adverse events

The retrospective Papa et al. 2020 study did not collect safety data on the pooled AAT comparator and therefore safety data from the ODAK trial was used. In the ODAK study, a total of 152 adverse events were reported in 60 of 134 patients. Adverse events were not included in the model as they occurred at a similar frequency in both treatment arms (44.9% in the polihexanide 0.8 mg/ml arm and 44.6% in the active comparator arm).⁴ Of note, the frequency of severe adverse events (Grade 3–5) was low across both treatment arms: 5.8% in the polihexanide 0.8 mg/ml treatment arm and 7.7% in active comparator arm.⁴ Adverse events are therefore expected to have negligible impact on the CEM results.

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life studies

As described in Section 3.1, a *de novo* economic SLR and subsequent update were conducted to identify cost-effectiveness, HSUVs and CRU data associated with the treatment options for patients with AK or MK. No studies, other than the ODAK trial were identified that reported EQ-5D outcomes in patients with AK. Three studies reporting on VFQ-25 were identified, two of which were in patients with AK, and one in patients with MK. Full details on the methods and results of this SLR are presented in Appendix F.

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

As discussed in Section 2.6.8, EQ-5D-5L and VFQ-25 were used in the ODAK trial to evaluate participant HRQoL, using a generic and disease-specific tool, respectively. In line with NICE's preference, EQ-5D-5L index scores were converted to utilities for use in the model, as described in Section 3.4.3.³ Additionally, given the 12-month period of the ODAK trial, additional disutilities associated with long-term complications have been included to ensure that the model reflects the long-term impact of AK on patients' HRQoL.

The ODAK trial provided utilities for the AK infection, cured with poor vision and cured with severe vision loss health states as detailed in Section 3.4.4. The ODAK trial was unable to

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provide utilities for the loss of eye functionality health state given that no patients experienced this within the trial. Therefore, data from published literature (Rentz et al.) were used to derive utilities for this health state.⁹⁸

3.4.3 Mapping

EQ-5D-5L scores obtained from the ODAK trial were mapped onto the EQ-5D-3L UK value set using the mapping function developed by the DSU based on the Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU) dataset,⁹² in alignment with NICE guidelines.³

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

Health-state specific utility values were assigned to patients in each of the health states in the CEM: AK infection, cured with good vision, cured with poor vision, cured with severe vision loss and loss of eye functionality. Patients enter the model with a utility value based on that of the general UK population (age- and gender- adjusted; 0.902). Utility values for each health state are then generated by applying a specific disutility associated with that health state. A summary of the disutility values included in the base case analysis is presented in Table 50.

Data from the ODAK trial was used to generate the disutility values for the cured with poor vision and cured with severe vision loss health states via a mixed-model repeated measures (MMRM) analysis. The analysis included only those visits where both visual acuity data and utility data were available for the same timepoint. The dependent variable was the EQ-5D score, and the independent variables (fixed effects) included visual acuity categories as defined in the model health states (i.e. good vision, poor vision, and severe vision loss), with good vision specified as the reference category (intercept). To model the within-subject correlations arising from repeated measurements over time, the model utilised an unstructured covariance matrix. This structure offers maximum flexibility by allowing each pair of timepoints to have a distinct covariance, without imposing any assumptions on the correlation pattern. The analysis was conducted without any formal data imputation procedures. Therefore, the model assumes a Missing at Random mechanism, where the probability of missing data is related only to the observed data and not the unobserved outcomes. Under this assumption, the distribution of missing (unobserved) EQ-5D scores is approximated by that of the observed scores. In line with best practices for analysing trial-based repeated measures data, the MMRM employed the “repeated” statement method rather than modelling random slopes. This choice reflects the design of the ODAK trial, where data are typically collected at fixed, prespecified timepoints, making pointwise estimation across time more appropriate than treating time as a continuous variable. While random effects models are suited for estimating slopes over continuous time, this is generally less compatible with clinical trial structures, which focus on estimating outcomes at discrete timepoints.

The disutility associated with each health state was applied for the duration that patients spend in each health state. Patients who were cured with good vision were assumed to have the same HRQoL as the general population (0.902), with no disutility applied. This seems to be supported by the utility of [REDACTED] obtained from the MMRM analysis for good vision (intercept). A constraint was imposed that utilities at any time cannot exceed the utility of the general population with corresponding age and sex.

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Published literature suggests that the EQ-5D may not capture all aspects of the impact of ophthalmological conditions.^{99, 100} To address this issue, additional ‘bolt-on’ dimensions have been proposed, namely the vision bolt-on for patients with vision problems.^{99, 101} In a scenario analysis, an additional bolt-on utility decrement of –0.0378 and –0.130 was added for patients in the PV and SVL health states. These utility decrements were based on the EQ + vision model reported in Longworth et al. 2014.⁹⁹

Table 50: Summary of utility values for the base case CEM

Health state	Disutility	Source
AK infection	████	Assumption based on utility value in good vision (MMRM on ODAK data; █████) population minus the average baseline utility from the ODAK trial (████)
Cured with poor vision	████	MMRM using GV as an intercept based on the ODAK trial data
Cured with severe vision loss	████	MMRM using GV as an intercept based on the ODAK trial data
Loss of eye functionality	-0.248	Rentz et al. 2014. ⁹⁸

Abbreviations: AK: Acanthamoeba keratitis; CEM: cost-effectiveness model; GV: good vision; MMRM: mixed-model repeated measures; UK: United Kingdom.

Sources: SIFI ODAK CSR 2022;² Rentz et al. 2014.⁹⁸

3.4.4.1 Ongoing disutilities associated with long-term complications of AK

As discussed in Section 1.3.3 and Section 3.3, patients may experience long-term pain, lacrimation, photophobia, anxiety and depression which leads to poorer HRQoL. Given that the ODAK trial had a 12-month duration, the impact of these long-term effects associated with AK were not captured in the EQ-5D utility data collected as part of the ODAK trial, with few patients experiencing these longer term impacts during the trial despite patient evidence from a patient roundtable supporting that these complications have a marked negative impact on HRQoL into the long-term.^{2, 13} Therefore, additional disutilities associated with these complications were derived from Van Wilder et al, 2019⁸¹ (a comprehensive catalogue of EQ-5D utility decrements associated with chronic disorders) and Ara and Brazier et al, 2011⁸² (Table 51) and combined using a multiplicative approach to calculate disutilities for patients with multiple conditions based on the prevalence of each (Section 3.3.3.6) and was applied to each of the health states, based on the proportion of patients experiencing each complication, as reported in the Delphi panel (see Table 48). A summary of the disutilities associated with long-term complications following AK resolution is presented in Table 52. Disutilities were applied to both the polihexanide 0.8 mg/ml and pooled AAT comparator arms of the model.

Table 51: Disutilities associated with long-term complications

Long-term effects	Model input	Source/Assumption
Intense and constant lacrimation/ Photophobia/ Pain	-0.0647	Average between -0.03 (Lacrimal system disorder, GBR, Van Wilder et al, 2019), -0.053 (Other eye complaints difference between 0.794 and 0.741, Ara and Brazier, 2011), -0.111 (migraine/headaches; difference between 0.888 and 0.777; Ara and Brazier, 2011)

Long-term effects	Model input	Source/Assumption
Depression/ Anxiety	-0.1910	Average between -0.1120 (depressive disorders, Van Wilder et al, 2019) and -0.272 (mental illness/anxiety/depression; difference between 0.878 and 0.606; Ara and Brazier, 2011)

Sources: Van Wilder et al, 2019;⁸¹ Ara and Brazier, 2011.⁸²

Table 52: Disutilities associated with long-term complications

Health state	Disutility
Cured with good vision	-0.031
Cured with poor vision	-0.079
Cured with severe vision loss	-0.125
Loss of eye functionality	-0.136

Sources: SIFI Delphi Panel 2023;¹¹ Van Wilder 2019;⁸¹ Ara and Brazier 2011.⁸²

3.4.4.2 Disutilities associated with events

A summary of the one-off disutilities associated with insomnia in the intensive treatment phase, therapeutic surgery, graft rejection and optical surgery are presented in Table 53, alongside the associated assumptions and sources for each disutility value.

Table 53: One-off disutilities associated with events

Event	Disutility	Duration (days)	Source/assumptions
Insomnia associated with the intensive treatment phase	-0.280	24.00	As discussed in Section 1.3.6, current therapeutic approaches are associated with a heavy administration burden, with patients required to administer drops at regular intervals (every 20–30 minutes) throughout the day and night which can cause sleep deprivation and severely impacts patients' ability to perform normal daily activities.¹³ Therefore, a disutility associated with the intensive treatment schedule was assumed to be the same as the UK EQ-5D-3L disutility associated with sleep deprivation due to a treatment schedule which requires day and night administration as reported in Van Wilder et al.⁸¹ The duration is assumed to be 24 days associated with the intensive treatment phase, reflecting current AAT use as per clinical expert opinion. Please note that this disutility is not applied to polihexanide 0.8 mg/ml given the less burdensome treatment regimen (which is only administered during daytime-hours); the intensive treatment phase disutility was therefore set to 0 for polihexanide 0.8 mg/ml. Disutility of the intensive treatment phase was included for polihexanide 0.8 mg/ml within a scenario analysis (see Section 3.11.3). In this scenario, the duration is assumed to be 19 days associated with the intensive treatment phase, in line with the treatment protocol for polihexanide 0.8 mg/ml.²

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Event	Disutility	Duration (days)	Source/assumptions
Therapeutic surgery	-0.140	121.75	Assumed to be same as the disutility reported for cataracts in NICE HST11. ⁸³ The duration is assumed to be between 2 weeks and 4 months, assuming that patients can return to work after 2 to 3 weeks if job does not involve physical strain, and 3 to 4 months if job involves manual labour. Therefore, the maximum duration of 4 months was applied in the model.
Graft rejection	-0.248	141.70	Assumed to be the same as the disutility associated with loss of eye functionality (Table 50). The duration is assumed to be the same as waiting time to therapeutic surgery, in line with the procedures reported after graft failure in Table 70. ¹¹
Optical surgery	-0.140	121.75	Assumed the same as therapeutic surgery.

Abbreviations: HST: highly specialised technology; NICE: National Institute for Health and Care Excellence; UK: United Kingdom.

3.4.4.3 Caregiver disutilities

As outlined in Section 1.3.3, AK also imposes a significant burden on caregivers and therefore caregiver disutilities was included in the base case analysis.

There were no studies identified in the *de novo* economic SLR (see Section 3.4.1) that reported caregiver disutilities in AK. Therefore, the utility decrement used in the model was based on NICE HST11 (Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations),⁸³ with a value of -0.04 applied for the entire cohort in the intensive treatment phase, undergoing therapeutic/optical surgery and in the severe vision loss and loss of eye functionality health states. The caregiver disutility value applied for graft failure was adjusted by the proportion of patients receiving further procedures after a graft failure based on data from the UK Delphi panel (-0.014). The caregiver disutility for AK was assumed to be similar to inherited retinal dystrophies due to both diseases having a burden associated with managing chronic vision impairment. Both ophthalmological conditions significantly impact daily life, with people with the disease requiring ongoing support with daily activities. The utility decrement associated with each event was estimated by multiplying the utility decrement by the proportion of patients for a certain duration. The proportion of patients to which the caregiver disutility is applied to all patients in the model. A summary of the caregiver disutilities used in the CEM is presented in Table 54.

Table 54: Caregiver disutilities

Event	Utility decrement	Duration (days)
Intensive treatment phase	-0.04	19.00 ^b
Therapeutic surgery	-0.04	121.75 ^c
Optical surgery	-0.04	121.75 ^c
Graft failure	-0.014 ^a	141.70 ^d

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Event	Utility decrement	Duration (days)
Severe vision loss or loss of eye functionality	-0.04	–

Footnote: ^aAdjusted by percentage of patients with further procedures after a graft failure (based on UK Delphi panel). ^bDuration of the intensive treatment phase (Table 53). ^cMaximum duration of 4 months was applied. ^dAssumed the same as waiting time to therapeutic surgery (based on UK Delphi panel).¹¹

3.4.4.4 Adverse reactions

As discussed in Section 3.3.5, adverse events were not included in the model, and therefore no associated disutilities have been included.

3.5 Cost and healthcare resource use identification, measurement and valuation

Published cost and resource use studies

As described in Section 3.1, an SLR and subsequent update were conducted to identify any relevant cost or resource use data associated with the treatment of AK or MK that should be included in the model. Full details of the SLR search strategy, study selection process and results are presented in Appendix G. The SLR and update identified 2014 unique records. Of these, only two studies reported on cost or resource use in the UK,^{102, 103} and only one of these was in a population containing people with AK.¹⁰²

Costs incorporated into the cost-effectiveness analysis

The cost-effectiveness analysis was conducted from an NHS and PSS perspective and therefore only included costs that would be directly incurred by the healthcare system. Appropriate sources of unit costs such as the British National Formulary (BNF) and the National Schedule of NHS Reference Costs (2023/2024) were used for cost inputs in the model.

The following cost types were included in the model:

- Drug acquisition costs
- Concomitant medication costs
- Hospitalisation costs
- Surgery (therapeutic and optical) costs
- Healthcare resource use costs

Full details of the costs included in the base-case economic analysis and how they are applied within the model are presented below.

3.5.1 Intervention and comparators' costs and resource use

3.5.1.1 Drug acquisition costs

The treatment regimens for polihexanide 0.8 mg/ml and the pooled AAT comparator are presented in Table 55.

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Table 55: Treatment regimen for polihexanide 0.8 mg/ml and pooled AAT

Treatment phase	Days	Dose frequency, hour interval	Number of drops per day
Polihexanide 0.8 mg/ml (daytime only)^a			
Intensive	0–5	1	16
	6–12	2	8
	13–19	3	6
Maintenance	20+	4	4
Pooled AAT^b			
Intensive	0–3	1 (day and night-time)	24
	4 –10	1 (daytime only)	16
	11–24	2 (daytime only)	8
Maintenance	25+	4	4

Abbreviations: AAT: Anti-amoebic therapy.

Source: ^aSIFI ODAK CSR 2022; ² ^bUK clinical expert feedback.

The treatment duration for polihexanide 0.8 mg/ml and the pooled AAT comparator was based on the mean duration of treatment data from a recent real-world evidence study (Franch et al. 2024) and median time-to-cure data from the Papa et al. retrospective study, respectively, and is summarised in Table 56.

Table 56: Duration of treatment

Treatment phase	Duration of treatment	Source
Polihexanide 0.8 mg/ml	101.00	Mean duration of treatment with polihexanide 0.8 mg/ml from real-world evidence study ⁶⁰
Pooled AAT	152.19	Median time-to-cure from Papa et al (2020). ²⁹

Abbreviations: AAT: anti-amoebic therapy.

Drug formulations and the unit costs for polihexanide 0.8 mg/ml as well as each therapy used as part of the pooled AAT comparator are presented in Table 57. It should be noted that the cost for hexamidine was assumed to be the same as that of propamidine, given that costs were not reported separately for hexamidine in the BNF.

Table 57: Drug acquisition costs

Treatment phase	Volume per bottle/sachet (ml)	Cost per bottle/sachet, £	Number of drops per bottle/sachet	Expiry once opened (days)	Source
Polihexanide 0.8 mg/ml	0.3	5,960.00	30	28 ^a	List price, SIFI-determined
Polihexanide 0.2 mg/ml	10	45.00	200	7	2023 Policy Matters, Market Intelligence Report. ¹⁰⁴

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Treatment phase	Volume per bottle/sachet (ml)	Cost per bottle/sachet, £	Number of drops per bottle/sachet	Expiry once opened (days)	Source
Polihexanide 0.6 mg/ml	10	50.00	200	7	2023 Policy Matters, Market Intelligence Report. ¹⁰⁴
Chlorhexidine 0.2 mg/ml	10	23.00	200	7	2023 Policy Matters, Market Intelligence Report. ¹⁰⁴
Propamidine 1 mg/ml	10	4.05	200	28	BNF 2025 ¹⁰⁵

Footnote: ^a28 days refers to the internal aluminum sachet that contains the single-dose vials. After the first sachet opening, the single-dose vials must be used within 28 days.

Abbreviations: BNF: British National Formulary.

As described in Section 1.3.6, currently available biguanides which require compounding have relatively short shelf lives. Therefore, the cost per treatment course for each treatment was calculated by firstly ascertaining the minimum number of bottles needed over the course of the treatment duration described in Table 57 to ensure treatments were taken before their expiry date. The additional number of drops (and therefore number of bottles) needed by patients to adhere to the treatment regimen detailed in Table 55 throughout the duration of treatment listed in Table 56 was then calculated. The cost per treatment course for polihexanide 0.8 mg/ml and the pooled AAT comparator is presented in Table 58. The cost per treatment course of polihexanide 0.8 mg/ml was calculated considering a PAS of [REDACTED]%, based on the use of 17 packs for 101 days of treatment.

Table 58: Drug acquisition costs per treatment course

Treatment phase	Cost per treatment course, £
Polihexanide 0.8 mg/ml	[REDACTED]
Pooled AAT	938.98

Abbreviations: AAT: anti-amoebic therapy.

3.5.1.2 Concomitant medication costs

During the ODAK trial, patients with AK received a range of concomitant medications, including various ophthalmological medications, anti-inflammatory and antirheumatic products, analgesics and antivirals. Concomitant medication was defined as ongoing medication or medication stopped on or after baseline.² Concomitant medication with incidence of greater than 10% in the polihexanide 0.8 mg/ml treatment arm in the ODAK trial were considered in the model, as presented in Table 59.

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Table 59: Concomitant medication used in at least 10% of patients in the polihexanide 0.8 mg/ml treatment arm of the ODAK trial

Concomitant medication (>10%)	Proportion of patients (%)
Ophthalmologicals	
Fluoroquinolones	51
Corticosteroids, plain	36
Other ophthalmologicals	29
Anticholinergics	14
Antibiotics	16
Other anti-infective	17
Anti-inflammatory and antirheumatic products	
Acetic acid derivatives and related substances	32
Propionic acid derivatives	16
Analgesics	
Anilides	16
Antivirals for systemic use	
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	13

Abbreviations: ODAK: Orphan Drug for Acanthamoeba Keratitis.

Source: SIFI ODAK CSR 2022.²

Information on the dosages and costs for the concomitant therapies was taken from the MIMS database and BNF, respectively, and is summarised in Table 60. Due to the lack of a SoC, and therefore heterogeneity in the types and duration of concomitant therapeutic approaches used, the cost of concomitant treatment was applied as a one-off cost of £17.78 across both the polihexanide 0.8 mg/ml and pooled AAT comparator arm when patients started one of the initial therapies or changed to an alternative AAT. A one-off cost for concomitant treatment based on the polihexanide 0.8 mg/ml treatment arm was considered to be a conservative assumption.

Table 60: Concomitant medication unit costs

Concomitant medication (>10%)	Name and dose	Dose per pack (ml)	Pack cost	Number of drops per pack	Number of drops required	Cost, £	Cost source
Ophthalmologicals (eye drops)							
Fluoroquinolones	Levofloxacin 5 mg/ml: 1 or 2 drops into affected eye(s) every 2 hours up to eight times daily while awake for first 2 days, then four times daily on days 3 to 5. ¹⁰⁶	5	10.03	100	56	5.62	BNF 2025 ¹⁰⁷
Corticosteroids, plain	Dexamethasone phosphate 1 mg/ml: 1 drop into affected eye(s) four to six times daily. If necessary, initiate with 1 drop hourly and reduce to 1 drop every 4 hours when inflammation subsides. Maximum duration 14 days. ¹⁰⁸	0.4	9.7	30	84	27.16	BNF 2025 ¹⁰⁹
Other ophthalmologicals	Carmellose sodium 0.5%: 1 or 2 drops into affected eye(s) as required. ¹¹⁰	10	1.68	200	42	0.35	BNF 2025 ¹¹¹
Anticholinergics	Atropine sulfate 1%: 1 drop as required. ¹¹²	10	70.01	200	42	14.70	BNF 2025 ¹¹³

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Concomitant medication (>10%)	Name and dose	Dose per pack (ml)	Pack cost	Number of drops per pack	Number of drops required	Cost, £	Cost source
Antibiotics	Chloramphenicol 0.5%: 1 or 2 drops into affected eye(s) up to 6 times daily, or more frequently if required. Continue for 48 hours after cure. ¹¹⁴	10	3.37	200	84	1.42	BNF 2025 ¹¹⁵
Other anti-infectives	Propamidine 0.1%: 1 or 2 drops into affected eye(s) four times daily. ¹¹⁶	10	4.05	200	56	1.13	BNF 2025 ¹⁰⁵
Anti-inflammatory and anti-rheumatic products (tablets)		Quantity per pack (mg)	Pack cost	Number of tablets per pack	Number of administrations	Cost (one-off), £	Cost source
Acetic acid derivatives and related substances	Aspirin: 300–900 mg every 4–6 hours as required with food; maximum 4 g daily. ¹¹⁷	300	7.09	100	56	3.9704	BNF 2025 ¹¹⁸
Propionic acid derivatives	Ibuprofen: 1.2–1.8 g daily in divided doses with food; maximum 2.4 g daily. ¹¹⁹	200	2.31	84	42	1.155	BNF 2025 ¹²⁰
Analgesics							
Anilides	Paracetamol: 500 mg–1 g every four to six hours as required; max 4 g daily. ¹²¹	500	2.09	100	42	0.88	BNF 2025 ¹²²

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Concomitant medication (>10%)	Name and dose	Dose per pack (ml)	Pack cost	Number of drops per pack	Number of drops required	Cost, £	Cost source
Antivirals for systemic use							
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	Aciclovir: Varicella or herpes zoster: 800 mg five times daily at four-hourly intervals, omitting the night time dose, for 7 days. Start treatment as soon as possible after onset of rash. ¹²³	200	1.16	25	140	6.50	BNF 2025 ¹²⁴

Abbreviations: BNF: British National Formulary.

3.5.1.3 Hospitalisation costs

The number of patients that were estimated to require hospitalisation and the number of hospitalisation days were based on data from the UK Delphi panel and are presented in Table 61. Data were used from the UK Delphi panel as opposed to those presented in Robaei et al. 2014 (a study reporting hospitalisation data which was identified in the economic SLR [see Section 3.5 and Appendix G]), given that the hospitalisation data reported in Robaei et al. were not limited to the intensive treatment phase in AK.¹⁰² As mentioned in Section 1.3.7, polihexanide 0.8 mg/ml is associated with a less burdensome dosing regimen compared with current AATs and only requires administration of eyedrops in the daytime. Therefore, it was assumed that patients administer polihexanide 0.8 mg/ml at home, with no hospitalisations or associated costs applied to polihexanide 0.8 mg/ml treatment within the CEM. A summary of the costs associated with hospitalisation during the intensive treatment period is presented in Table 62.

Table 61: Proportion of patients requiring hospital admission during the intensive treatment phase

Treatment	Patients requiring hospitalisation (%)	Number of hospitalisation days
Polihexanide 0.8 mg/ml	0.00 ^a	0.00 ^a
Pooled AAT	26.60 ^b	4.20 ^b

Footnote: ^aFor polihexanide 0.8 mg/ml, it was assumed that hospitalisation is not required given that the treatment is only administered in the daytime. ^bEstimates based on UK Delphi panel.¹¹

Abbreviations: AAT: anti-amoebic therapy

Table 62: Cost of hospitalisation during the intensive treatment phase

Treatment	Cost, £	Source
Cost per hospitalisation day	484.00	National Schedule of NHS Costs 2023/24, Summary: HRG – Daytime, BZ24G: Non-surgical ophthalmology without interventions, with CC score 0–1 ⁸⁸
Total cost of hospitalisation during intensive treatment period		
Polihexanide 0.8 mg/ml	0.00 ^a	–
Pooled AAT	540.72 ^b	

Footnote: ^aFor polihexanide 0.8 mg/ml, it was assumed that hospitalisation is not required given that the treatment is only administered in the daytime. ^bCalculated by multiplying the proportion of patients requiring hospitalisation (26.60%) by the number of hospitalisation days (4.20) and the cost per hospitalisation day (£484.00).

Abbreviations: AAT: anti-amoebic therapy; CC: critical care; HRG: healthcare resource group; NHS: National Health Service.

3.5.1.4 Costs associated with therapeutic surgery

A one-off cost of £11,633.56 was incorporated into the model to account for the costs associated with therapeutic surgery. This included pre-surgery costs, costs associated with the different types of therapeutic surgery and the overall costs for post-surgery patient management, including treatment of surgical complications and post-surgical adjuvant systemic and immunosuppressive

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therapies. The total cost was then multiplied by the average number of therapeutic surgeries (1.20) as reported in the UK Delphi panel.¹¹ A breakdown of these costs is presented below.

Pre-therapeutic surgery costs

A one-off cost was applied in the model to account for the management of patients before therapeutic surgery. This cost was calculated from the average of NHS outpatient expenses related to ophthalmology, anaesthetic and pain management services as summarised in Table 63.

Table 63: Pre-therapeutic surgery costs

Pre-operation consultation	Cost, £	Source
Ophthalmology Service	140.01	National Schedule of NHS Costs 2023/24, Summary: Outpatient Attendances, Code 130
Anaesthetic Service	141.42	National Schedule of NHS Costs 2023/24, Summary: Outpatient Attendances, Code 190
Pain Management Service	228.49	National Schedule of NHS Costs 2023/24, Summary: Outpatient Attendances, Code 191
Total pre-therapeutic surgery cost (one-off)	169.97	Average of pre-operation consultation services

Abbreviations: NHS: National Health Service.

Therapeutic surgery costs

The unit costs for different types of therapeutic surgeries are presented in Table 64. The distribution of patients receiving therapeutic surgeries (based on the UK Delphi panel: Table 39 in Section 3.3.2.3) was accounted for in the total one-off cost.

Table 64: Unit costs by type of therapeutic surgery

Therapeutic surgery	Cost, £	Source
Therapeutic keratoplasty	5,123.25	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of the costs for following codes: BZ60A, BZ60B, BZ62A, BZ62B ⁸⁸
Enucleation	5,690.33	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ50Z, BZ53A, BZ53B ⁸⁸

Therapeutic surgery	Cost, £	Source
Deep lamellar keratoplasty	5,123.25	Assumed to be the same cost as therapeutic keratoplasty
Evisceration	3,538.25	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ61A, BZ61B, BZ63A, BZ63B ⁸⁸
Amniotic membrane	5,347.00	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ51A, BZ51B, BZ54A, BZ54B ⁸⁸
Amniotic membrane and penetrating keratoplasty	10,470.25	Assumed to be the sum of the costs for two procedures
Conjunctival flap	1,597.50	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ64A and BZ64B ⁸⁸

Abbreviations: HRG: healthcare resource group; NHS: National Health Service.

Post-therapeutic surgery costs

Complications after therapeutic surgery

As discussed in Section 1.3.5, patients can experience complications during or following therapeutic surgeries which may require further procedures. The complications associated with therapeutic surgeries and the respective proportion of patients estimated to experience these complications, based on the UK Delphi panel, are presented in Table 65. The costs associated with these complications are subsequently presented in Table 66; a one-off cost of £2,291.88 was applied in the model.

Table 65: Complications associated with therapeutic surgeries

Complications	Proportion (%)
Glaucoma	42.6
Scleritis	11.2
Corneal melt	5.9
Neurotrophic keratopathy	4.7
Perforation, wound leak	1.5
Re-suturing	1.8
Corneal vascularisation	12.0
Optic atrophy	1.8

Source: SIFI Delphi Panel 2023.¹¹

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Table 66: Cost of complications associated with therapeutic surgeries

Complications	Cost, £	Source
Glaucoma	3,633.11	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ90Z, BZ91A, BZ91B, BZ92A, BZ92B, BZ93A, BZ93B, BZ94A, BZ94B, BZ95Z ⁸⁸
Scleritis	2,113.28	Brolucizumab for treating diabetic macular oedema [TA820]. Assumed the same as the cost for endophthalmitis (Table 45) ¹²⁵
Corneal melt	3,092.34	Assumed as the average of intermediate corneal procedures (National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Code BZ64A) ⁸⁸ and therapeutic keratoplasty cost presented in Table 64)
Neurotrophic keratopathy	948.65	Brolucizumab for treating diabetic macular oedema [TA820]. Assumed the same cost as 'visual acuity reduced' in Table 45 ¹²⁵
Perforation, wound leak	1,256.00	UH Bristol NHS Foundation Trust Private Patient Tariff 2014-15 Version 1. Assumed same as Descemet's Stripping Automated Endothelial Keratoplasty (DSAEK) Corneal Transplant costs (C4640) ¹²⁶
Re-suturing	1,597.50	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ64A and BZ64B ⁸⁸
Corneal vascularisation	948.65	Brolucizumab for treating diabetic macular oedema [TA820]. Assumed the same cost as 'visual

Complications	Cost, £	Source
		acuity reduced' in Table 45 ¹²⁵
Optic atrophy	948.65	Brolucizumab for treating diabetic macular oedema [TA820]. Assumed the same cost as 'visual acuity reduced' in Table 45 ¹²⁵
Total cost to treat surgical complications (one-off)	2,291.88	—

Abbreviations: HRG: healthcare resource group; NHS: National Health Service; TA: technology appraisal.

Systemic therapies

The use of adjuvant systemic therapies and systemic immunosuppressants after therapeutic surgery is important to reduce the risk of rejection and other complications. The proportion of patients requiring these therapies and the mean treatment duration, based on the UK Delphi panel, are presented in Table 67. The costs associated with systemic therapies are subsequently presented in Table 68. One-off costs of £1,637.36 and £463.92 were applied in the model for systemic immunosuppressants and adjuvant systemic therapies, respectively.

Table 67: Systemic therapies post-therapeutic surgery

Systemic therapies	Proportion (%)	Mean treatment duration (days)
Systemic immunosuppressive		
Cyclosporine	17	217.5
Azathioprine	1	23.4
Mycophenolate	26	309.4
Steroids	25	27.5
Tacrolimus	14	284.5
Adjuvant systemic therapies		
Miltefosine	1	9.7
Voriconazole	20	37.3
Prednisolone	52	54.2
Polihexanide 0.6 mg/ml	26	79.4
Doxycycline	15	76.5

Source: SIFI Delphi Panel 2023.¹¹

Table 68: Costs associated with systemic therapies

Systemic therapies	Quantity per unit (mg)	Units per pack	Pack cost, £	Cost per mg, £	Dose per administration	Number of administrations per day	Cost per treatment, £	Source
Systemic immunosuppressive								
Cyclosporine	50	30	25.5	0.0170	1,140.64	1	4,217.51	BNF 2025 ¹²⁷
Azathioprine	50	56	1.33	0.0005	114.06	1	1.27	BNF 2025 ¹²⁸
Mycophenolate	500	50	5.78	0.0002	1,000.00	2	143.07	BNF 2025 ¹²⁹
Steroids	10	28	9.70	0.0346	40.00	1	38.11	BNF 2025 ¹³⁰
Tacrolimus	1	50	71.59	1.4318	7.60	2	6,195.14	BNF 2025 ¹³¹
Total cost (one-off), £	1,637.36							
Adjuvant systemic therapies								
Miltefosine	Cost not available ^a							
Voriconazole	50	28	193.53	0.1382	200	2	2,062.48	BNF 2025 ¹³²
Prednisolone	10	28	9.70	0.0346	40	1	75.11	BNF 2025 ¹³⁰
Polihexanide 0.6 mg/ml	-	200	50.00	0.2500	1	4	79.40	2023 Policy Matters, Market Intelligence Report. ¹⁰⁴
Doxycycline	50	28	1.44	0.0010	200	1	15.74	BNF 2025 ¹³³
Total cost (one-off), £	463.92							

Footnote: ^aCost for miltefosine was not found on the MIMS database or BNF.

Abbreviations: BNF: British National Formulary.

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3.5.1.5 Costs associated with optical surgery

Pre-optical surgery costs

As with therapeutic surgery, a one-off cost of £169.97 was applied in the model to account for the management of patients before optical surgery. This cost was calculated from the average of NHS outpatient expenses related to ophthalmology, anaesthetic and pain management services as summarised in Section 3.5.1.4 in Table 63.

Optical surgery costs

A total one-off cost of £4,205.99 was incorporated into the model to account for the costs associated with optical surgery. This cost was calculated based on the proportion of patients undergoing each intervention, based on the UK Delphi panel (Table 43 in Section 3.3.3.2) multiplied by the unit costs presented in Table 69. Unlike therapeutic surgery (Section 3.5.1.4), post-surgery costs are not included for optical surgeries in the model, as post-therapeutic surgery costs primarily relate to adjuvant systemic medication and immunosuppressive therapies specific to therapeutic procedures. In contrast, the aim of optical surgeries focuses on visual rehabilitation, and they do not typically involve subsequent ongoing treatment. Therefore, post-surgery costs were not applied for optical surgeries. This was confirmed during the UK Delphi panel, where experts discussed the proportion of patients needing medication after therapeutic surgeries and the expected treatment durations.¹¹

Table 69: Unit costs by type of optical surgery

Optical surgery	Cost, £	Source
Optical keratoplasty	5,123.25	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of the costs for following codes: BZ60A, BZ60B, BZ62A, BZ62B ⁸⁸
Evisceration	3,538.25	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ61A, BZ61B, BZ63A, BZ63B ⁸⁸
Cataract	3,025.80	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ30A, BZ30B, BZ31A, BZ31B, BZ32A, BZ32B, BZ33Z, BZ34A, BZ34B, BZ34C ⁸⁸
Deep anterior lamellar keratoplasty	5,123.25	Assumed the same cost as optical keratoplasty
Surgical correction for astigmatism	3,025.80	Assumed the same cost as cataract given that refractive lens exchange is considered to be the same procedure as cataract surgery ¹³⁴
Total costs associated with optical surgery (one-off)	4,205.99	

Abbreviations: HRG: healthcare resource group; NHS: National Health Service.

3.5.1.6 Graft failure

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A graft failure cost of £899.60 is applied as a one-off cost within the model. This cost was calculated based on the proportion of patients undergoing procedures after a graft failure reported in the UK Delphi panel multiplied by the graft failure procedure unit costs. The patient distribution and associated unit costs are reported in Table 70.

Table 70: Unit costs by procedures after graft failure

Procedures after graft failure	Proportion of patients (%) ^a	Cost, £	Source
Endothelial keratoplasty	24.41	1,256.00	UH Bristol NHS Foundation Trust Private Patient Tariff 2014-15 Version 1. Assumed same as Descemet's Stripping Automated Endothelial Keratoplasty (DSAEK) Corneal Transplant costs (C4640; includes day case rate) ¹²⁶
Enucleation	5.25	5,690.33	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ50Z, BZ53A, BZ53B ⁸⁸
Evisceration	5.38	3,538.25	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ61A, BZ61B, BZ63A, BZ63B ⁸⁸
No further procedures	64.96	0.00	In the event that a patient does not undergo any further procedures after a graft failure, no further costs are assumed.
Total costs associated with graft failure (one-off)	899.60		

Abbreviations: HRG: healthcare resource group; NHS: National Health Service.

Source: ^aSIFI Delphi Panel 2023.¹¹

3.5.1.7 Healthcare resource use costs

HCRU unit costs were based on Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care 2024 and the wider literature and are presented in Table 71. The HCRU required for monitoring and follow-up were derived from the UK Delphi panel, with the frequency of HCRU and the patient distribution presented in Table 72 and Table 73, respectively.

The HCRU costs by health state and per cycle applied in the model are presented in Table 74.

Table 71: HCRU unit costs

HCRU	Cost, £	Source
Ophthalmologist/Optometrist visit	103.00	PSSRU 2024. Cost per working hour (including qualifications) of a consultant (medical) as per Table 11.3.2 ⁸⁹
Psychiatrist visits	289.00	PSSRU 2024. Cost of general psychiatry service as per Table 2.1.1 ⁸⁹
Nurse visits	64.00	PSSRU 2024. Cost per working hour (including qualifications) for Band 6 as per Table 9.2.1 ⁸⁹
Intraocular pressure check	73.00	NHS Payment Scheme. Outpatient attendances – unit prices, 2024/25.

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HCRU	Cost, £	Source
		(WF01A Follow Up Attendance – Single Professional) 130 – Ophthalmology Service ⁹⁰
Scraping of the eye	73.00	NHS Payment Scheme. Outpatient attendances – unit prices, 2024/25. (WF01A Follow Up Attendance – Single Professional) 130 – Ophthalmology Service ⁹⁰
Ophthalmoscopy	73.00	NHS Payment Scheme. Outpatient attendances – unit prices, 2024/25. (WF01A Follow Up Attendance – Single Professional) 130 – Ophthalmology Service ⁹⁰
Low vision rehabilitation sessions	323.30	NICE Macular degeneration Appendix J: Health Economics ¹³⁵
Visual aids – magnifiers	214.69	NICE Macular degeneration Appendix J: Health Economics ¹³⁵
In vivo confocal microscopy	123.34	Gov.UK: Hospital eye service maximum charges ¹³⁶
Visual aids – contact lens clinic (rigid gas permeable contact lens)	61.77	Gov.UK, Annex A: Contact lenses for which a prescription is given in consequences of a sight test by an NHS trust or NHS foundation trust ¹³⁶

Abbreviations: NHS: National Health Service; NICE: National Institute for Health and Care Excellence; HCRU: healthcare resource utilisation; PSSRU: Personal Social Services Research Unit.

Table 72: Frequency of HCRU

Resource	Frequency of the intervention (times/year)							Loss of eye functionality
	AK infection	AK infection resolved with pharmacological treatment			AK infection resolved with surgical treatment			
		GV	PV	SVL	GV	PV	SVL	
Ophthalmologist/Optometrist visit	19	4.3	9	10.2	9.4	11.8	12	7.3
Psychiatrist visits	1.1	0.1	0.9	1.4	0.2	1.9	1.4	1.7
Nurse visits	7.2	1.7	7	3.7	2.9	4.4	4.2	3
Intraocular pressure check	16.1	4	8.5	9.8	9.2	11.5	11.8	7.3
Scraping of the eye	1.6	0.3	0.6	0.7	0.7	0.6	0.6	0.6
Ophthalmoscopy	9.6	2.7	5.7	8.2	4.9	6	7.4	4.3
Low vision rehabilitation sessions	1.9	0	1.4	2.6	0.1	1.7	1.8	1.3
Visual aids – magnifiers	1.4	0	0.8	1.4	0	1	0.9	0
In vivo confocal microscopy	1.6	0.5	0	0	0	0	0	0
Visual aids – contact lens clinic (rigid gas permeable contact lens)	0	0	0	0	0	1.9	1.3	0

Abbreviations: AK: *Acanthamoeba* keratitis; GV: good vision; HCRU: healthcare resource utilisation; PV: poor vision; SVL: severe vision loss.

Source: SIFI Delphi Panel 2023.¹¹

Table 73: Patient distribution by HCRU

Resource	Patients (%)							Loss of eye functionality
	AK infection	AK infection resolved with pharmacological treatment			AK infection resolved with surgical treatment			
		GV	PV	SVL	GV	PV	SVL	
Ophthalmologist/Optometrist visit	86.60	77.10	72.80	78.80	83.20	82.60	80.80	62.20
Psychiatrist visits	9.90	17.60	18.20	26.90	7.10	23.20	25.10	25.20
Nurse visits	24.20	33.80	35.30	32.50	41.60	43.60	41	33.30
Intraocular pressure check	79.40	82.30	74.70	78.50	87.30	85.30	83.50	66.40
Scraping of the eye	72.10	19.50	49.10	41.10	22.60	30.50	32.70	21.50
Ophthalmoscopy	58.50	68.30	63.50	56.20	52.90	53.80	57	45.90
Low vision rehabilitation sessions	8	13.50	27.50	50	15.10	25.30	33.60	18.20
Visual aids – magnifiers	5.40	0	14.10	23.40	0	7.10	9.70	0
In vivo confocal microscopy	32	48.50	0	0	0	0	0	0
Visual aids – contact lens clinic (rigid gas permeable contact lens)	5.40	0	14.10	23.40	0	17.80	17.80	0

Abbreviations: AK: *Acanthamoeba* keratitis; GV: good vision; HCRU: healthcare resource utilisation; PV: poor vision; SVL: severe vision loss.

Source: SIFI Delphi Panel 2023.¹¹

Table 74: HCRU cost per cycle

Health state	HCRU cost per cycle, £
AK infection	3,415.80
Good vision after medical resolution of AK infection	792.45
Poor vision after medical resolution of AK infection	1,828.67
Severe vision loss after medical resolution of AK infection	2,587.37
Good vision after surgical resolution of AK infection	1,680.47
Poor vision after surgical resolution of AK infection	2,446.68
Severe vision loss after surgical resolution of AK infection	2,553.16
Loss of eye functionality	1,265.19

Abbreviations: AK: *Acanthamoeba* keratitis; HCRU: healthcare resource utilisation.

3.5.2 Adverse reaction unit costs and resource use

As discussed in Section 3.3.5, adverse events and their associated costs were not included in the model.

3.6 Severity

Despite the severity of the condition and large unmet need in people with AK – a very rare condition that can result in profound and lifelong impacts such as vision loss – polihexanide 0.8 mg/ml does not meet the criteria for a severity modifier in this indication.

3.7 Uncertainty

NICE has accepted that AK is a very rare condition, distinct from IK more broadly, with AK recognised as an orphan disease affecting 1:50,000 people in England, with <300 people in England eligible for the technology. It is therefore vital that the challenges associated with an appraisal in a very rare condition, such as small sample sizes in clinical trials, and any resulting uncertainty is considered when evaluating the evidence.

As discussed in Section 1.3.7, polihexanide 0.8 mg/ml is the first treatment to be appraised in AK. Consequently, no previous economic evaluations in this condition have been conducted. AK-specific data sources to inform the model are scarce and where available, usually limited to smaller sample sizes, giving rise to uncertainty around mean parameter values. For model inputs which could not be informed by either the wider literature, or the ODAK and Papa et al studies, these were largely informed by a robust two-round Delphi panel of 10 ophthalmologists with extensive experience treating AK patients within the NHS.¹¹ Although the evidence generated by expert elicitation is subject to risk of bias and uncertainty, use of a Delphi panel which is a structured expert elicitation technique recognised by NICE,³ ensured that any uncertainty was minimised. For any assumptions which were not validated by the Delphi panel, clinical input from experts in AK was sought to validate these parameters to ensure model inputs were clinically appropriate (as detailed in Section 3.14).

For AK in particular, the lack of a standard of care or established treatment pathway results in heterogeneity in current therapeutic regimens across the UK and therefore, modelling all possible

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treatment combinations is a significant challenge. Consequently, a pooled treatment comparator was deemed the most appropriate approach, allowing for a comprehensive evaluation that reflects the diversity of real-world treatment scenarios, in line with the results from the aforementioned Delphi Panel.¹¹

Therefore, SIFI asks the Committee to consider the strength of the data presented in light of the rarity of the condition. Flexibility in NICE's STA process is therefore expected to be relevant in this submission, when compared to products being assessed through STA for conditions with a much higher prevalence.

3.8 *Managed access proposal*

SIFI does not wish to present a managed access proposal for polihexanide 0.8 mg/ml at this stage.

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

3.9.1 **Summary of base-case analysis inputs**

A summary of the base-case model inputs is presented in Table 75.

Table 75: Summary of base-case model inputs

Variable	Value	Reference to section in submission
Model settings		
Time horizon (years)	Lifetime (up to 100 years)	Section 3.2.2
Model cycle length	1 year (with half cycle correction)	
Discount rate (costs), %	3.5	
Discount rate (benefits), %	3.5	
Population characteristics		
Mean initial age (years)	36.70	Section 3.3.1
Male (%)	41.73	
Mean body weight (kg)	76.04	
Clinical inputs for the first 12 months		
12-month MCR		Section 3.3.2.1
Polihexanide 0.8 mg/ml (%)	84.85	
RR for 12-month MCR polihexanide 0.8 mg/ml versus pooled AAT	████(resultant MCR [%]: █████)	
Change to alternative AAT		Section 3.3.2.2
Polihexanide 0.8 mg/ml (%)	3.55	
Pooled AAT (%)	████	
Therapeutic surgery		Section 3.3.2.3
Polihexanide 0.8 mg/ml (%)	2.50	
Pooled AAT (%)	████	

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Variable	Value	Reference to section in submission
<i>BCVA outcomes after clinical resolution of AK infection with pharmacological treatment</i>		Section 3.3.2.4
Good vision (%)	████	
Poor vision (%)	████	
Severe vision loss (%)	████	
<i>BCVA outcomes after clinical resolution with therapeutic keratoplasty</i>		
Good vision (%)	34.68	
Poor vision (%)	11.56	
Severe vision loss (%)	35.56	
Loss of eye functionality (%)	18.20	
<i>BCVA outcomes after clinical resolution with deep lamellar keratoplasty</i>		
Good vision (%)	34.68	
Poor vision (%)	11.56	
Severe vision loss (%)	35.56	
Loss of eye functionality (%)	18.20	
<i>BCVA outcomes after enucleation</i>		
Good vision (%)	0.00	
Poor vision (%)	0.00	
Severe vision loss (%)	0.00	
Loss of eye functionality (%)	100.00	
<i>BCVA outcomes after evisceration</i>		
Good vision (%)	0.00	
Poor vision (%)	0.00	
Severe vision loss (%)	0.00	
Loss of eye functionality (%)	100.00	
<i>BCVA outcomes after other surgeries^a</i>		
Good vision (%)	34.68	
Poor vision (%)	11.56	
Severe vision loss (%)	35.56	
Loss of eye functionality (%)	18.20	
Clinical inputs beyond 12 months		
<i>Optical surgery</i>		Section 3.3.3.2
Proportion of patients who achieve AK resolution with poor vision and undergo optical surgery (% [lifetime])	41.90	
Proportion of patients who achieve AK resolution with severe vision loss and undergo optical surgery (% [lifetime])	46.00	
<i>Graft failure after therapeutic surgery</i>		Section 3.3.3.3
Probability in Year 0	—	
Probability in Year 1	0.362	

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Variable	Value	Reference to section in submission
Probability in Year 2	0.179	
Probability in Year 3	0.170	
Graft failure after optical surgery		
Probability in Year 0	—	
Probability in Year 1	0.082	
Probability in Year 2	0.078	
Probability in Year 3	0.071	
BCVA outcomes after optical surgery		Section 3.3.3.4
Improved to the next BCVA range (%)	49.70	
Remain in the same BCVA range (%)	27.30	
Worsened to the next BCVA range (%)	16.30	
Loss of eye functionality (%)	6.70	
BCVA outcomes after graft failure		
Good vision (%)	8.46	
Poor vision (%)	2.82	
Severe vision loss (%)	8.68	
Loss of eye functionality (%)	80.03	
Per-cycle probability of recurrence of AK infection		
Polihexanide 0.8 mg/ml (Year 1, %)	■	
Pooled AAT (Year 1, %)	11.5	
Polihexanide 0.8 mg/ml (Year 2+, %)	■	
Pooled AAT (Year 2+, %)	3.0	
Intense and constant lacrimation/photophobia/pain		Section 3.3.3.6
Cured with good vision (%)	19	
Cured with poor vision (%)	34	
Cured with severe loss (%)	33	
Loss of eye functionality (%)	32	
Depression/anxiety		
Cured with good vision (%)	10	
Cured with poor vision (%)	31	
Cured with severe loss (%)	55	
Loss of eye functionality (%)	62	
Mortality (HR versus general population)		
Cured with poor vision	1.23	Section 3.3.4
Cured with severe loss	1.54	
Loss of eye functionality		
Utility values		
AK infection	■	Section 3.4.4
Cured with poor vision	■	
Cured with severe vision loss	■	

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Variable	Value	Reference to section in submission
Loss of eye functionality	-0.248	
Disutilities associated with long-term conditions		
Cured with good vision	-0.031	Section 3.4.4.1
Cured with poor vision	-0.079	
Cured with severe vision loss	-0.125	
Loss of eye functionality	-0.136	
Disutilities associated with events		
Insomnia associated with the intensive treatment phase	-0.280	Section 3.4.4.2
Therapeutic surgery	-0.140	
Graft rejection	-0.248	
Optical surgery	-0.140	
Caregiver disutilities		
Intensive treatment phase	-0.04	Section 3.4.4.3
Therapeutic surgery	-0.04	
Optical surgery	-0.04	
Graft failure	-0.014	
Severe vision loss or loss of eye functionality	-0.04	
Duration of treatment (days)		
Polihexanide 0.8 mg/ml	101.00	Section 3.5.1.1
Pooled AAT	152.19	
Drug acquisition costs per treatment course (£)		
Polihexanide 0.8 mg/ml		Section 3.5.1.1
Pooled AAT	938.98	
Concomitant medication costs (£)		
One-off cost	17.78	Section 3.5.1.2
Hospitalisation costs during intensive treatment period (£)		
Polihexanide 0.8 mg/ml	0.00	Section 3.5.1.3
Pooled AAT	540.72	
Therapeutic surgery costs (£)		
Total one-off cost	11,633.56	Section 3.5.1.4
Optical surgery costs (£)		
Total one-off cost	4,205.99	Section 3.5.1.5
Graft failure costs (£)		
Total one-off cost	899.60	Section 3.5.1.6
HCRU cost per cycle (£)		
AK infection	3,415.80	Section 3.5.1.7
Good vision after medical resolution of AK infection	792.45	

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Variable	Value	Reference to section in submission
Poor vision after medical resolution of AK infection	1,828.67	
Severe vision loss after medical resolution of AK infection	2,587.37	
Good vision after surgical resolution of AK infection	1,680.47	
Poor vision after surgical resolution of AK infection	2,446.68	
Severe vision loss after surgical resolution of AK infection	2,553.16	
Loss of eye functionality	1,265.19	

Abbreviations: AAT: anti-amoebic therapy; AK: Acanthamoeba keratitis; BCVA: best-corrected visual acuity; HCRU: healthcare resource utilisation; HR: hazard ratio; MCR: medical cure rate; RR: relative risk.

3.9.2 Assumptions

A list of the key assumptions and inputs used in the base case analysis of the economic model is provided in Table 76.

Table 76: List of key assumptions and inputs used in the base case analysis model

Variable	Assumption	Justification
Clinical effectiveness		
Probability of recurrence	The probability of recurrence of AK infection is only applied up to Year 15 of the time horizon	- Beyond Year 1, a lower probability of recurrence is applied in the model to reflect that if recurrence does not occur within the first months after stopping treatment, then the likelihood of a recurrence thereafter is smaller - Recent published case studies have documented instances of recurrence at 15 months after initial AK resolution, with instances of 'late' recurrence documented after five years.^{94, 95} However, given the lack of robust data in AK, the probability of recurrence of AK infection in the model is applied up to 15 years as a conservative approach - This assumption was validated by a UK clinician who agreed that 15 years appropriately represents the latest possible timepoint that AK may reoccur after an initial cure
Recurrence for patients receiving polihexanide 0.8 mg/ml	Patients receiving polihexanide 0.8 mg/ml [REDACTED] recurrence of infection within the model	This assumption was based on the fact that [REDACTED]
Treatment switching	Patients can only switch to an alternative AAT once	Clinical input from the Delphi panel indicated that 23.4% of patients who do not respond to initial AAT may receive an alternative treatment regimen.¹¹ However, given the limited treatment options available and the lack of demonstrated differences in efficacy, further switching is unlikely. Additionally, by this point, disease progression often requires surgical intervention. This approach was validated by two UK clinicians
Surgery		

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Variable	Assumption	Justification
Therapeutic surgery waiting time	All patients that did not achieve medical resolution within two years underwent therapeutic surgery and entered the sub health state for 'waiting for therapeutic surgery' in the semi-Markov model	This assumption was validated with a UK clinician, who confirmed that a surgical intervention would remain the only option at this stage, with enucleation most likely to be performed
BCVA outcomes after clinical resolution of infection with therapeutic surgery	BCVA outcomes for people with AK undergoing deep lamellar keratoplasty, amniotic membrane, combined amniotic membrane and penetrating keratoplasty, and conjunctiva flap are assumed to be the same as those resulting from therapeutic keratoplasty	There were no available studies identified in the <i>de novo</i> economic SLR (see Section 3.4.1) to inform visual outcomes after each therapeutic procedure, only to inform BCVA outcomes after therapeutic keratoplasty (based on the publication by Robaei et al. 2015 and feedback from the UK Delphi panel).^{11, 34} It was assumed that the BCVA outcomes for all the therapeutic surgeries (including deep lamellar keratoplasty, amniotic membrane, combined amniotic membrane and penetrating keratoplasty, and conjunctiva flap) were the same as the ones described for therapeutic keratoplasty
Optical surgery waiting time	Within the model, the mean waiting time for optical surgery is assumed to be 1 year	This assumption was validated by a UK clinician
Graft failure	Graft failure was assumed to only occur within 3 years of surgery	The number of patients at risk from Year 3 onwards was relatively small and therefore this conservative assumption was used to avoid unnecessary complexity in the model
Costs		
Hospitalisation costs for polihexanide 0.8 mg/ml	No hospitalisations or associated costs were applied to polihexanide 0.8 mg/ml treatment within the model	Polihexanide 0.8 mg/ml is associated with a less burdensome regimen (with no overnight administration required), therefore patients can administer the treatment at home, with no hospitalisations required
AE costs	AE costs were not included in the model	In the ODAK study, a total of 152 adverse events were reported in 60 of 134 patients. Adverse events were not included in the model as they occurred at a similar frequency in both treatment arms (44.9% in the polihexanide 0.8 mg/ml arm and 44.6% in the active comparator arm) and therefore are not expected to have a large impact on the CEM results⁴

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Variable	Assumption	Justification
Post-optical surgery costs	Unlike therapeutic surgery (Section 3.5.1), post-surgery costs for optical surgeries were not included in the model	Post-therapeutic surgery costs primarily relate to adjuvant systemic medication and immunosuppressive therapies specific to therapeutic procedures. In contrast, the aim of optical surgeries focuses on visual rehabilitation, and they do not typically involve subsequent ongoing treatment. Therefore, post-surgery costs were not applied for optical surgeries. This was confirmed during the UK Delphi panel, where experts discussed the proportion of patients needing medication after therapeutic surgeries and the expected treatment durations¹¹
HRQoL		
Intensive treatment phase	Disutility for the intensive treatment phase was not applied to polihexanide 0.8 mg/ml	- Polihexanide 0.8 mg/ml is associated with a less burdensome treatment regimen, requiring administration only in the daytime - Disutility of the intensive treatment phase was included for polihexanide 0.8 mg/ml within a scenario analysis (see Section 3.11.3)
Disutilities associated with the intensive treatment phase	Assumed to be the same as disutility for insomnia associated with sleep deprivation due to treatment schedule (which requires day and night administration) reported in Van Wilder et al. ⁸¹	There were no studies identified in the <i>de novo</i> economic SLR (see Section 3.4.1) that reported disutilities for the intensive treatment phase in AK. During the initial days of treatment with AATs, the administration regimen is highly demanding, with patients needing to administer eyedrops throughout the day and night. Therefore, insomnia/disruption to sleep is likely to be the key aspect of the intensive treatment phase in which polihexanide 0.8 mg/ml is able to improve quality of life compared with the pooled comparator (given that polihexanide 0.8 mg/ml administration is not required during the night). As a result, this conservative approach was taken to capture the disutility associated with the intensive treatment phase and account for the impact of this intensive treatment regimen on patients' QoL
Disutilities associated with therapeutic surgery	Assumed to be same as cataract reported on NICE HST11 (Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations) ⁸³	There were no studies identified in the <i>de novo</i> economic SLR (see Section 3.4.1) that reported disutilities for therapeutic surgery in AK. Therefore, the disutility derived from cataract surgery reported in NICE

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Variable	Assumption	Justification
		HST11, ⁸³ representing a utility decrement applicable to any eye surgical procedure, including therapeutic or optical surgeries. The aim was to reflect the disutility associated to the eye surgical procedure itself independently of the type of procedure
Disutilities associated with graft rejection	Assumed to be the same as disutilities associated with loss of eye functionality	There were no available studies identified in the <i>de novo</i> economic SLR (see Section 3.4.1) to quantify the utility decrement associated with graft rejection. Therefore, it was assumed that the same disutilities as those associated with loss of eye functionality could be used as a proxy. This assumption is supported by the fact that graft failure after eye surgery can significantly impair visual capacity. When a corneal graft fails, the cornea may become cloudy due to persistent oedema, scarring or irregularities, resulting in blurred vision or severe visual impairment. Consequently, patients experiencing graft failure may require additional interventions to restore visual function. Based on the visual deterioration associated with graft failure, using loss of eye functionality disutilities as a proxy was deemed reasonable
Disutilities associated with optical surgery	Assumed to be the same as disutilities associated with therapeutic surgery	As above, the utility decrement for cataract reported in the NICE HST11 was used to inform the utility decrement associated to any eye surgical procedure, including therapeutic or optical surgeries.⁸³ This is a conservative assumption given that the disutility is assumed to be the same for all surgeries despite the fact that therapeutic surgeries are more complex procedures
Caregiver disutilities	The utility decrement for caregivers was assumed to be the same as that reported in NICE HST11 (Voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations), ⁸³ applied for all patients	There were no studies identified in the <i>de novo</i> economic SLR (see Section 3.4.1) that reported caregiver disutilities in AK. Therefore, the utility decrement used in the model was based on NICE HST11,⁸³ and a value of -0.04 applied to entire cohort in the intensive treatment phase, undergoing therapeutic/optical surgery and in the severe vision loss and loss of eye functionality health states. The caregiver disutility value applied for graft failure was adjusted by the proportion of patients

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Variable	Assumption	Justification
		receiving further procedures after a graft failure based on data from the UK Delphi panel (-0.014).The caregiver disutility for AK was assumed to be similar to disutilities associated with inherited retinal dystrophies due to both diseases having a burden associated with managing chronic vision impairment. Both conditions significantly impact daily life, with people with the disease requiring ongoing support with daily activities

Abbreviations: AAT: anti-amoebic therapy; AE: adverse event; AK: Acanthamoeba keratitis; BCVA: best-corrected visual acuity; CEM: cost-effectiveness model; HRQoL: health-related quality of life; HST: highly specialised technology; NICE: National Institute for Health and Care Excellence; QoL: quality of life; SLR: systematic literature review; UK: United Kingdom.

3.10 **Base-case results**

3.10.1 **Base-case incremental cost-effectiveness analysis results**

A summary of the deterministic base case results for polihexanide 0.8 mg/ml versus the pooled AAT comparator is presented in Table 77. Probabilistic base case results are shown in Table 78. For all results, polihexanide 0.8 mg/ml has been included at proposed PAS price.

In the base case at the proposed PAS price, polihexanide 0.8 mg/ml was associated with increased health benefits compared with the pooled AAT comparator of 2.56 more QALYs, reflecting the higher efficacy of polihexanide 0.8 mg/ml as demonstrated by the ITC presented in Section 2.10. Polihexanide 0.8 mg/ml was associated with higher incremental costs (£1,000) than the pooled AAT comparator and the resulting proposed PAS price ICER versus pooled AATs was £1,000 per QALY gained (Table 77).

The incremental net-health benefit (INHB) of polihexanide 0.8 mg/ml at a willingness-to-pay (WTP) threshold of £20,000 and £30,000 has been included. INHB represents the sum of the incremental QALYs and incremental costs valued in health terms, with a positive INHB indicating the intervention is cost-effective at the selected WTP threshold. INHB was selected in line with the preference expressed in the NICE manual for health technology evaluations.³ In the base case (deterministic, with PAS), INHB for polihexanide 0.8 mg/ml versus pooled AAT was -£1,000 and 2.56 QALYs at WTP thresholds of £20,000 and £30,000, respectively.

As discussed in Sections 1.3, AK is a very rare disease, with no approved treatments available despite being associated with severe impairment of quality of life and potential permanent vision loss. In light of the challenges associated with very rare conditions and in recognition of NICE's acceptance of polihexanide 0.8 mg/ml meeting Criterion 1 and 2 of the HST checklist, additional flexibility is requested during this technology evaluation.

The disaggregated base case cost-effectiveness results are presented in Appendix H.

Table 77: Deterministic base-case results for polihexanide 0.8 mg/ml versus the pooled AAT comparator (with PAS)

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INHB at £20k	INHB at £30k
Polihexanide 0.8 mg/ml	■	22.65	17.31	-	-	-	-	-	-
Pooled AAT	■	22.37	14.76	■	0.28	2.56	■	-■	■

Abbreviations: 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.

3.11 *Exploring uncertainty*

As detailed in Section 3.7, model parameters were associated with uncertainty as would be expected in a rare disease. In order to assess the impact of parameter uncertainty on the economic model results, both probabilistic and deterministic sensitivity analyses were conducted, the results of which are presented in Sections 3.11.1 and 3.11.2, respectively. In addition, key assumptions in the model were explored in several scenario analyses, the results of which are presented in Section 3.11.3.

Overall, it is considered that relevant uncertainties included in the analyses have been adequately accounted for and the base case results were found to be robust to uncertainty in the key model inputs and assumptions.

3.11.1 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was conducted to assess the impact of uncertainty around parameter values on the results of the base-case model. In the PSA, 1,000 simulations were performed in which model parameters were varied simultaneously by sampling at random from hypothetical distributions. Population characteristics were not included in the PSA since they represent first order uncertainty.

Where data were available, probability distributions were assigned to parameters, to characterise uncertainty associated with the precision of the mean values, based on the nature of each parameter. Where empirical probability distributions were not available, the standard error was assumed to take a value equal to 10% of that of the mean.

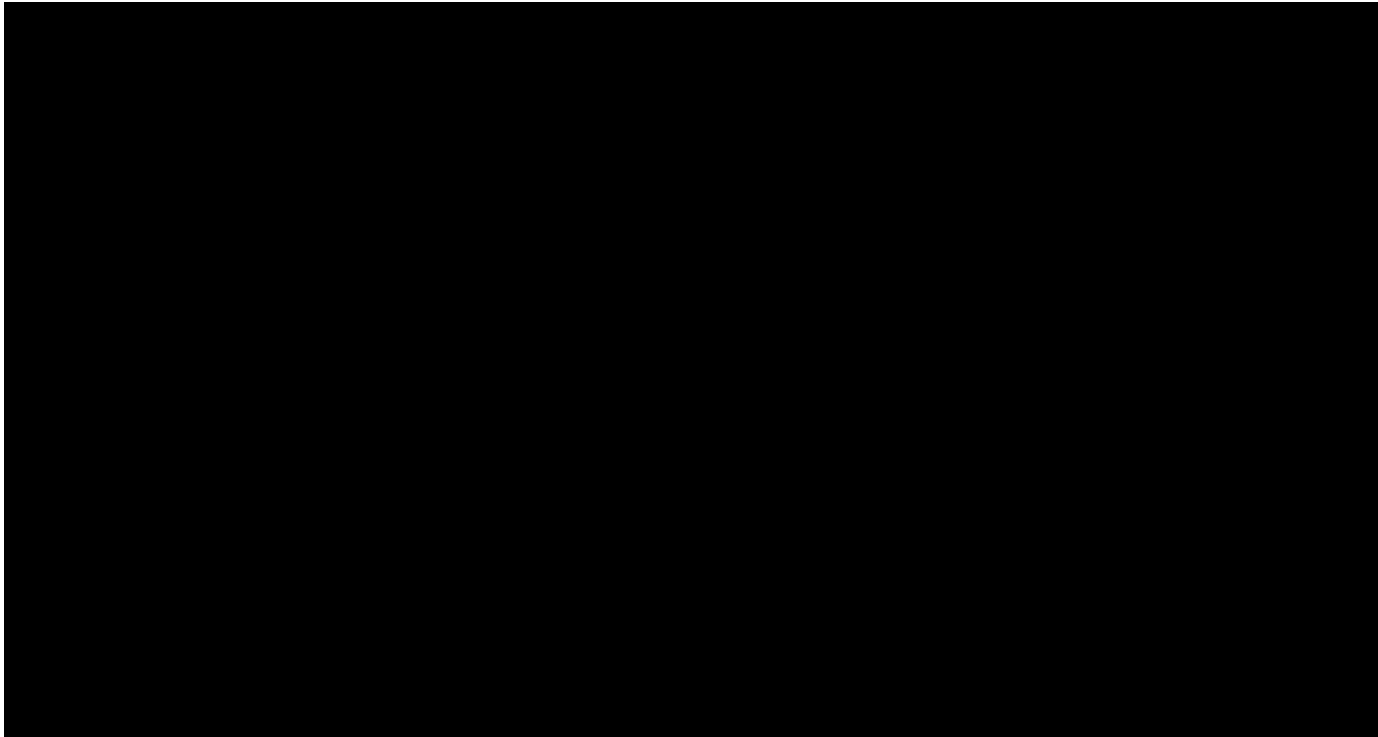
In the probabilistic analysis at its proposed PAS price, polihexanide 0.8 mg/ml was associated with more health benefits (2.52 more QALYs), at an incremental cost of [REDACTED] versus pooled AAT. The resulting PAS price ICER was [REDACTED] per QALY gained (Table 78). Overall, the mean PSA results were similar to the base case results. The cost-effectiveness plane and acceptability curves are presented in Figure 7 and Figure 8, respectively. These results use the proposed PAS price for polihexanide 0.8 mg/ml.

Table 78: Probabilistic results for polihexanide 0.8 mg/ml versus the pooled AAT comparator (with PAS)

	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)	INHB at £20k	INHB at £30k
Polihexanide 0.8 mg/ml		22.65	17.31	-	-	-	-	-	-
Pooled AAT	37,751	22.38	14.79		0.27	2.52		-	

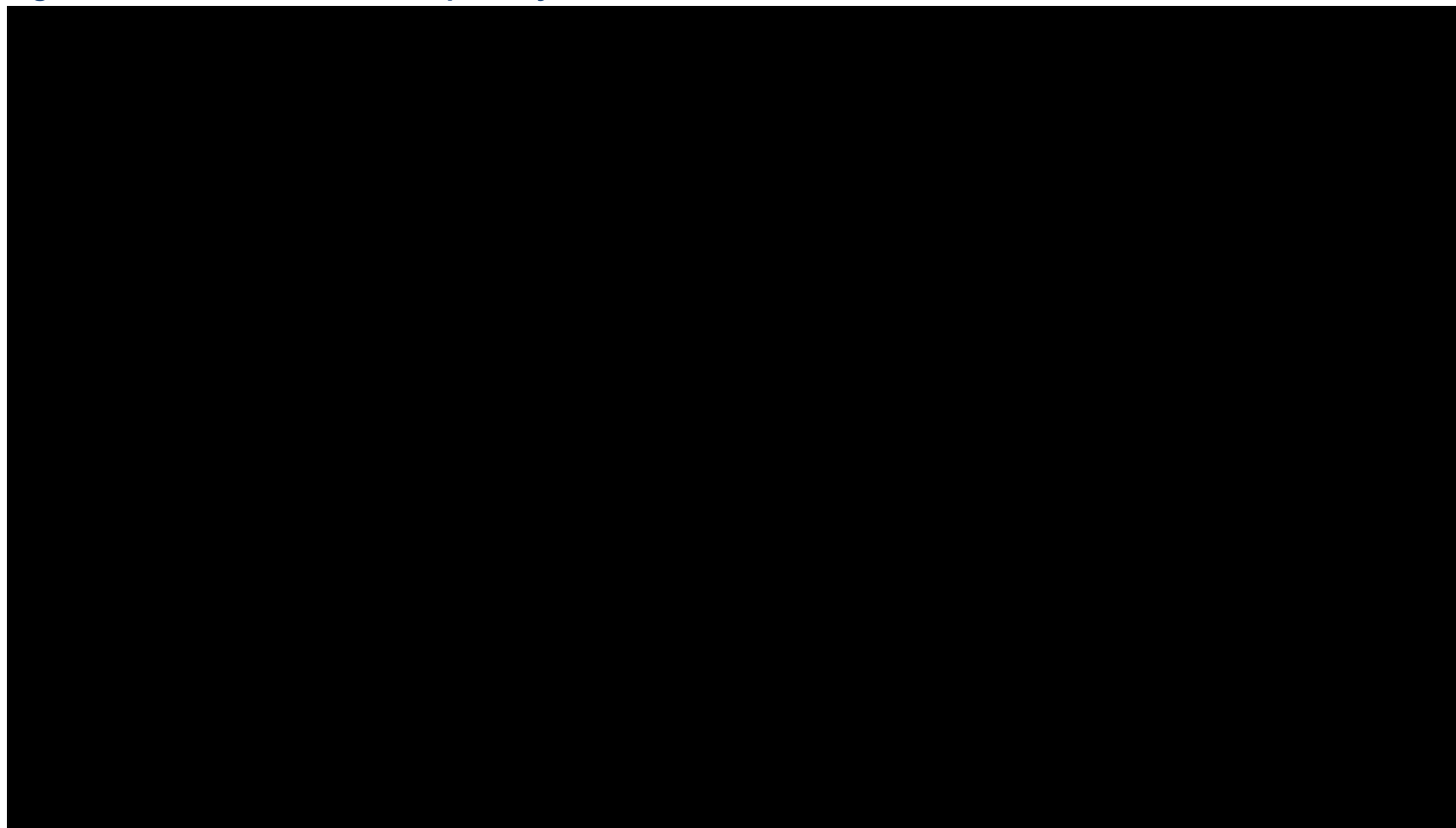
Abbreviations: AAT: anti-amoebic therapy; ICER; incremental cost-effectiveness ratio; INHB: incremental net health benefit; LYG; life years gained; PAS: patient access scheme; QALYs; quality-adjusted life years.

Figure 7: Cost-effectiveness scatter plot from base-case PSA



Abbreviations: CE: cost-effectiveness; GBP: Great British Pound; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year.

Figure 8: Cost-effectiveness acceptability curve from base-case PSA



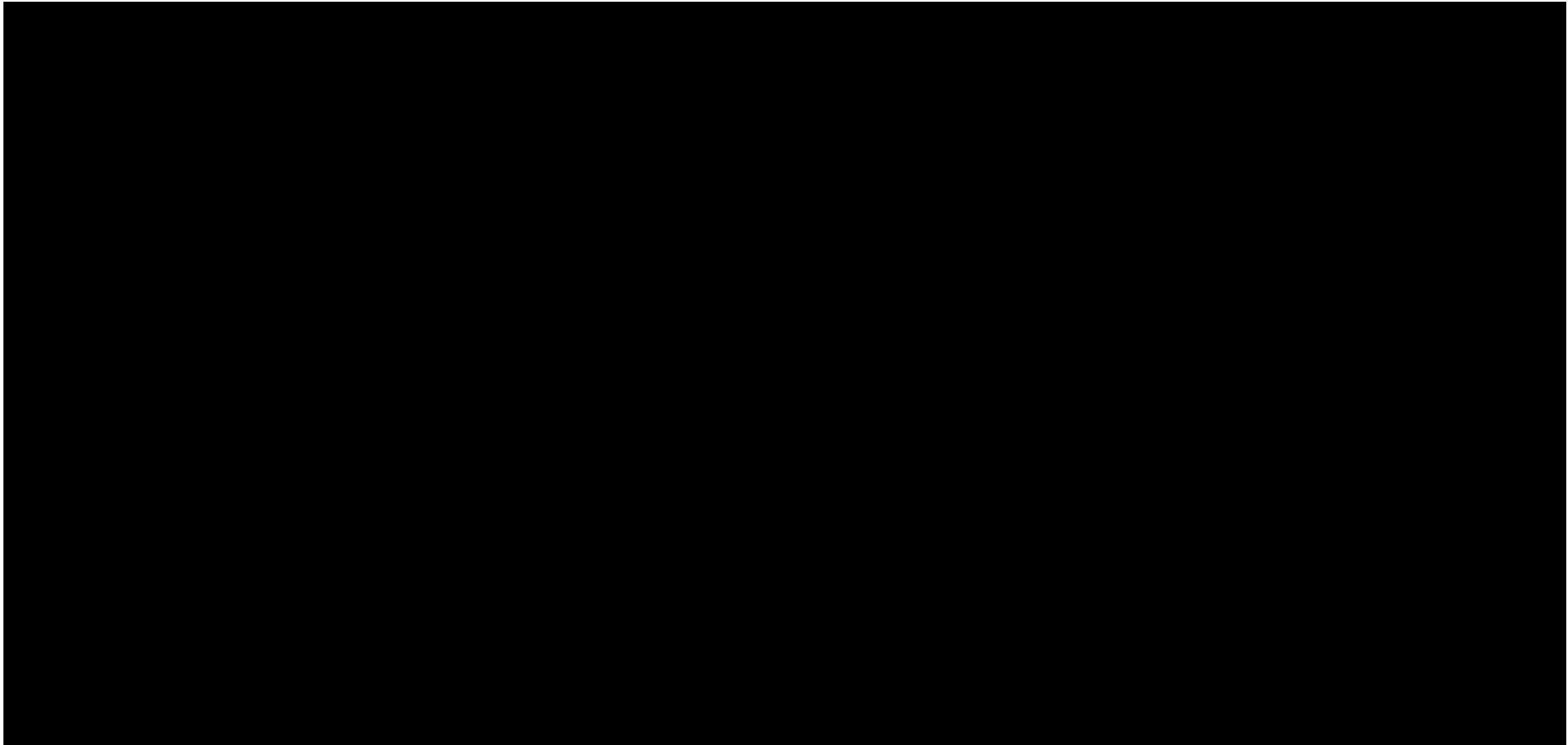
Abbreviations: GBP: Great British Pound; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; WTP: willingness-to-pay.

3.11.2 Deterministic sensitivity analysis

To evaluate the sensitivity of model results to variation in input parameters, a series of one-way (deterministic) sensitivity analyses were performed in which key model parameters were varied one at a time around their base-case values. The 95% confidence limits were used as the maximum and minimum values, where reported in the source data. If not reported, the 95% CI was approximated by setting maximum and minimum values at the base-case value $\pm 1.96 \times$ standard error (SE). When the SE was not reported, $\pm 10\%$ of the base-case value was used as a proxy.

The percentage change in base-case results following lower and upper variation in the 10 most influential model parameters is presented in Figure 9. Results of the DSA show that the parameters with the greatest influence on the base-case ICER was the discount rate applied for outcomes, the RR for the 12-month MCR for polihexanide 0.8 mg/ml versus the pooled AAT comparator (ODAK trial versus Papa et al. 2020) and treatment duration.

Figure 9: DSA tornado plot for absolute change in ICER (with PAS)



Abbreviations: BCVA: best-corrected visual acuity; DSA: deterministic sensitivity analysis; GBP: Great British Pound; GV: good vision; ICER: incremental cost-effectiveness ratio; ITC: indirect treatment comparison; MCR: medical cure rate; QALY: quality adjusted life year; RR: relative risk.

3.11.3 Scenario analysis

A range of scenario analyses were conducted to test the robustness of the model results to alternative model inputs and assumptions. A list of all the scenarios and a justification for their inclusion is provided in Table 79. The probabilistic and deterministic base case results were similar (Section 3.10 and Section 3.11.1), indicating that the economic model is linear; therefore, all scenario analyses were run deterministically.

Table 79: Scenario analyses conducted

Scenario	Scenario detail	Rationale
Pooled comparator distribution	Distribution of AATs in pooled comparator arm sourced from Papa et al. (2020)	To explore an alternative distribution of therapeutic approaches derived from the published Papa et al. (2020) study instead of the UK Delphi panel, (Table 31 in Section 3.2.3).
Treatment effectiveness inputs	12-month MCR for pooled AAT comparator sourced from ITC of polihexanide 0.8 mg/ml RWD (Franch et al. 2024) and pooled AAT (Papa et al. 2020), imputing age and % males, based on average values reported for the entire cohort	To explore the impact of using treatment effectiveness inputs from available RWD for polihexanide 0.8 mg/ml versus from the ODAK trial (Table in Section 3.3.2).
	12-month MCR for pooled AAT comparator sourced from ITC of polihexanide 0.8 mg/ml RWD (Franch et al. 2024) and pooled AAT (Papa et al. 2020), not adjusted for age or sex	
Mortality	General population mortality applied to all health states	This scenario was explored to model a conservative approach to mortality risk for the GV, SVL and loss of eye functionality health states, instead of applying mortality HRs derived from the published literature, associated with direct and indirect effects of visual impairment on mortality (Table 49 in Section 3.3.4).
Utility data inputs	Inclusion of disutility associated with intensive treatment phase in polihexanide 0.8 mg/ml arm	This scenario explores the impact of applying disutilities associated with insomnia in the intensive treatment phase to patients treated with polihexanide 0.8 mg/ml, although the intervention does not require administration during the night hours (Table 53 in Section 3.4.4). This scenario therefore models a conservative approach to disutilities.

Scenario	Scenario detail	Rationale
	Utility for PV and SVL health states informed by MMRM using cured GV as intercept, from ODAK trial with vision bolt-on disutilities	This scenario explores the use of a vision 'bolt-on' utility decrement for the PV and SVL health states, as the published literature suggests the EQ-5D may not capture all the impacts of ophthalmological conditions (Table 50 in Section 3.4.4). ⁹⁹⁻¹⁰¹

Abbreviations: AAT: anti-amoebic therapy; AK: Acanthamoeba keratitis; BCVA: best corrected visual acuity; GV: good vision; HR: hazard ratio; ICER: incremental cost-effectiveness ratio; ITC: indirect treatment comparison; MCR: medical cure rate; MMRM: mixed-models repeated measures; ODAK: Orphan Drug for Acanthamoeba Keratitis; PV: poor vision; QALY: quality-adjusted life year; RR: relative risk; SVL: severe vision loss; TA: technology assessment.

A list of all scenario analyses and their results are presented in Table 80. These results show that the scenario analyses with the greater impact on the base-case ICER were those using an ITC treatment effectiveness input for polihexanide 0.8 mg/ml from published real-world data (RWD) (Franch et al. 2024), either adjusted for age and sex or unadjusted, which decreased the ICER by █████% and █████%, respectively. These scenarios using RWD for polihexanide 0.8 mg/ml support that the effectiveness observed in the ODAK trial is likely to be replicable and, potentially, conservative versus real-world clinical practice.

The next largest change was observed when vision bolt-on disutilities were applied to the PV and SVL health states, which decreased the ICER by █████%. The scenario using the distribution of AATs from Papa et al. 2020 versus the distribution sourced from the Delphi panel (base case) had little impact on the ICER (█████), which is supportive of alignment and generalisability of the two sources of data.

Table 80: Results of the scenario analyses (deterministic, with PAS)

Scenario	Incremental costs, £	Incremental QALYs	ICER (£/QALY)	Absolute % Change in ICER	INHB at £20k	INHB at £30k
Base case	█████	2.56	█████	NA	-█████	█████
Distribution of AATs in pooled comparator arm sourced from Papa et al. (2020)	█████	2.56	█████	█████	-█████	█████
12-month MCR for pooled AAT comparator sourced from ITC of polihexanide 0.8 mg/ml RWD (Franch et al. 2024) and pooled	█████	3.36	█████	█████	-█████	█████

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Scenario	Incremental costs, £	Incremental QALYs	ICER (£/QALY)	Absolute % Change in ICER	INHB at £20k	INHB at £30k
AAT (Papa et al. 2020), imputing age and % males						
12-month MCR for pooled AAT comparator sourced from ITC of polihexanide 0.8 mg/ml RWD (Franch et al. 2024) and pooled AAT (Papa et al. 2020), not adjusted for age or sex	■	3.29	■	■	-■	■
General population mortality applied to all health states	■	2.46	■	■	-■	■
Inclusion of disutility associated with intensive treatment phase in polihexanide 0.8 mg/ml arm	■	2.54	■	■	-■	■
Utility for PV and SVL health states informed by MMRM using cured GV as intercept, from ODAK trial with vision bolt-on dis-utilities	■	2.67	■	■	-■	■

Abbreviations: AAT: anti-amoebic therapy; BCVA: best corrected visual acuity; GV: good vision; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; ITC: indirect treatment comparison; ODAK: Orphan Drug for Acanthamoeba Keratitis; QALY: quality-adjusted life year.

3.12 **Subgroup analysis**

As discussed in Section 1.1, the submission focuses on the total population of adults and children from 12 years of age with AK, in line with the expected marketing authorisation for polihexanide 0.8 mg/ml and the total population considered in the NICE scope.

There are no subgroups that are clinically relevant and for which polihexanide 0.8 mg/ml is expected to be more clinically or cost-effective. Furthermore, the population of patients with AK is very small, and it is therefore not appropriate to further reduce the population size by considering subgroups in terms of clinical outcomes or cost effectiveness. Therefore, subgroups were not analysed for cost-effectiveness.

3.13 **Benefits not captured in the QALY calculation**

The economic analysis has attempted to include all the potential benefits related to polihexanide 0.8 mg/ml within the QALY calculation. There are, however, several potential benefits of treatment with polihexanide 0.8 mg/ml which are not captured within the assessment.

As discussed in Section 1.3.5, when pharmacological approaches fail to clear the *Acanthamoeba* infection, people with AK may have to resort to surgical interventions, including therapeutic surgery. The prospect of surgery brings heightened anxiety and stress due to the uncertainty of the outcomes and the fear of potential vision loss, which can dramatically affect a patient's QoL. Additionally, undergoing these procedures can result in a significant psychological burden such as PTSD.⁷ Patients may experience distress while waiting for surgery, with extended wait times exacerbating feelings of helplessness and uncertainty about their future vision health.¹³⁷ Ophthalmologists consulted as part of a Delphi panel estimated an average wait time of 141.7 days prior to receiving surgical treatment, the psychological impact of which may be difficult to quantify and capture in the QALY analysis.¹¹

AK is also associated with a number of societal impacts which were not captured in the economic analysis, given the base case took an NHS and PSS perspective, in line with the NICE reference case. As discussed in Section 1.3.3, AK has significant physiological and functional impacts on patients, due to increasing worsening symptoms, including vision loss. The symptoms can result in isolation and impacts on their work environment, with challenges in performing job duties potentially leading to high levels of absenteeism and decreased productivity, affecting both personal livelihoods and broader economic productivity.¹³ Specifically, patients with AK who have experienced vision loss or blindness as a result of the disease may be eligible for disability benefits in the UK such as Personal Independence Payment (PIP) and/or Employment and Support Allowance (ESA).^{138, 139} The amount of benefits received via PIP and ESA depends on how much the condition affects activities of daily life, mobility tasks and the work capability of the individual. Patients with AK could be eligible for a weekly allowance of between £73.90–£110.40 for daily living and between £29.20–£77.05 for mobility under PIP benefits and up to a maximum of £140.55 per week if entitled to ESA.^{138, 139} However, these costs have not been captured as part of the cost-effectiveness analysis.

Care of people with AK in the UK is currently mainly provided by specialist centres, such as the Moorfields Eye Hospital, London.²⁹ Therefore, patients are required to travel long distances at considerable cost, in order to access specialist care. Furthermore, due to the lack of standard treatment protocol for treatment of AK, disease management strategies and therefore treatment Company evidence submission template for polihexanide eye drops for treating acanthamoeba keratitis in people 12 years and over [ID6497]

outcomes differ between treatment centres. This ‘postcode lottery’ is therefore a potential driver of health inequalities in AK, particularly given that rapid diagnosis and treatment in line with a standardised protocol is crucial to improve eventual prognosis.⁵³ The reimbursement of polihexanide 0.8 mg/ml would enable a standardised, rapid treatment approach, improving the equality of care for people with AK across England and Wales.

3.14 Validation

3.14.1 Validation of cost-effectiveness analysis

Clinical validation

SIFI utilised expert elicitation methods, in the form of a two-round Delphi panel, to address the limitations in available data for key model inputs. This is a structured expert elicitation methodology which is recognised by NICE and the wider community as a robust approach which is especially useful in research areas where knowledge is scarce.³ The Delphi panel included 10 ophthalmologists with experience treating AK patients in the UK and were affiliated with the UK NHS institutions in different regions of the country, ensuring insights were gathered from a broad range of clinical practices in the UK. Further details on the methodology of the Delphi Panel are presented in Appendix K.

For model inputs which could not be informed by existing literature, the ODAK and Papa et al studies, or the aforementioned Delphi Panel, assumptions were validated from a clinical perspective by two UK-based clinical experts, who agreed to participate in web-based interviews: Prof. Dart (Consultant Ophthalmologist who has researched AK disease for 30 years) and Dr. Sajjad Ahmad (Consultant Ophthalmic Surgeon in Moorfields Hospital).

Technical validation

The model was developed in accordance with ‘Modelling Good Research Practices’ disseminated by the International Society of Pharmacoeconomics and Outcomes Research and the Society for Medical Decision Making (ISPOR-SMDM).¹⁴⁰ Once fully developed, the model underwent an independent quality control and technical validation process which included checking of all model calculations including standalone formulae, equations and Excel macros programmed in Visual Basic for Applications (VBA). The correct functioning of the sensitivity and scenario analyses was also reviewed, and a checklist were completed to ensure that the model generated accurate results which were consistent with input data and robust to extreme values.

3.15 Interpretation and conclusions of economic evidence

3.15.1 Cost-effectiveness of polihexanide 0.8 mg/ml in people with AK

In the deterministic base-case economic analysis, polihexanide 0.8 mg/ml (with the proposed PAS discount) was associated with +2.56 incremental QALYs at an incremental cost of £[REDACTED] versus the pooled AAT comparator. The resulting ICER was £[REDACTED] per QALY gained. Therefore, considering the cost-effectiveness threshold of £20,000–£30,000 per QALY, the economic model results demonstrate that polihexanide 0.8 mg/ml is a cost-effective use of NHS resources versus relevant AAT comparators. In the PSA based on 1,000 simulations, the mean PSA results were

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similar to the base case results. In the DSA, the most influential parameters on the cost-effectiveness results were the discount rate applied for outcomes, the RR for the 12-month MCR for polihexanide 0.8 mg/ml versus the pooled AAT comparator (ODAK trial versus Papa et al. 2020) and treatment duration.

The majority of scenario analyses conducted remained cost-effective, illustrating the robustness of the model to the variation in inputs and further supports the cost-effectiveness of polihexanide 0.8 mg/ml to the NHS.

3.15.2 Strengths and limitations of the evidence

This is the first NICE TA in AK, and the model developed to support this submission is the first economic evaluation to model the cost effectiveness of a treatment for AK.

The Papa et al. (2020) study used to inform inputs within the model was considered a major strength given that this approach enabled real-world data to be directly leveraged from a large observational study. The Papa et al. (2020) study comprised outcome data from N=277 patients with AK, providing a large and robust sample of patients, with the majority of participants treated in the UK (177/277; 64%). The study also provided outcome data for AATs currently used in the UK, making it a representative assessment of the real-world treatment effectiveness in UK clinical practice.

Whilst AK is a very rare disease with associated evidence generation challenges, key model inputs were informed by a Delphi panel. This is a structured expert elicitation methodology which is recognised by NICE and the wider community as a robust approach which is especially useful in research areas where knowledge is scarce.³ The two-round Delphi panel included 10 ophthalmologists with experience treating AK patients in the UK and were affiliated with the UK NHS institutions in different regions of the country, ensuring insights were gathered from a broad range of clinical practices enhancing the credibility and reliability of the key model inputs used in this evaluation.

Furthermore, EQ-5D utility data were able to be generated from the ODAK trial, providing utility data from a directly relevant patient population, in line with NICE's preferences. EQ-5D-5L scores were mapped onto the EQ-5D-3L UK value set using the mapping function developed by the DSU based on the EEPRU dataset in alignment with NICE guidelines.^{3, 92} Therefore, unlike with evaluations for many other rare conditions, this evaluation is aligned with NICE's established standards for HRQoL.

However, this evaluation is not without limitation. As is expected in the study of rare diseases, there was limited availability of AK-specific data in the wider literature that was suitable to inform the inputs of the cost-effectiveness model. Subsequently, evidence from a number of different sources, including expert elicitation, were used in the economic model. To ensure robust collection of data using expert elicitation, data were sourced from a Delphi panel (Appendix K), which is an expert elicitation methodology recognised by NICE and the wider community which uses a structured and iterative approach to understand clinician perspectives. The Delphi panel participants were based in the UK working in the NHS, and all had experience treating patients with AK, ensuring that all responses were well informed with respect to the UK setting.

Given the heterogeneity of the current therapeutic approaches (a combination of off-label, compounded and unlicensed anti-amoebic agents), modelling all possible therapeutic combinations for AK is a significant challenge. A pooled AAT comparator was deemed the most

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appropriate approach to modelling current therapeutic options, allowing for a comprehensive yet streamlined evaluation that reflects the diversity of real-world treatment scenarios. In addition, some assumptions were required to avoid unnecessary complexity in the model (e.g. the model assumed that patients could only switch treatment once) which were validated by UK clinicians.

3.15.3 Conclusions

The results of the base case cost-effectiveness analysis demonstrate that polihexanide 0.8 mg/ml (with PAS) is associated with health benefits versus currently available treatments over a lifetime horizon, whilst also demonstrating an ICER that lies within NICE's cost-effective threshold of £20,000–£30,000. Uncertainty was demonstrated to be low. Therefore, polihexanide 0.8 mg/ml is likely to provide a cost-effective use of NHS resources. Given that the ODAK clinical trial data are generalisable to the UK, the modelling approach has been validated by clinical experts in England and UK-specific cost and resource use inputs were obtained from the aforementioned Delphi Panel, the model and its results are considered to be generalisable to clinical practice in England.

Crucially, data from the ODAK trial and the ITC with Papa et al. (2020) demonstrate that polihexanide 0.8 mg/ml provides a clear benefit in the treatment of AK. Results of the ITC showed that polihexanide 0.8 mg/ml had a statistically significantly higher MCR without surgery compared with the pooled AAT comparator from Papa et al. before weighting (RR: ■■■ [95% CI: ■■■, ■■■]) and in PSA analyses after adjustment (RR: ■■■ [95% CI: ■■■, ■■■]).³³ Improvements compared with baseline were also observed across a range of secondary endpoints for patients treated with polihexanide 0.8 mg/ml in the ODAK trial. These included improvements in visual acuity and corneal abnormality, with the rates of surgery and adjunctive therapy remaining low. Polihexanide 0.8 mg/ml is well-tolerated, with an acceptable safety profile in patients with AK, which aligns with EMA's overview of polihexanide 0.8 mg/ml in their EPAR report.⁵

As well as offering improved cure rates, polihexanide 0.8 mg/ml will provide a less burdensome dosing regimen (avoiding the need to regularly administer eye drops overnight and thereby avoiding sleep disruption and hospitalisation), compared with currently available therapeutic approaches. Individuals with AK rely on compounded, unlicensed treatments which are often not available at the point of diagnosis, leading to delays in treatment that significantly affect their prognosis. Moreover, these treatments lack safety and efficacy assessments and do not meet GMP standards, leading to suboptimal outcomes. Polihexanide 0.8 mg/ml meets GMP quality standards and is a stable treatment, removing the need for compounding of biguanide treatment on request as polihexanide 0.8 mg/ml could be kept in stock by treating centres. This would allow centres to treat AK more rapidly and consistently which is crucial given that delayed treatment is associated with poorer prognosis and clinical outcome. Reimbursement of polihexanide 0.8 mg/ml by NICE would represent an important step in formalising treatment for AK, providing patients with faster access to a long-overdue effective treatment and giving people an equal chance for cure across England and Wales.

Given the absence of effective therapeutic options indicated for AK, it is clear that there remains a critical unmet need for treatments in this population. Individuals with AK, caregivers, patient organisation representatives and clinicians have expressed a need for newer and better treatment options as soon as possible, highlighting the urgent remaining unmet need for an effective treatment.⁷ Polihexanide 0.8 mg/ml is therefore expected to provide a vital treatment for patients with AK.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Summary of Information for Patients (SIP)

24th June 2025

File name	Version	Contains confidential information	Date
ID6497_AKANTIOR _SIP_24June25	1.0	No	24 th June 2025

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#)

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Polihexanide 0.8 mg/ml

Brand name: Akantior®

Please note: Further explanations for the words and phrases highlighted in **bold text** are provided in the glossary (**Section 4b**). Cross-references to other sections or other appraisal documents are highlighted in **orange**. Cross-references to figures and tables are highlighted in **teal**.

1b) Population this treatment will be used by: Please outline the main patient population that is being appraised by NICE:

Adults and children from 12 years of age with a condition called ***Acanthamoeba keratitis***.
(Please see **Section 2a** for an explanation of what *Acanthamoeba keratitis* is).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

On 15 May 2025, the **Medicines and Healthcare products Regulatory Agency** granted **marketing authorisation** for polihexanide 0.8 mg/ml as a treatment for individuals 12 years and over with *Acanthamoeba keratitis* (<https://www.gov.uk/government/news/mhra-approves-poli-hexanide-to-treat-acanthamoeba-keratitis>). More information on this can be found in **Section 1.2 of the Company Submission**.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

SIFI collaborates with a range of stakeholders with an interest in *Acanthamoeba* keratitis. This includes collaboration with patient groups to support improvements in health and care for individuals with *Acanthamoeba* keratitis.

SIFI would like to disclose the following collaborations with patient groups:

- SIFI has a multi-year collaboration with and supports the “*Acanthamoeba* Keratitis Eye Foundation”, based in The Netherlands with representation in the UK (<https://akeyefoundation.com/>). This collaboration is aimed at raising awareness of the disease, mainly at clinical congresses. Beyond this, SIFI provided a donation of €5,000 in 2023.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Polihexanide 0.8 mg/ml is being considered for the treatment of *Acanthamoeba* keratitis

What is *Acanthamoeba* keratitis?

- *Acanthamoeba* keratitis is a very rare and serious eye disease which can result in vision and/or eye loss. It is caused by *Acanthamoeba* (a **free-living protozoan**) which sticks to the surface of the eye (**cornea**) and moves progressively deeper into it, damaging the eye. This can cause symptoms such as red and swollen eyes, unbearable pain, blurred vision, tearing and prolonged and severe sensitivity to light.(1, 2) *Acanthamoeba* keratitis usually affects one eye but can sometimes involve both. In about one-third of cases, it can lead to vision loss that is permanent or very long lasting.(3) **Therapeutic surgery** is often necessary to remove the infected part of the cornea and to prevent further damage. If there are scars on the cornea, **optical surgery** may be needed for help restore vision once the infection is resolved (see **Section 2c** for more information).
- *Acanthamoeba* has two life stages: an active, moving form that multiplies quickly and can damage the eye and a dormant, resting form that is very tough and resistant to treatment. Because *Acanthamoeba* can switch between these two stages, it can be hard to eliminate them, and the infection might come back, even after treatment (**recurrence**).

What causes *Acanthamoeba* keratitis?

The main risk factor for developing *Acanthamoeba* keratitis is the inappropriate use of contact lenses. Poor contact lens hygiene includes wearing contact lenses overnight, using them for too long, or keeping them on during swimming or showering. Poor contact lens hygiene is linked to 87% of cases of *Acanthamoeba* keratitis.(4-6)

How many people have *Acanthamoeba* keratitis?

Acanthamoeba keratitis is a very rare disease. It is estimated that there are around 1 in 425,500 people across the UK that are affected by *Acanthamoeba* keratitis every year.(6) Therefore, there are approximately 126 people in the UK who are affected by *Acanthamoeba* keratitis each year.(7)

What is the impact of *Acanthamoeba* keratitis for people living with the condition?

Physical impact

Acanthamoeba keratitis has a severe negative impact on an individuals' wellbeing and daily life. Symptoms like intense pain, severe light sensitivity, eye redness and swelling worsen over time, making it hard for people with *Acanthamoeba* keratitis to keep their eyes open.(8) This can make day-to-day life very difficult, making everyday activities hard and unsafe.(8) Therefore, prompt treatment of *Acanthamoeba* keratitis is important to reduce the impact of symptoms on individuals and their daily lives.

As *Acanthamoeba* keratitis is a very rare disease, many doctors are not familiar with this condition. Therefore, many people with *Acanthamoeba* keratitis may receive a wrong or late diagnosis. Over half of individuals with *Acanthamoeba* keratitis are misdiagnosed with a viral infection, called Herpes Simplex keratitis.(9) As a consequence, the treatment for Herpes Simplex keratitis would be ineffective in *Acanthamoeba* keratitis, leading to more damage to the eye and poorer outcomes for individuals.(10)

Emotional impact

Living with *Acanthamoeba* keratitis can seriously impact a persons' mental health. Some people may feel anxious, sad and depressed due to constant pain, lack of sleep and isolation.(11) Many people with *Acanthamoeba* keratitis also fear losing their eyesight which increases anxiety. The condition often keeps individuals at home, reducing social interactions and their ability to live independent lives, which makes feelings of loneliness and depression worse.(8, 11) People with *Acanthamoeba* keratitis may also feel embarrassed or unhappy with how they look, which can make it hard for them to feel "normal" and confident.

Impact on quality of life

As the main risk factor for *Acanthamoeba* keratitis is improper contact lens hygiene, *Acanthamoeba* keratitis affects mainly young people. Vision impairment can greatly impact the **quality of life** of individuals as well as their future plans. It can make daily activities like reading or getting around difficult, with individuals often needing help or special aids to remain independent.(8) People with *Acanthamoeba* keratitis may also feel less able to join social activities and their ability to work or study may be affected, sometimes requiring changes to their job, and frequently, individuals lose their job, unless they can go on sick leave for long periods of time.(8) Individuals may feel like their lives are put 'on hold' whilst they are waiting to be cured, even though this may take several months or even years.

What is the impact of *Acanthamoeba* keratitis on families and carers?

Carers dedicate a large amount of time providing support to people with *Acanthamoeba* keratitis.(8) People with *Acanthamoeba* keratitis may need help with everyday tasks like getting out of bed, moving around the home, cooking and household chores. People with *Acanthamoeba* keratitis often need support with attending appointments and managing their medications.(8) The severe pain, vision problems and light sensitivity associated with *Acanthamoeba* keratitis and uncertainty around possible permanent vision impairment in individuals with *Acanthamoeba* keratitis can also cause stress for caregivers.(8) The uncertainty about the future and whether the person's eyesight will be permanently damaged can make individuals and their families feel isolated, anxious and afraid.(12)

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is *Acanthamoeba* keratitis diagnosed?

In the UK, *Acanthamoeba* keratitis is diagnosed by using corneal scraping and corneal scans to look for signs of the disease:(13, 14)

- In corneal scans, the eyes are scanned using a confocal microscope to look for *Acanthamoeba* cysts.(13, 15)
- **Corneal scraping** is performed to collect cells from the cornea. These can be analysed using various methods such as growing the organisms in a **culture** and applying special stains to see them under a microscope, or using a technique called **Polymerase Chain Reaction** to test for *Acanthamoeba*.(16)

There are no additional diagnostic tests required before individuals are treated with polyhexanide **0.8 mg/ml**.(17)

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

- if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the therapeutic approaches available for *Acanthamoeba* keratitis?

Treatment with eye drops

In England and Wales, there were no approved treatments available for *Acanthamoeba* keratitis before polyhexanide 0.8 mg/ml. Therefore, individuals receive combinations of **off-label** and **unlicensed** eye drops which are not specifically designed to be used together and are not part of a standard treatment plan.(18) The **therapeutic approaches** currently used include **compounded** solutions containing substances called **biguanides** (such as chlorhexidine and polyhexanide at lower amounts than 0.8 mg/ml) and solutions based on **diamidines** that are used off-label (such as propamidine and hexamidine). These eye drops can be used alone, or in combination with one another,(19) and they work by killing the *Acanthamoeba* organisms in the eye.(20-22) These eye drops are administered regularly (hourly) throughout the day and night for several days. This can disturb sleep for individuals with *Acanthamoeba* keratitis, making them feel tired. Moreover, the compounded products used in the current therapeutic approaches are not always readily available to people with *Acanthamoeba* keratitis as they have to be specially prepared each time they are used. This can lead to safety issues like lack of **sterility** or wrong doses and delays in starting treatment.(23) Treatment delays have a negative impact on individuals, who continue to experience severe pain, discomfort and the worsening of their vision. Research has shown that treatment delays result in worse outcomes for people with *Acanthamoeba* keratitis.(10) Additionally, compounded products do not meet **Good Manufacturing Practice standards** which may negatively affect their safety or effectiveness when treating *Acanthamoeba* keratitis. In addition to eye drops, pain relief and **corticosteroids** are often used to manage the pain and swelling caused by *Acanthamoeba* keratitis.(9, 11)

There is no clear medical guidance for how these unapproved products should be given to people with *Acanthamoeba* keratitis in the UK. As a result, individuals receive different care depending on their doctor, including different types of treatment and treatment schedules.(9) This often leads to varying health outcomes for individuals.

Eye surgery

Individuals are considered for eye surgery in multiple circumstances: to restore vision when *Acanthamoeba* keratitis is cured or when treatments fail to cure *Acanthamoeba* keratitis. Eye surgery for individuals with *Acanthamoeba* keratitis include two different types, both of which involve replacing the damaged eye surface with a **donor eye surface** (known as **corneal transplant**):

- **Therapeutic surgery** aims to clear the *Acanthamoeba* keratitis infection. These surgeries are performed when the eye surface is severely damaged or as a last option to clear the *Acanthamoeba* keratitis infection if other treatments have failed.(24)
- **Optical surgery** aims to repair the eye surface and to try to improve the person's vision once the infection, swelling and redness are cleared.(24)

It is anticipated that polyhexanide 0.8 mg/ml will replace the off-label and unlicensed eye drops currently given to people with *Acanthamoeba* keratitis in the UK. Polyhexanide 0.8 mg/ml has been developed to be used as **monotherapy**, with a well standardised treatment protocol which does not need to be administered during the night. In the ODAK trial (see **Section 3d**), 84.8% of individuals were cured without the need for surgery when treated with polyhexanide 0.8 mg/ml.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

***Acanthamoeba* keratitis from the patient perspective**

People with *Acanthamoeba* keratitis face the reality of losing part or all of their eyesight. Living with *Acanthamoeba* keratitis can be very challenging and impact quality of life. The Global Alliance Against *Acanthamoeba* Keratitis is a collaboration of people with *Acanthamoeba* Keratitis, doctors, scientists and regulators who work to improve outcomes for *Acanthamoeba* keratitis. They interviewed people with *Acanthamoeba* keratitis as part of a study in 2024 to raise awareness about *Acanthamoeba* keratitis. Within this study, one individual with *Acanthamoeba* keratitis commented that: *“Acanthamoeba keratitis 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.”*(11)

Additionally, one individual with *Acanthamoeba* keratitis noted that *“Acanthamoeba keratitis is a living nightmare in excruciating pain, light sensitivity, isolated from the world, depressed and afraid of the future.”* *“Some days you want to give up. Or pull your eye out.”*(11)

People with *Acanthamoeba* keratitis often face anxiety, frustration and anger due to the uncertainties associated with varied treatments, surgeries and the potential of losing their eyesight in the long-term. One person with *Acanthamoeba* keratitis explained: *“I had four corneal transplants. As I am still very young, my body rejects all the transplants and when I was 20 years old, I had to start taking steroids alongside my regular medication.”*(11) The emotional impact of undergoing surgery is further illustrated by another person with *Acanthamoeba* keratitis who stated *“Through all the traumatic surgeries at a relatively young age, PTSD came fairly soon. It grew from fears of never leaving the cycle of surgery and doctor appointments and manifested in nightmares.”*(11)

Therefore, there is a clear unmet need for an effective treatment for *Acanthamoeba* keratitis that individuals can access quickly after diagnosis.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

As mentioned in **Section 2a**, *Acanthamoeba* keratitis is caused by *Acanthamoeba* organisms sticking to the surface of the eye, causing an infection. The treatment under consideration by NICE, polihexanide 0.8 mg/ml, works against both the active and dormant forms of *Acanthamoeba* (see **Section 2a** for an explanation of these). Polihexanide 0.8 mg/ml works by damaging the membrane (outer skin) of the *Acanthamoeba*, which destroys the protozoan. Polihexanide 0.8 mg/ml also binds to the **deoxyribonucleic acid** (DNA) of the *Acanthamoeba* to stop it from growing and multiplying. Polihexanide 0.8 mg/ml has been approved by the Medicines and Healthcare products Regulatory Agency (**Section 1c**). It has also been granted orphan status, a Promising Innovative Medicine designation and New Active Substance status which are all special recognitions for new medicines, recognising their innovative nature and potential to address unmet need. The availability of polihexanide 0.8 mg/ml will change how *Acanthamoeba* keratitis is treated. It will give patients direct access to a treatment that is of high quality, which is specifically developed and approved to treat *Acanthamoeba* keratitis.(25)

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Polihexanide 0.8 mg/ml is not intended to be used with any other therapeutic approach for the treatment of *Acanthamoeba* keratitis.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How is polihexanide 0.8 mg/ml taken?

Polihexanide 0.8 mg/ml should be used exactly as explained by the Summary of Product Characteristics.(17) Proper use of the product, as described in the instructions for use, increases the likelihood of a good outcome of the treatment with polihexanide 0.8 mg/ml.

Polihexanide 0.8 mg/ml is taken in the form of eyedrops, applied directly to the eye by the person using a dropper bottle.

How much medicine do individuals take and when?

The recommended dose is one drop of polihexanide 0.8 mg/ml in the affected eye according to the following regimen:(17)

First 19 days of treatment ('intensive treatment phase'):

- Days 1–5: Apply 16 times a day, once every hour during the day.
- Days 6–12: Apply 8 times a day, once every two hours during the day.
- Days 13–19: Apply 6 times a day, once every three hours during the day.

After first 19 days ('continuation treatment phase'):

- Apply 4 times a day, once every four hours, until the eye is healed and not for more than 12 months.

The 19-day intensive treatment phase should be restarted if swelling and redness worsens during the continuation phase and there is no more *Acanthamoeba* present. Treatment with polihexanide 0.8 mg/ml should be stopped if *Acanthamoeba* keratitis is not cured within 12 months.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Studies of polihexanide 0.8 mg/ml in *Acanthamoeba* keratitis

In England and Wales, there were no approved treatments available for *Acanthamoeba* keratitis before polihexanide 0.8 mg/ml. The Orphan Drug for *Acanthamoeba* Keratitis (ODAK) trial was the first primary **clinical trial** studying how well polihexanide 0.8 mg/ml works in people with *Acanthamoeba* keratitis.(25) A summary of the key information about the ODAK trial is provided in **Table 1**.

The ODAK trial was a **Phase 3, randomised clinical trial**, investigating how well polihexanide 0.8 mg/ml plus **placebo** worked to treat *Acanthamoeba* keratitis (its **efficacy**) and how safe the medicine was compared to a combination of polihexanide 0.2 mg/ml and propamidine 1 mg/ml (the **active comparator**). The trial also investigated the impact of polihexanide 0.8 mg/ml on participants' quality of life.(25)

An active comparator was used in the ODAK trial after a request by the **European Medicines Agency**. The European Medicines Agency asked for this group to be included to make sure all individuals received some form of treatment during the trial, addressing ethical concerns. However, the effectiveness of the active comparator in the clinical trial does not reflect how current therapeutic approaches work in the real-world, as in the trial they were provided more quickly than in the real-world and in a more standardised way, which would improve how well they work (please see **Section 3e** for more details).(22, 26)

In the trial, participants were randomly chosen to take either polihexanide 0.8 mg/ml (plus **placebo**) or polihexanide 0.2 mg/ml and propamidine 1 mg/ml for one year. The trial was **assessor-masked**, which means the person assessing participant's results did not know which treatment each participant was receiving.(25)

Participants whose *Acanthamoeba* keratitis infection was cured during the trial were assessed at two follow-up visits after they had finished treatment: one visit 30 days after

stopping treatment and one visit 90 days after stopping treatment. For individuals who were not cured within a year of treatment, it was considered that the treatment had not worked.(25)

Table 1. Trials investigating polihexanide 0.8 mg/ml for *Acanthamoeba* keratitis

Trial name and number	ODAK (NCT03274895)(27)
Location	Six sites in three countries: UK, Italy and Poland
Participant population	People aged 12 years or over with <i>Acanthamoeba</i> keratitis
Number of participants included	127
Treatment being tested	Polihexanide 0.8 mg/ml (plus placebo)
Comparator (the medicine being compared against)	Polihexanide 0.2 mg/ml and propamidine 1 mg/ml

Abbreviations: ODAK: Orphan Drug for Acanthamoeba Keratitis.

Source: ClinicalTrials.gov (NCT03274895).(27)

More information about the ODAK trial can be found here:

- Dart et al. 2024 ([https://www.aaojournal.org/article/S0161-6420\(23\)00710-8/fulltext](https://www.aaojournal.org/article/S0161-6420(23)00710-8/fulltext)).
- ClinicalTrials.gov (<https://clinicaltrials.gov/study/NCT03274895>).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

How was the efficacy of polihexanide 0.8 mg/ml in *Acanthamoeba* keratitis measured in the trial?

For individuals with *Acanthamoeba* keratitis, the main goal is to cure the infection. Since many individuals currently need to be treated for several years with available therapeutic approaches and sometimes surgery, reducing the time taken to be cured is also important. It is also important to measure how well a patient is able to see and to understand if their eyesight is getting worse.

In the ODAK trial, the efficacy of polihexanide 0.8 mg/ml was measured according to how well it improved these three key measures after 12 months of treatment:(25)

- Medical cure rate at 12 months: This was the percentage of individuals that were cured without needing surgery or a change in treatments within 12 months. Being "cured" meant that the eye infection caused by *Acanthamoeba* was cleared, and the eye looked healthy—specifically, the surface of the eye was intact, and there were no signs or symptoms of swelling and redness. This was confirmed after

stopping treatment and waiting 30 days, and then checked again at the final visit, 90 days after stopping treatment.

- Time to cure: the time (in days) taken for the individual's *Acanthamoeba* keratitis infection to be cured.
- Best-corrected visual acuity: a measure of how clearly a subject can see with correction (glasses or contact lenses). Best-corrected visual acuity is tested by asking an individual to look at an eye chart from a certain distance and to read the smallest letters they can see. This helps doctors understand an individual's true level of vision with the best possible correction.

Within 12 months of treatment with polyhexanide 0.8 mg/ml, 84.8% of individuals with *Acanthamoeba* keratitis were cured (in line with the medical cure rate definition above), taking an average (median) of 140 days to be cured. On average, participants' vision got better during the trial, with an average improvement of 0.29 in their best-corrected visual acuity measurement compared to when they first started the trial.

More efficacy results from the ODAK trial can be found in **Section 2.6 of the Company Submission**.

Comparison of polyhexanide 0.8 mg/ml to current therapeutic approaches

The ODAK trial compared polyhexanide 0.8 mg/ml to polyhexanide 0.2 mg/ml combined with propamidine 1 mg/ml (the comparator). However, the trial results comparing polyhexanide 0.8 mg/ml to the comparator are not fully relevant to how *Acanthamoeba* keratitis is treated in the real-world. Current therapeutic approaches in the UK are often not made to Good Manufacturing Practice standards and need to be prepared before being used, causing delays to treatment which can lead to worse outcomes. In the ODAK trial, individuals received both the products in the active comparator faster than they would in the real-world, and treatment was given in a standardised way, which is not how the treatment is given in real-world practice. Polyhexanide 0.8 mg/ml is a ready-to-use product made to Good Manufacturing Practice standards so its use in practice would likely be similar to how it was tested in the trial. Therefore, while randomised clinical trials are seen as the gold standard for comparing how well medicines work, the differences described above mean that the ODAK clinical trial may not have fully captured the differences in efficacy between polyhexanide 0.8 mg/ml and to polyhexanide 0.2 mg/ml with propamidine 1 mg/ml.

As such, data for polyhexanide 0.8 mg/ml from the ODAK trial were compared to another study: the Papa et al. 2020 study.(22) This was a **retrospective** study looking back at data from 1991 to 2012, to see how well different treatments work for people with *Acanthamoeba* keratitis in clinical practice.(22) In this study, individuals were treated with a range of therapeutic approaches, either by themselves, or in different combinations. As clinical practice can vary widely, the Papa et al. 2020 study presented combined results for all therapeutic approaches used referred to as a '**pooled comparator**'.(22)

To compare the efficacy between polyhexanide 0.8 mg/ml and currently used therapeutic approaches, information on how quickly people receiving polyhexanide 0.8 mg/ml were cured was taken from the ODAK trial. Information for how quickly people were cured with current therapeutic approaches was taken from Papa et al. 2020. These were then compared using a technique called an **indirect treatment comparison**. An indirect treatment comparison is a way to compare the effects of different treatments that were not included in the same study. The data from ODAK and Papa et al. 2020 could be compared because they both used the same definition for medical cure rate.

Results of the indirect treatment comparison showed that polyhexanide 0.8 mg/ml cured more individuals with *Acanthamoeba* keratitis than the pooled comparator. This result was **statistically significant**, suggesting that polyhexanide 0.8 mg/ml can be more effective

than current therapeutic approaches at curing *Acanthamoeba* keratitis. More information can be found in **Section 2.10 of the Company Submission**.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQoL-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Impact of polyhexanide 0.8 mg/ml on quality of life

During the ODAK trial, individuals were asked to answer questions about their quality of life, using questionnaires called the EQ-5D and visual functioning questionnaire (VFQ-25).⁽²⁵⁾ The EQ-5D is a questionnaire that is recommended by NICE for measuring a person's quality of life. The VFQ-25 is a questionnaire which specifically asks about the effect of vision problems on a person's quality of life, including the ability to see and participate in everyday activities. The results of EQ-5D and VFQ-25 showed that people with *Acanthamoeba* keratitis experienced a significant improvement in their quality of life when treated with polyhexanide 0.8 mg/ml compared to treatment with polyhexanide 0.2 mg/ml with propamidine 1 mg/ml.⁽²⁵⁾ Further information can be found in **Section 2.6.8 of the company submission**.

By achieving a quicker cure, further damage from the *Acanthamoeba* organism is prevented, which helps reduce pain and the fear of losing eyesight. As a result, overall quality of life for people with *Acanthamoeba* keratitis is likely to improve with polyhexanide 0.8 mg/ml treatment as polyhexanide 0.8 mg/ml improves cure rates compared to current therapeutic approaches (**Section 3e**).

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Every medicine has the potential to result in **side effects** and the same medicine can produce different reactions in different people. In the ODAK trial, polyhexanide 0.8 mg/ml was generally well **tolerated** (individuals were able to put up with the side effects of their treatment) and most of the side effects were mild or moderate.⁽²⁵⁾

In ODAK, the most common side effects experienced by individuals receiving polyhexanide 0.8 mg/ml were eye pain (13.0%), **infections** and **infestations** (13.0%; harmful germs

entering the eye), **ocular hyperaemia** (11.6%; red eyes), increased **lacrimation** (8.7%; eyes watering more than usual) and general effects throughout the body and at the site of treatment administration (5.8%). Doctors in the trial considered that these side effects were not related to taking polihexanide 0.8 mg/ml. There were seven individuals who stopped taking polihexanide 0.8 mg/ml due to side effects they experienced during the ODAK trial. There were no serious side effects (side effects that result in death, hospital stays, cause lasting disability or pose a threat to life) or deaths caused by other things during the trial, according to the ODAK protocol.(25) The side effects were re-evaluated by the **European Medicines Agency** using a different criteria which re-categorised four side effects in the ODAK trial to serious side effects. These were the formation of a hole in the cornea (one case in the polihexanide 0.8 mg/ml arm and one case in the polihexanide 0.2 mg/ml and propamidine 1 mg/ml arm), **corneal transplant** and vision impairment (each with one case in the polihexanide 0.8 mg/ml arm).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

There is an urgent unmet need for an effective treatment for individuals with *Acanthamoeba* keratitis

Acanthamoeba keratitis is an extremely painful and devastating disease, in which symptoms worsen over time, with the potential for life-long vision impairment and eye loss.(11) Despite this, there were no approved treatments, before polihexanide 0.8 mg/ml, specifically available for people with *Acanthamoeba* keratitis in England and Wales. As a result, there are no standard treatment types or treatment patterns that doctors use to treat the condition, so treatment varies depending on the doctor seen by the person with *Acanthamoeba* keratitis. As well as this, current therapeutic approaches may not meet Good Manufacturing Practice standards, so their safety or ability to treat *Acanthamoeba* keratitis could be negatively affected.(28) They also must be specially prepared each time they are used which can cause lack of sterility, incorrect doses and delays in treatment.(23) Current therapeutic approaches have to be taken very frequently (hourly) throughout the day and night for several days, which can disrupt sleep and daily activities.(8) During this intensive treatment phase, approximately 27% of individuals must go to hospital.(29) Following treatment with current medications, many people with *Acanthamoeba* keratitis require surgery which carries multiple risks such as post-surgical infections and **graft rejection** with a need for further surgery.(29) These surgeries can also cause a lot of emotional and physical stress for individuals.(29) There is therefore a high unmet need for readily available treatments that can clear the *Acanthamoeba* infection and improve the quality of life of people affected by *Acanthamoeba* keratitis.

Polihexanide 0.8 mg/ml is effective for treating individuals with *Acanthamoeba* keratitis

In the ODAK trial, polihexanide 0.8 mg/ml was shown to be effective with 84.8% of individuals cured.(12, 25) When compared to current therapeutic approaches, the cure rate in patients treated with polihexanide 0.8 mg/ml was statistically significantly higher than for people taking these therapeutic approaches in the real-world.(12) Based on the

results from the ODAK trial and the indirect treatment comparison, it was found that patients treated with polihexanide 0.8 mg/ml:(22, 25)

- Experienced higher cure rates.
- Had improved quality of life.
- Had mild or moderate side effects that were manageable.

How polihexanide 0.8 mg/ml addresses the unmet need

Polihexanide 0.8 mg/ml would be the first treatment available in England and Wales specifically developed for *Acanthamoeba* keratitis. This will reduce the variability in the clinical outcome experienced by individuals with *Acanthamoeba* keratitis when treated with the therapeutic approaches currently used in the clinical practice. Polihexanide 0.8 mg/ml is a well-tolerated treatment that is manufactured to Good Manufacturing Practice standards. It is also stable up to 24 months and does not require any particular storage conditions, so it does not need to be specially prepared each time it is used, unlike current therapeutic approaches. Instead, polihexanide 0.8 mg/ml can be stored and supplied directly by treatment centres when required. This allows people with *Acanthamoeba* keratitis to be treated more quickly and reliably, which is important because treatment delays can lead to worse health outcomes.(10) It also helps reduce mistakes that can happen when preparing current therapeutic approaches, such as contamination or incorrect doses.(23)

Polihexanide 0.8 mg/ml is easier to use than current therapeutic approaches because it requires a less intense treatment course, with eye drops given every hour during the day in the initial treatment period, unlike current therapeutic approaches that require administration throughout the day and night for several days.(17) This makes it easier for individuals to take polihexanide 0.8 mg/ml properly and reduces the disruption to their sleep and daily lives.

By increasing the cure rate and reducing the length of time it takes to reach a cure in *Acanthamoeba* keratitis, individuals receiving polihexanide 0.8 mg/ml are less likely to progress to surgery, with low rates of surgery found in the ODAK trial with respect to current clinical practice.(12)

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Like all medicines, some individuals may experience side effects while they are taking polihexanide 0.8 mg/ml. The main side effects associated with polihexanide 0.8 mg/ml are listed in **Section 3g**. However, the side effects associated with polihexanide 0.8 mg/ml are considered to be manageable, and most people do not need to stop treatment because of side effects. Beyond these side effects, there are no additional key disadvantages with treatment.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Overview of the economic model

The role of NICE is to evaluate whether a new medicine would represent 'good value for money' to the NHS if it is recommended for use. To do this, NICE will look at the costs of a new medicine for a particular condition and how the health and quality of life of people is likely to improve if they take it, compared to if people with the same condition carried on taking the medicines that are currently available.

The costs and benefits of a new medicine are considered together within a **health economic model** and are compared to the costs and benefits of an existing medicine. In this submission, an economic model was used to compare the costs and benefits of polihexanide 0.8 mg/ml, versus a combination of the most commonly used therapeutic approaches in UK clinical practice (referred to as a 'pooled comparator'), to understand whether polihexanide 0.8 mg/ml would represent 'good value for money' for the NHS, if it was recommended by NICE. The pooled comparator included the following off-label and/or compounded therapeutic approaches:

- Polihexanide 0.2 mg/ml.
- Polihexanide 0.2 mg/ml with diamidine.
- Polihexanide 0.6 mg/ml.
- Polihexanide 0.6 mg/ml with diamidine.
- Chlorhexidine 0.2 mg/ml with diamidine.
- Chlorhexidine 0.2 mg/ml.
- Diamidine.
- Chlorhexidine 0.2 mg/ml with polihexanide 0.2 mg/ml.
- Chlorhexidine 0.2 mg/ml with polihexanide 0.2 mg/ml with diamidine.

How the economic model reflects *Acanthamoeba* keratitis

The *Acanthamoeba* keratitis disease course was split into different stages known as 'health states.' The economic model looked at how individuals with *Acanthamoeba* keratitis moved through these health states.

All calculations in the model were done twice:

- once for a hypothetical group of adults and children aged ≥ 12 years with *Acanthamoeba* keratitis who received the pooled comparator, and
- once for a hypothetical group of adults and children aged ≥ 12 years with *Acanthamoeba* keratitis who received polyhexanide 0.8 mg/ml.

The economic model includes a 'hypothetical' group of people with *Acanthamoeba* keratitis using information from the ODAK study and general population data to determine their characteristics e.g. their age, mean body weight etc. These people move through the economic model depending on if and when *Acanthamoeba* infection is cured and the treatments or surgeries they receive. The model is used to explore the difference in costs and benefits between the two treatment scenarios.

To capture the lived experiences of people with *Acanthamoeba* keratitis over an entire lifetime, the health economic model captured:

- How many people with *Acanthamoeba* keratitis were cured.
- How many people with *Acanthamoeba* keratitis changed treatments or received surgery (therapeutic or optical).
- The likelihood of the surgery not working (graft failure) or the likelihood of the *Acanthamoeba* infection returning (recurrence).
- The costs to the NHS of treating *Acanthamoeba* keratitis.
- The impact on the quality of life of individuals with *Acanthamoeba* keratitis.

The model used data from the ODAK trial, the Papa et al. 2020 study and a **Delphi panel** of UK eye doctors conducted by SIFI in 2023 to inform these inputs in the model.

Modelling the effectiveness and safety of polyhexanide 0.8 mg/ml

Based on the results from the ODAK trial and the Papa et al. 2020 study (see **Section 3e**), individuals treated with polyhexanide 0.8 mg/ml experience higher and faster rates of medical cure than individuals treated with the pooled comparator.(22, 25) Therefore, individuals in the model who are treated with polyhexanide 0.8 mg/ml are less likely to move to health states associated with higher rates of surgery and lower visual ability, and fewer individuals in this group need therapeutic surgery or experience the return of *Acanthamoeba* infection over time.

Modelling other important clinical data in *Acanthamoeba* keratitis

In addition to modelling the rates of medical cure achieved in individuals treated with the pooled comparator and individuals treated with polyhexanide 0.8 mg/ml, the model also captured information on:

- The risk of death occurring. As *Acanthamoeba* keratitis is not typically a life-threatening disease, it was assumed that the risk of death occurring was the same as for the UK general population.
- How often long-term problems occur (e.g. depression, anxiety, pain, excessive eye watering and sensitivity to light).

Modelling how much polihexanide 0.8 mg/ml improves quality of life

Participants of the ODAK trial completed the EQ-5D questionnaire (described in [Section 3f](#)) which provided information on their quality of life. The responses to this questionnaire were used to calculate quality of life scores (**utility values**) which were used in the economic model.

An improvement in quality of life was modelled when an individual experienced cure of their *Acanthamoeba* keratitis. This reflects the fact that the mental and emotional impact of disease would likely be reduced when an individual experiences cure. Since more people treated with polihexanide 0.8 mg/ml are cured, (22, 25) this group generally has an improved quality of life compared to those receiving the pooled comparator treatment.

Modelling how the costs of treatment differ with the new treatment

Various NHS costs were included in the model for the treatment of *Acanthamoeba* keratitis. These costs include:

- The cost of polihexanide 0.8 mg/ml itself.
- The cost of medications in the pooled comparator and how much it costs to give them to people with *Acanthamoeba* keratitis in hospital.
- The cost of other medications taken alongside *Acanthamoeba* keratitis treatments, such as medicines that reduce swelling, fight viruses and provide pain-relief.
- The cost of therapeutic surgery and optical surgery, and the costs for post-surgery management and treating complications.
- The cost of managing disease including:
 - The cost of regular doctor/hospital visits.
 - The cost of visual aids (such as contact lens clinics and magnifiers).

The costs associated with treatment for *Acanthamoeba* keratitis are estimated using information about the type of care provided and how often that type of care is given. This information was provided by expert UK eye doctors in the Delphi panel mentioned above, with the unit costs for different types of care being taken from published sources including NHS reference costs.

The results of the economic model

The economic model calculates the average total costs and average total health outcomes for a hypothetical group of individuals with *Acanthamoeba* keratitis receiving the pooled comparator, and for a hypothetical group of individuals with *Acanthamoeba* keratitis receiving polihexanide 0.8 mg/ml. The total costs and total health outcomes of these two groups are then compared to calculate the differences. For this calculation, health outcomes are expressed using a measure called **quality-adjusted life years (QALYs)**, which considers how long people live and their quality of life.

Based on the calculations of the pharmaceutical company, treatment with polihexanide 0.8 mg/ml is associated with more costs and more health benefits (more QALYs) than treatment with the pooled comparator. This means that whilst polihexanide 0.8 mg/ml costs more on average to the NHS, those individuals treated with polihexanide 0.8 mg/ml are expected to have improved quality of life and may live longer than individuals treated with the pooled comparator.

NICE will need to decide whether this expected improvement in quality and length of life is worth the additional costs.

Uncertainty in the economic model

All economic models are associated with some uncertainty because their development involves using data from a number of different sources and making assumptions. This assessment has considerable challenges and related uncertainty, as this is the first time that NICE has assessed a treatment for *Acanthamoeba* keratitis. As a very rare disease, *Acanthamoeba* keratitis is not a condition that most people are familiar with. There is a lack of information available in the published literature to say exactly what typical treatment for people with *Acanthamoeba* keratitis entails, how families and carers are impacted more widely, and how health-related quality of life is impacted for people affected by *Acanthamoeba* keratitis. SIFI has tried to reduce this uncertainty by getting advice from UK clinicians who have years of experience in treating people with *Acanthamoeba* keratitis in the NHS.(29) Because *Acanthamoeba* keratitis is a very rare disease, it is more difficult to conduct clinical trials. Therefore, the number of individuals in the ODAK clinical trial was smaller than it tends to be for more common diseases.(25)

The company requests that NICE takes uncertainty into account for *Acanthamoeba* keratitis as a very rare disease currently lacking a specific available treatment, as well as the severity of the disease and the significant impact it has on people's lives. This uncertainty will need to be considered in light of the challenges of conducting clinical trials in rare conditions, the limited published evidence in this disease and limited resources available to inform economic models in *Acanthamoeba* keratitis.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Innovation

Polihexanide 0.8 mg/ml is the first and only approved therapy for *Acanthamoeba* keratitis in the UK. Polihexanide 0.8 mg/ml has been awarded orphan drug designations by the Food and Drug Administration, the European Medicines Agency and Medicines and Healthcare products Regulatory Agency.(20, 30) These designations are given to drugs treating serious conditions where there is a high unmet medical need.

The novel nature of polihexanide 0.8 mg/ml is also highlighted by its Promising Innovative Medicine designation and New Active Substance status awarded by the Medicines and Healthcare products Regulatory Agency in May 2025. Therefore, polihexanide 0.8 mg/ml is an innovative, **patented** treatment which is expected to provide more benefit to people with *Acanthamoeba* keratitis than current therapeutic approaches.

Benefits not captured in the economic model

The economic model did not capture all of the benefits of polihexanide 0.8 mg/ml:

- The care and treatment types that individuals with *Acanthamoeba* keratitis currently receive in the UK can vary at different centres, which may lead to inequality in care across the population. Polihexanide 0.8 mg/ml would be the first and only treatment

available for *Acanthamoeba* keratitis specifically, supporting equal access to treatment for individuals with *Acanthamoeba* keratitis in the UK.

- Current therapeutic approaches are not always readily available as they have to be specially prepared before being given to individuals.(28) This can introduce errors and cause treatment delays which negatively impacts individuals with *Acanthamoeba* keratitis. Current therapeutic approaches also may not meet Good Manufacturing Practice quality standards, which could lead to safety and lack of efficacy issues. (28) Polihexanide 0.8 mg/ml is readily available and meets Good Manufacturing Practice standards.
- The emotional effects of surgery on individuals, including stress, anxiety and distress with long waiting times, the uncertainty of outcomes and the fear of potential vision loss.(11) With higher cure rates than current therapeutic approaches, polihexanide 0.8 mg/ml is expected to reduce the likelihood of surgery, reducing the impact on the mental health of individuals with *Acanthamoeba* keratitis.(22, 25)
- The positive impact polihexanide 0.8 mg/ml provides on aspects of everyday life for individuals with *Acanthamoeba* keratitis. The symptoms of *Acanthamoeba* keratitis can cause individuals to feel isolated and can impact the ability to carry out daily activities and work, with many people with *Acanthamoeba* keratitis having to take time off work.(8) This affects overall productivity and can have financial implications. By improving cure rates and reducing the consequences of *Acanthamoeba* keratitis (including poor vision and the need for surgery), polihexanide 0.8 mg/ml is expected to reduce the impact of *Acanthamoeba* keratitis on everyday life.(22, 25)

Given the above, additional benefits of polihexanide 0.8 mg/ml may not be captured in the model results and the model might underestimate the potential benefits of polihexanide 0.8 mg/ml. It will be important for NICE to take these factors into consideration when making its decision.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues [here](#)

SIFI strongly believes that individuals with *Acanthamoeba* keratitis should have access to polihexanide 0.8 mg/ml as the only treatment approved by the MHRA specifically for *Acanthamoeba* keratitis. It is important to make sure everyone with *Acanthamoeba* keratitis that is eligible for treatment can access polihexanide 0.8 mg/ml, no matter where

they live or their financial situation, their age, gender or ethnicity and for SIFI and NICE to consider any challenges different patient groups might face.

The care of individuals with *Acanthamoeba* keratitis in the UK is currently mainly provided by a few specialist centres, such as the Moorfields Eye Hospital, London.(22) SIFI is aware of individuals who are required to travel long distances to access specialist care, which can be expensive. Variable access to treatment centres is therefore a potential driver of health inequalities in *Acanthamoeba* keratitis, particularly given that rapid treatment is crucial to improve outcomes.(10)

Additionally, as discussed in **Section 2d**, there are currently no treatments available in England and Wales specifically for people with *Acanthamoeba* keratitis, with no standard type of treatment or treatment patterns.(18) As a result, individuals with *Acanthamoeba* keratitis often receive different combinations of treatments, resulting in differences in individual care. Differences in care between centres and doctors leads to a range of treatment delays and poorer quality product, leading to varying outcomes for individuals depending on the centre or doctor they visit.

By improving cure rates and reducing the problems associated with *Acanthamoeba* keratitis (including poor vision and the need for surgery), polyhexanide 0.8 mg/ml is expected to improve the clinical management of individuals with *Acanthamoeba* keratitis and potentially reduce the strain on the healthcare system. As the first approved treatment, it is expected that polyhexanide 0.8 mg/ml would improve equality of access to treatment for individuals with *Acanthamoeba* keratitis in England and Wales.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.

Where possible, please provide open access materials or provide copies that patients can access.

Further information about *Acanthamoeba* keratitis:

Acanthamoeba keratitis Eye Foundation: [Home - Acanthamoeba Keratitis Eye Foundation](#)

Fight for Sight: [Acanthamoeba keratitis | Discover causes, symptoms and treatments | Fight For Sight](#)

Moorfields Eye Hospital: [Acanthamoeba keratitis - Moorfields Eye Hospital](#)

Further information on NICE and the role of patients:

Public Involvement at NICE [Public involvement | NICE and the public | NICE Communities | About | NICE](#)

NICE's guides and templates for patient involvement in HTAs [Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)

EUPATI guidance on patient involvement in the HTA decision-making process: [Patient involvement in the HTA decision-making process - EUPATI Toolbox](#)

EFPIA – Working together with patient groups:

<https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>

National Health Council Value Initiative. <https://nationalhealthcouncil.org/issue/value/>

INAHTA: <http://www.inahta.org/>

European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: [Health technology assessment: an introduction to objectives, role of evidence, and structure in Europe](#)

4b) Glossary of terms

This glossary explains terms highlighted in **blue bold text** in this summary of information for patients. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

0.8 mg/ml

This relates to the amount of active medicine in a treatment. In this instance, there are 0.8 milligrams of medicine in every millilitre of a liquid.

Acanthamoeba

A tiny organism found in the environment, like water, soil, or air.

Acanthamoeba keratitis

An eye infection caused by **Acanthamoeba**, which can lead to pain, redness, and in serious cases, vision problems.

Active comparator

A medication or treatment used in studies to compare against another treatment, rather than using no treatment or a **placebo**.

Assessor-masked

When the person checking or measuring progress in a **clinical trial** does not know which treatment or therapy each person is receiving, to help make the results fair and unbiased.

Biguanides	Medicines that help control infections by preventing certain germs from growing, often used as eye drops to treat eye infections.
Clinical trial	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease.
Contamination	Unwanted substances accidentally getting into the medicine, which can make the treatment unsafe or less effective.
Cornea	The clear, front part of the eye that helps focus light so people can see clearly; it acts like a protective window for the eye.
Corneal transplant	A surgical procedure where a damaged or diseased cornea (the clear front part of the eye) is replaced with healthy tissue from a donor to improve vision.
Corneal scrape	A medical procedure where a small sample of cells is gently taken from the surface of the cornea to help diagnose infections or other eye problems.
Corticosteroids	Medicines that help reduce inflammation, swelling, and redness, often used to treat allergies, asthma, or skin conditions.
Culture	A laboratory technique that involves growing organisms, like bacteria or cells in special conditions so that scientists can study them
Delphi panel	A study design in which a group of experts (such as doctors) answer questions based on their experience and share their opinions

	anonymously, often over several rounds, to reach a shared agreement or consensus on a specific topic.
Deoxyribonucleic acid (DNA)	The set of instructions inside your body's cells that tell your body how to grow and function.
Diamidines	Medicines that kill or stop the growth of germs, commonly used to treat infections caused by specific parasites or organisms.
Donor eye surface	The outer surface of an eye that has come from someone who donated their eye tissue, and it can be used to help repair or replace parts of another person's eye.
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a clinical trial .
European Medicines Agency	The organisation in Europe responsible for evaluating and monitoring medicines to ensure they are safe, effective, and of good quality before they are allowed to be used.
Free-living protozoan	A tiny single-celled living organism that moves around and lives in nature by itself, and does not require a host organism to survive
Good Manufacturing Practice standards	Strict quality rules that ensure medicines are made safely, consistently, and to a high quality, so individuals can trust that their treatment is safe and effective.
Graft rejection	When the body recognises the transplanted tissue as unwanted and tries to attack it, which can cause it to stop working properly.
Graft failure	When a transplanted tissue, such as a corneal transplant, does not function

	properly or is rejected by the body, leading to the loss of the transplant's intended benefit.
Health economic model	A way to predict the costs and effects of a technology over time or in patient groups not covered in a clinical trial .
Indirect treatment comparison	A way to compare two different treatments when they haven't been directly tested against each other in the same clinical study, by looking at how each one compares to a common treatment or group.
Infections	Illnesses caused by harmful germs like bacteria, viruses, fungi, or parasites that invade your body and make you sick.
Infestations	The presence and overwhelming of a persons' body or skin by larger parasites, such as lice, mites, or ticks.
Lacrimation	The production and release of tears from the eyes, often in response to irritation, emotion, or other stimuli.
Marketing authorisation	The legal approval by a regulatory body that allows a medicine to be given to individuals in a particular country.
Medicines and Healthcare products Regulatory Agency	The regulatory body that evaluates, approves and supervises medicines throughout the United Kingdom.
Microscope	An instrument used to see tiny objects or details that cannot be seen with the naked eye.
Monotherapy	Treatment that uses only one medication or method to treat a disease or condition (as

	opposed to a combination of two or more treatments).
Ocular hyperaemia	Tiny blood vessels in the eye enlarge and dilate, causing the eye to appear red.
Off-label	Using a medicine for a purpose, dosage, or in a way that has not been officially approved by the regulatory authority.
Optical surgery	A type of surgery performed to improve vision by replacing or repairing the cornea affected by <i>Acanthamoeba</i> keratitis, helping the person see more clearly.
Patented	Refers to a new, innovative invention, product, or process that has been granted legal protection by a patent, giving the patent holder exclusive rights to use, make, or sell the invention for a specific period of time
Polymerase Chain Reaction	A test that makes lots of copies of an organism's DNA so it can be analysed
Phase 3	This type of clinical trial that tests the safety and how well a new treatment works compared with a standard treatment. For example, it evaluates which group of individuals has better survival rates or fewer side effects .
Placebo	A 'dummy' treatment that appears real but has no therapeutic benefit. It is used in clinical trials to compare treatments to.
Pooled comparator	A combination of multiple current therapeutic approaches into a single comparison group, to evaluate a new treatment against all therapeutic

	approaches currently used rather than individual treatments separately. A measure of the state of health of a person, where the length of life is adjusted to reflect the quality of life. One quality-adjusted life year (QALY) is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for an individual following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.
Quality-adjusted life year	
Quality of life	The overall enjoyment of life. Many clinical trials assess the effects of a disease and its treatment on the quality of life of individuals. These studies measure aspects of an individual's sense of well-being and their ability to carry out activities of daily living.
Randomised clinical trial	A trial where a drug is compared to one or more comparators, which can include a placebo, and people are randomly allocated to one treatment group
Recurrence	The return of a disease or condition after it has improved or gone away.
Regulatory bodies	These are legal bodies that review the quality, safety and efficacy of medicines and medical technologies.
Retrospective	Looking back at past events or information that has already happened or has been recorded.

Side effect (also called adverse event)	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe.
Statistically significant	A result in data analysis that is unlikely to have occurred by chance, indicating a high likelihood that the observed effect is real, based on a predefined threshold.
Sterility	When a product or environment is completely free from germs, bacteria, viruses, and other living microorganisms, making it safe and clean.
Therapeutic approaches	Different ways or methods used by doctors to treat and help improve health problems or illnesses.
Therapeutic surgery	A surgical procedure done to treat serious eye problems caused by <i>Acanthamoeba</i> keratitis, such as removing damaged tissue to help save the eye or corneal transplant to clear the <i>Acanthamoeba</i> keratitis infection.
Tolerated	The ability of an individual to put up with the side effects of treatment.
Unlicensed	A medicine that has not been officially approved or licensed for use at all and may not have passed all the safety and effectiveness tests required for official approval.
Utility value	A number which expresses quality of life and is used in economic models. It is generally a number between 0 (representing death) and 1 (perfect health).

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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21. Shing B, Balen M, McKerrow JH, Debnath A. Acanthamoeba Keratitis: An update on amebicidal and cysticidal drug screening methodologies and potential treatment with azole drugs. *Expert Review of Anti-infective Therapy*. 2021;19(11):1427-41.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

July 2025

File name	Version	Contains confidential information	Date
ID6497 polihexanide EAG clarification letter_Company Response_31Jul25_[noCON]	Final draft	Yes	31 July 2025

Section A: Clarification on effectiveness data

Literature searching (clinical effectiveness)

A1. Please provide references (and PDFs, if available) of the identified systematic literature reviews (SLRs) of which references lists were searched for further studies of interest (CS Appendix B.1.1 Bibliography searches)

The reference lists of any SLRs identified during the title/abstract review process (see Table 1) were reviewed to identify additional studies of interest, supplementing articles retrieved from the databases searches. The available PDFs for the relevant SLRs are now included in the reference pack folder, for the EAG's consideration.

Table 1: SLRs screened as part of bibliography searches

Reference	Link	Notes
Alkharashi M, Lindsley K, Law HA, Sikder S. Medical interventions for acanthamoeba keratitis. Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD010792. DOI: 10.1002/14651858.CD010792.pub2.	https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010792.pub2/full	PDF available
Hanet MS, Jamart J, Chaves AP. Fluoroquinolones or fortified antibiotics for treating bacterial keratitis: systematic review and meta-analysis of comparative studies. Can J Ophthalmol. 2012 Dec;47(6):493-9. doi: 10.1016/j.jcjo.2012.09.001. PMID: 23217502.	https://www.canadianjournalofophthalmology.ca/article/S0008-4182(12)00423-1/abstract	PDF available
Büchele MLC, Nunes BF, Filippin-Monteiro FB, Caumo KS. Diagnosis and treatment of Acanthamoeba Keratitis: A scoping review demonstrating unfavorable outcomes. Cont Lens Anterior Eye. 2023 Aug;46(4):101844. doi: 10.1016/j.clae.2023.101844. Epub 2023 Apr 26. PMID: 37117130.	https://www.contactlensjournal.com/article/S1367-0484(23)00048-6/abstract	Full text not available
Germán Mejía-Salgado, Juan Daniel Ribero, Joaquín Alonso Pérez-Vivas, Emmanuel Vazquez, Ana María Amaya-Sánchez, Alejandro Tello, Virgilio Galvis, Clinical and management factors linked to good visual outcomes in Acanthamoeba keratitis: A Systematic review and meta-analysis, AJO International, Volume 2, Issue 1, 2025, 100095, ISSN 2950-2535,	https://www.sciencedirect.com/science/article/pii/S2950253524000959	PDF available
Aaron R. Kaufman, Elmer Y. Tu, Advances in the management of Acanthamoeba keratitis: A review of the literature and synthesized algorithmic approach, The Ocular Surface, Volume 25, 2022, Pages 26-36,ISSN 1542-0124, https://doi.org/10.1016/j.jtos.2022.04.003 .	https://www.sciencedirect.com/science/article/pii/S1542012422000295	Full text not available
Kim CK, Karslioglu MZ, Zhao SH, Lee OL. Infectious Keratitis in Patients Over 65: A Review on Treatment and Preserving Eyesight. Clin Interv Aging. 2024;19:1393-1405 https://doi.org/10.2147/CIA.S467262	https://www.dovepress.com/infectious-keratitis-in-patients-over-65-a-review-on-treatment-and-peer-reviewed-fulltext-article-CIA	PDF available

Bodicoat DH, Papa V, Alves R, Duarte AA, Tofani L. Current Clinical Evidence for Agents used in Acanthamoeba Keratitis: Systematic Literature Reviews J Rare Dis Res Treat. (2023) 8(2): 1-12	https://www.rarediseasesjournal.com/article/s/current-clinical-evidence-for-agents-used-in-acanthamoeba-keratitis-systematic-literature-reviews.pdf	PDF available
Marques-Couto,P.; Monteiro, M.; Ferreira, A.M.; Pinheiro-Costa, J.; Vilares-Morgado, R. AcanthamoebaKeratitisManagement andPrognosticFactors: ASystematic Review. J. Clin. Med. 2025,14,2528. https://doi.org/10.3390/jcm14072528	https://pmc.ncbi.nlm.nih.gov/articles/PMC11989993/pdf/jcm-14-02528.pdf	PDF available
Shakib P, Kalani H, Tahir Aleem M, Faridnia R, Zebardast Pour M, Moradpour K, Cheraghipour K. New Strategies in the Treatment of Diseases Caused by <i>Acanthamoeba</i> Based on Nanoparticles: A Systematic Review. Curr Rev Clin Exp Pharmacol. 2023;19(1):68-77. doi: 10.2174/277243281866622111155119. PMID: 36372923.	https://www.eurekaselect.com/article/127527	Full text not available
N. Szentmáry, S. Goebels, P. Matoula, F. Schirra, B. Seitz. Die Akanthamöbenkeratitis – ein seltenes und oft spät diagnostiziertes Chamäleon. Klin Monbl Augenheilkd 2012; 229(5): 521-528 DOI: 10.1055/s-0031-1299539	https://www.thieme-connect.de/products/ejournals/abstract/10.1055/s-0031-1299539	PDF available
Alkharashi M, Lindsley K, Law HA, Sikder S. Medical interventions for acanthamoeba keratitis. Cochrane Database Syst Rev. 2015 Feb 24;2015(2):CD010792. doi: 10.1002/14651858.CD010792.pub2. PMID: 25710134; PMCID: PMC4730543.	https://pubmed.ncbi.nlm.nih.gov/25710134/	PDF available

A2. Please clarify which element of the search strategy targeted literature review (TLR) in the PRISMA flow diagram (CS Appendix B, figure 1) is referring to.

As part of SIFI's search strategy for adequately scoping polihexanide 0.8 mg/ml monotherapy for the treatment of AK, a TLR was conducted with the aim of identifying the efficacy outcomes used in the literature for current therapeutic approaches for AK. The findings of the TLR then informed the indirect treatment comparison (ITC) feasibility assessment and the protocol for the subsequent clinical SLR. The targeted searches were conducted in February 2022, using Wolters Kluwer's OVID platform and limited to articles published in English language. No time limitations were imposed.

To supplement the electronic database searches and ensure that as many relevant articles as possible were considered in the TLR, published and unpublished articles were identified from the grey literature sources and conference proceedings listed below:

- ARVO (Association for Research in Vision and Ophthalmology) via IOVS (Investigative Ophthalmology & Visual Science)
- EVER (European Association for Vision and Eye Research)
- AAO (American Association of Ophthalmology)

- AOA (American Optometric Association)
- ASCRS (American Society of Corneal and refractive Surgery)
- ESCRS (European Society of Corneal and refractive Surgeons)
- Cornea Society

The conference proceedings were limited to articles published in the last three years (2019-2022), since it is generally believed that full-text manuscripts are often developed within three years of congress abstract publication. The eligibility criteria for the targeted literature review are summarised in Table 2.

Table 2: Eligibility criteria for the TLR

PICOS	Inclusion criteria	Exclusion criteria
Population	• Patients of at least 12 years of age • Patients with a confirmed diagnosis of acanthamoeba keratitis	• Age <12 years • No confirmed diagnosis
Intervention/ Comparators	• Polihexanide 0.8 mg/ml • Polihexanide 0.2 mg/ml • Polihexanide 0.6 mg/ml • Polihexanide 0.2 mg/ml and diamidine • Polihexanide 0.2 mg/ml and propamidine 1 mg/ml and moxifloxacin 5 mg/ml • Polihexanide 0.2 mg/ml and hexamidine 1 mg/ml • Chlorhexidine 0.2 mg/ml • Chlorhexidine 0.2 mg/ml and propamidine 1 mg/ml • Chlorhexidine and diamidine • Propamidine • Propamidine and neomycin • Propamidine and neomycin-polymyxin-gramicidin • Miltefosine • Imidazole • Neomycin • Hexamidine • Miconazole 1% • Clotrimazole 1% • Ketoconazole • Itraconazole • Voriconazole • Fluconazole • Pentamidine • Povidone Iodine 0.5%	• Surgery^a • Any other treatments
Outcomes	Criteria specifically related to outcomes were not used in the TLR screening. Given the exploratory nature of the TLR, efficacy outcomes from the literature were instead screened on the basis of (but not limited to) the statistical analysis plan for	

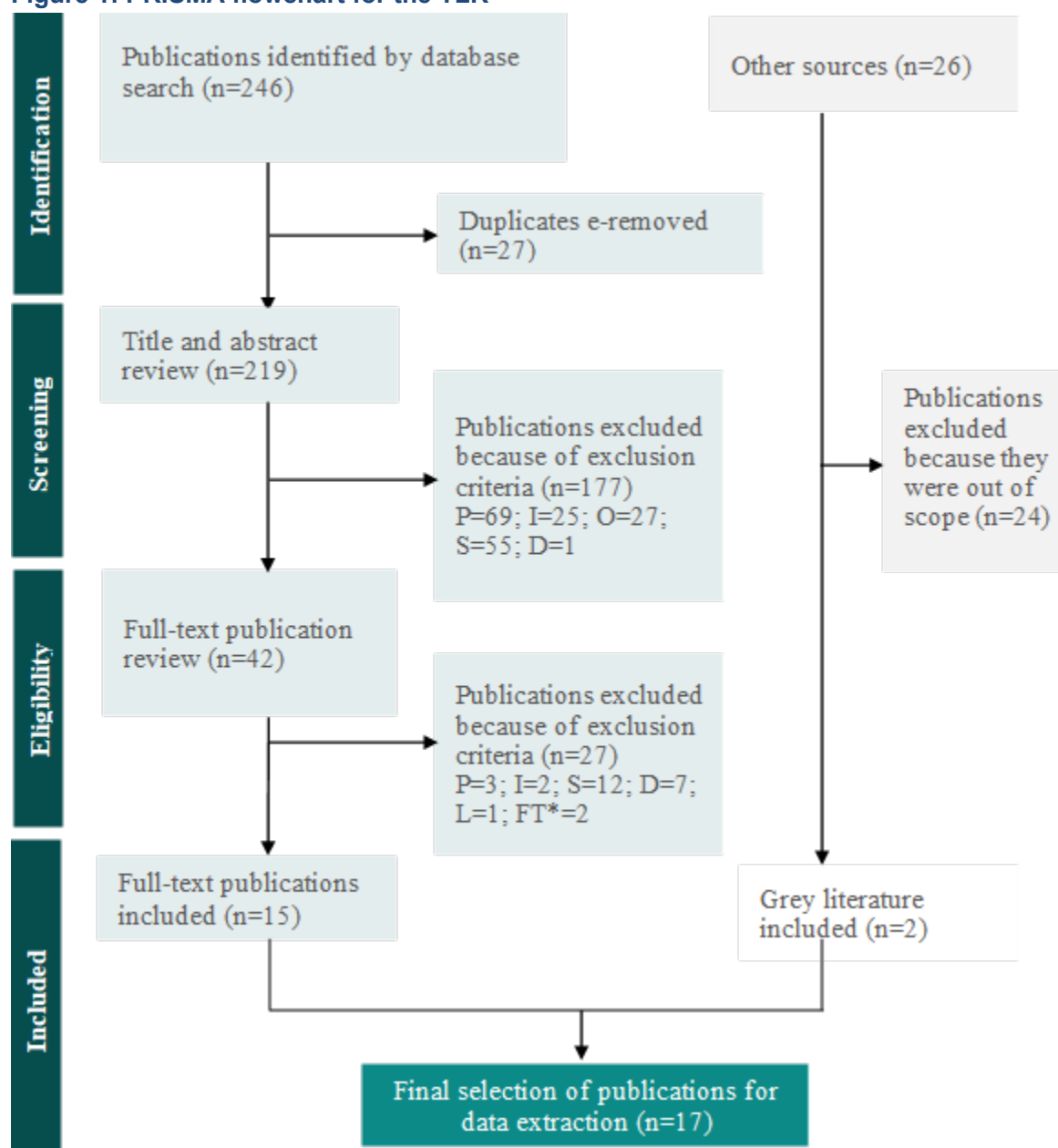
	the pivotal ODAK trial. Note that studies with outcomes unrelated to efficacy or safety were not eligible for the TLR.	
Study design	• Randomised controlled trials • Observational cohort studies • Cross sectional studies • Case reports and series with ≥ 5 participants	• Any type of literature review^b • Editorial • Letters • Expert opinions • News • Economic evaluations • Case series or case report with < 5 participants • Animal or in vitro studies • Pharmacokinetic or pharmacodynamic studies • Clinical guidelines • Commentary • Any study design not listed in the inclusion criteria
Limitation	Full text and abstract publication in English language	Full text and abstract publication in any other languages

Footnotes: ^aSurgery included amniotic membrane transplants, superficial keratectomy, application of cyanoacrylate glue, therapeutic penetrating, lamellar keratoplasty, cataract surgery, evisceration, or enucleation.

^bLiterature reviews were used for hand searching, ensuring all relevant studies were covered.

Overall, electronic searches yielded 219 unique records (after removal of duplicates). Following the title and abstract screen, a total of 177 records were excluded. This was followed by a detailed examination of the full texts of the remaining 42 records. After the full text screen, 15 references were included. Additionally, two references were added from manual searches from the grey literature sources and conference proceedings. Therefore, 17 publications met the eligibility criteria for inclusion in the TLR (see Figure 1).

Figure 1: PRISMA flowchart for the TLR



Abbreviations: D, Duplicate; FT*, Full Text not available; I, intervention; O, Outcome not relevant (unrelated to efficacy or safety); P, Population; S, Study design.

Based on the findings of the TLR, a total of 17 studies were included in the clinical SLR, as reflected in the PRISMA diagram presented in Appendix B, Figure 1 of the CS. References for the included studies are in Table 3 below. The TLR report has been included in the reference pack folder, for the EAG's consideration.

Table 3: References included in the TLR

1	Azuara-Blanco A, Sadiq AS, Hussain M, Lloyd JH, Dua HS. Successful medical treatment of Acanthamoeba keratitis. <i>Int Ophthalmol</i> . 1997;21(4):223-7.
2	Bacon AS, Frazer DG, Dart JK, Matheson M, Ficker LA, Wright P. A review of 72 consecutive cases of Acanthamoeba keratitis, 1984-1992. <i>Eye (Lond)</i> . 1993;7 (Pt 6):719-25.

3	Bagga B, Joseph J, Garg P, Chandran K, Jayabhasker P, Manjulatha K, et al. Efficacy of Topical Miltefosine in Patients with Acanthamoeba Keratitis: A Pilot Study. <i>Ophthalmology</i> . 2019;126(5):768-70.
4	Bagga B, Sharma S, Gour RPS, Mohamed A, Joseph J, M Rathi V, et al. A randomized masked pilot clinical trial to compare the efficacy of topical 1% voriconazole ophthalmic solution as monotherapy with combination therapy of topical 0.02% polyhexamethylene biguanide and 0.02% chlorhexidine in the treatment of Acanthamoeba keratitis. <i>Eye (Lond)</i> . 2021;35(5):1326-33.
5	Bouheraoua N, Gaujoux T, Goldschmidt P, Chaumeil C, Laroche L, Borderie VM. Prognostic factors associated with the need for surgical treatments in acanthamoeba keratitis. <i>Cornea</i> . 2013;32(2):130-6.
6	Caruso C, Eletto D, Rinaldi M, Pacente L, Troisi S, Semeraro F, et al. Effectiveness and Safety of Topical Chlorhexidine and Vitamin E TPGS in the Treatment of. <i>J Clin Med</i> . 2020;9(11).
7	Chew HF, Yildiz EH, Hammersmith KM, Eagle RC, Rapuano CJ, Laibson PR, et al. Clinical outcomes and prognostic factors associated with acanthamoeba keratitis. <i>Cornea</i> . 2011;30(4):435-41.
8	Duguid IG, Dart JK, Morlet N, Allan BD, Matheson M, Ficker L, et al. Outcome of acanthamoeba keratitis treated with polyhexamethyl biguanide and propamidine. <i>Ophthalmology</i> . 1997;104(10):1587-92.
9	Hargrave SL, McCulley JP, Hussein Z. Results of a trial of combined propamidine isethionate and neomycin therapy for Acanthamoeba keratitis. <i>Brolene Study Group. Ophthalmology</i> . 1999;106(5):952-7.
10	Illingworth CD, Cook SD, Karabatsas CH, Easty DL. Acanthamoeba keratitis: risk factors and outcome. <i>Br J Ophthalmol</i> . 1995;79(12):1078-82
11	Lim N, Goh D, Bunce C, Xing W, Fraenkel G, Poole TR, et al. Comparison of polyhexamethylene biguanide and chlorhexidine as monotherapy agents in the treatment of Acanthamoeba keratitis. <i>Am J Ophthalmol</i> . 2008;145(1):130-5.
12	Megha K, Thakur A, Khurana S, Sehgal R, Gupta A. Acanthamoeba keratitis: A 4-year review from a tertiary care hospital in North India. <i>Nepal J Ophthalmol</i> . 2020;12(23):83-90.
13	Musayeva A, Riedl JC, Schuster AK, Wasilica-Poslednik J, Pfeiffer N, Gericke A. Topical Voriconazole as Supplemental Treatment for Acanthamoeba Keratitis. <i>Cornea</i> . 2020;39(8):986-90.
14	Naranjo A, Martinez JD, Miller D, Tonk R, Amescua G. Systemic Miltefosine as an Adjunct Treatment of Progressive. <i>Ocul Immunol Inflamm</i> . 2021;29(7-8):1576-84.
15	Papa V, Rama P, Ferrario F, Ramoni A, Matuska S, Radford C, et al. Orphan Drug for Acanthamoeba Keratitis (ODAK) project: results of a 10-Year retrospective study in Italy and in the United Kingdom. <i>IOVS</i> . 2014;55(13).
16	Papa V, Rama P, Radford C, Minassian DC, Dart JKG. Acanthamoeba keratitis therapy: time to cure and visual outcome analysis for different antiamebic therapies in 227 cases. <i>Br J Ophthalmol</i> . 2020;104(4):575-81.
17	Rahimi F, Hashemian SM, Tafti MF, Mehjerdi MZ, Safizadeh MS, Pour EK, et al. Chlorhexidine Monotherapy with Adjunctive Topical Corticosteroids for Acanthamoeba Keratitis. <i>J Ophthalmic Vis Res</i> . 2015;10(2):106-11.

A3. Regarding CS Appendix B.1.1 Bibliography searches, please clarify: a) whether 'eligible articles' in citation chasing is referring to all the included studies in the original 2022 SLR and if not, please provide a list of the studies used; b) which

studies the backward and forward searching was conducted on in the 2025 update.

a) To supplement the studies retrieved from databases searches, a citation chasing process was conducted for both the original SLR conducted in 2022 and the SLR update conducted in 2025. This process included reviewing the reference lists from:

- Bibliographies of SLRs identified during the screening phase (13 studies in total – see response to question A1)
- Eligible full-text articles following the screening process (48 studies in total from the original [n=34] and update [n=14] clinical SLR)

Therefore, all eligible studies in the original/update economic SLR were considered for citation chasing, as well as the reference lists of relevant SLRs.

Any potentially relevant articles identified through citation chasing underwent the same eligibility assessment i.e. a title and abstract review followed by a full-text review, conducted independently by two reviewers. In addition, references found in published SLRs of AK were subjected to both backward and forward citation searching. This iterative cycle continued until no new eligible articles were found.

In 2022, citation chasing was conducted manually by a single reviewer, including hand-searching the reference lists of eligible articles and identified SLRs, along with forward citation searching via Google Scholar. For the 2025 update, both backward and forward citation searches were performed using the Citation Chaser Shiny app. All identified abstracts were uploaded to Covidence and screened independently by two reviewers, ensuring consistency and traceability.

b) Table 4 summarises the studies (n=14) that were used for backward forward citation chasing in the 2025 SLR update.

Table 4: Records used for citation chasing in the 2025 clinical SLR update

1	Agarwal S, Srinivasan B, Iyer G, Pandey S, Agarwal M, Dhiman R, Surya J, Anand AR; Sankara Nethralaya Cornea Emergency Team (SNCET). Depth, size of infiltrate, and the microbe - The trio that prognosticates the outcome of infective keratitis. Indian J Ophthalmol. 2024 Jan 1;72(1):44-50. doi: 10.4103/IJO.IJO_1022_23. Epub 2023 Dec 22. PMID: 38131568; PMCID: PMC10841783.
2	Ahmed NH, Rathod PG, Satpathy G, Tandon R, Sharma N, Titiyal JS. <i>Acanthamoeba</i> keratitis: Experience from a tertiary eye care center in North India. Trop Parasitol. 2022 Jul-Dec;12(2):119-123. doi: 10.4103/tp.tp_16_22. Epub 2022 Nov 24. PMID: 36643983; PMCID: PMC9832494.
3	Arnalich-Montiel F, Lorenzo-Morales J, Irigoyen C, Morcillo-Laiz R, López-Vélez R, Muñoz-Negrete F, Piñero JE, Valladares B. Co-isolation of Vahlkampfia and acanthamoeba in acanthamoeba-like keratitis in a Spanish population. Cornea. 2013 May;32(5):608-14. doi: 10.1097/ICO.0b013e31825697e6. PMID: 22929156.
4	Arnalich-Montiel F, Lumbreras-Fernández B, Martín-Navarro CM, Valladares B, Lopez-Velez R, Morcillo-Laiz R, Lorenzo-Morales J. Influence of Acanthamoeba genotype on clinical course and outcomes for patients with Acanthamoeba keratitis in Spain. J Clin Microbiol. 2014 Apr;52(4):1213-6. doi: 10.1128/JCM.00031-14. Epub 2014 Jan 15. PMID: 24430449; PMCID: PMC3993498.
5	Blaser F, Bajka A, Grimm F, Metzler S, Herrmann D, Barthelmes D, Zweifel SA, Said S. Assessing PCR-Positive Acanthamoeba Keratitis-A Retrospective Chart Review.

	Microorganisms. 2024 Jun 17;12(6):1214. doi: 10.3390/microorganisms12061214. PMID: 38930596; PMCID: PMC11205950.
6	Chen DZ, Chai C, Tan A, Ray M. Microbial patterns of <i>Acanthamoeba</i> keratitis at a Singapore ophthalmic referral hospital: A 5-year retrospective observational study. Ann Acad Med Singap. 2021 Jun;50(6):494-496. doi: 10.47102/annals-acadmedsg.2020507. PMID: 34195759.
7	Chen LL, Young AL, Lau TT, et al. Review of <i>Acanthamoeba</i> keratitis associated with contact lenses in Hong Kong Chinese people. Hong Kong Journal of Ophthalmology 2009;13:9-14.
8	Dart JK, Papa V, Rama P, et al. The orphan drug for <i>Acanthamoeba</i> keratitis (ODAK) trial: PHMB 0.08%(polihexanide) and placebo versus PHMB 0.02% and propamidine 0.1%. Ophthalmology 2024;131:277-287
9	Franch A, Knutsson KA, Pedrotti E, et al. Treatment of <i>Acanthamoeba</i> keratitis with high dose PHMB (0.08%) monotherapy in clinical practice: A case series. European Journal of Ophthalmology 2024;0:7
10	Li S, Bian J, Wang Y, et al. Clinical features and serial changes of <i>Acanthamoeba</i> keratitis: an in vivo confocal microscopy study. Eye (Lond) 2020;34:327-334.
11	Messina M, Tucci D, Mocini S, et al. Increasing incidence of contact-lens-related <i>Acanthamoeba</i> keratitis in a tertiary ophthalmology department in an Italian population. European Journal of Ophthalmology 2024;34:1875-1883.
12	Orosz E, Kriskó D, Shi L, et al. Clinical course of <i>Acanthamoeba</i> keratitis by genotypes T4 and T8 in Hungary. Acta Microbiol Immunol Hung 2019;66:289-300.
13	Roth M, Balasiu A, Daas L, et al. Impact of implementation of polymerase chain reaction on diagnosis, treatment, and clinical course of <i>Acanthamoeba</i> keratitis. Graefes Archive for Clinical and Experimental Ophthalmology 2023;261:1951-1959
14	Zhao N, Liang L, Hao M, et al. A case series of overnight orthokeratology-related <i>Acanthamoeba</i> keratitis in Northwest China: Clinical presentation, management, and outcomes. Contact Lens and Anterior Eye 2025:102406.

A4. Regarding CS Appendix B.1.1 Congress proceedings (and same section in CS Appendix E.1.1), please provide the search terms used to hand-search the conference proceedings.

To ensure the SLR was as robust as possible and included all relevant published and grey literature, a search of relevant conference proceedings was conducted for both the original and updated SLR, to identify additional primary publications. The search used the term “*Acanthamoeba* keratitis”. Therefore, all proceedings pertaining to AK were included in the title/abstract screening. Proceedings were hand-searched by one reviewer on 25th July 2022 (proceedings from 2017–2022) and on 24th March 2025 (proceedings from 2022–2024) for potential eligible abstracts.

Systematic literature review (clinical effectiveness)

A5. In the SLR, corresponding authors were emailed for 32 (66.7%) studies to see if they reported primary outcome. Please provide the details of responses from authors for all studies including Papa 2020.

The corresponding authors of 32 studies were emailed during the clinical SLR process to verify if in their studies the primary outcome of the ODAK trial (medical cure rate at 12 months) was reported. Only three authors replied to the email. A summary of the responses is provided in the table below. The full responses are attached as PDF, that are now included in the reference package folder for your consideration.

Corresponding author	Study title	Response
David Chen Zoyou	Microbial patterns of Acanthamoeba keratitis at a Singapore ophthalmic referral hospital: A 5-year retrospective observational study	Details on the number of patients medically cured at 12 months were not available
Alvin Young	Review of Acanthamoeba keratitis associated with contact lenses in Hong Kong Chinese people	Study details not available
Vincenzo Papa	Acanthamoeba keratitis therapy: time to cure and visual outcome analysis for different antiamebic therapies in 227 cases	Additional cure data requested and provided by the author.

A6. In the SLR, please describe the process (e.g. were the criteria pre-stated; how many reviewers) for the additional step taken to identify studies for the indirect treatment comparison.

As noted in the company's response to Question A2, an initial TLR followed by a SLR (and update in 2025), was undertaken to identify all relevant evidence on the efficacy of polyhexanide 0.8 mg/ml and currently available therapeutic approaches for AK. These reviews were conducted to support evidence submissions to healthcare authorities and payers, including the current NICE evidence appraisal.

Based on the findings from the SLR, a feasibility assessment for an ITC was carried out to determine the most appropriate methodological approach for estimating the relative efficacy of polyhexanide 0.8 mg/ml versus existing therapeutic approaches for AK. Therefore, there were no additional steps taken during the SLR to identify the studies for the ITC, since this part was conducted in a separate ITC feasibility assessment. Please refer to the company's response to question A21 for further information on the ITC feasibility assessment.

Included studies (clinical effectiveness)

A7. **Priority question:** Please provide the report from the Delphi survey to include details of the panel membership, the questions asked, median and minimum-maximum values of responses, see also clarification question C1).

The UK Delphi panel report has been updated in line with the EAG's request and version 3.0 is now included in the reference pack folder. Each summary table at the end of the respective sections now presents the range of estimates (minimum and maximum values) provided by the panel responders.

A8. Priority question: The CS makes the case for not using the active comparator arm from the ODAK trial because it is not reflective of real-world practice. Please also provide a summary of the points of critique made by the European Medical Agency (EMA) about the ODAK trial.

The EMA critique of the ODAK trial, as outlined in the European Public Assessment Report (EPAR),¹ was primarily focused on the value of the active comparator. Specifically, the EMA noted that the active comparator used in the ODAK trial, a combination of polihexanide 0.2 mg/ml plus propamidine 1 mg/ml, is an unlicensed regimen and does not constitute a standardised or licensed therapy for AK within the EU. Additionally, there were no historical data available to compare this active comparator against placebo, meaning an indirect assessment of superiority of polihexanide 0.8 mg/ml over placebo could not be established. The EMA stated that *“Considering that the active arm as applied in the ODAK trial contained a medicinal product [polihexanide 0.2 mg/ml] manufactured to GMP quality, with immediate availability and a standardised treatment protocol, it could not be considered representative of current practice”*.¹ Current practice consists of unstandardised prescriptions of biguanides (chlorhexidine, polihexanide 0.2 mg/ml and polihexanide 0.6 mg/ml [as a compounded formulation made to order]) and diamidines (propamidine and hexamidine).²

These limitations restricted the interpretability of the trial results and led the EMA to conclude that comparative efficacy of polihexanide 0.8 mg/ml could not be inferred through non-inferiority testing against the ODAK active comparator due to *“methodological uncertainties”*. Therefore, the ODAK trial was considered by the EMA as a pseudo single-arm study and an indirect comparison to alternative efficacy data reflective of the proposed ‘current practice’ pooled AAT comparator was performed. As superiority to unapproved treatment options is difficult to establish in a well-managed clinical trial setting and, as stated by the EMA, it would be *“unethical to randomise to placebo”*, the EMA regarded the indirect comparison to historical patients treated with the AAT comparator as a valid approach to demonstrate treatment benefit, and this methodology was subsequently presented in the company's submission to NICE.¹ This approach aligns with the NICE RWE framework which recognises the need to use real-world data to inform efficacy data, particularly in rare, severe diseases where conducting placebo-controlled RCTs is unfeasible or unethical and where comparators do not reflect standard of care in the NHS.³

When interpreting the indirect comparison results, the EMA acknowledged that even under a conservative assumption of a 50.3% resolution rate in untreated cases, the difference in treatment effect with polihexanide 0.8 mg/ml and the AAT comparator was sufficiently large to support that the treatment provides a beneficial effect compared to treatment with the AAT comparator.¹

A9. In the ODAK trial full analysis set, baselines are defined as the last valid evaluation prior to the first dose of study medication:

A. What does a ‘valid’ evaluation consist of?

B. What is the range of time prior to first study dose?

As defined in the SAP and CSR, a 'valid' evaluation is defined as the last non-missing value before the first dose of the investigational medicinal product was administered.⁴

Regarding the range of time prior to first dose, baseline assessments and first dose were normally conducted on the same day. However, as stated in the protocol for the ODAK trial, baseline assessments were permitted to have taken place up to two days before randomisation and study drug administration (both took place in the same visit; Day 0).⁴

A10. Priority question: Please provide the baseline characteristics seen in CS Table 6 for both study arms from the intention-to-treat (ITT) population (All 135 randomised patients).

The baseline demographics and clinical characteristics of the 135 randomised patients across both the polihexanide 0.8 mg/ml and active comparator treatment arms are presented in Table 5. Overall, these baseline characteristics are consistent with those reported for the full analysis set (n=127) in the Company Submission.

Table 5: Baseline demographics and clinical characteristics of the 135 randomised patients

Characteristics	Polihexanide 0.8 mg/ml (n=69)	Polihexanide 0.2 mg/ml with propamidine 1 mg/ml (n=66)
Age, years		
Mean (SD)	35.1 (13.0)	37.8 (14.0)
Median (IQR)	33 (25–43)	36 (26–49)
Minimum–maximum	15–73	17–71
15–35 n (%)	38 (55.1)	31 (47.0)
36–73 n (%)	31 (44.9)	35 (53.0)
Sex, n (%)		
Female	41 (59.4)	37 (56.1)
Male	28 (40.6)	29 (43.9)
BCVA (in metres) before AK, n (%) ^a		
≥ 6/6	60 (96.8)	49 (92.5)
< 6/6–6/12	1 (1.6)	3 (5.7)
6/15–6/30	1 (1.6)	1 (1.9)
Unknown	7	13
Study centre, n (%)		
Moorfields Eye Hospital, United Kingdom	29 (42.1)	34 (51.5)
Manchester Eye Hospital, United Kingdom	2 (2.9)	1 (1.5)
University Hospital Southampton, United Kingdom	1 (1.4)	3 (4.5)
Ospedale San Raffaele, Milano, Italy	23 (33.3)	17 (25.8)

Characteristics	Polihexanide 0.8 mg/ml (n=69)	Polihexanide 0.2 mg/ml with propamidine 1 mg/ml (n=66)
Ospedale SS Giovanni e Paolo, Venice, Italy	10 (14.5)	5 (7.6)
Medical University of Silesia, Katowice, Poland	4 (5.8)	6 (9.1)
Risk factors for keratitis CL wear, n (%)		
No	2 (3.0)	3 (4.8)
Yes	65 (97.0)	59 (95.2)
Unknown	2	4
Ocular trauma, n (%)		
No	64 (95.5)	60 (96.8)
Yes	3 (4.5)	2 (3.2)
Unknown	2	4
Time from onset of symptoms, days ^b		
Mean (SD)	33.6 (39.0)	36.7 (54.6)
Median (IQR)	20 (8–42)	20 (8 - 37)
Unknown	2	4
Time from first treatment for keratitis, days		
Mean (SD)	11.5 (21.9)	12.7 (21.6)
Median (IQR)	4 (0–16)	3 (0–20)
Antibiotics for keratitis before baseline, n (%)		
No	11 (15.9)	13 (19.7)
Yes	58 (84.1)	53 (80.3)
Antivirals for keratitis before baseline, n (%)		
No	51 (73.9)	47 (71.2)
Yes	18 (26.1)	19 (28.8)
Antifungals for keratitis before baseline, n (%)		
No	68 (98.6)	66 (100)
Yes	1 (1.4)	0
Corticosteroids before baseline (any cause), n (%)		
No	37 (53.6)	46 (69.7)
Yes	32 (46.4)	20 (30.3)
Disease stage at baseline, n (%)		
I	15 (21.7)	9 (13.6)
II	43 (62.3)	49 (74.2)
III	11 (15.9)	8 (12.1)
Severe inflammatory disease: scleritis or hypopyon	0	0
Bilateral disease, n (%)		
Absent	56 (84.8)	58 (93.5)
Present	10 (15.2)	4 (6.5)
Unknown	3	4

Footnotes: ^aThe BCVA before AK was obtained from patients' history, optometry or hospital records. For those without a past history of eye disease, when written records were not available, the acuity was recorded as 20/20; ^bThe metric 'days from onset of symptoms, grouped, n (%)' from Table 6 of the CS is not available for the ITT.
Abbreviations: AK: Acanthamoeba keratitis; BCVA: best-corrected visual acuity; CL: contact lens; IQR: interquartile range; SD: standard deviation.
Source: Dart et al. 2024 (Supplementary Table 2).⁵

A11. The ODAK trial's principal inclusion criteria specified that participants could be of 'any race', could you please clarify if racial demographic data was collected for the trial, and if so, please provide the relevant data?

Racial demographic data were not collected from participants in the ODAK trial and therefore, cannot be provided. Based on currently available epidemiological data, race/ethnicity is not a known risk factor for, or associated with differences in outcomes in AK.^{6,7}

A12. Section 2.11.2 reports that 11 participants prematurely discontinued the study treatment:

A. Did any of these receive alternative treatments?

B. What were the reasons for those discontinuing the study classed as 'other'?

In the safety analysis set of the ODAK trial (134 patients), 11 patients receiving polyhexanide 0.8 mg/ml prematurely withdrew from the study. According to the protocol for the ODAK trial, all patients who discontinued study treatment received the treatment used by clinicians at the participating centre at the time.⁴ However, no further details as to the specific treatments these patients received is available.

There were two patients who discontinued polyhexanide 0.8 mg/ml study treatment who were classed as 'other' within Table 27 of the Company Submission. This included one patient with a viral infection (an exclusion criterion of the ODAK trial) and one patient who remained on study treatment after 12 months from randomisation (the maximum time frame of treatment), which was classed as a treatment failure.

A13. Priority question: Please provide the trial outcomes from both study arms using the ITT population (All 135 randomised patients).

In the ODAK trial, N=135 patients were randomised to receive study treatment. Of these, 134 patients received at least one dose of the study drug, forming the safety analysis population. The Company Submission presented trial efficacy outcomes for the full analysis set (n=127 patients). The full analysis set included all but seven patients who were included within the safety analysis set. These seven patients were only evaluated for safety outcomes and were excluded from the full analysis set as their AK diagnosis was unconfirmed upon expert review of *in vitro* confocal microscopy (IVCM) results and both culture and PCR were negative.⁵ The inclusion of these patients in the efficacy analysis could potentially introduce bias, a concern recognised by the EMA, with the EMA basing all efficacy evaluations using data from the full analysis set of n=127.¹

Trial outcomes are not available for the ITT (N=135) population. For the EAG's reference, the MCR results for both arms of the ODAK trial, including all randomised patients who received at least one dose of study treatment (n=134) are presented in Table 6 below.

Table 6: Summary of 12-month MCR (safety analysis set: n=134)

12-month MCR	Polihexanide 0.8 mg/ml + placebo (n=69)	Polihexanide 0.2 mg/ml + propamidine 1 mg/ml (n=65)
Resolved, n (%)	58 (84.1)	58 (89.2)
Relative risk (95% CI)	0.94 (0.82, 1.08)	
p-value	0.452	

Abbreviations: CI: confidence interval; MCR: medical cure rate.

A14. Why was the assessment of corneal staining, which showed a dose-dependent effect in healthy volunteers, not included as a specific safety endpoint in the pivotal Phase III ODAK trial for AK patients? What is the company's confidence that this potential effect does not represent a significant safety concern in the patient population, especially considering the long treatment durations for AK?

Corneal staining was analysed during the ODAK trial and was captured within the efficacy assessment of corneal inflammation as "corneal epithelial defects". These are rarely reported adverse events, which is why they were not formally analysed within the ODAK trial. Specifically, within the safety analysis population, punctate keratitis (preferred term for corneal epithelial defects) was reported as an adverse event in one patient receiving polihexanide 0.8 mg/ml, with no instances in the active comparator arm. Corneal staining is therefore not anticipated to represent a significant safety concern for patients with AK, with no additional toxicity expected in patients with AK than was observed in healthy volunteers.

A15. Priority question: The CS includes eye pain as an adverse event of treatment with 0.8 mg/ml of polyhexanide, indicating its clinical relevance. Furthermore, it was reported that 50% of patients suffered corneal scarring, which is a marker of significant ocular surface damage. Therefore, please provide clarity as to why pain was not measured systematically as a trial outcome. Furthermore, please explain how pain could be adequately captured through EQ-5D (one item on pain/discomfort) or VFQ-25 (functional vision).

Pain was assessed in the ODAK trial using both patient-reported outcomes (EQ-5D-5L and VFQ-25) and safety outcomes (AEs coded according to MedDRA version 20.0–24.0). Both the EQ-5D-5L and VFQ-25 tools have been used for other ophthalmic conditions appraised by NICE (HST11: Voretigene neparovec for treating inherited retinal dystrophies caused by RPE65 gene mutations).⁸

Pain was captured using the EQ-5D questionnaire (which included the 5-level pain/discomfort dimension, asking patients to rate their pain from 'no pain' to 'extreme pain'), as well as the ocular pain dimension of the VFQ-25 tool, which asked patients to rate pain in and around their eyes on 5 levels from 'none' to 'very severe'. Both tools were assessed at each patient visit during the ODAK trial i.e. on study Days 0, 7 (±2), 14 (±2), 21 (±2), 30 (±3), 60 (±3) and every 30 days (±5) until resolution, in addition to follow-up and end-of-study visits. It should be noted that

in the FAS, 65/66 patients in the polihexanide 0.8 mg/ml treatment arm completed the EQ-5D and VFQ-55 questionnaires, with the questionnaires not compiled for one patient (see response to question B11).

There was a statistically significant improvement ($p < 0.0001$) in the EQ-5D-5L pain/discomfort dimension from baseline to the end-of-study visit, in patients treated with polihexanide 0.8 mg/ml, indicating that the treatment led to a significant improvement of the pain/discomfort associated with AK in the trial population; even accounting for any pain associated with adverse events arising from treatment (Table 7). The EQ-5D-5L pain/discomfort scores for the active comparator arm and the associated comparative analysis are presented in Table 14.2.5.10 and 14.2.5.9 in the CSR, respectively, for reference.

Table 7: Analysis of EQ-5D-5L pain/discomfort dimension (full analysis set)

EQ-5D-5L pain/discomfort dimension	Polihexanide 0.8 mg/ml (n=65)
Baseline^a	
No pain or discomfort	9 (13.8%)
Slight pain or discomfort	12 (18.5%)
Moderate pain or discomfort	30 (46.2%)
Severe pain or discomfort	12 (18.5%)
Extreme pain or discomfort	1 (1.5%)
Missing	1 (1.5%)
Number of patients with a score higher than 1 ^b	55 (84.6%)
End-of-study visit	
No pain or discomfort	41 (63.1%)
Slight pain or discomfort	14 (21.5%)
Moderate pain or discomfort	3 (4.6%)
Severe pain or discomfort	0
Extreme pain or discomfort	0
Missing	7 (10.8%)
Number of patients with a score higher than 1 ^b	17 (26.2%)
p-value ^c	<0.0001

Footnote: ^aBaseline is defined as the last valid evaluation prior to the first dose of study medication.

^bAny answer except 'no pain or discomfort'.

^cThe p-values are based on paired t-tests where the baseline value is compared to the value at end-of-study.

Source: SIFI ODAK CSR 2022 (Table 14.2.5.10).⁹

Additionally, there was a statistically significant improvement ($p < 0.0001$) in the change in the VFQ-25 ocular pain score from baseline to end-of-study visit within the polihexanide 0.8 mg/ml treatment arm (Table 8). The VFQ-25 ocular pain scores for the active comparator arm are presented in Table 14.2.6.4 in the CSR for reference.

Table 8: Analysis of VFQ-25 ocular pain scores (full analysis set)

VFQ-25 score – ocular pain	Polihexanide 0.8 mg/ml (n=65)
Baseline^a	
Number assessed/number missing	64/1
Mean (SD)	49.4 (23.7)

VFQ-25 score – ocular pain	Polihexanide 0.8 mg/ml (n=65)
Median	42.5
Q1–Q3	30.0–62.5
Min, Max	0, 100
End-of-study visit	
Number assessed/number missing	60/5
Mean (SD)	86.8 (17.0)
Median	100.0
Q1–Q3	75.0–100.0
Min, Max	43, 100
Change from baseline to end-of-study visit	
Number assessed/number missing	60/5
Mean (SD)	37.4 (24.6)
Median	37.5
Q1–Q3	18.8, 50.0
Min, Max	-13–100
p-value ^b	<0.0001

Footnote: ^aBaseline is defined as the last valid evaluation prior to the first dose of study medication.

^bThe p-values are based on paired t-tests where the baseline value is compared to the value at end-of-study.

Abbreviations: SD: standard deviations; VFQ: visual functioning questionnaire.

Source: SIFI ODAK CSR 2022 (Table 14.2.6.4).⁹

Therefore, pain was adequately and regularly evaluated as a systematic trial outcome, captured through the aforementioned patient reported outcomes and through AE monitoring. Overall, the two different measurement tools yielded consistent results, with both demonstrating a statistically significant decrease in pain observed in patients treated with polihexanide 0.8 mg/ml compared with baseline, indicative of an improvement in this impactful symptom of AK.

A16. Please quality assess the ODAK study, which is being treated as a single arm study, with the same questions with which the Papa et al study is assessed (CS Table 10).

Table 9 below describes the critical appraisal and quality assessment of the pivotal ODAK trial using the Quality Assessment Tool for Case Series Studies, aligned with the tool used for the assessment of the Papa et al study.¹⁰ Based on the assessment, the ODAK study is of good quality and low risk of bias.

Table 9: Critical appraisal and quality assessment of the ODAK trial (Dart et al, 2024)

Question	Description
Was the study question or objective clearly stated?	Yes
Was the study population clearly and fully described, including a case definition?	Yes
Were the cases consecutive?	Yes
Were the subjects comparable?	Yes
Was the intervention clearly described?	Yes
Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes

Question	Description
Was the length of follow-up adequate?	Yes
Were the statistical methods well-described?	Yes
Were the results well-described?	Yes
Overall quality	Good

A17. Table 24: AEs by causality – the accompanying text states ‘by investigator’ but how was this determined to be related, unrelated etc to the study drug? Also, ‘AEs by action taken with study treatment’, please provide details of the doses given to those who had a dose increase and the duration of the dose increase. Please also provide the same detail for dose interruption; and explain what is N/A n=6, 12 events?

For each AE occurring in the ODAK trial, the investigator was responsible for obtaining sufficient information to determine the seriousness, causality and outcome of each AE. The relationship of any AE to the study drug was assessed and graded on the following five-point scale, and as outlined in the ODAK protocol.⁴

- **Unrelated:** Sufficient information exists to indicate that causality is unrelated to drug i.e. the event is due to extraneous causes (an underlying medical condition, concurrent drugs, environmental factors etc.)
- **Unlikely:** The AE is likely to have been produced by the subject's clinical state, environmental or toxic factors or other therapeutic interventions but an effect of drug cannot be ruled out.
- **Possible:** The AE follows a reasonable temporal sequence from drug administration; is unlikely to have been produced by the subject's clinical state, environmental or toxic factors or other therapeutic interventions.
- **Probable:** The AE follows a reasonable temporal sequence from drug administration or is associated with established drug concentration in body tissues; improves on stopping or reducing drug dosage (de-challenge); and could not reasonably be explained by the study subject's clinical state environmental or toxic factors, or other therapeutic interventions.
- **Related:** As for "probable" - but on the basis of the observation of objective clinical signs any other cause may be excluded.

Details of the doses given to those who had a dose increase and the duration of the dose increase for the ‘AEs by action taken with study treatment’ (Table 24 of CS and Table 14.3.3.1 of the CSR) in the ODAK trial are not available and therefore cannot be provided.

Investigators provided no further detail for the AEs by action taken with study treatment classed as ‘not applicable’ (N/A; n=6, 12 events).

A18. Please explain how adjunctive therapy use (45.5%) was accounted for in the interpretation of outcomes like inflammation, ulceration and quality of life?

Adjunctive therapy use was defined as new use after baseline or any increase of at least one of the following medications: topical steroid (dexamethasone, prednisolone, fluorometholone, loteprednol), oral NSAIDs (diclofenac, ibuprofen, flurbiprofen, naproxen). There is no evidence that oral NSAIDs interfere with the effect of the immune system or AAT in clearing AK infection.¹¹ Therefore, an analysis of MCR in the ODAK trial stratified by adjuvant steroid use was conducted, given that steroids were the only adjunctive therapy used that were anticipated to affect MCR. Overall, there was no statistically significant difference ($p=1.000$) in MCR between the treatment groups for patients without prior steroid treatment and with steroid treatment starting after baseline and without any prior steroid treatment (Table 10).

Table 10: 12-month MCR stratified by adjuvant steroid use (full analysis set)

12-month MCR	Polihexanide 0.8 mg/ml (n=66)	Polihexanide 0.2 mg/ml + propamidine 1 mg/ml (n=61)	Total (n=127)
Patient without prior steroid treatment and with steroid treatment starting after baseline			
Not resolved	2 (18.2%)	3 (23.1%)	5 (20.8%)
Resolved	9 (81.8%)	10 (76.9%)	19 (79.2%)
Fisher exact test for difference between treatment	p=1.0000		
Patient without any steroid treatment			
Not resolved	1 (4.2%)	2 (7.1%)	3 (5.8%)
Resolved	23 (95.8%)	26 (92.9%)	49 (94.2%)
Fisher exact test for difference between treatment	p=1.0000		

Footnote: Any of the following medications is defined as steroid treatment: Corticosteroids and anti-infectives in combination or corticosteroids alone

Abbreviations: MCR: medical cure rate

Source: SIFI ODAK CSR 2022 (Table 14.2.1.5).⁹

Inflammation, ulceration and quality of life outcomes are inherently linked with MCR, however cure is considered the most clinically relevant outcome for patients with AK, as discussed in the Company Submission. Subsequently, in light of time constraints, it was agreed during the clarification meeting with the EAG that presentation of the analysis exploring the relationship between adjuvant steroid use and MCR (Table 3) should be prioritised and further analyses regarding secondary outcomes would be deprioritised for submission.

A19. The CS reports that 50% of patients developed corneal scarring, please explain how this result can be interpreted with regards to MCR and visual function outcomes?

The response to question A19 is captured within the response to question A20 below.

A20. Please provide results of MCR and best corrected visual acuity (BCVA) outcomes stratified by both the presence and absence of corneal scarring at the culmination of the study.

Please find the Company's combined response to questions A19 and A20 below.

Corneal scarring is a corneal opacity, characterised by the presence of scar tissue on the cornea. It is a complication of corneal infections, such as AK, and can persist even after the infection has resolved.¹²

A crude analysis of cured patients and BCVA outcomes stratified by the presence and absence of corneal scarring is presented in Table 11 and Table 12, respectively. It is important to note that any association between cure rates or BCVA and corneal scarring are likely to be affected by baseline factors, such as disease severity. This is highlighted by the data in Table 11 and Table 12, in which patients with corneal scars at the end of the study had higher MCR and better BCVA (lower LogMAR) than those without scarring; these data imply that there are other baseline factors impacting these outcomes not accounted for in the analysis and as such, these data are inappropriate for making conclusions on the relationship between scarring, MCR and BCVA.

As a result, a crude (unadjusted) analysis for the comparison is potentially misleading and only a multivariable analysis may clarify the eventual association between the outcomes. As discussed at the clarification meeting, SIFI is unable to complete this analysis within the clarification period timelines. Therefore, these data should be interpreted with caution.

Table 11 Table 11: MCR stratified by the presence or absence of corneal scars at the end of the study

	Polihexanide 0.8 mg/ml (n=64) ^a	
	Corneal scars at the end of the study (n=33)	No corneal scars at the end of the study (n=31)
Number of patients cured, n	31	24
Percentage of patients cured, % (95% CI)	93.9 (80.4, 98.3)	77.4 (60.2, 88.6)

Footnote: Corneal scarring data was unavailable for n=2 patients.

Abbreviations: CI: confidence interval; MCR: medical cure rate.

Source: SIFI. Data on File. Outcomes stratified by presence or absence of corneal scars.¹³

Table 12 Table 12: BCVA (LogMAR) stratified by the presence or absence of corneal scars at the end of the study

	Polihexanide 0.8 mg/ml (n=64)	
	Corneal scars at the end of the study (n=33)	No corneal scars at the end of the study (n=31)
LogMAR, mean (SD)	0.07 (0.23)	0.31 (0.49)
LogMAR, median (min, max)	0.00 (-0.18, 1.00)	0.00 (-0.08, 1.30)

Abbreviations: BCVA: best-corrected visual acuity; LogMAR: Logarithm of the Minimum Angle of Resolution; max: maximum; min: minimum; SD: standard deviation.

Source: SIFI. Data on File. Outcomes stratified by corneal scars.¹⁴

Indirect treatment comparison (clinical effectiveness)

A21. What steps if any, were taken to ensure consistency in the definition of treatment success (MCR) between studies beyond simple alignment of criteria?

Based on the results from the clinical SLR update in 2025, an ITC feasibility assessment was conducted to determine whether it was feasible to conduct ITC analyses comparing polihexanide 0.8 mg/ml from the pivotal ODAK study with current therapeutic approaches used in clinical practice for treating AK, in terms of cure without surgery.

The key outcome included in the ITC was the clinical resolution of AK infection. To ensure consistency between studies in the definition of this key outcome and to determine whether ITC analyses could reasonably be conducted, the feasibility assessment included a heterogeneity assessment phase, considering that high levels of heterogeneity can limit the robustness of ITC analyses. This assessment included the evaluation of clinical resolution definitions among studies, determining if studies were reporting the same (or similar) endpoint with consistent definition. An evaluation of the populations was also performed to identify any notable imbalances across studies.

Of the 48 eligible studies in the clinical SLR, 28 studies reported clinical resolution as an outcome. Considering that clinical resolution was measured at 12 months in the polihexanide 0.8 mg/ml pivotal trial (ODAK), the timepoint included in the outcome definition was included as part of the criteria for heterogeneity assessment.

Following comparison of the clinical resolution outcome and timing of the assessments, three studies were considered for the ITC analyses: Dart 2024 (index study), Papa 2020 and Skarin 1996. In these three studies, clinical resolution was defined as:

- Dart et al, 2024: Percentage of subjects cured 30 days after discontinuing all study therapies, within 12 months of randomisation
- Papa et al, 2020: Cure without surgery, independent of visual acuity (including blindness). Cure was defined as clinical evidence of elimination of *Acanthamoeba* - an intact corneal epithelium with no clinical signs of ocular inflammation after discontinuing AAT for 30 days and treating discontinuations of baseline AAT as failures
- Skarin et al, 1996: Healed without surgery

In terms of outcome definition, it was concluded that Dart 2024 and Papa 2020 are similar, with both requiring treatment to be discontinued for 30 days before cure could be confirmed. The study by Skarin et al (1996) was therefore, not considered in the analysis.

The heterogeneity in study populations was explored for studies which were judged to be comparable in terms of definition and timing of the clinical resolution outcome only. The average age and sex distributions were similar in the pivotal trial (Dart et al, 2024) and in the observational study (Papa et al, 2020). The proportions of patients with prior corticosteroid use, a large delay from diagnosis to AAT initiation, and advanced disease were higher in the Papa et al, 2020 study population than in the pivotal ODAK trial. The most important observed difference was the proportion of advanced (Stage 3) disease at baseline (27.3% in Papa 2020 versus 14.2% in the pivotal trial). However, as AK disease stage was identified as a covariate in the ITC analysis, the differences between studies were accounted for in the analysis weighting.

A22. Priority question: Are any additional baseline characteristics available from Papa et al, other than those reported in CS Table 21? Could these be requested from the authors? Please also provide a CSR or other full report for the Papa et al study.

As requested, additional baseline characteristics available from Papa et al, 2020 study have been included in Table 13. Two additional items have been included in this table versus Table 21 of the CS: ethnicity (% Caucasian) and prior use of antibiotics (%). A CSR is not available for the Papa et al, 2020 publication, since it is a retrospective scientific paper.

Table 13: Comparison of baseline characteristics in the ODAK trial and Papa et al. 2020 study

Baseline characteristic	Polihexanide 0.8 mg/ml (ODAK, FAS)	Pooled AAT (Papa et al. 2020)
Number of patients	66	227
Age, years		
Mean (SD)	35.2 (13.2)	35.7 (13.8)
Median (min, max)	33.5 (15.0, 73.0)	33.0 (13.0, 76.0)
Male, %	40.9	44.1
Ethnicity, % of Caucasian ^a	NR	59.5
AK disease Stage 3, %	16.7	27.3
Treatment delay,^b days		
Mean (SD)	33.5 (39.2)	44.9 (48.4)
Median (min, max)	19.0 (1.0, 177.0)	30.0 (0.0, 330.0)
Prior use of corticosteroids, (%)	47.0	44.5
Prior use of antibiotics, (%)	84.8	67.5
Prior use of topical antivirals, (%)	25.8	44.9

Footnote: ^aRace/ethnicity data were not collected as part of the ODAK trial; ^bTime from symptoms onset to treatment initiation.

Abbreviations: AAT: anti-amoebic therapy; AK: Acanthamoeba keratitis; FAS: full analysis set; NR: Not reported; ITC: indirect treatment comparison; SD: standard deviation.

Source: Papa et al. 2020; Dart et al. 2023.

A23. Please can the company clarify whether there were any other outcomes analysed in the ITC? If so, please present the results in the same format at the results for the MCR ITC in Table 23 of the CS.

No other outcomes were analysed in the ITC, since the key endpoint of interest was the cure of AK infection, defined as MCR at 12 months, as per the ODAK trial protocol (please see the company's response to question A21 for further information). MCR was the primary endpoint for the ODAK trial and the only outcome of interest in the ITC as it represents a highly important outcome measure for both patients and clinicians. Achieving a cure and avoiding prolonged damage to the eye associated with long AK exposure is a key treatment priority for patients.

A24. Priority question: Given potential changes in diagnostics and management of AK, how do you justify using a comparator dataset (Papa et al) that predominantly predates 2012?

AK is a relatively new disease first identified in 1972 in the US¹⁵ and in 1974 in the UK.¹⁶ Following the characterisation of AK, the therapeutic approaches commonly used were based on a mix of corticosteroids, antivirals, antibiotics and antifungals but, in most cases, therapeutic keratoplasty was used to control the infection.¹⁷ Although diagnostic technologies and understanding of the complexity of AK (including epidemiological patterns) have significantly improved over the years, the core treatment pathway has remained largely unchanged. A summary of the therapeutic approaches for AK, as summarised in the literature and Royal College of Ophthalmologists guidelines, pre- and post-2012 is presented in Table 14. The first patient to be cured with propamidine was reported in 1985¹⁸ and traditional therapeutic approaches with anti-amoebic activity, such as biguanides (chlorhexidine, polyhexamethylene biguanide [PHMB]) and diamidines (propamidine isethionate, hexamidine), are the mainstay of current clinical management.¹⁹

The literature also emphasises the importance of prompt treatment in AK,²⁰ with delays associated with poorer prognosis, which is common with the current therapeutic approaches that require compounding or importing from other countries.²¹ Moreover, the unapproved current therapeutic approaches for AK lack safety and are often not manufactured to GMP standards and are not subject to pharmacovigilance monitoring, leading to suboptimal outcomes and potential safety concerns. Consequently, patients often fail to avoid the need for surgical intervention, which is associated with high levels of anxiety and burden for patients.

Analyses of individual patient data from Papa et al. 2020 (presented in the response to question A25 below) demonstrates that clinical management remained similar independent of the year of AK diagnosis and similarly, the distribution of therapeutic approaches in the recent Delphi panel conducted by SIFI (in 2023)²² and the Papa et al. distribution were comparable (see Company's response to question B6). Hence, changes in terms of AK management over the past decades are not considered to be a limitation of the Papa et al dataset.

Table 14: The treatment and management of AK pre- and post-2012

	Kumar et al. 2002²³	Dart et al. 2009²⁴	Lorenzo-Morales et al. 2015²⁵	The College of Optometrists Clinical Management Guidelines²⁶
Diagnosis	• Rapid diagnosis is critical; early detection reduces the need for penetrating keratoplasty. • Initiate combination drug therapy promptly at diagnosis to improve prognosis.	• Consider AK in any case of corneal trauma with exposure to soil or contaminated water, especially in contact lens wearers. • Prompt and accurate diagnosis within 3 weeks of symptom onset is critical for a good prognosis. • Use clinical features, confocal microscopy, culture, histology, or PCR for diagnosis.	• Recognise AK promptly, especially in contact lens wearers or following corneal trauma; early detection leads to better outcomes. • Diagnosis procedures include microscopy, culture or PCR.	• Acanthamoeba keratitis can be difficult to treat, and delayed diagnosis is associated with worse visual outcomes; therefore prompt, aggressive therapy is vital. • Make an emergency (same day) referral to ophthalmologist without intervention. • Diagnosis will usually be confirmed by histology (corneal scrape) and culture or by PCR. Cystic form can also be imaged by confocal microscopy.
Therapeutic approaches	• Combination therapy is most effective, typically involving: 0.02% PHMB 0.1% propamidine isethionate (Brolene) or chlorhexidine	• First-line topical agents: Biguanides (0.02–0.06%, chlorhexidine 0.02–0.2%) and diamidines (propamidine 0.1%, hexamidine 0.1%). • Combination therapy is common, but monotherapy with	• Biguanides (e.g., PHMB 0.02% and chlorhexidine 0.02% as first-line approaches. • Combinations with diamidines (propamidine, hexamidine) in combination. • In the case of a persistent infection with inflammation, corticosteroids may be used.	• Intensive (day and night) topical medical treatment with either a biguanide or a diamidine or a combination of the two. ○ Biguanides include: PHMB and chlorhexidine. ○ Diamines: propamidine, dibromopropamidine, hexamidine. • A range of other agents can also be used including:

		PHMB alone may suffice. • Use of other drugs (antibiotics, antifungals, antivirals) is generally ineffective against <i>Acanthamoeba</i> cysts. • Use systemic immunosuppression (e.g., corticosteroids and ciclosporin) for scleritis and severe inflammation, after controlling infection.		○ Antifungals and topical antibiotics ○ Systemic analgesia and/or topical cycloplegics for pain relief as necessary. ○ Topical steroids to limit inflammation if severe.
Surgical intervention	• Penetrating keratoplasty is generally reserved for severe, unresponsive cases or when corneal perforation occurs. • Keratoplasty with adjunctive medical therapy can be effective in eliminating infection and restoring vision.	• Therapeutic keratoplasty should be reserved for advanced complications such as corneal perforation, persistent severe inflammation, or failed medical therapy. • Anti-amoebic therapy should be used before surgery and be continued postoperatively using drugs and doses that will minimise or avoid signs of toxicity.	• Keratoplasty considered when topical treatment has failed and infection spreads or when corneal integrity is compromised. • DALK has been proposed to increase graft survival and prevent entry of pathogenic organisms at the time of surgery.	• Lamellar or penetrating keratoplasty if corneal irregularity, thinning and/or scarring is severe following complete control of infection.

Abbreviations: AK: Acanthamoeba keratitis; DALK: deep anterior lamellar keratoplasty; PCR: polymerase chain reaction; PHMB: polyhexamethylene biguanide.

A25. Priority question: Please provide a sensitivity analysis excluding data prior to 2000 or 2005 to test the robustness of results.

To address the EAG's question around potential uncertainty related to the management of AK, we tested the robustness of the base case analysis (Propensity scores adjusted analysis [PSA] with overlap weights [OW] including the full population from Papa et al. 2020 study in the pooled AAT arm for the assessment), conducting the following sensitivity analyses:

- PSA analysis with OW excluding data from Papa et al. 2020 prior to 2005
- PSA analysis with OW excluding data from Papa et al. 2020 prior to 2000

The results of the PSA analysis (OW) excluding data prior to 2000 or 2005 when compared with the original analysis including the full cohort are presented in Table 15. Results show a consistent effect in terms of relative risk, as well as a similar magnitude of effect across the estimates, which indicates a robust and stable finding across populations. In addition, all p-values < 0.0001, strongly suggesting that the observed effects are highly statistically significant and unlikely due to chance. Last, each 95% CI is relative narrow, suggesting precise estimates with reasonable certainty about where the true effect lies. Importantly, all CIs are above 1, reinforcing that the effect is consistently in the same direction (increased risk).

To test the impact of the sensitivity analyses on the ICER, the relative risk estimates obtained from the PSA with OW analyses excluding data prior to 2005 and prior to 2000 were implemented in the cost effectiveness model. Compared to the base case analysis, applying the weighted relative risk considering only the cohort for subjects since 2005 and since 2000 from the study by Papa et al. 2020 resulted in an increment in the ICER of [REDACTED] and [REDACTED] respectively, as shown in Table 16.

Table 15. Propensity scores adjusted analysis (OW) of ODAK study (polihexanide 0.8 mg/ml and placebo) vs. Papa et al. 2020 study (pooled AAT cohort): full cohort, subjects since 2005 only and subjects since 2000 only

PSA analyses (OW)	ODAK vs. Papa et al. 2020 study - full cohort		ODAK vs. Papa et al. 2020 study - pooled AAT subjects since 2005		ODAK vs. Papa et al. 2020 study – pooled AAT subjects since 2000	
	ODAK	Papa et al. 2020	ODAK	Papa et al. 2020	ODAK	Papa et al. 2020
N. of patients	66	227	66	153	66	192
Unweighted MCR at 12 months: proportion [95% CI]	84.8% [76.2%;93.5%]	43.6% [37.2%;50.1%]	84.8% [76.2%;93.5%]	47.7% [39.8%;55.6%]	84.8% [76.2%;93.5%]	45.3% [38.3%;52.4%]
Weighted RR [95% CI] p-value	1.754 [1.457;2.111] <.0001		1.675 [1.376;2.039] <.0001		1.712 [1.417;2.068] <.0001	

Footnote: Variables adjusted for: Age, Male sex, Disease Stage 3, Prior Corticosteroids, Prior antivirals and Delay Days [Onset to symptoms].

Abbreviations: AAT: anti-amoebic therapy; MCR: medical cure rate; N: Number; OW: Overlap Weights; PSA: Propensity scores adjusted; RR: Relative risk.

Table 16. Results of additional scenario analysis for relative efficacy estimates when stratifying Papa et al. 2020 population by period: including subjects since 2005 and since 2000

Scenario	Incremental costs, £	Incremental QALYs	ICER (£/QALY)	Absolute % Change in ICER	INHB at £20k	INHB at £30k
Updated base case*	■■■■	2.56	■■■■	NA	■■■■	■■■■
ODAK vs. Papa et al. 2020 study - pooled AAT subjects since 2005 (PSA-OW)	■■■■	2.41	■■■■	■■■■	■■■■	■■■■
ODAK vs. Papa et al. 2020 study – pooled AAT subjects since 2000 (PSA-OW)	■■■■	2.48	■■■■	■■■■	■■■■	■■■■

Footnote: *Updated base case also includes the EAG updates requested in question B16.

Abbreviations: AAT: anti-amoebic therapy; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; NA: not applicable; OW: Overlap Weights; PSA: Propensity scores adjusted; QALY: quality-adjusted life years.

As the EAG requested (in question A30) to provide sensitivity analyses considering alternative weighting methods for the base case ITC, we have conducted sensitivity analysis testing propensity scores methodologies, excluding data from Papa et al. 2020 study prior to 2005 and 2000, specifically inverse weighting average treatment effect (ATE) and-inverse weighting effect of treated (ATT), the results of which are presented in Table 17 and Table 18 for ATE and ATT analyses, respectively.

The resultant estimates consistently show a statistically significant elevated relative risk ($RR > 1$) among PSA methodologies; however, ATE based RR estimates are slightly higher than the OW-based estimates, suggesting the treatment effect may appear stronger with this inverse weighting methodology. On the other hand, AAT-based estimates are slightly lower than OW estimates but remain consistently significant and in the same direction ($RR > 1$), still indicating a consistent, meaningful effect. All methods (ATE and ATT) yield relatively narrow CIs, reinforcing precision. All intervals exclude 1.0, confirming significance across methodologies. However, as mentioned in the response to question A30, PSA analysis with OW tends to produce more stable estimates and better covariate balance compared with other propensity scores methodologies (i.e., ATE and ATT), therefore, PSA analysis with OW was selected for the base case.

The impact of the estimates from alternative propensity scores methodologies considering the full cohort from Papa et al. 2020 study and considering only subjects since 2005 and since 2000, were assessed as part of the scenario analyses (see Table 19 and Table 20 below).

Table 17. Propensity scores adjusted analysis (Inverse weighted - ATE) of ODAK study (polihexanide 0.8 mg/ml and placebo) vs. Papa et al. 2020 study (pooled AAT cohort): full cohort, subjects since 2005 only and subjects since 2000 only

PSA analyses, inverse weighted (ATE)	ODAK vs. Papa et al. 2020 study- full cohort		ODAK vs. Papa et al. 2020 study - pooled AAT subjects since 2005		ODAK vs. Papa et al. 2020 study – pooled AAT subjects since 2000	
Parameter	ODAK	Papa et al. 2020	ODAK	Papa et al. 2020	ODAK	Papa et al. 2020
N. of patients	66	227	66	153	66	192
Unweighted MCR at 12 months: proportion [95% CI]	84.8% [76.2%;93.5%]	43.6% [37.2%;50.1%]	84.8% [76.2%;93.5%]	47.7% [39.8%;55.6%]	84.8% [76.2%;93.5%]	45.3% [38.3%;52.4%]
Weighted RR [95% CI] p-value	1.884 [1.557; 2.280] <.0001		1.744 [1.432; 2.123] <.0001		1.821 [1.501; 2.208] <.0001	

Footnote: Variables adjusted for: Age, Male sex, Disease Stage 3, Prior Corticosteroids, Prior antivirals and Delay Days [Onset to symptoms].

Abbreviations: ATE: Average treatment effect; CI: confidence interval; MCR: medical cure rate; N: Number; PSA: Propensity scores adjusted; RR: Relative risk

Table 18. Propensity scores adjusted analysis (Inverse weighted - ATT of ODAK study (polihexanide 0.8 mg/ml and placebo) vs. Papa et al. 2020 study (pooled AAT cohort): full cohort, subjects since 2005 only and subjects since 2000 only

PSA analyses, inverse weighted (ATT)	ODAK vs. Papa et al. 2020 study- full cohort		ODAK vs. Papa et al. 2020 study - pooled AAT subjects since 2005		ODAK vs. Papa et al. 2020 study – pooled AAT subjects since 2000	
Parameter	ODAK	Papa et al. 2020	ODAK	Papa et al. 2020	ODAK	Papa et al. 2020
N. of patients	66	227	66	153	66	192
Unweighted MCR at 12 months: proportion [95% CI]	84.8% [76.2%; 93.5%]	43.6% [37.2%; 50.1%]	84.8% [76.2%; 93.5%]	47.7% [39.8%; 55.6%]	84.8% [76.2%; 93.5%]	45.3% [38.3%; 52.4%]

Weighted RR [95% CI] p-value	1.709 [1.416; 2.062] <.0001	1.620 [1.325; 1.980] <.0001	1.654 [1.368; 2.000] <.0001

Footnote: Variables adjusted for: Age, Male sex, Disease Stage 3, Prior Corticosteroids, Prior antivirals and Delay Days [Onset to symptoms].

Abbreviations: ATT: Average treatment effect of treated; CI: confidence interval; MCR: medical cure rate; N: Number; PSA: Propensity scores adjusted; RR: Relative risk

Table 19. Results of additional scenario analysis for alternative propensity scores methodologies (ATE): full cohort, subjects since 2005 only and subjects since 2000 only

Scenario	Incremental costs, £	Incremental QALYs	ICER (£/QALY)	Absolute % Change in ICER	INHB at £20k	INHB at £30k
Updated base case*	■■■■	2.56	■■■■	NA	■■■■	■■■■
ODAK vs. Papa et al. 2020 study- full cohort (PSA-ATE)	■■■■	2.77	■■■■	■■■■	■■■■	■■■■
ODAK vs. Papa et al. 2020 study - pooled AAT subjects since 2005 (PSA-ATE)	■■■■	2.54	■■■■	■■■■	■■■■	■■■■
ODAK vs. Papa et al. 2020 study – pooled AAT subjects since 2000 (PSA-ATE)	■■■■	2.67	■■■■	■■■■	■■■■	■■■■

Footnote: *Updated base case also includes the EAG updates requested in question B16.

Abbreviations: ATE: Average treatment effect; AAT: anti-amoebic therapy; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; NA: not applicable; OW: Overlap Weights; PSA: Propensity scores adjusted; QALY: quality-adjusted life years.

Table 20. Results of additional scenario analysis for alternative propensity scores methodologies (ATT): full cohort, subjects since 2005 only and subjects since 2000 only

Scenario	Incremental costs, £	Incremental QALYs	ICER (£/QALY)	Absolute % Change in ICER	INHB at £20k	INHB at £30k
*Updated base case	■■■■	2.56	■■■■	NA	■■■■	■■■■
ODAK vs. Papa et al. 2020 study- full cohort (PSA-ATT)	■■■■	2.48	■■■■	■■■■	■■■■	■■■■
ODAK vs. Papa et al. 2020 study - pooled AAT subjects since 2005 (PSA-ATT)	■■■■	2.31	■■■■	■■■■	■■■■	■■■■
ODAK vs. Papa et al. 2020 study – pooled AAT subjects since 2000 (PSA-ATT)	■■■■	2.37	■■■■	■■■■	■■■■	■■■■

Footnote: Updated base case includes the EAG updates requested in question B16.

Abbreviations: ATT: Average treatment effect of treated; AAT: anti-amoebic therapy; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; NA: not applicable; OW: Overlap Weights; PSA: Propensity scores adjusted; QALY: quality-adjusted life years.

A26. How was heterogeneity in the comparator regimens addressed beyond pooling? Were subgroup analyses conducted?

The population characteristics of the regimens included in the comparator arm are summarised in Table 21, as reported in the publication by Papa et al. 2025.¹⁷ In addition, the rates of MCR within 12 months for patients with AK treated with each of the regimens of the comparator arm based on the results from the ITC are described.

Since the population characteristics were relatively similar among treatment regimens included in the comparator arm from Papa et al. 2020, and since the outcomes in terms of MCR were consistent among populations, no additional analyses were conducted.²⁷

Table 21. Summary of unweighted characteristics for patients with AK treated with any initial AAT, polihexanide 0.2 mg/ml plus a diamidine 1 mg/ml or chlorhexidine 0.2 mg/ml alone or plus a diamidine 1 mg/ml

Parameter	Papa et al. 2025		
	Any initial AAT	Polihexanide 0.2 mg/ml plus diamidine 1 mg/ml	Chlorhexidine 0.2 mg/ml alone or plus diamidine 1 mg/ml
Population characteristics			
Number of patients Age, years	227	111	35
Age, Mean (SD)	35.7 (13.8)	34.4 (13.6)	36.2 (13.8)
Age, Median (min, max)	33.0 (13.0, 76.0)	32.0 (13.0, 75.0)	35.0 (17.0, 74.0)
Male, n (%)	100 (44.1)	49 (44.1)	19 (54.3)

AK disease stage 1-2, n (%)	149 (72.7)	86 (77.5)	20 (66.7)
AK disease stage 3, n (%)	56 (27.3)	25 (22.5)	10 (33.3)
AK disease stage missing, n (%)	22	0	5
Treatment delay, days, Mean (SD)	44.9 (48.4)	51.3 (52.6)	45.6 (45.7)
Treatment delay, days, Median (min, max)	30.0 (0.0, 330.0)	31.0 (2.0, 330.0)	30.0 (0.0, 233.0)
Prior use of corticosteroids, n (%)	101 (44.5)	46 (41.4)	14 (40.0)
Prior use of topical antivirals, n (%)	102 (44.9)	48 (43.2)	19 (54.3)
MCR within 12 months – estimates from the ITC*			
	Polihexanide 0.8 mg/ml vs any initial AAT	Polihexanide 0.8 mg/ml vs polihexanide 0.2 mg/ml plus diamidine 1 mg/ml	Polihexanide 0.8 mg/ml vs chlorhexidine 0.2 mg/ml alone or plus diamidine 1 mg/ml
% MCR (95% CI) - PHMB 0.08%	84.7 (76.1, 93.4)	85.1 (76.6, 93.7)	83.3 (74.3, 92.3)
% MCR (95% CI) – treatment regime	48.3 (41.8, 54.8)	60.9 (51.9, 70.0)	46.4 (29.9, 63.0)
% Difference in MCR (95% CI)	36.4 (24.9, 47.9)	24.2 (11.3, 37.1)	36.8 (14.2, 59.5)
P value	<0.001	<0.001	0.002

Footnote: *Results were adjusted for the following confounders: age, sex, disease stage, prior corticosteroid use, prior antiviral use and treatment delay.

Abbreviations: AAT, anti-amoebic treatment; AK, Acanthamoeba keratitis; max, maximum; ITC: indirect treatment comparison; MCR: medical cure rate; min, minimum; n, number of patients.

A27. Appendix Table 5 has all 48 included studies (References 3-49) but no details of all their interventions – please provide summary details. Please also provide the pdfs

The PDFs for the 48 studies included in the clinical SLR are included in the reference pack folder for the EAG's consideration. Table 22 summarises the included studies alongside information about the interventions assessed in each study.

Table 22: Studies included in the clinical SLR, including treatments considered

Study	Country	Study years	AK Population	Treatments included per study	Sample size (N)	Mean (range) ^a			Proportion (%)				Stages
						Follow-up (days)	Age (years)	Diagnosis delay, (days) ^b	Male	CLs	Bilateral keratitis	Prior CS treatment	
Randomised controlled trial													
Dart, 2024 ⁵	Italy, Poland, UK	2017–21	All	Polihexanide 0.8 mg/ml; Polihexanide 0.2 mg/ml + Propamidine 1 mg/ml	134	NR (NR-95)	36.5 (15-73)	NR	42	NR	0	21	I: 17 II: 69 III: 14
Bagga, 2021 ²⁸	India	2016–18	All	Polihexanide 0.02% + Chlorhexidine 0.02%; Voriconazole 1%	23	85 (14-NR)	39.8 (19-67)	NR	61.1	NR	NR	11.1	NR
Lim, 2008 ²⁹	UK	1995–2001	All	Polihexanide 0.02%; Chlorhexidine 0.02%;	50	NR	31 (NR)	NR	46	98	2.00	NR	NR
Retrospective analyses of routine data													
Arnaiz-Camacho, 2025 ³⁰	Spain	2014–24	Contact lens-associated AK	Chlorhexanide 0.02%+/- propamidine 0.1%	13	660 (90-NR)	30 (15-44)	5 (NR)	38.5	100	0	46.2	NR
Zhao, 2025 ³¹	China	2021–24	Overnight Orthokeratology-related AK	PHMB, Metronidazole and Voriconazole	11	396 (234-888)	14.7 (11-22)	5 (2-150)	27.3	100	27.3	NR	NR
Blaser, 2024 ³²	Switzerland	2010–23	All	Polihexanide and Propamidine	52	NR	33 (13-90)	18 (3-70)	40.4	92.3	7.7	NR	NR
Messina, 2024 ³³	Italy	2020–21	Contact lens-associated AK	Polihexanide and Propamidine	8	NR (60-180)	27.8 (18-45)	NR	37.5	100	12.5	25	Severe: 12.5%
Agarwal, 2023 ³⁴	India	2015–19	All	Polihexanide and Propamidine	24	NR	NR	42 (NR)	NR	NR	NR	NR	NR
Roth, 2023 ³⁵	Germany	1993–2021	All	Polihexanide and Propamidine	75	NR	37 (15-73)	47 (14-100)	30.3	84	1.3	NR	NR

Study	Country	Study years	AK Population	Treatments included per study	Sample size (N)	Mean (range) ^a			Proportion (%)				Stages
						Follow-up (days)	Age (years)	Diagnosis delay, (days) ^b	Male	CLs	Bilateral keratitis	Prior CS treatment	
Ahmed, 2022 ³⁶	India	2016–20	All	0.02% Polihexanide + natamycin + voriconazole; 0.02% Polihexanide + moxifloxacin + voriconazole; 0.02% Polihexanide + propamidine + moxifloxacin; 0.02% Polihexanide + propamidine	7	NR	35 (20-55)	NR	100	NR	0	25	NR
Bonini, 2021 ²⁰	Italy	1994–2012	All	Polihexanide 0.2 mg/ml + Propamidine 1 mg/ml	35	4782 (NR)	30 (12-67)	81.6 (28-366)	55.56	NR	18	NR	I: 22.2% II: 40.7% III: 47.0%
Chen, 2021 ³⁷	Singapore	2012–16	All	Chlorhexanide and hexamidine	18	NR	24.4 (15-40)	NR	33.3	77.8	0	26.7	NR
Nasef, 2021 ³⁸	Egypt	2016–20	All	Polihexanide 0.2 mg/ml + Propamidine 1 mg/ml	42	NR	31.6 (18-65)	20.2 (1-40)	28.5	77	NR	25	NR
Jo, 2020 ³⁹	Korea	2013–18	Contact lens-associated AK	Polihexanide 0.2 mg/ml; Chlorhexanide 0.02%; Chlorhexanide 0.02%+ Polihexanide 0.2 mg/ml	16	NR	21.1 (13-42)	7.1 (1-21)	12.5	100	15.8	NR	I: 68.4% II: 31.6%
Megha, 2020 ⁴⁰	India	2014–18	All	Polihexanide 0.2 mg/ml	11	NR	33 (21-73)	22.2 (3-84)	72.73	27.3	9.09	NR	NR
Musayeva, 2020 ⁴¹	Germany	2014–17	All	Polihexanide 0.02%, propamidine 0.1%,	28	NR	41.7 (21-80)	18.2 (1-138)	42.9	57.1	0	NR	I: 7.1% II: 50.0% III: 42.9%

Study	Country	Study years	AK Population	Treatments included per study	Sample size (N)	Mean (range) ^a			Proportion (%)				Stages
						Follow-up (days)	Age (years)	Diagnosis delay, (days) ^b	Male	CLs	Bilateral keratitis	Prior CS treatment	
				voriconazole 1%, Gentamicin 1.4% or moxifloxacin 0.5%, dexamethasone 0.13% and other (mydriatics, ganciclovir, autologous serum, bevacizumab)									
Papa, 2020 ²⁷	Italy UK	1991–2012	All	Polihexanide 0.2 mg/ml +/- Propamidine 1 mg/ml; Polihexanide 0.6 mg/ml +/- Propamidine 1 mg/ml; other combinations (Polihexanide, chlorhexidine, propamidine and/or hexamidine in various combinations).	227	NR (31-NR)	35.7 (13-76)	45.6 (NR-330)	44.05	NR	NR	44.49	Non-severe: 66% Severe: 34%
Hassan, 2019 ⁴²	UK	2017–18	All	Polihexanide 0.02% + Propamidine 0.1%; Chlorhexidine 0.02% + Propamidine 0.1%; Polihexanide 0.02% + Propamidine 0.1% + Chlorhexidine 0.02%; Polihexanide 0.02% +	9	NR	33.6 (22-61)	NR (NR-10)	11.11	100	0	NR	NR

Study	Country	Study years	AK Population	Treatments included per study	Sample size (N)	Mean (range) ^a			Proportion (%)				Stages
						Follow-up (days)	Age (years)	Diagnosis delay, (days) ^b	Male	CLs	Bilateral keratitis	Prior CS treatment	
				Propamidine 0.1%+ Hexamidine 0.1%; Chlorhexidine 0.02% + Polihexanide 0.02%									
Li, 2019 ⁴³	China	2007–15	All	Chlorhexidine 0.02% and metronidazole	37	NR	48.8 (18-76)	NR	51.4	NR	0	NR	NR
Orosz, 2019 ⁴⁴	Hungary	2015–18	Contact lens-associated AK	Polihexanide 0.02%; Propamidine 0.1%; metronidazole	7	NR	30.7 (NR)	1.4 (NR)	43.0	100	NR	NR	NR
Randag, 2019 ^{c,45}	Netherlands	2009–15	All	Propamidine 0.1% monotherapy or +/- Chlorhexidine 0.02%; Polihexanide 0.02% monotherapy or +/- Chlorhexidine 0.02%; Chlorhexidine 0.02% monotherapy	224	353 (12-1682)	34 (11-75)	29 (2-319)	37.5	95.1	4.5	63.8	I: 25.9% II: 42.4% III: 28.6%
Carnt, 2018 ⁴⁶	UK	1991–2012	All	Polihexanide 0.02% monotherapy or + diamidine or + chlorhexidine 0.02%; Diamidine monotherapy or + chlorhexidine 0.02%; chlorhexidine 0.02% monotherapy	194	Bad outcome s: 896 (420-1624) Better outcome s: 196 (112-308)	34 (15-76)	NR (8-65)	48	94	NR	47	I: 10% II: 56% III: 34%

Study	Country	Study years	AK Population	Treatments included per study	Sample size (N)	Mean (range) ^a			Proportion (%)				Stages
						Follow-up (days)	Age (years)	Diagnosis delay, (days) ^b	Male	CLs	Bilateral keratitis	Prior CS treatment	
Zhong, 2017 ⁴⁷	China	2004–14	All	Neomycin 0.5% and propamidine 0.1%	15	840 (168-1008)	42.3 (19-63)	52 (20-120)	66.67	6.67	0	NR	NR
Jiang, 2015 ⁴⁸	China	1991–2013	Advanced stage	Polihexanide 0.04% and chlorhexidine 0.04%;	259	NR	NR (7-82)	NR	56.37	29.8	0.39	NR	Advanc-ed: 100%
Arnalich-Montiel, 2014 ¹³	Spain	2009–13	All	Chlorhexidine 0.02% + PHMB and propamidine 0.1%	17	NR	38 (13-60)	NR	23.5	88.2	5.9	NR	NR
Erdem, 2014 ⁴⁹	Turkey	2010–12	Non–contact lens–wearing	Chlorhexidine 0.02% and propamidine 0.1%	26	NR (NR-672)	49.3 (10-83)	24.8 (5-123)	61.54	0	0	0	NR
Cheng, 2009 ⁵⁰	Hong Kong	2005–07	All	Propamidine 0.1% monotherapy; Polihexanide 0.02% monotherapy; Propamidine 0.1% + Polihexanide 0.02%; Polihexanide 0.02% + Neosporin; Polihexanide 0.02% + Propamidine 0.1% + Neosporin	7	369 (NR)	23.1 (14-38)	7.6 (NR-28)	0	100	28.6	14.3	NR
Ku, 2009 ⁵¹	Australia	2003–07	All	Polihexanide 0.02% or 0.04% +/- Brolene	13	386 (84-1484)	35 (23-56)	NR	62	92	0	69	NR
Lin, 2009 ⁵²	Taiwan	2001–06	All	Propamidine 0.1% + Polihexanide 0.02% ; Propamidine 0.1% + Polihexanide	11	NR	23.7 (7-66)	26.1 (7-56)	82	NR	0	NR	NR

Study	Country	Study years	AK Population	Treatments included per study	Sample size (N)	Mean (range) ^a			Proportion (%)				Stages
						Follow-up (days)	Age (years)	Diagnosis delay, (days) ^b	Male	CLs	Bilateral keratitis	Prior CS treatment	
				0.02% + Clotrimazole									
Mathers, 2006 ⁵³	USA	NR	All	Chlorhexidine 0.02%	8	NR	NR	NR	NR	NR	NR	NR	Mild: 86.2% Severe:13.8 %
Sun, 2006 ⁵⁴	China	1997–2003	All	Chlorhexanide 0.02%, neomycin 0.5% and metronidazole 0.4%; Chlorhexanide 0.02%, neomycin 0.5% and metronidazole 0.4% with adjunctive chlorhexidine 0.1% 2x weekly	20	266 (77-770)	26 (12-50)	42 (7-182)	60	60	0	NR	NR
Perez-Santonja, 2003 ⁵⁵	UK	1990–2000	Positive cultures after treatment ^c	Polihexanide 0.02% + hexamidine 0.1%; Polihexanide 0.02% + hexamidine 0.1% + Chlorhexanide 0.02%; Polihexanide 0.02% monotherapy; Polihexanide 0.02% + propamidine 0.1%	8	375 (126-868)	36.4 (26-56)	9.75 (1-24)	50	75	NR	NR	NR
Donoso, 2002 ⁵⁶	Chile	NR	All	Polihexanide 0.02% + propamidine 0.1%	27	NR	NR	NR (28-140)	NR	96	14.81	NR	NR
Parija, 2001 ⁵⁷	India	1997–2000	All	Neosporin	11	NR	NR (15-57)	NR	73	0	NR	NR	NR
Azuara-Blanco,	UK	1994–97	All	Polihexanide 0.02% +	10	NR	30 (19-40)	12.7 (2-26)	60	100	0	NR	NR

Study	Country	Study years	AK Population	Treatments included per study	Sample size (N)	Mean (range) ^a			Proportion (%)				Stages
						Follow-up (days)	Age (years)	Diagnosis delay, (days) ^b	Male	CLs	Bilateral keratitis	Prior CS treatment	
1997 ⁵⁸				propamidine 0.1% + polyfax; Chlorhexanide 0.02% (then PHMB 0.02%), propamidine and polyfax									
Duguid, 1997 ⁵⁹	UK	1992–95	All	Polihexanide 0.02% and propamidine 0.1%	105	NR	32 (16-64)	NR	57.14	91.9	5.4	NR	NR
Skarin, 1996 ⁶⁰	Sweden	1991–93	All	Polihexanide 0.02% + Propamidine 0.1% + Neomycin + Polymyxin B; Propamidine 0.1% + Neomycin + Polymyxin B; Propamidine 0.1% + Neomycin + Polymyxin B + oral ketoconazole + miconazole + paromomycin; Polihexanide 0.02% + Propamidine 0.1% + Neomycin + Polymyxin B + oral ketoconazole + paromomycin; Polihexanide 0.02% + Propamidine 0.1% + Neomycin + Polymyxin B + oral ketoconazole + paromomycin + clotrimazole	8	NR (NR-672)	37 (22-69)	81.2 (28-308)	62.5	62.5	0	25	NR
Prospective single-arm interventional study													

Study	Country	Study years	AK Population	Treatments included per study	Sample size (N)	Mean (range) ^a			Proportion (%)				Stages
						Follow-up (days)	Age (years)	Diagnosis delay, (days) ^b	Male	CLs	Bilateral keratitis	Prior CS treatment	
Franch, 2024 ⁶¹	Italy	2023	Contact lens-associated AK	Polihexanide 0.08%	11	NR	41.4 (17-67)	NR	36	100	9.1	91	I: 17% II: 33% III: 50%
Caruso, 2020 ⁶²	Italy	2018–19	All	Chlorhexidine 0.02% and Vitamin E 0.2%	29	NR (NR-84)	27.0 (NR)	NR	31.04	55.17	NR	NR	III: 100%
Bagga, 2019 ⁶³	India	2018–18	All	Miltefosine 4 mg/ml	5	NR	41.5 (30-58)	33 (10-90)	0	NR	NR	NR	NR
Revathi, 2018 ⁶⁴	NR	NR	All	Polihexanide 0.04% and chlorhexidine 0.04%	25	NR	NR	23 (NR)	NR	NR	NR	NR	NR
Rahimi, 2014 ⁶⁵	Iran	NR	All	Polihexanide 0.02%	25	NR	NR	NR	NR	NR	8	NR	NR
Hargrave, 1999 ⁶⁶	USA	NR	All	Propamidine 0.1% and Neomycin-polymyxin B-gramicidin (Neotricin)	83	NR	33 (18-72)	68 (NR)	NR	75	3	35	NR
Kosirukvongs, 1999 ⁶⁷	Thailand	1996–96	Not responded to neomycin	Chlorhexidine 0.006%	5	NR	53 (33-77)	NR	40	20	20	NR	NR
Seal, 1996 ⁶⁸	UK	NR	All	Chlorhexidine 0.02% and propamidine 0.1%	12	NR (168-NR)	30.9 (14-50)	30.9 (7-98)	41.67	100	NR	25	NR
Case-control study													
Hsu, 2022 ⁶⁹	Taiwan	2001–16	Contact lens-associated AK	Chlorhexidine 0.02% monotherapy, Chlorhexidine 0.02% + Voriconazole 1%; Chlorhexidine 0.02% + Voriconazole 1% + oral voriconazole;	35	NR	22.9 (11-55)	18.3 (7-56)	37.14	100	11.43	NR	NR

Study	Country	Study years	AK Population	Treatments included per study	Sample size (N)	Mean (range) ^a			Proportion (%)				Stages
						Follow-up (days)	Age (years)	Diagnosis delay, (days) ^b	Male	CLs	Bilateral keratitis	Prior CS treatment	
				Polihexanide + Propamidine 0.1%; Polihexanide + Chlorhexidine 0.02% + Propamidine 0.1%; Chlorhexidine 0.02% + Propamidine 0.1%; Chlorhexidine 0.02% + Propamidine 0.1% + Voriconazole 1%									
Wouters, 2022 ^{d,70}	Netherlands	2003–17	All	Chlorhexidine 0.02% + Propamidine 0.1%; Chlorhexidine 0.02% + Propamidine 0.1% + Corticosteroids	109	504 (28-5796)	41 (15-70)	23 (7-303)	58.49	92	9	0	I-II: 60% III-IV: 40%
							35 (11-74)	62 (0-295)	46.43	98	7	100	I-II: 34% III-IV: 66%
Cohort study													
Radford, 1998 ⁷¹	UK	1992–96	All	Polihexanide + propamidine; Chlorhexidine + propamidine; Polihexanide + neomycin + propamidine	243	NR	31.5 (4-64)	NR	56	88	7	NR	NR

Footnote: ^aValues in italics are medians. ^bTime from symptom initiation to diagnosis. ^cTwo patients with missing treatment data are included in the demographic summary but not in summaries by treatment.

Abbreviations: AK: *Acanthamoeba* keratitis; CS: corticosteroid; CLs: contact lens wearers; NR: not reported; UK: United Kingdom

A28. Priority question: Please can the company provide the distribution of the propensity score and weights used in the indirect treatment comparison (ITC). This should include:

- A. A table summarising key statistics (for example mean, standard deviation, range, median and interquartile range)**
- B. A histogram or density plot showing the distribution of propensity scores for each study arm (before weighting), and the overlap weights (after weighting).**

To fully answer this question, Table 23 presents the baseline characteristics of the patients included in the analysis (those treated with polihexanide 0.8 mg/ml [ODAK trial] and those in the pooled AAT arm from the Papa et al. 2020 study), both before and after propensity score weighting. The PSA adjusted analysis with OW demonstrates more stable estimates and better covariate balance compared with ATE and ATT methods.

In Table 24, a summary of the distribution of propensity scores and derived weighting variables is provided, as requested in part A of the question. In addition, Figure 2 presents the distribution of propensity scores for each study arm as requested in part B. The figure demonstrates strong overlap in propensity scores between the two populations, indicating that they are sufficiently comparable to allow for effective propensity score matching. As a result, the overlap weight approach yielded near-perfect matching, and the analyses using both ATE and ATT produced well-balanced matches. This level of consistency across weighting methods supports the overall stability and robustness of the results.

Table 23. Demographic characteristics of patients from the ODAK trial and from Papa et al. 2020 study: unadjusted and after propensity score weighting (OW, ATE and ATT methodologies)

Propensity scores	Unadjusted analyses		Propensity scores adjusted analyses (OW)*		Propensity scores adjusted analyses (Inverse weighted - ATE)*		Part 4: Propensity scores adjusted analyses (Inverse weighted - ATT)*	
	ODAK	Papa et al. 2020	ODAK	Papa et al. 2020	ODAK	Papa et al. 2020	ODAK	Papa et al. 2020
Age (years), Mean $\pm$ SD	35.2 $\pm$ 13.2	35.7 $\pm$ 13.8	34.87 $\pm$ 13.02	34.87 $\pm$ 14.09	34.17 $\pm$ 12.61	35.82 $\pm$ 14.56	35.23 $\pm$ 13.24	34.37 $\pm$ 13.86
Male sex	40.91% (27/66)	44.05% (100/227)	40.55% (27/66)	40.55% (92/227)	41.16% (27/66)	42.72% (97/227)	40.91% (27/66)	39.04% (89/227)
Disease Stage 3	16.67% (11/66)	27.32% (56/205)	18.76% (12/66)	18.76% (43/227)	24.01% (16/66)	24.74% (56/227)	16.67% (11/66)	16.73% (38/227)

Prior Corticosteroids	46.97 % (31/66)	44.49 % (101/227)	45.23% (30/66)	45.23% (103/227)	44.10% (29/66)	45.30% (103/227)	46.97% (31/66)	46.61% (106/227)
Prior antivirals	25.76 % (17/66)	44.93 % (102/227)	29.99% (20/66)	29.99% (68/227)	40.83% (27/66)	40.64% (92/227)	25.76% (17/66)	25.93% (59/227)
Delay Days [Onset to symptoms] Mean $\pm$ SD	33.5 $\pm$ 39.2	44.9 $\pm$ 48.4	35.56 $\pm$ 41.33	35.56 $\pm$ 36.70	40.33 $\pm$ 45.34	41.74 $\pm$ 44.65	33.55 $\pm$ 39.25	33.99 $\pm$ 34.68
Unweighted MCR at 12 months – proportion, 95% CI	NA	NA	84.8% (56/66) [76.2%;93.5%]	43.6% (99/227) [37.2%;50.1%]	84.8% (56/66) [76.2%;93.5%]	43.6% (99/227) [37.2%;50.1%]	84.8% (56/66) [76.2%;93.5%]	43.6% (99/227) [37.2%;50.1%]
Weighted MCR at 12 months – proportion, 95% CI	NA	NA	84.7% (55.9/66) [76.1%;93.4%]	48.3% (109.7/227) [41.8%;54.8%]	84.7% (55.9/66) [76.0%;93.4%]	44.9% (102.0/227) [38.5%;51.4%]	84.8% (56.0/66) [76.2%;93.5%]	49.7% (112.7/227) [43.2%;56.2%]
Weighted analysis [ESS]	NA	NA	64.8	174.4	53.9	201.2	66.0	155.8
Weighted RR [95% CI] p-value	NA		1.754 [1.457; 2.111] <.0001		1.884 [1.557; 2.280] <.0001		1.709 [1.416; 2.062] <.0001	

Footnote: Variables adjusted for (*): Age, Male sex, Disease Stage 3, Prior Corticosteroids, Prior antivirals and Delay Days (Onset to symptoms).

Abbreviations: ATE: average treatment effect; ATT: average treatment effect of treated; CI: confidence interval; ESS: Effective Sample Size; MCR: medical cure rate; OW: overlap weights; RR: Relative risk; SD: standard deviation.

Table 24. Analysis of ODAK study (polihexanide 0.8 mg/ml and placebo) vs. Papa et al. 2020 study (pooled AAT cohort): distribution of propensity scores and derived weighting variables

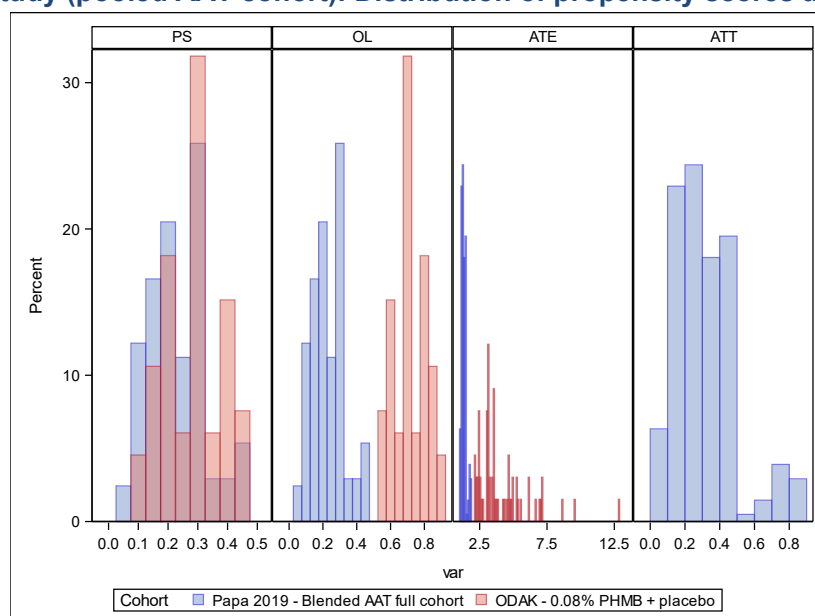
Outcome	ODAK study (polihexanide 0.8 mg/ml and placebo)	Papa et al. 2020 study (pooled AAT full cohort)
Propensity score		
Mean $\pm$ SD (N)	0.285 $\pm$ 0.099 (66)	0.230 $\pm$ 0.097 (205)
Median (Min, Max)	0.287, (0.078, 0.471)	0.219, (0.051, 0.467)
IQR (Q1, Q3)	0.207, 0.328	0.149, 0.292
PSM weight [OW]		
Mean $\pm$ SD (N)	0.715 $\pm$ 0.099 (66)	0.230 $\pm$ 0.097 (205)
Median (Min, Max)	0.713, (0.529, 0.922)	0.219, (0.051, 0.467)

IQR (Q1, Q3)	0.672, 0.793	0.149, 0.292
PSM weight [ATE]		
Mean $\pm$ SD (N)	4.108 $\pm$ 1.962 (66)	1.322 $\pm$ 0.181 (205)
Median (Min, Max)	3.489, (2.125, 12.831)	1.281, (1.053, 1.875)
IQR (Q1, Q3)	3.046, 4.823	1.176, 1.412
PSM weight [ATT]		
Mean $\pm$ SD (N)	1.000 $\pm$ 0.000 (66)	0.322 $\pm$ 0.181 (205)
Median (Min, Max)	1.000, (1.000, 1.000)	0.281, (0.053, 0.875)
IQR (Q1, Q3)	1.000, 1.000	0.176, 0.412

Footnote: The ATT analysis does not show the data on 'treated' arm, as its weight for each subject is equal to 1 per definition. Variables adjusted for (*): Age, Male sex, Disease Stage 3, Prior Corticosteroids, Prior antivirals and Delay Days [Onset to symptoms].

Abbreviations: AAT: anti-amoebic therapy; ATE: average treatment effect; ATT: average treatment effect for the treated; IQR: interquartile range; OW: Overlap Weights; PS: propensity scores matching; SD: standard deviation.

Figure 2. Analysis of ODAK study (polihexanide 0.8 mg/ml and placebo) vs. Papa et al. 2020 study (pooled AAT cohort): Distribution of propensity scores and derived weights



Footnote: The ATT analysis does not show the data on 'treated' arm, as its weight for each subject is equal to 1 per definition. Variables adjusted for: Age, Male sex, Disease Stage 3, Prior Corticosteroids, Prior antivirals and Delay Days [Onset to symptoms].

Abbreviations: AAT: anti-amoebic therapy; PS: propensity scores; OW: overlap weights; ATE: Average treatment effect; ATT: average treatment effect for the treated.

A29. Priority question: Please conduct both multivariate and bivariate logistic regression analyses for the primary binary outcome: whether a patient achieved medical cure. Specifically:

A. Fit one multivariate logistic regression model, including:

- A binary treatment indicator: polihexanide vs pooled AAT
- All six baseline prognostic variables used in the ITC.

B. Fit six bivariate logistic regression models, each including:

- The treatment indicator variable
- One of the six prognostic variables used in the ITC (one for each model)

C. For each model, please provide:

- A table and/or forest plot summarising the odds ratios, 95% confidence intervals and p-value for the treatment effect and each covariate
- The number of patients in each subgroup (where applicable)
- The number of medical cure events in each subgroup

The analyses requested for both multivariate and bivariate logistic regression analyses were conducted. The results of the multivariate analyses are provided in Table 25, and for the bivariate analyses considering the prognostic variables used in the ITC from Table 26 to Table 31.

It is important to note that with logistic regression methods, even when adjusting for covariates, the odds ratio (OR) tends to remain relatively stable. In contrast, when performing propensity score matching, the populations are more balanced, and a decrease in the OR is observed, though it remains strongly in favour of polihexanide 0.8 mg/ml. This suggests that matching may provide a more refined estimate of treatment effect, as it directly accounts for differences between groups. This is particularly relevant given that the polihexanide 0.8 mg/ml had fewer patients in Disease Stage 3 and less prior exposure to antivirals at baseline.

Table 25. Multivariable logistic regression analysis using treatment and all covariates as fixed effects

Outcome: MCR at 12 months		
N observations used in model		
ODAK polihexanide 0.8 mg/ml	66	
Papa et al. 2020 pooled AAT	205	
Logistic Regression Model Results		
Variable Label	Parameter Estimate (SE), p-value	Odds ratio [95% CI]
Model Intercept	1.579 (0.449), p=0.0004	
Treatment [ODAK polihexanide 0.8 mg/ml] vs. [Papa et al. 2020 pooled AAT]	2.007 (0.400), p<.0001	7.442 [3.396; 16.311]
Age (years)	-0.027 (0.011), p=0.0147	0.974 [0.953; 0.995]
Age (years)	-0.027 (0.011), p=0.0147	0.974 [0.953; 0.995]
Male sex	-0.093 (0.286), p=0.7435	0.911 [0.520; 1.594]
Disease Stage 3	-1.246 (0.349), p=0.0004	0.288 [0.145; 0.570]
Prior Corticosteroids	-0.371 (0.317), p=0.2418	0.690 [0.371; 1.284]

Prior antivirals	0.079 (0.330), p=0.8105	1.082 [0.567; 2.066]

Abbreviations: AAT: anti-amoebic therapy; CI: confidence interval; MCR: medical cure rate; SE: standard error.

Table 26. Bivariate logistic regression analysis using treatment and age (years) as fixed effects

Outcome: MCR at 12 months		
N observations used in model		
ODAK polihexanide 0.8 mg/ml	66	
Papa et al. 2020 pooled AAT	227	
Logistic Regression Model Results		
Variable Label	Parameter Estimate (SE), p-value	Odds ratio [95% CI]
Model Intercept	0.893 (0.365), p=0.0145	
Treatment [ODAK polihexanide 0.8 mg/ml] vs. [Papa et al. 2020 pooled AAT]	2.046 (0.377), p<.0001	7.737 [3.697; 16.192]
Age (years)	-0.033 (0.010), p=0.0008	0.968 [0.949; 0.987]
Outcome by subgroups		
Age (years) >=33 (overall median of analyzed set)	ODAK - polihexanide 0.8 mg/ml + placebo	Papa et al. 2020 - Pooled AAT full cohort
Overall	56/66 (84.8%)	99/227 (43.6%)
No	30/33 (90.9%)	62/118 (52.5%)
Yes	26/33 (78.8%)	37/109 (33.9%)

Abbreviations: AAT: anti-amoebic therapy; CI: confidence interval; SE: standard error.

Table 27. Bivariate logistic regression analysis using treatment and male sex as fixed effects

Outcome: MCR at 12 months		
N observations used in model		
ODAK polihexanide 0.8 mg/ml	66	
Papa et al. 2020 pooled AAT	227	
Logistic Regression Model Results		
Variable Label	Parameter Estimate (SE), p-value	Odds ratio [95% CI]
Model Intercept	-0.160 (0.173), p=0.3561	
Treatment [ODAK polihexanide 0.8 mg/ml] vs. [Papa et al. 2020 pooled AAT]	1.977 (0.369), p<.0001	7.223 [3.506; 14.881]
Male sex	-0.223 (0.252), p=0.3761	0.800 [0.488; 1.311]
Outcome by subgroups		
Male sex	ODAK – polihexanide 0.8 mg/ml + placebo	Papa et al. 2020 - Pooled AAT full cohort
Overall	56/66 (84.8%)	99/227 (43.6%)

No	34/39 (87.2%)	58/127 (45.7%)
Yes	22/27 (81.5%)	41/100 (41.0%)

Abbreviations: AAT: anti-amoebic therapy; CI: confidence interval; SE: standard error.

Table 28. Bivariate logistic regression analysis using treatment and disease Stage 3 as fixed effects

Outcome: MCR at 12 months		
N observations used in model		
ODAK polihexanide 0.8 mg/ml	66	
Papa et al. 2020 pooled AAT	205	
Logistic Regression Model Results		
Variable Label	Parameter Estimate (SE), p-value	Odds ratio [95% CI]
Model Intercept	0.074 (0.161), p=0.6470	
Treatment [ODAK polihexanide 0.8 mg/ml] vs. [Papa et al. 2020 pooled AAT]	1.982 (0.384), p<.0001	7.255 [3.416; 15.408]
Disease Stage 3	-1.399 (0.331), p<.0001	0.247 [0.129; 0.472]
Outcome by subgroups		
Disease Stage 3	ODAK – polihexanide 0.8 mg/ml + placebo	Papa et al. 2020 - Pooled AAT full cohort
Overall	56/66 (84.8%)	89/205 (43.4%)
No	49/55 (89.1%)	77/149 (51.7%)
Yes	7/11 (63.6%)	12/56 (21.4%)

Abbreviations: AAT: anti-amoebic therapy; CI: confidence interval; SE: standard error.

Table 29. Bivariate logistic regression analysis using treatment and prior corticosteroids as fixed effects

Outcome: MCR at 12 months		
N observations used in model		
ODAK polihexanide 0.8 mg/ml	66	
Papa et al. 2020 pooled AAT	227	
Logistic Regression Model Results		
Variable Label	Parameter Estimate (SE), p-value	Odds ratio [95% CI]
Model Intercept	0.029 (0.173), p=0.8661	
Treatment [ODAK polihexanide 0.8 mg/ml] vs. [Papa et al. 2020 pooled AAT]	2.041 (0.374), p<.0001	7.701 [3.703; 16.019]
Prior Corticosteroids	-0.660 (0.256), p=0.0099	0.517 [0.313; 0.853]
Outcome by subgroups		
Prior Corticosteroids	ODAK - polihexanide 0.8 mg/ml + placebo	Papa et al. 2020 - Pooled AAT full cohort
Overall	56/66 (84.8%)	99/227 (43.6%)

No	32/35 (91.4%)	63/126 (50.0%)
Yes	24/31 (77.4%)	36/101 (35.6%)

Abbreviations: AAT: anti-amoebic therapy; CI: confidence interval; SE: standard error.

Table 30. Bivariate logistic regression analysis using treatment and prior antivirals as fixed effects

Outcome: MCR at 12 months		
N observations used in model		
ODAK polihexanide 0.8 mg/ml	66	
Papa et al. 2020 pooled AAT	227	
Logistic Regression Model Results		
Variable Label	Parameter Estimate (SE), p-value	Odds ratio [95% CI]
Model Intercept	-0.003 (0.174), p=0.9863	
Treatment [ODAK polihexanide 0.8 mg/ml] vs. [Papa et al. 2020 pooled AAT]	1.897 (0.371), p<.0001	6.666 [3.220; 13.798]
Prior antivirals	-0.578 (0.256), p=0.0239	0.561 [0.340; 0.926]
Outcome by subgroups		
Prior antivirals	ODAK – polihexanide 0.8 mg/ml + placebo	Papa et al. 2020 - Pooled AAT full cohort
Overall	56/66 (84.8%)	99/227 (43.6%)
No	41/49 (83.7%)	64/125 (51.2%)
Yes	15/17 (88.2%)	35/102 (34.3%)

Abbreviations: AAT: anti-amoebic therapy; CI: confidence interval; SE: standard error.

Table 31. Bivariate logistic regression analysis using treatment and delay days [onset to symptoms] as fixed effects

Outcome: MCR at 12 months		
N observations used in model		
ODAK polihexanide 0.8 mg/ml	66	
Papa et al. 2020 pooled AAT	227	
Logistic Regression Model Results		
Variable Label	Parameter Estimate (SE), p-value	Odds ratio [95% CI]
Model Intercept	0.204 (0.187), p=0.2752	
Treatment [ODAK polihexanide 0.8 mg/ml] vs. [Papa et al. 2020 pooled AAT]	1.954 (0.377), p<.0001	7.059 [3.373; 14.773]
Delay Days [Onset to symptoms]	-0.011 (0.003), p=0.0009	0.989 [0.983; 0.995]
Outcome by subgroups		
Delay Days [Onset to symptoms] >=28 (overall median of analysed set)	ODAK – polihexanide 0.8 mg/ml + placebo	Papa et al. 2020 - Pooled AAT full cohort
Overall	56/66 (84.8%)	99/227 (43.6%)

No	38/43 (88.4%)	55/107 (51.4%)
Yes	18/23 (78.3%)	44/120 (36.7%)

Abbreviations: AAT: anti-amoebic therapy; CI: confidence interval; SE: standard error.

A30. Please can the company clarify whether sensitivity analyses were conducted for the ITC? For example, using alternative methods (IPTW, unweighted) or with alternative model specifications (complete case only, interactions, reweighting using different prognostic variables). If so, please present these results. If not, please mention why they were not conducted.

Initially, sensitivity analyses using alternative weighting methods or with alternative model specifications, were not conducted given the appropriateness of the ITC methodology selected (ITC with PSM method with OW to obtain comparative efficacy estimates). To provide clarification of the ITC methodology selected and additional analyses conducted, this question has been addressed in three separate points:

- Description of the ITC methodology selected and decision-making process
- Alternative methods tested to address potential uncertainty
- Alternative model specifications

Description of the ITC methodology selected and decision-making process

The decision to pursue an unanchored methodology was driven by the characteristics and limitations of the available data, which preclude the use of anchored ITC methods. The key requirement for an anchored ITC is the presence of a common comparator across studies of the treatments to be compared indirectly. In this case, such a common comparator is not available. Regulatory authorities (i.e. CHMP) have also acknowledged that the ODAK comparator arm does not reflect clinical practice, reinforcing the conclusion that the ODAK trial does not provide a suitable anchor.

In light of this, and in accordance with current methodological guidelines (Philippo et al. 2018), we conducted a feasibility assessment of all available studies identified via a SLR conducted in 2022 and updated in May 2025 (n=48 studies).⁷² Among the studies identified, Papa et al. 2020 was the only study with comparable definition of clinical resolution to the ODAK trial. IPD were available for both the ODAK trial and the Papa et al. 2020 study. This allowed the implementation of a population-adjusted comparison method, aligning populations by weighting patients in both studies based on the similarity of their covariates. Specifically, an ITC with PSM method with OW was conducted to obtain comparative efficacy estimates between polihexanide 0.8 mg/ml from ODAK trial (n=66) and pooled AAT from Papa et al. 2020 (n=227). The ITC estimated the adjusted relative risk (RR) of achieving a MCR within 12 months (MCR_12) from start of the AAT, between polihexanide 0.8 mg/ml and pooled AAT.

The PSM with OW used a weighted regression methods with adjustment for key effect modifiers and prognostic factors of AK (age, sex, stage 3 AK, prior use of corticosteroid, prior use of antivirals and treatment delay) to balance study populations before estimation of the treatment effect to ensure populations are comparable and control for selection biases when combining sources of non-randomised evidence. Propensity scores are used as weights to account for selection assignment differences between treatment groups (Desai et al. 2019).⁷³ This approach is well-established in the scientific literature and increasingly accepted by HTA bodies such as

NICE. It allows for the alignment of patient populations between studies by adjusting for confounding variables and balancing effect modifiers. Propensity score methods such as the overlap weighting technique offer a principled and statistically sound solution in cases where there are no common comparators. Compared to naïve comparisons or anchored methods without adjustments that rely on questionable assumptions about comparator equivalence, this method provides greater internal validity and more reliable estimates of treatment effect. Moreover, in the absence of a common comparator, the PSM also represents a higher level of robustness compared with population-adjustment methods that applies weights to only one of the two treatments compared, such as matching-adjusted indirect comparison (MAIC) (Philippo et al. 2018, Truong et al. 2023).^{72, 74}

The selection of this method followed a structured methodology selection process. Given the absence of a connected trial network, the lack of a valid common comparator, and the availability of IPD from both studies, unanchored PSM with overlap weighting was determined to be the most robust and appropriate method to conduct an indirect comparison between the intervention and the comparator of interest. This method tends to produce more stable estimates and better covariate balance compared with other propensity scores methodologies (i.e. inverse weighting ATE and inverse weighting ATT).

Alternative methods tested to address potential uncertainty

In order to address the risk of potential bias/uncertainty, we have tested the robustness of the findings testing other propensity scores methodologies, such as ATE and ATT. The results of these analyses were presented in the response to question A28.

Alternative model specifications to address potential uncertainty

The following analyses were conducted to address potential uncertainty. Overall, results indicate that despite the variability in terms of effect size in each of the sensitivity analysis (RR variable), the results were aligned demonstrating a statistically significant increased relative risk with narrow CIs, suggesting precision and statistical significance across all results (as presented from Table 32 to Table 37).

Table 32. Analysis of ODAK study [polihexanide 0.8 mg/ml + placebo] vs Papa 2020 study [pooled AAT full cohort] excl. disease stage

Propensity scores	Unadjusted analyses		Propensity scores adjusted analyses (OW)*		Propensity scores adjusted analyses (Inverse weighted - ATE)*		Propensity scores adjusted analyses (Inverse weighted - ATT)*	
Source	ODAK	Papa 2020	ODAK	Papa 2020	ODAK	Papa 2020	ODAK	Papa 2020
Age (years), Mean $\pm$ SD	35.2 $\pm$ 13.2	35.7 $\pm$ 13.8	34.80 $\pm$ 12.97	34.80 $\pm$ 13.27	34.17 $\pm$ 12.54	35.44 $\pm$ 13.64	35.23 $\pm$ 13.24	34.52 $\pm$ 13.08
Male sex	40.91% (27/66)	44.05% (100/227)	40.97% (27/66)	40.97% (93/227)	40.31% (27/66)	43.13% (98/227)	40.91% (27/66)	39.95% (91/227)
Disease Stage 3	16.67% (11/66)	27.32% (56/205)	16.82% (11/66)	25.87% (53/205)	16.85% (11/66)	26.95% (55/205)	16.67% (11/66)	25.67% (53/205)
Prior corticosteroids	46.97% (31/66)	44.49% (101/227)	45.91% (30/66)	45.91% (104/227)	46.04% (30/66)	45.14% (102/227)	46.97% (31/66)	47.39% (108/227)
Prior antivirals	25.76% (17/66)	44.93% (102/227)	29.70% (20/66)	29.70% (67/227)	41.76% (28/66)	40.70% (92/227)	25.76% (17/66)	26.09% (59/227)
Delay Days [onset to symptoms] Mean $\pm$ SD	33.5 $\pm$ 39.2	44.9 $\pm$ 48.4	35.67 $\pm$ 41.38	35.67 $\pm$ 36.06	43.71 $\pm$ 47.88	42.51 $\pm$ 45.77	33.55 $\pm$ 39.25	34.16 $\pm$ 34.06
Weighted analysis [ESS]	NA	NA	65.1	196.9	55.0	224.1	66.0	180.5
Weighted RR [95% CI] p-value	NA		1.829 [1.527; 2.191] <.0001		1.934 [1.616; 2.315] <.0001		1.802 [1.497; 2.169] <.0001	

Footnote: Variables adjusted for (*): Age, Male sex, Prior Corticosteroids, Prior antivirals and Delay Days [Onset to symptoms].

Abbreviations: AAT: anti-amoebic therapy; ATE: average treatment effect; ATT average treatment effect of treated; CI: confidence interval; ESS effective sample size; OW: overlap weights; SD: standard deviation.

Table 33. Analysis of ODAK study [polihexanide 0.8 mg/ml + placebo] vs Papa 2020 study [pooled AAT full cohort] – complete cases analysis

Propensity scores	Unadjusted analyses	Propensity scores adjusted analyses (OW)*	Propensity scores adjusted analyses (Inverse weighted - ATE)*	Propensity scores adjusted analyses (Inverse weighted - ATT)*

Source	ODAK	Papa 2020	ODAK	Papa 2020	ODAK	Papa 2020	ODAK	Papa 2020
Age (years), Mean ± SD	35.2±13.2	36.3±14.0	34.88±13.02	34.88±13.42	34.23±12.62	35.80±13.86	35.23±13.24	34.39±13.20
Male sex	40.91% (27/66)	42.93% (85/198)	40.26% (27/66)	40.26% (80/198)	40.41% (27/66)	41.95% (83/198)	40.91% (27/66)	39.02% (77/198)
Disease Stage 3	16.67% (11/66)	27.78% (55/198)	18.89% (12/66)	18.89% (37/198)	24.04% (16/66)	25.02% (50/198)	16.67% (11/66)	16.74% (33/198)
Prior Corticosteroids	46.97% (31/66)	44.95% (89/198)	45.26% (30/66)	45.26% (90/198)	44.32% (29/66)	45.36% (90/198)	46.97% (31/66)	46.60% (92/198)
Prior antivirals	25.76% (17/66)	45.45% (90/198)	30.06% (20/66)	30.06% (60/198)	40.47% (27/66)	40.57% (80/198)	25.76% (17/66)	25.91% (51/198)
Delay Days [Onset to symptoms] Mean ± SD	33.5±39.2	44.7±45.5 (198)	35.66±41.41	35.66±35.39	40.47±45.46	42.05±43.03	33.55±39.25	33.96±33.38
Weighted analysis [ESS]	NA	NA	64.7	168.9	54.4	194.2	66.0	151.2
Weighted RR [95% CI] p-value	NA		1.712 [1.423; 2.058] <.0001		1.837 [1.519; 2.222] <.0001		1.670 [1.385; 2.013] <.0001	

Footnote: Variables adjusted for (*): Age, Male sex, Prior Corticosteroids, Prior antivirals and Delay Days [Onset to symptoms].

Abbreviations: AAT: anti-amoebic therapy; ATE: average treatment effect; ATT average treatment effect of treated; CI: confidence interval; ESS effective sample size; OW: overlap weights; SD: standard deviation.

Table 34. Analysis of ODAK study [polihexanide 0.8 mg/ml + placebo] vs Papa 2020 study [pooled AAT full cohort] with zero-imputation for disease stage 3

Propensity scores	Unadjusted analyses		Propensity scores adjusted analyses (OW)*		Propensity scores adjusted analyses (Inverse weighted - ATE)*		Propensity scores adjusted analyses (Inverse weighted - ATT)*	
Source	ODAK	Papa 2020	ODAK	Papa 2020	ODAK	Papa 2020	ODAK	Papa 2020
Age (years), Mean ± SD	35.2±13.2	35.7±13.8	34.75±12.98	34.75±13.32	33.86±12.49	35.42±13.65	35.23±13.24	34.44±13.15

Male sex	40.91% (27/66)	44.05% (100/227)	40.79% (27/66)	40.79% (93/227)	41.30% (27/66)	43.04% (98/227)	40.91% (27/66)	39.55% (90/227)
Disease Stage 3	16.67% (11/66)	24.67% (56/227)	18.19% (12/66)	18.19% (41/227)	22.31% (15/66)	22.88% (52/227)	16.67% (11/66)	16.71% (38/227)
Prior corticosteroids	46.97% (31/66)	44.49% (101/227)	45.51% (30/66)	45.51% (103/227)	44.67% (29/66)	45.04% (102/227)	46.97% (31/66)	46.91% (106/227)
Prior antivirals	25.76% (17/66)	44.93% (102/227)	29.68% (20/66)	29.68% (67/227)	41.36% (27/66)	40.69% (92/227)	25.76% (17/66)	26.06% (59/227)
Delay days [onset to symptoms] Mean ± SD	33.5±39.2	44.9±48.4 (227)	35.52±41.26	35.52±36.19	41.45±46.27	42.48±45.81	33.55±39.25	33.99±34.19
Weighted analysis [ESS]	NA	NA	65.0	194.5	54.1	223.8	66.0	176.7
Weighted RR [95% CI] p-value	NA		1.769 [1.479; 2.116] <.0001		1.899 [1.582; 2.279] <.0001		1.734 [1.445; 2.080] <.0001	

Footnote: Variables adjusted for (*): Age, Male sex, Prior Corticosteroids, Prior antivirals and Delay Days [Onset to symptoms].

Abbreviations: AAT: anti-amoebic therapy; ATE: average treatment effect; ATT average treatment effect of treated; CI: confidence interval; ESS effective sample size; OW: overlap weights; SD: standard deviation.

Table 35. Analysis of ODAK study [polihexanide 0.8 mg/ml + placebo] vs Papa 2020 study [pooled AAT full cohort] – Sensitivity excl. Delay

Propensity scores	Unadjusted analyses		Propensity scores adjusted analyses (OW)*		Propensity scores adjusted analyses (Inverse weighted - ATE)*		Propensity scores adjusted analyses (Inverse weighted - ATT)*	
	ODAK	Papa 2020	ODAK	Papa 2020	ODAK	Papa 2020	ODAK	Papa 2020
Age (years), Mean ± SD	35.2±13.2	35.7±13.8	34.88±13.06	34.88±14.11	33.98±12.69	35.82±14.56	35.23±13.24	34.39±13.89
Male sex	40.91% (27/66)	44.05% (100/227)	40.55% (27/66)	40.55% (92/227)	41.88% (28/66)	42.71% (97/227)	40.91% (27/66)	39.01% (89/227)
Disease Stage 3	16.67% (11/66)	24.67% (56/227)	18.89% (12/66)	18.89% (43/227)	25.87% (17/66)	24.76% (56/227)	16.67% (11/66)	16.80% (38/227)

Prior corticosteroids	46.97% (31/66)	44.49% (101/227)	44.87% (30/66)	44.87% (102/227)	42.61% (28/66)	45.19% (103/227)	46.97% (31/66)	46.16% (105/227)
Prior antivirals	25.76% (17/66)	44.93% (102/227)	29.72% (20/66)	29.72% (67/227)	40.28% (27/66)	40.55% (92/227)	25.76% (17/66)	25.59% (58/227)
Delay days [onset to symptoms] Mean ± SD	33.5±39.2	44.9±48.4 (227)	34.28±40.00	39.74±42.65	35.19±40.13	42.91±45.85	33.55±39.25	38.80±41.38
Weighted analysis [ESS]	NA	NA	64.9	176.0	52.8	201.4	66.0	157.7
Weighted RR [95% CI] p- value	NA		1.788 [1.485; 2.153] <.0001		1.908 [1.580; 2.304] <.0001		1.737 [1.437; 2.100] <.0001	

Footnote: Variables adjusted for (*): Age, Male sex, Prior Corticosteroids, Prior antivirals and Delay Days [Onset to symptoms].

Abbreviations: AAT: anti-amoebic therapy; ATE: average treatment effect; ATT average treatment effect of treated; CI: confidence interval; ESS effective sample size; OW: overlap weights; SD: standard deviation.

Table 36. Analysis of ODAK study [polihexanide 0.8 mg/ml + placebo] vs Papa 2020 study [pooled AAT full cohort] excl. disease stage – Sensitivity excl. Delay

Propensity scores	Unadjusted analyses		Propensity scores adjusted analyses (OW)*		Propensity scores adjusted analyses (Inverse weighted - ATE)*		Propensity scores adjusted analyses (Inverse weighted - ATT)*	
	ODAK	Papa 2020	ODAK	Papa 2020	ODAK	Papa 2020	ODAK	Papa 2020
Age (years), Mean ± SD	35.2±13.2	35.7±13.8	34.81±13.01	34.81±13.30	34.02±12.65	35.44±13.65	35.23±13.24	34.54±13.13
Male sex	40.91% (27/66)	44.05% (100/227)	41.02% (27/66)	41.02% (93/227)	41.01% (27/66)	43.15% (98/227)	40.91% (27/66)	40.05% (91/227)
Disease Stage 3	16.67% (11/66)	24.67% (56/227)	16.87% (11/66)	26.60% (54/205)	18.04% (12/66)	27.13% (56/205)	16.67% (11/66)	26.47% (54/204)
Prior corticosteroids	46.97% (31/66)	44.49% (101/227)	45.59% (30/66)	45.59% (104/227)	44.66% (29/66)	45.03% (102/227)	46.97% (31/66)	46.90% (106/227)

Prior antivirals	25.76% (17/66)	44.93% (102/227)	29.46% (19/66)	29.46% (67/227)	40.87% (27/66)	40.63% (92/227)	25.76% (17/66)	25.81% (59/227)
Delay days [onset to symptoms] Mean ± SD	33.5±39.2	44.9±48.4 (227)	34.41±40.10	41.42±44.47	37.13±41.55	43.95±47.30	33.55±39.25	40.57±43.21
Weighted analysis [ESS]	NA	NA	65.2	199.9	56.5	224.4	66.0	184.7
Weighted RR [95% CI] p- value	NA		1.877 [1.567; 2.249] <.0001		1.967 [1.651; 2.343] <.0001		1.844 [1.529; 2.222] <.0001	

Footnote: Variables adjusted for (*): Age, Male sex, Prior Corticosteroids, Prior antivirals and Delay Days [Onset to symptoms].

Abbreviations: AAT: anti-amoebic therapy; ATE: average treatment effect; ATT average treatment effect of treated; CI: confidence interval; ESS effective sample size; OW: overlap weights; SD: standard deviation.

Table 37. Analysis of ODAK study [polihexanide 0.8 mg/ml + placebo] vs Papa 2020 study [pooled AAT full cohort] – complete cases analysis – Sensitivity excl. Delay

Propensity scores	Unadjusted analyses		Propensity scores adjusted analyses (OW)*		Propensity scores adjusted analyses (Inverse weighted - ATE)*		Propensity scores adjusted analyses (Inverse weighted - ATT)*	
	ODAK	Papa 2020	ODAK	Papa 2020	ODAK	Papa 2020	ODAK	Papa 2020
Source	ODAK	Papa 2020	ODAK	Papa 2020	ODAK	Papa 2020	ODAK	Papa 2020
Age (years), Mean ± SD	35.2±13.2 (66)	36.3±14.0 (198)	34.89±13.06	34.89±13.44	34.05±12.70	35.81±13.87	35.23±13.24	34.40±13.22
Male sex	40.91% (27/66)	42.93% (85/198)	40.26% (27/66)	40.26% (80/198)	41.10% (27/66)	41.94% (83/198)	40.91% (27/66)	38.97% (77/198)
Disease Stage 3	16.67% (11/66)	27.78% (55/198)	19.02% (13/66)	19.02% (38/198)	25.91% (17/66)	25.04% (50/198)	16.67% (11/66)	16.82% (33/198)
Prior Corticosteroids	46.97% (31/66)	44.95% (89/198)	44.90% (30/66)	44.90% (89/198)	42.83% (28/66)	45.25% (90/198)	46.97% (31/66)	46.14% (91/198)
Prior antivirals	25.76% (17/66)	45.45% (90/198)	29.79% (20/66)	29.79% (59/198)	39.94% (26/66)	40.49% (80/198)	25.76% (17/66)	25.57% (51/198)

Delay days [onset to symptoms] Mean ± SD	33.5±39.2 (66)	44.7±45.5 (198)	34.31±40.01	40.10±41.27	35.22±40.13	43.32±44.24	33.55±39.25	39.08±40.02
Weighted analysis [ESS]	NA	NA	64.8	170.6	53.4	194.5	66.0	153.3
Weighted RR [95% CI] p- value	NA		1.748 [1.453; 2.103] <.0001		1.862 [1.543; 2.247] <.0001		1.700 [1.408; 2.053] <.0001	

Footnote: Variables adjusted for (*): Age, Male sex, Prior Corticosteroids, Prior antivirals and Delay Days [Onset to symptoms].

Abbreviations: AAT: anti-amoebic therapy; ATE: average treatment effect; ATT average treatment effect of treated; CI: confidence interval; ESS effective sample size; OW: overlap weights; SD: standard deviation.

- A31. Please can the company clarify whether any interactions between the six prognostic variables tested or explored in the propensity score model? If so,
- Please specify which interaction terms and how they were chosen (pre-specified vs data-driven).
 - Provide the estimated interaction effects, 95% CIs, and p-values
 - Describe how any statistically or clinically significant interactions were handled in the analysis.
 - If interactions were not tested, please confirm whether this was due to clinical rationale, statistical power, model complexity constraints, or any other reason.

Since the propensity score adjusted analysis with OW methodology provided a good match, additional analyses to assess interaction effect were not conducted. This decision was supported by the fact that including covariate subgroup interactions in the propensity score model until subgroup balance is achieved is a theoretical approach that has not been implemented in practice, given that it is cumbersome to manually check interactions and it may amplify the classic bias-variance trade-off.⁷⁵

A32. Priority question: The company mentioned that patients with missing treatment delay data were imputed with the median value, missing age data imputed with the mean value.

- Please justify why these values were imputed (for example mean age instead of median age).
- Were other imputation methods utilised (such as multiply imputation)?
- Furthermore, why was imputation used for only two of the six covariates that were selected in the ITC?

For the “Delay Days” variable, missing data was minimal. For those few cases, an imputation of the expected value (30 days) was applied as a reasonable assumption based on available data.

In contrast, the “Disease Stage” variable had a higher proportion of missing values. To address this, the main analysis using complete cases only (N=205) were run (please refer to our response to question A30, Table 37), where the propensity score weights were calculated. Following this, we reweighted the results to N=227 for the descriptive and outcome analyses to reflect the full study population. Importantly, the analytical precision was retained by calculating outcomes using GENMOD with the weights, grounded in the N=205 sample.

This approach (complete case analysis for Disease Stage coupled with a modest imputation for Delay Days) strikes a balance between methodological rigor and data completeness. We also ran sensitivity analyses to test the robustness of this strategy (please refer to our response to question A30 for the results tables):

- Sensitivity analysis excluded Delay Days from the matching algorithm to assess the impact (Table 35).

- Sensitivity analysis removed Disease Stage from the matching step, allowing full use of the N=227 sample (Table 32).
- Sensitivity analysis included only complete cases (Table 33).
- Sensitivity analysis applied a “zero-imputation” approach for Disease Stage 3, enabling inclusion of all 227 subjects (Table 34).

This suite of analyses helps ensure transparency and confidence in the conclusions, even in the presence of minor data limitations.

Section B: Clarification on cost-effectiveness data

Literature searching (cost-effectiveness)

B1. Re. CS Appendices E.1.1 Bibliography searches, please clarify: a) whether ‘eligible articles’ in citation chasing is referring to all the included studies in the original 2022 cost-effectiveness SLR and if not, please provide a list of the studies used; b) which studies the backward and forward searching was conducted on in the 2025 cost-effectiveness update.

a) The same methodology for citation chasing was conducted for the clinical and economic SLRs (original and updates). See the company’s responses to question A3 for details; to summarise, citation chasing was conducted for:

- Bibliographies of SLRs identified during the screening phase (13 studies in total – please see question A1)
- Eligible full-text articles following the screening process (32 studies in total from the original SLR and update economic SLR)

Therefore, all the eligible studies in the original/update economic SLR were considered for citation chasing, as well as the reference lists of relevant SLRs.

Any potentially relevant articles identified through citation chasing underwent the same eligibility assessment i.e. a title and abstract review followed by a full-text review, conducted independently by two reviewers. In addition, references found in published SLRs of AK were subjected to both backward and forward citation searching. This iterative cycle continued until no new eligible articles were found.

In 2022, citation chasing was manually conducted by a single reviewer, including hand-searching the reference lists of eligible articles and identified SLRs, along with forward citation searching via Google Scholar. For the 2025 update, both backward and forward citation searches were performed using the Citation Chaser Shiny app. All identified abstracts were uploaded to Covidence and screened independently by two reviewers, ensuring consistency and traceability.

b) Table 38 summarises the studies (n=18) that were used for backward forward citation chasing in the 2025 economic SLR update.

Table 38: Records used for citation chasing in the 2025 economic SLR update

1	AlMahmoud T, Elhanan M, Elshamsy MH, Alshamsi HN, Abu-Zidan FM. Management of infective corneal ulcers in a high-income developing country. <i>Medicine (Baltimore)</i> . 2019;98(51):e18243.
2	Arunga S, Wiafe G, Habtamu E, Onyango J, Gichuhi S, Leck A, et al. The impact of microbial keratitis on quality of life in Uganda. <i>BMJ Open Ophthalmol</i> . 2019;4(1):e000351.
3	Daley JR, Lee MK, Wang X, Ly M, Samarawickrama C. Epidemiology and Economic Cost Analysis of Microbial Keratitis from a Tertiary Referral Hospital in Australia. <i>Pathogens</i> . 2023;12(3)
4	Gangopadhyay N, Daniell M, Weih L, Taylor HR. Fluoroquinolone and fortified antibiotics for treating bacterial corneal ulcers. <i>Br J Ophthalmol</i> . 2000;84(4):378-84.
5	Harbiyeli İ, Çelebi D, Erdem E, Kibar F, Yağmur M. Etiological and Clinical Features of Contact Lens-Associated Microbial Keratitis. <i>Turk J Ophthalmol</i> . 2022;52(5):309-17.
6	Keay L, Edwards K, Naduvilath T, Forde K, Stapleton F. Factors affecting the morbidity of contact lens-related microbial keratitis: a population study. <i>Invest Ophthalmol Vis Sci</i> . 2006;47(10):4302-8.
7	Knyazer B, Krakauer Y, Tailakh MA, Achiron A, Hecht I, Lifshitz T, et al. Accelerated Corneal Cross-linking as an Adjunct Therapy in the Management of Presumed Bacterial Keratitis: A Cohort Study. <i>J Refract Surg</i> . 2020;36(4):258-64.
8	Koh YY, Sun CC, Hsiao CH. Epidemiology and the Estimated Burden of Microbial Keratitis on the Health Care System in Taiwan: A 14-Year Population-Based Study. <i>Am J Ophthalmol</i> . 2020;220:152-9.
9	Lim Wen Siang J, Wu Zhuan O, Yi Chen N, Sok Lin N. Profile of Microbial Keratitis. <i>Cureus</i> . 2021;13(12):e20663.
10	Lin TY, Yeh LK, Ma DH, Chen PY, Lin HC, Sun CC, et al. Risk Factors and Microbiological Features of Patients Hospitalized for Microbial Keratitis: A 10-Year Study in a Referral Center in Taiwan. <i>Medicine (Baltimore)</i> . 2015;94(43):e1905.
11	Marasini S, Wang MT, Swift S, Dean SJ, Ormonde SE, Gamble GD, et al. Clinical and microbiological profile of <i>Pseudomonas aeruginosa</i> keratitis admitted to a New Zealand tertiary centre. <i>Clin Exp Ophthalmol</i> . 2018;46(4):441-4.
12	Obrubov AS, Slonimskii AY. [Contact lens-related keratitis and purulent corneal ulcers]. <i>Vestn Oftalmol</i> . 2018;134(4):17-24.
13	Prajna VN, Nirmalan PK, Saravanan S, Srinivasan M. Economic analysis of corneal ulcers in South India. <i>Cornea</i> . 2007;26(2):119-22.

14	Prajna NV, Radhakrishnan N, Lalitha P, Rajaraman R, Abdelrahman S, Arnold B, et al. Vision-Related Quality of Life Outcomes in Patients Treated for Filamentous Fungal Keratitis in the CLAIR Trial. <i>Journal of EuCornea</i> . 2023;12(2).
15	Przybek-Skrzypecka J, Ryk-Adamska M, Szewczuk A, Skrzypecki J, Izdebska J, Udziela M, et al. Severe Microbial Keratitis in Virgin and Transplanted Cornea- Probability of Visual Acuity Improvement. <i>J Clin Med</i> . 2024;14(1).
16	Ting DSJ, Galal M, Kulkarni B, Elalfy MS, Lake D, Hamada S, et al. Clinical Characteristics and Outcomes of Fungal Keratitis in the United Kingdom 2011-2020: A 10-Year Study. <i>J Fungi (Basel)</i> . 2021;7(11).
17	Tutaş Günaydın, Nesrin & KANDEMİR, Baran & Doğan Gökçe, Gizem & ÖZEN, Mehmet & Dönmez Gün, Raziye & HACISEYİTOĞLU, Demet. (2022). Comparison of culture-positive and culture-negative severe infectious keratitis leading to hospitalization: a tertiary referral center experience. <i>Journal of Health Sciences and Medicine</i> . 5. 1612-1618. 10.32322/jhsm.1176813.
18	Wong T, Ormonde S, Gamble G, McGhee CN. Severe infective keratitis leading to hospital admission in New Zealand. <i>Br J Ophthalmol</i> . 2003;87(9):1103-8.

B2. The cost-effectiveness SLR search strategy includes the source 'University of York Centre for Reviews and Dissemination Database'. Please clarify which specific CRD database was searched?

The University of York Centre for Reviews and Dissemination Database search covered the three key databases that support evidence-based healthcare decision-making, including the database of abstracts of reviews of effects (DARE), the NHS economic evaluation database (NHS EED) and the health technology assessment database (HTA). The link to access this database is the following: <https://www.crd.york.ac.uk/crdweb>.

Model Structure

B3. Company submission (CS), Figure 5. Please can the company clarify whether the structure presented represents one of the strategies being compared. If so, are the illustrative structures identical in both strategies?

The model structure presented in CS Figure 5 represents both strategies being compared. Within the decision tree structure (model for the first 12 months after initial AK treatment), all patients starting in the AK infection node are assigned to receive treatment with either polihexanide 0.8 mg/ml or the pooled AAT comparator. The cohort with AK infection in each treatment arm can follow different pathways. Even though the structure represents both strategies being compared, the probability of transitioning through the decision tree changes depending on whether patients are receiving polihexanide 0.8 mg/ml or the pooled AAT comparator, based on the associated MCR at 12 months. A summary of the proportion of patients by treatment arm who move through each of the pathways of the decision tree is provided in Table 39 below.

Table 39: Summary of transition probabilities for decision tree model (first 12 months following AK treatment initiation)

Pathways after AK treatment initiation	Proportion of the cohort transitioning by treatment arm	
	Polihexanide 0.8 mg/ml	Pooled AAT
MCR_12 m	84.85%	48.37%
Source of the estimate	Dart et al, 2024	Calculation: (MCR_12 m polihexanide 0.8 mg/ml / RR for MCR_12 m ITC ODAK vs Papa et al, 2020)
Switch to another AAT regime (treatment switch)	3.55%	12.08%
Source of the estimate	Calculation based on the proportion of patients switching therapy within 12 months advanced from the UK Delphi panel: ((1-MCR_12 m)* proportion of patients switching therapy within 12 months)	
Therapeutic surgery (within 12 months)	2.50%	8.50%
Source of the estimate	Calculation based on the proportion of patients who underwent therapeutic surgery advanced from the UK Delphi panel: (1-m_MCR_12m - % of patients switching therapy within 12 months)* Proportion of patients who underwent therapeutic surgery)	
Remaining patients without treatment switch, nor therapeutic surgery and not medically cured at 12 months	9.11%	31.04%
Source of the estimate	Calculation: remaining proportion of patients when excluding the previous three pathways: (1-(sum of % MCR_12m , % of patients switching therapy within 12 months and % of patients who underwent therapeutic surgery))	

A description of the pathways after AK treatment initiation is provided:

1. For the cohort who achieved a medical resolution of AK infection within 12 months on initial AAT (MCR_12 m), a proportion of patients will transition to a corresponding visual category after AK resolution of the infection (i.e. good vision, poor vision, or severe vision loss) defined based on best-corrected visual acuity (BCVA) threshold.
2. A proportion of the cohort who do not achieve a medical cure with initial treatment may switch AAT. Under treatment with the new AAT, patients can then either:
 - a. Achieve a medical cure of AK infection after switching AAT within 12 months
 - b. Undergo therapeutic surgery after not achieving medical cure with the switched regime. For patients who switched AAT within the first year, if the duration of initial treatment plus the duration of treatment with alternative AAT plus the waiting time for the therapeutic surgery is less than one year, the cohort will undergo therapeutic surgery within the first year, modelled as part of the decision tree. If not, patients enter the sub health state for 'waiting for therapeutic surgery' in the semi-Markov model.

- c. Remaining patients are classified as “Not cured”, which includes the proportion of patients after treatment switch that are not medically cured nor undergoing to therapeutic surgery. This resulting cohort is assumed to be awaiting therapeutic surgery after Year 1.
 3. In addition, a proportion of patients who are unresponsive to medical treatment will undergo therapeutic surgery (without switching AAT). Similarly, if the duration of initial therapy plus the waiting time for the therapeutic surgery is less than one year, then the cohort is assumed to undergo therapeutic surgery within the first year and the proportion of the cohort in each of the BCVA levels and who experience loss of eye functionality after surgery are estimated using the decision tree
 4. A proportion of the cohort are assumed not to achieve a resolution of the AK infection during the first year, with no change in AAT nor therapeutic surgery prescribed during this time; this cohort are assumed to be awaiting therapeutic surgery
- B4. CS, Figure 5. Please can the company explain what is the difference between people waiting for therapeutic surgery immediately emanating from the change to an alternative AAT compared to people not cured, then waiting for therapeutic surgery?

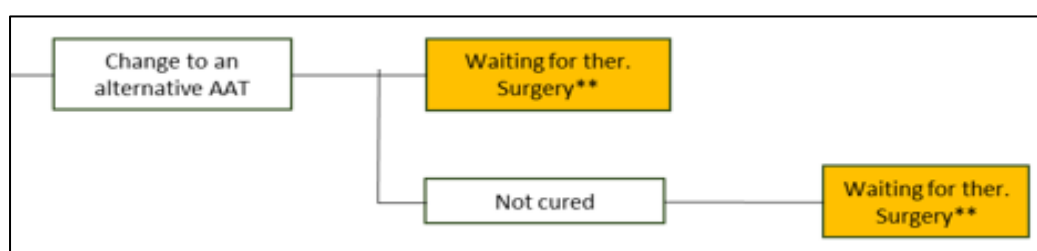


Figure 1: Section of the pathway emanating from the change to an alternative AAT

A proportion of the cohort who do not achieve a medical cure with initial treatment may switch AAT. This proportion was sourced from the UK Delphi panel, which determined that of the cohort of patients who do not achieve medical resolution of AK infection within 12 months on initial AAT, 23.40% will switch to an alternative AAT.²² As mentioned in the company’s response to question B3, the overall proportion of patients switching therapy by treatment arm differs considering the proportion of patients achieving medical cure with the initial treatment (84.85% for polihexanide 0.8 mg/ml and 48.37% for the pooled AAT comparator). The proportion of patients that switch treatment by treatment arm is 3.55% and 12.08% for polihexanide 0.8 mg/ml and pooled AAT, respectively.

As shown in the figure provided with the EAG’s question, after treatment switch, patients can then either:

- a) Achieve a medical cure of AK infection after switching AAT within 12 months
- b) Undergo therapeutic surgery after not achieving medical cure with the switched regime. The model assumes there is waiting time for performing therapeutic surgeries, based on the feedback provided by the Delphi panel. The calculation of this proportion is based on the following formula:

(1-proportion of the cohort medically cured after treatment switch) proportion of patients who underwent therapeutic surgery*

This refers to the first box named “Waiting for therapeutic surgery” in the figure.

- c) Remaining patients are classified as “Not cured”, which includes the proportion of patients after treatment switch that are not medically cured and did not undergo to therapeutic surgery. The calculation of this proportion is based on the following formula:

1- proportion of the cohort medically cured after treatment switch - proportion of patients who underwent therapeutic surgery

In the model, all patients who are not cure at the end of year 1 will undergo therapeutic surgery. Therefore, the resulting cohort is assumed to be awaiting therapeutic surgery, captured in the semi-Markov subsection of the model. This refers to the second box “Waiting for therapeutic surgery” in the figure.

It is important to highlight that the model assumes there is a waiting time for undergoing therapeutic surgery, based on the feedback provided by the UK Delphi panel. Therefore, for patients who switched AAT within the first year, if the duration of initial treatment plus the duration of treatment with alternative AAT plus the waiting time for the therapeutic surgery is less than one year, the cohort may undergo to therapeutic surgery within the first year, modelled as part of the decision tree. If the duration is over one year, patients enter the sub health state for ‘waiting for therapeutic surgery’ in the semi-Markov model.

In question B5 below, the model diagram showing the section of the pathway emanating from the change to an alternative AAT has been modified to make a clear differentiation between people waiting for therapeutic surgery immediately emanating from the change to an alternative AAT compared to people not cured, then waiting for therapeutic surgery.

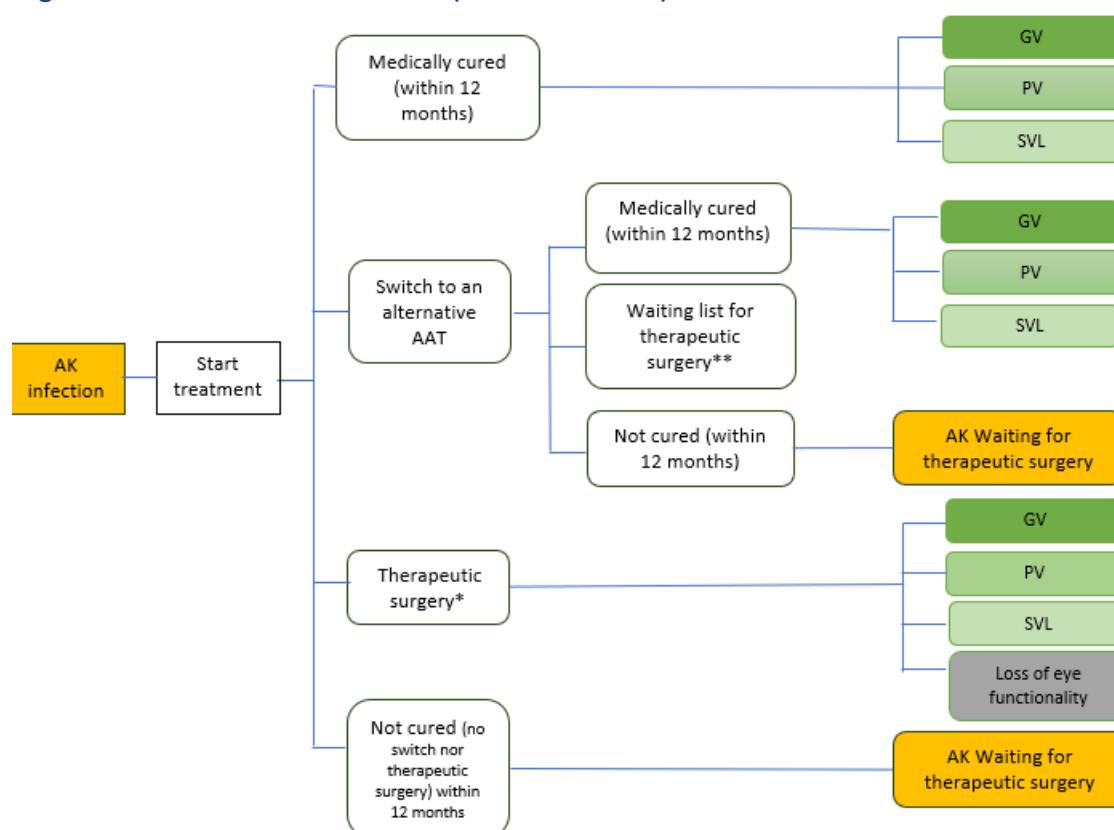
B5. There appears to be discrepancy between the health state ‘waiting list for therapeutic surgery*’ in the illustrative structure in the ‘Introduction’ worksheet compared to CS Figure 5, which states ‘Waiting for thera. Surgery **.’ For clarity, please can the company suggest which is correct, given that that footnotes suggest:

*“*Depending on the waiting time and treatment duration of initial treatment, patients may undergo therapeutic surgery within the first year (captured in the decision tree subsection of the model), or between Year 1 and Year 2 (captured in the semi-Markov subsection of the model).*

***Depending on the waiting time, treatment duration of initial treatment and alternative AAT, patients may undergo therapeutic surgery within the first year (captured in the decision tree subsection of the model), or between Year 1 and Year 2 (captured in the semi-Markov subsection of the model).’*

To clarify the footnotes included in the decision tree structure of the model, please find an updated diagram in Figure 3 below.

Figure 3: Decision tree structure (first 12 months)



* Depending on the waiting time and treatment duration of initial treatment, patients may undergo therapeutic surgery within the first year (captured in the decision tree subsection of the model) or between Year 1 and Year 2 (captured in the semi-Markov subsection of the model)

** Depending on the waiting time, treatment duration of initial treatment and alternative AAT, patients may undergo therapeutic surgery within the first year (captured in the decision tree subsection of the model), or between Year 1 and Year 2 (captured in the semi-Markov subsection of the model).

Intervention and comparators

B6. CS, Table 30 reports the distribution along with 90% confidence intervals (CIs) of the current therapeutic approaches for treating people with AK in the UK, which were based on a UK Delphi panel. Additionally, in Table 31, the company reported current therapeutic approaches based on information obtained from the Papa et al study.

A. Please can the company clarify whether these are 90%CI?

B. Please can the company provide the 95% CIs around the proportions obtained from the Papa et al. 2020 study?

The confidence intervals reported in Table 30 of the Company Submission are 90% CI values, as reported in the UK Delphi panel report for the distribution of the current therapeutic approaches for treating patients with AK in the UK.²²

The 95% CIs cannot be provided for the proportions derived from the Papa et al. (2020) study, as this study only reports the number and percentage of patients receiving each therapeutic approach, without providing distributional data. In contrast, the UK Delphi panel data included a distribution of clinician responses, which enabled the calculation and presentation of a mean proportion along with a corresponding 90% CI.

The table provided by the EAG in their clarification questions has been revised accordingly (Table 40): the heading for the Papa et al. (2020) study has been updated to 'Proportion (%)' consistent with its presentation in Table 31 of the Company Submission.

Table 40: AAT distribution obtained from the Delphi panel and Papa et al.

AAT distribution	Delphi panel	Papa et al., 2020
	Mean (90% CI)	Proportion (%)
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

Abbreviations: AAT: anti-amoebic therapy; CI: confidence interval.

Clinical inputs beyond 12 months

B7. Please can the company provide a scenario analysis results where the probability of recurrence of AK infection for the pooled AAT is set to zero.

The requested scenario is provided in Table 41 below. Setting the probability of recurrence of AK infection to 0% for the comparator arm leads to an [REDACTED] in the ICER, however based on available evidence, this scenario is not clinically plausible.

It is important to highlight that recurrence of AK infection following medical or surgical cure is a well-documented feature of the disease, observed in real-world clinical practice.^{76, 77} As such, incorporating the probability of recurrence for the pooled AAT comparator reflects observed clinical patterns, as supported by insights from the SIFI-led Delphi panel (incorporated in the model base case as best reflection of the current real world clinical practice in England).²²

Additionally, literature on recurrence rates after therapeutic surgery supports similar recurrence rates as those estimated in the UK Delphi panel. For instance, in patients achieving infection resolution following therapeutic keratoplasty, Bagga et al. (2020) documented a recurrence rate of 13.04% within a median time of 3 years, further underscoring the relevance of including recurrence risk in the comparator arm.⁷⁸

In the base case, for the cohort receiving pooled AAT who achieved medical cure, a probability of recurrence is applied. Recurrence of AK infection is not applied for the polihexanide 0.8 mg/ml arm as this reflects observations in the ODAK trial, where no recurrence of AK infection after medical cure was observed.⁵

Table 41: Results of additional scenario analysis for recurrence rate

Scenario	Incremental costs, £	Incremental QALYs	ICER (£/QALY)	Absolute % Change in ICER	INHB at £20k	INHB at £30k
*Updated base case		2.56		NA		
Probability of recurrence of AK infection for the pooled AAT set to zero		2.06				

Footnote: *Updated base case includes the updates requested in question B16.

Resource use and costs

B8. Priority question: The company stated that the proportion of patients requiring hospitalisation and number of hospitalisation days were elicited from the Delphi panel rather than information presented in Robaei et al., 2014, ‘a study reporting hospitalisation data...’ Please can the company provide this information, which could have been obtained from the Robaei et al., 2014 study.

The study by Robaei et al. 2014 provides data on the number of hospital visits among AK patients treated with AATs (biguanide plus diamidine), with or without the use of topical corticosteroids.⁷⁹ Notably, patients who had received corticosteroids prior to their AK diagnosis had significantly more clinic visits compared to those without prior steroid use (median of 20 visits versus 8, respectively [$P < 0.001$]).

However, the publication does not include information on the proportion of patients requiring hospitalisation or the duration of hospital stays. As such, the estimates provided by the UK Delphi panel are considered the most suitable proxy for informing hospitalisation rates and the average length of stay within the UK context.

One additional source has been identified in the literature that provides information on the hospitalisation requirement during the AK active infection phase, focused on the Italian setting. The study by Messina et al. 2024, reported that 50% of AK patients in an Italian sample required hospitalisation during the intensive treatment period when treated with current AATs.³³ Table 42

below presents the results of a scenario analysis, using hospitalisation rates for the comparator arm sourced from Messina et al. 2024; the alternative scenario had minimal impact on the ICER.

Table 42: Results of additional scenario analysis for hospitalisation rate

Scenario	Incremental costs, £	Incremental QALYs	ICER (£/QALY)	Absolute % Change in ICER	INHB at £20k	INHB at £30k
*Updated base case	■	2.56	■	NA	■	■
Proportion of patients on pooled AAT arm requiring hospitalisation during intensive treatment phase from Messina et al. 2024 ³³	■	2.56	■	■	■	■

Abbreviations: AAT: anti-amoebic therapy; ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; NA: NA; QALY: quality-adjusted life years.

B9. Hospitalisation costs were not apportioned to the polyhexanide 0.8mg/ml arm.

Please can the company provide clarification/justification for this assumption?

The response to question B9 is captured within the response to question B10 below.

B10. Please can the company outline the cause(s) of people requiring hospitalisation in people treated with pooled AAT?

Please find the Company's combined response to questions B9 and B10 below.

Treatment with the therapeutic approaches included in the 'pooled AAT' comparator involves a significant administration burden, as patients are required to administer drops at regular intervals throughout the day and night. During the initial treatment phase, patients are often required to administer drops every 20–30 minutes during the nighttime.⁸⁰ As a result, patients treated with these therapeutic approaches are often hospitalised during the initial treatment period to ensure they receive support with the demanding overnight treatment regimen, with the Royal College of Ophthalmologists guidelines acknowledging that hospital admission is common under current clinical management.^{26, 80} Specifically, an Italian study by Messina et al. reported that 50% of patients required hospitalisation during the intensive treatment period when treated with current AATs.³³ Additionally, current therapeutic approaches can involve dual or triple combination regimens which increase the complexity of administration, with patients having to manage different drops, each with its own specific dosage and timing. Adherence to the prescribed treatment schedule is essential for effectively managing AK, as delays in effective treatment are associated with poorer outcomes for patients.²⁰ According to patient testimonies, it can be challenging to adhere to these regimens precisely and hospital supervision can help ensure patients receive the correct treatment schedule, thereby improving treatment adherence and contributing to improved prognosis and HRQoL.⁸⁰

However, polyhexanide 0.8 mg/ml is associated with a less burdensome dosing regimen. It requires the administration of eyedrops every hour in the daytime only, for the initial 5-day treatment period, with no overnight administration necessary.⁸¹ Additionally, as a monotherapy, it

offers a simplified administration schedule. It was therefore assumed that patients can self-administer polihexanide 0.8 mg/ml at home, without the need for hospitalisation to manage a burdensome overnight treatment regimen. As such, no hospitalisations or associated costs were applied to polihexanide 0.8 mg/ml treatment within the CEM.

Health-related quality of life

B11. Please report CS Table 7 (trial populations) with numbers per study arm.

Please explain how EQ-5D is reported for n=65 participants in the intervention arm, which does not appear to align with the analysis sets in Table 7.

The populations analysed in the ODAK trial, including the number of patients per study arm, are presented in Table 43. As presented below, there were n=66 patients in the polihexanide 0.8 mg/ml treatment arm in the FAS. EQ-5D and VFQ-25 questionnaires were not completed by one patient receiving polihexanide 0.8 mg/ml within the FAS. Consequently, EQ-5D and VFQ-25 data were only reported for 65 patients within the polihexanide 0.8 mg/ml arm in the Company Submission. Nonetheless, achieving an estimated 98% completion rate for these measures reflects a very high response rate.

Table 43: Trial populations of the ODAK trial by study arm

Analysis population	Polihexanide 0.8 mg/ml + placebo (N=69)	Polihexanide 0.2 mg/ml + propamidine 1 mg/ml (N=66)	Total (N=135)
All randomised, n (%) All eligible patients who were randomised to receive study treatment, either arm	69 (100.0%)	66 (100.0%)	135 (100.0%)
Efficacy results			
Full analysis set, n (%) All randomised patients for whom the primary efficacy variable had been assessed. This population was used in all efficacy analyses	66 (95.7%)	61 (92.4%)	127 (94.1%)
Per-protocol, n (%) A subset of patients from the full analysis population, for whom no major protocol deviation was deemed to impact the primary efficacy analysis was reported or identified. This population was used in the analysis of the primary efficacy endpoint only	62 (89.9%)	57 (86.4%)	119 (88.1%)
Safety results			

Analysis population	Polihexanide 0.8 mg/ml + placebo (N=69)	Polihexanide 0.2 mg/ml + propamidine 1 mg/ml (N=66)	Total (N=135)
Safety, n (%) All randomised patients who had received at least one dose of the study drug. This population was used in all safety analyses	69 (100.0)	65 (98.5%)	134 (99.3%)

Source: SIFI ODAK SAP⁸² and SIFI ODAK CSR 2022 (Table 10.1).⁹

B12. Please provide more details about the VFQ-25 measure, including if it is a validated scale.

The VFQ-25 is a patient survey that evaluates the impact of visual impairment on daily functioning and quality of life.⁸³ The VFQ-25 consists of a core set of 25 vision-targeted questions covering 11 vision-related constructs: global vision rating, difficulty with near vision activities, difficulty with distance vision activities, limitations in social functioning due to vision, role limitations due to vision, dependency on others due to vision, mental health symptoms due to vision, driving difficulties, limitations with peripheral and colour vision and ocular pain.⁸³ Additionally, the VFQ-25 contains a single general health rating question which is included to provide researchers with a minimum amount of information about an individual's general health status (as similar question is included in other HRQoL measures, such as in the 36-Item Short Form Health Survey [SF-36]).⁸³

Currently, there are no disease-specific HRQoL measures for AK. The VFQ-25 represents the most appropriate available instrument for measuring disease-specific HRQoL, having been previously used in a retrospective observational study of patients with AK,²⁰ and in multiple randomised clinical trials of ophthalmological conditions with similar visual impacts. In these trials, the VFQ-25 has shown strong internal consistency, reliability, as well as convergent and known group validity⁸⁴ and has proven to be a valid measure of vision-related functioning.⁸⁴⁻⁸⁶ Subscales and total scores derived from the VFQ-25 have been found to be highly responsive to changes in visual acuity, supporting its suitability for use in the ODAK trial.⁸⁴⁻⁸⁶

B13. Priority question: Please can the company provide the output of the mixed-model repeated measures (MMRM) analysis.

To ensure clarity, we have structured the response to this question into the following sections:

- Mapping of ODAK data on EQ-5D-5L to EQ-5D-3L to derive utility values
- Estimation of the utility decrement for AK infection (-0.24)
- Estimation of the utility decrements for “cured with poor vision” and “cured with severe vision loss” (-0.106 and -0.123, respectively)
- Estimation of the utility decrement for loss of eye functionality (-0.)

Mapping of ODAK data on EQ-5D-5L to EQ-5D-3L to derive utility values

EQ-5D-5L data collected in the ODAK trial were mapped onto the EQ-5D-3L UK value set using a method developed by the NICE Decision Support Unit (DSU), based on the Policy Research Unit in Economic Evaluation of Health and Care Interventions (EEPRU) dataset.⁸⁷ This approach uses the crosswalk method originally proposed by van Hout et al. (2012), which estimates the proportion of EQ-5D-3L levels corresponding to each EQ-5D-5L level for each health dimension.⁸⁸ These proportions are then used to compute a weighted average of EQ-5D-3L utility values, for each EQ-5D-5L utility.

To facilitate implementation of this mapping approach, the NICE DSU has developed R commands and tools, available at: <https://www.sheffield.ac.uk/nice-dsu/methods-development/mapping-eq-5d-5l-3l>. These values are also adjusted for age and sex.

This pre-calculated value set, incorporating the Hernández-Alava mapping, allows direct transformation of EQ-5D-5L data into utility values. Accordingly, it was used to convert each EQ-5D-5L observation in the ODAK trial into utility values for the cost-effectiveness model. In this case it was sufficient to assign the corresponding reported utility for each combination of the EQ-5D-5L in the ODAK trial, considering the age of the sex and age of the patient (e.g. a 35-year-old, male with EQ-5D-5L domains of 11113 corresponds to a utility of 0.817).

Estimation of the utility decrement for AK infection

The disutility associated with the AK infection health state in the cost-effectiveness analysis (CEA) was estimated using EQ-5D-5L data from the ODAK trial, transformed into utility values using the Hernández-Alava et al. (2023) value set, as described in the previous section.⁸⁷ Only EQ-5D-5L data collected at baseline in the ODAK trial were used in this analysis, as they reflect the health status of all patients during active AK infection.

A simple average of the mean baseline utility across all ODAK trial participants (n=123) was calculated, resulting in a mean utility of 0.658, standard error [SE] = 0.020). Using the average utility of patients in the ODAK trial who had good vision, estimated at 0.906 as the anchor, the disutility of AK infection was:

$$\text{Disutility} = 0.658 - 0.906 = -0.249$$

Estimation of the utility decrements for “cured with poor vision” and “cured with severe vision loss”

EQ-5D-5L data from the ODAK trial were used to generate the disutility values for the “cured with poor vision” and “cured with severe vision loss health states” via a mixed-model for repeated measures (MMRM) analysis. As a first step, EQ-5D-5L data collected in the ODAK trial were transformed into utility values using the Hernández-Alava et al. (2023) value set, as described above.⁸⁷

The visual acuity data were converted into the 3 Snellen Fraction vision loss subgroups, in alignment with the CEA health states: good vision with best-corrected visual acuity (BCVA) $\geq 20/40$, poor vision with BCVA $\geq 20/200$ and $< 20/40$, and severe vision loss with BCVA $< 20/200$. The analysis included only those visits where both visual acuity data and utility data were available for the same timepoint. The utility data of the corresponding visits was linked to the visual acuity data.

The MMRM model used the utility data as outcome and the derived vision health states as fixed effects. Therefore, the dependent variable was the utility value, and the independent variables (fixed effects) included visual acuity categories as defined in the model health-states (i.e. good vision, poor vision, and severe vision loss), with good vision specified as the reference category (intercept).

To model the within-subject correlations arising from repeated measurements over time, the model utilised an unstructured covariance matrix. This structure offers maximal flexibility by allowing each pair of timepoints to have a distinct covariance, without imposing any assumptions on the correlation pattern. The analysis was conducted without any formal data imputation procedures. Therefore, the model assumes a Missing at Random (MAR) mechanism, where the probability of missing data is related only to the observed data and not the unobserved outcomes. Under this assumption, the distribution of missing (unobserved) EQ-5D scores is approximated by that of the observed scores. In line with best practices for analysing trial-based repeated measures data, the MMRM employed the “repeated” statement method rather than modelling random slopes. This choice reflects the trial's design, where data are typically collected at fixed, prespecified timepoints, making pointwise estimation across time more appropriate than treating time as a continuous variable. While random effects models are suited for estimating slopes over continuous time, this is generally less compatible with clinical trial structures, which focus on estimating outcomes at discrete timepoints.

The resulting MMRM coefficients for “poor vision” and “severe vision loss” represent reductions in utility relative to the reference category of “good vision” (the MMRM intercept; see Table 44. These coefficients were therefore used as utility decrements for the “cured with poor vision” and “cured with severe vision loss” health states in the model.

Table 44: MMRM analysis of EQ-5D utility values and BCVA categories in the ODAK trial

Visual acuity category	Estimate	Standard Error	Number of observations
Good vision [BCVA $\geq$ 20/40] (<i>INTERCEPT</i>)	0.906	0.012	146
Poor vision [BCVA $\geq$ 20/200 and $<$ 20/40]	-0.106	0.029	54
Severe vision loss [BCVA $<$ 20/200]	-0.123	0.083	7

Abbreviations: BCVA: best corrected visual acuity

Estimation of the utility decrement for loss of eye functionality

The ODAK trial was unable to provide utilities for the loss of eye functionality health state given that no patients experienced this within the trial. Therefore, data from published literature (Rentz et al. 2014) were used to derive utilities for this health state.⁸⁹

Rentz et al (2014) utilised a cross-sectional design, recruiting 607 adult participants from Australia, Canada, the UK and the US to derive preference-based health utility scores related to vision-specific quality of life (the National Eye Institute Visual Function Questionnaire-25 - NEI VFQ-25). The design captures health state preferences associated with varying degrees of visual function, which align with a priori expectations that vision impairment impacts health-related quality of life (HRQoL). The clinical rationale was that deteriorating vision would predictably result in reduced HRQoL scores. The NEI VFQ-25 was selected due to its established validity and reliability in assessing vision-related HRQoL in several different

populations. It has been validated for measuring outcomes specific to ocular conditions, making it suitable for developing a preference-based index.

Potential risks of bias included the limited number of health states directly assessed and reliance on the time trade-off (TTO) technique, which requires subjective value judgments that might vary across populations. While the sample represented a several populations, differences between this group and typical patient populations with severe ocular conditions could introduce bias. The use of item response theory (IRT) mitigated these risks by modelling a broader continuum of health states.

Participants rated eight pre-selected health states using the TTO method, which measures the trade-off individuals are willing to make between longevity and health quality. The selection of health states was informed by the VFQ-Utility Index (VFQ-UI) classification framework.

The utility decrement associated with loss of eye functionality in the current CEA was estimated as two-fifths of the difference between the utility in good vision from Rentz et al. (0.8835=the average of the utility values for domains “111111” and “211111” in Rentz et al. 2014) and the utility in the complete loss of eye function (0.264 = the utility associated with the “555555” domain in Rentz et al. 2014). This 2/5 factor was applied to reflect the relative QoL impact of unilateral versus bilateral blindness.

B14. Priority question: Please can the company provide a summary of the level and the pattern of missingness observed in the data used for the MMRM.

Regarding the pattern of missingness observed in the data used for the MMRM, it is important to note that BCVA data are available for only two timepoints: baseline and end-of-study. Given this constraint, a descriptive summary table for each timepoint is presented in Table 45.

Table 45: Descriptive summary of baseline and end of study BCVA data

Outcome	Polihexanide 0.8 mg/ml + placebo	Polihexanide 0.2 mg/ml + propamidine 1 mg/ml	All patients
Baseline			
Nr of patient records	58	49	107
Mapped EQ-5D index UK – Hernández-Alava et al, 2023 ⁸⁷			
Mean ± SE (N)	0.6711±0.0285 (58)	0.6628±0.0315 (49)	0.6673±0.0210 (107)
Median (Min, Max)	0.7046, (0.0854, 0.9871)	0.7185, (0.0851, 0.9871)	0.7148, (0.0851, 0.9871)
IQR (Q1, Q3)	0.5529, 0.8005	0.5547, 0.8051	0.5529, 0.8051
[95% CI] (normal)	[0.61, 0.73]	[0.60, 0.73]	[0.63, 0.71]
Snellen Fraction Group			
(1) Good vision [BCVA >=20/40]	50.00% (29 / 58)	63.27% (31 / 49)	56.07% (60 / 107)
(2) Poor vision [BCVA >=20/200 and <20/40]	46.55% (27 / 58)	30.61% (15 / 49)	39.25% (42 / 107)
(3) Severe vision loss [BCVA <20/200]	3.45% (2 / 58)	6.12% (3 / 49)	4.67% (5 / 107)
End-of-study visit			

Nr of patient records	52	47	99
Mapped EQ-5D index UK – Hernández-Alava et al, 2023 ⁸⁷			
Mean ± SE (N)	0.9275±0.0124 (52)	0.9176±0.0172 (47)	0.9228±0.0104 (99)
Median (Min, Max)	0.9845, (0.5638, 0.9871)	0.9845, (0.3860, 0.9879)	0.9845, (0.3860, 0.9879)
IQR (Q1, Q3)	0.8825, 0.9854	0.8598, 0.9859	0.8763, 0.9854
[95% CI] (normal)	[0.90, 0.95]	[0.88, 0.95]	[0.90, 0.94]
Snellen Fraction Group			
(1) Good vision [BCVA ≥20/40]	86.54% (45 / 52)	87.23% (41 / 47)	86.87% (86 / 99)
(2) Poor vision [BCVA ≥20/200 and <20/40]	11.54% (6 / 52)	12.77% (6 / 47)	12.12% (12 / 99)
(3) Severe vision loss [BCVA <20/200]	1.92% (1 / 52)		1.01% (1 / 99)

Abbreviations: BCVA: best-corrected visual acuity; CI: confidence interval IQR: interquartile range; Nr: number; SE: standard error; UK: United Kingdom.

Resource use and costs

B15. CS, Table 6. Please can the company provide rationale for using the mean duration of treatment with polihexanide 0.8mg/ml from the real-world Franch et al. study rather than using the median time to cure from their studies?

The modelled treatment duration of 101 days for polihexanide 0.8 mg/ml is based on real-world evidence (RWE) reported by Franch et al. (2024), where the mean duration of polihexanide 0.8 mg/ml treatment was observed under routine clinical practice.⁶¹ This estimate is the most appropriate for the economic model, as it reflects the period during which patients are exposed to polihexanide 0.8 mg/ml in real-world clinical practice. Patients in the Franch et al, 2024 case series received polihexanide 0.8 mg/ml as part of a name-based compassionate use programme, which used the same treatment protocol for polihexanide 0.8 mg/ml as that of the ODAK trial, making it an appropriate source of data to inform the model alongside data from the ODAK trial.

Importantly, the MCR reported in Franch et al. (91.7%) is broadly consistent with the MCR observed in the ODAK trial (84.9%), indicating that a shorter treatment duration in real-world practice than observed in the ODAK trial is achievable, without compromising efficacy of polihexanide 0.8 mg/ml. Real-world treatment exposure is likely to be a more accurate reflection of clinical practice than trial-based estimates, which may be affected by protocol-driven factors.

The data from Franch et al. (2024) therefore represent real-world use of polihexanide 0.8mg/ml under protocols aligned with those used in the ODAK trial, but without the limitations of a clinical trial. Treatment was appropriately discontinued at the point of confirmed cure. As such, the mean treatment duration of 101 days observed in Franch et al. provides a more accurate and relevant estimate for modelling purposes.

B16. Priority question: In CS Table 60, concomitant medications (ophthalmological eye drops) were costed based on the number of drops required for the treatment duration not the number of bottles required for

the treatment duration. This was also seen with tablet medications where costs were provided for number of tablets not packets required. Please can the company provide the costs for the number of bottles/packets required for the treatment durations as available for purchase and treatment of patients in real world practice.

The EAG's request has been implemented for the estimation of the cost associated with systemic therapies, including immunosuppressives and adjuvant medications (please refer to question B18). After this update, the ICER is [REDACTED], representing a reduction of [REDACTED] in comparison with the ICER presented in the model previously submitted (Table 46).

Table 46. Updated results after the adjustment of concomitant and systemic medications cost calculation based on total number of bottles/packages per treatment course

Scenario	Incremental costs, £	Incremental QALYs	ICER (£/QALY)	Absolute % Change in ICER	INHB at £20k	INHB at £30k
Previous base case	[REDACTED]	2.56	[REDACTED]	NA	[REDACTED]	[REDACTED]
Concomitant and systemic medications cost updated based on total number of bottles/packages per treatment course: Updated base case	[REDACTED]	2.56	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: ICER: incremental cost-effectiveness ratio; INHB: incremental net health benefit; NA: not applicable; QALY: quality-adjusted life years

B17. Please can the company confirm the presentation of Aciclovir is dose per pack ml or mg. (NICE technical team comment: we noticed that in the final row of Table 60 in the CS, columns 3, 5 and 6 imply that this is an eye drop formulation, but columns 2 and 4 imply that it is tablets (the unit price of £1.16 cited from the BNF seems to relate to a pack of 25 x 200mg tablets). Please clarify the correct formulation, pack size and unit cost for concomitant use of aciclovir).

Table 60 of the CS presents a list of concomitant medications, divided into two categories:

- **Ophthalmological medications:** These are listed in the first part of the table, with doses provided in millilitres per pack. This section includes agents such as levofloxacin, dexamethasone, carmellose sodium, atropine sulphate, chloramphenicol, and propamidine
- **Non-ophthalmological medications (oral administration):** Shown in the second part of the table, with doses presented in milligrams per pack. This includes anti-inflammatory and antirheumatic drugs (e.g. aspirin, ibuprofen), analgesics (e.g. paracetamol), and systemic antivirals (e.g. acyclovir).

Accordingly, the presentation of acyclovir is in milligrams per pack, specified as 25 tablets of 200 mg each. As requested in question B16, the costs of the concomitant ophthalmological and non-ophthalmological medications based on the number of bottles and packages respectively, have been estimated in Table 47.

Table 47. Concomitant ophthalmological and non-ophthalmological medications with costs

Concomitant medication (>10%)	Name and dose	Dose per pack (ml)	Pack cost £	Number of drops per pack	Number of drops required	Cost, £*	Cost source
Ophthalmologicals (eye drops)							
Fluoroquinolones	Levofloxacin 5 mg/ml: 1 or 2 drops into affected eye(s) every 2 hours up to eight times daily while awake for first 2 days, then four times daily on days 3 to 5. ⁹⁰	5	10.03	100	56	10.03	BNF 2025 ⁹¹
Corticosteroids, plain	Dexamethasone phosphate 1 mg/ml: 1 drop into affected eye(s) four to six times daily. If necessary, initiate with 1 drop hourly and reduce to 1 drop every 4 hours when inflammation subsides. Maximum duration 14 days. ⁹²	0.4	9.7	30	84	29.10	BNF 2025 ⁹³
Other ophthalmologicals	Carmellose sodium 0.5%: 1 or 2 drops into affected eye(s) as required. ⁹⁴	10	1.68	200	42	1.68	BNF 2025 ⁹⁵
Anticholinergics	Atropine sulfate 1%: 1 drop as required. ⁹⁶	10	70.01	200	42	70.01	BNF 2025 ⁹⁷
Antibiotics	Chloramphenicol 0.5%: 1 or 2 drops into affected eye(s) up to 6 times daily, or	10	3.37	200	84	3.37	BNF 2025 ⁹⁹

Concomitant medication (>10%)	Name and dose	Dose per pack (ml)	Pack cost £	Number of drops per pack	Number of drops required	Cost, £*	Cost source
	more frequently if required. Continue for 48 hours after cure. ⁹⁸						
Other anti-infectives	Propamidine 0.1%: 1 or 2 drops into affected eye(s) four times daily. ¹⁰⁰	10	4.05	200	56	4.05	BNF 2025 ¹⁰¹
Non-ophthalmological medications (orally administered)							
Anti-inflammatory and anti-rheumatic products (tablets)		Quantity per pack (mg)	Pack cost	Number of tablets per pack	Number of administrations	Cost (one-off), £	Cost source
Acetic acid derivatives and related substances	Aspirin: 300–900 mg every 4–6 hours as required with food; maximum 4 g daily. ¹⁰²	300	7.09	100	56	7.09	BNF 2025 ¹⁰³
Propionic acid derivatives	Ibuprofen: 1.2–1.8 g daily in divided doses with food; maximum 2.4 g daily. ¹⁰⁴	200	2.31	84	42	2.31	BNF 2025 ¹⁰⁵
Analgesics							
Anilides	Paracetamol: 500 mg–1 g every four to six hours as required; max 4 g daily. ¹⁰⁶	500	2.09	100	42	2.09	BNF 2025 ¹⁰⁷
Antivirals for systemic use							
Nucleosides and nucleotides excl. reverse	Aciclovir: Varicella or herpes zoster: 800 mg five times daily at	200	1.16	25	140	6.96	BNF 2025 ¹⁰⁹

Concomitant medication (>10%)	Name and dose	Dose per pack (ml)	Pack cost £	Number of drops per pack	Number of drops required	Cost, £*	Cost source
transcriptase inhibitors	four-hourly intervals, omitting the night time dose, for 7 days. Start treatment as soon as possible after onset of rash. ¹⁰⁸						

Footnote: Costs calculated based on the number of bottles/packets required for the treatment durations.

B18. Please can the company provide clarity on the values provided in CS, Table 68, column 6, dose per administration and state the unit for the values presented.

The values presented in Table 68, column 6 of the CS represent the calculated total dose per administration (in mg) for systemic immunosuppressive agents and adjuvant systemic therapies, derived from the recommended dosage for each medication. For certain medications listed, dosing is specified in mg/kg; therefore, calculations were performed using the average baseline weight assumed in the model. To enhance transparency, Table 33 below has been updated to indicate the relevant units for column 6. To align to the EAG's request in Question B16, Table 49 also presents the costs for systemic therapies by the number of packages/bottles required for the treatment duration.

Table 48: Costs associated with systemic therapies

Systemic therapies	Quantity per unit (mg)	Units per pack	Pack cost, £	Cost per mg, £	Dose per administration in mg*	Number of administrations per day	Cost per treatment, £	Source
Systemic immunosuppressive								
Cyclosporine	50	30	25.5	0.0170	1,140.64	1	4,233.00	BNF 2025 ¹¹⁰
Azathioprine	50	56	1.33	0.0005	114.06	1	1.33	BNF 2025 ¹¹¹
Mycophenolate	500	50	5.78	0.0002	1,000.00	2	144.50	BNF 2025 ¹¹²
Steroids	10	28	9.70	0.0346	40.00	1	38.80	BNF 2025 ¹¹³
Tacrolimus	1	50	71.59	1.4318	7.60	2	6,228.33	BNF 2025 ¹¹⁴
Total cost (one-off), £	1,637.36							
Adjuvant systemic therapies								
Miltefosine	Cost not available ^a							
Voriconazole	50	28	193.53	0.1382	200	2	2,128.83	BNF 2025 ¹¹⁵
Prednisolone	10	28	9.70	0.0346	40	1	77.60	BNF 2025 ¹¹³
Doxycycline	50	28	1.44	0.0010	200	1	15.84	BNF 2025 ¹¹⁶
Adjuvant therapies								

Systemic therapies	Quantity per unit (mg)	Units per pack	Pack cost, £	Cost per mg, £	Dose per administration in mg*	Number of administrations per day	Cost per treatment, £	Source
Polihexanide 0.6 mg/ml	-	200	50.00	0.2500	1	4	150.00	2023 Policy Matters, Market Intelligence Report. ¹¹⁷
Total cost (one-off), £	463.92							

Footnote: *Dose per administration in mg, represent the calculated total dose derived from the recommended dosage for each medication.

Table 49: Dose per administration calculation for systemic immunosuppressives and adjuvant therapies

Systemic therapies	Recommended dose – full description	Calculation	Dose per administration in mg	Number of administrations per day	Source
Cyclosporine	Initial dose: 15 mg/kg orally 4 to 12 hours prior to transplantation; although a single dose of 14 to 18 mg/kg was used in most clinical trials, most clinicians favour the lower end of the scale; lower initial doses are usually used for renal transplantation in the ranges of 10 to 14 mg/kg/day Maintenance dose: The initial single daily dose is continued postoperatively for 1 to 2 weeks and then tapered by 5% per week to a maintenance dose of 5 to 10 mg/kg/day; some clinicians prefer to reduce the maintenance dose to 3 mg/kg/day in some renal transplant patients without an apparent rise in rejection rate	15 mg * 76.04 Kg	1,140.64	1	Link: https://www.drugs.com/dosage/cyclosporine.html#Usual_Adult_Dose_for_Organ_Transplant_Rejection_Prophylaxis
Azathioprine	1 to 1.5 mg/kg orally per day, in combination with prednisolone and cyclosporine	1.5 mg * 76.04 Kg	114.06	1	Link: https://www.drugs.com/dosage/azathioprine.html#Usual_Adult_Dose_for_Uveitis
Mycophenolate	1 g orally or IV 2 times a day (2 gm per day); [in clinical trials, 1.5 g orally or IV 2 times a day	Not required	1,000.00	2	Link: https://www.drugs.com/dosage/mycophenolate-

	(3 gm per day) was used effectively, however, the safety profile for 3 gm a day was lower]				mofetil.html#Usual_Adult_Dose_for_Organ_Transplant___Rejection_Prophylaxis
Steroids	5—60mg daily	Not required, value from the recommended range used	40.00	1	MIMS database. Prednisolone. (https://www.mims.co.uk/drugs/endocrine/inflammatory-disorders/prednisolone). Accessed 02/08/2023
Tacrolimus	In combination with azathioprine: Initial dose: 0.1 mg/kg orally every 12 hours; initiate within 24 hours of surgery but delay until renal function has recovered	0.1 mg * 76.04 Kg	7.60	2	Link: https://www.drugs.com/dosage/tacrolimus.html#Usual_Adult_Dose_for_Organ_Transplant___Rejection_Prophylaxis
Voriconazole	Treatment: loading dose for first 24 hrs, 400mg every 12 hrs (≥40kg) or 200mg every 12 hrs (< 40kg). Maintenance, 200mg twice daily (≥40kg) or 100mg twice daily (< 40kg). If response inadequate, maintenance dose may be increased to 300mg twice daily (≥40kg) or 150mg twice daily (< 40kg). Reassess risk–benefit after 6 months.	Not required, maintenance dose used	200	2	MIMS database. Voriconazole. (https://www.mims.co.uk/drugs/infections-and-infestations/fungal-infections/voriconazole). Accessed 02/08/2023
Prednisolone	5—60mg daily	Not required, value from the recommended range used	40	1	MIMS database. Prednisolone. (https://www.mims.co.uk/drugs/endocrine/inflammatory-disorders/prednisolone). Accessed 02/08/2023
Doxycycline	Usually, 200mg on the first day, then 100—200 mg daily. Dose for STD and misc. infections, see SPC.	Not required	200	1	MIMS database. Doxycycline. (https://www.mims.co.uk/drugs/infections-and-infestations/bacterial-infections/doxycycline). Accessed 02/08/2023
Ophthalmological medications					

Adjuvant therapy	Recommended dose – full description	Calculation	Dose per administration in mg	Number of administrations per day	Source
Polihexanide 0.6 mg/ml	Assuming 4 drops per day (as in the maintenance phase)	Not required	1	4	Assumption

Abbreviations: IV: intravenous; MIMS: Monthly Index of Medical Specialities; STD: sexually transmitted diseases; SPC: summary of product characteristics.

Section C: Textual clarification and additional points

C1. Please provide the documents for the following three 'data on file' references (or clarify their filenames and location in the reference pack):

- A. 11. SIFI. Data on File. Technical Report. Results from two-round Delphi panel on *acanthamoeba keratitis* in the United Kingdom. 2023. (see also clarification question A7).

The requested file is named 'SIFI. Data on File. Technical Report. Results from two-round Delphi panel on *acanthamoeba keratitis* in the United Kingdom. 2023.' This has been uploaded to NICE Docs alongside this response within the folder 'Data on File'.

- B. 72. SIFI. Data on File. ITC Report. 2024.

This was a referencing error and should instead refer to the most recent version of the ITC report, found in the following file: 'SIFI. Data on File. ITC Report 2025'. This has been uploaded to NICE Docs alongside this response within the 'Data on File' folder in the reference pack.

- C. 104. SIFI. Data on File. Policy Matters. Market Intelligence Report: Product and pricing information to inform the UK economic model for polihexanide in AK. 2023.

The requested file is named 'SIFI. Data on File. Policy Matters Market Intelligence Report.' This has been uploaded to NICE Docs alongside this response within the folder 'Data on File'.

C2. Appendix B Figure 1 PRISMA, the numbers in the flow diagram and text do not appear to be correct. 2250 records minus 704 duplicates = 1546 (not 1539). Please clarify this discrepancy.

Microsoft Excel, in combination with specialist literature screening software (Covidence), was used to monitor the progress of publications throughout the stages of the SLR, including identification, de-duplication and eligibility assessment. To clarify the numbers reported in the "Identification phase" of the PRISMA diagram, the counts for the number of titles/abstracts screened, full-text articles reviewed, and total studies included in the final analysis are accurate.

A total of 2250 records were initially identified and imported into Covidence from various databases and trial registries. These records included:

- PubMed (n = 221)
- CENTRAL (n = 16)
- PROSPERO (n = 15)
- ClinicalTrials.gov (n = 15)
- TLR references (n = 17)

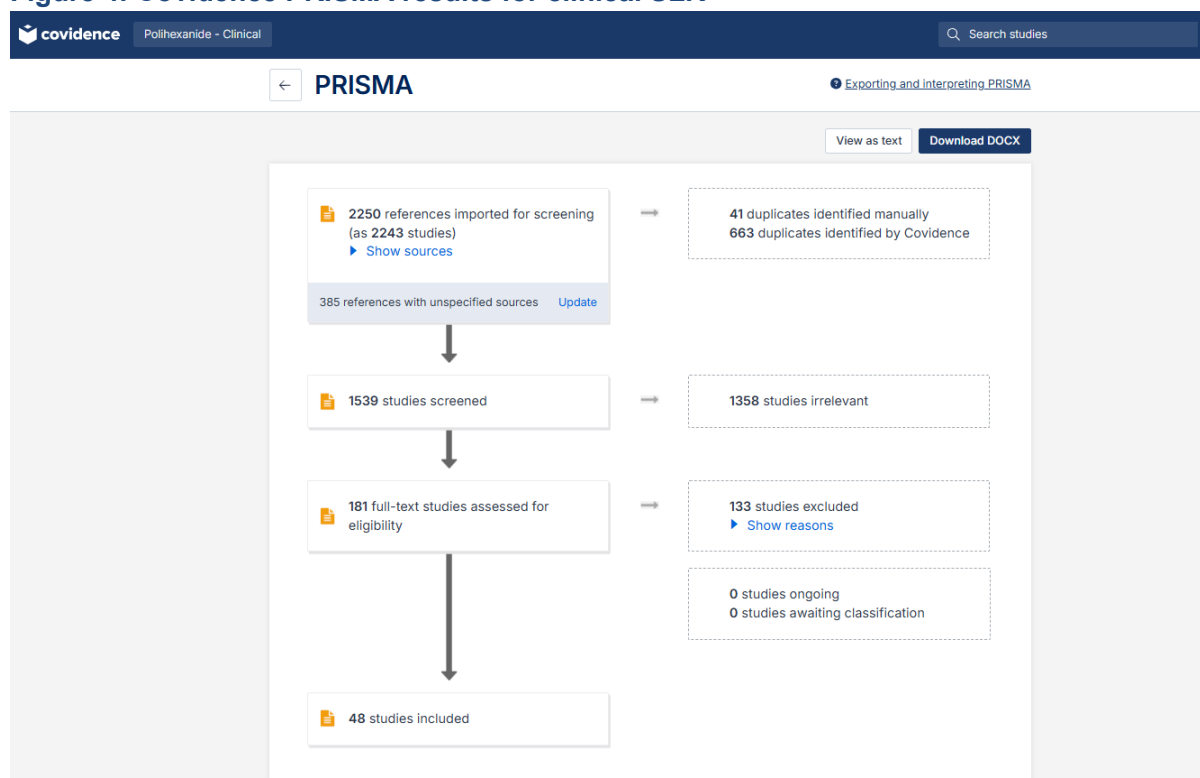
- Manufacturer websites (n = 0)
- Conference proceedings (n = 15)
- Citation chasing process (n = 1951)

These 2250 records represent the raw import total, which may have included duplicate records, conference abstracts, ineligible publications, or entries with incomplete metadata. Following import, Covidence automatically performed deduplication using metadata fields such as title, author, journal, publication year and DOI. This process produced 2243 unique records, that is the number of studies entering the screening phase.

Of the 2243 records, 41 were manually identified as duplicates and 663 duplicates were flagged by Covidence, resulting in a total of 704 excluded records. The remaining 1539 studies proceeded to title/abstract screening. After excluding 1358 studies, 181 records underwent full-text review. Subsequently, 133 publications were excluded during this phase, leaving 48 studies eligible and included in the clinical SLR for data extraction and analysis.

This screening process aligns with the PRISMA diagram presented in Appendix B, Figure 1 of the CS. A screenshot of the Covidence platform is also provided to corroborate the reference and study counts.

Figure 4: Covidence PRISMA results for clinical SLR



Additionally, a dedicated Excel workbook ("SLR Tracker") was created to document each stage of the publication selection process, ensuring full traceability. This file is included with the Clinical SLR report provided in the reference pack in the 'Data on File' folder.

C3. Please provide the pdfs of the 133 excluded studies in the clinical SLR.

The PDFs for the excluded studies are now included in the reference pack. Please note that only 107 PDFs are included in the folder, since several references were sourced from online-only materials, and therefore, PDF copies could not be provided for those entries (in total 26 sources; Table 17). Additionally, some references were excluded as duplicates. For these cases, a clarification note has been added to the Table 17, which lists the online references and corresponding remarks for your consideration.

Table 17. Excluded records not included in references pack

Title; year	Link to the source	Notes
Retrospective Chart Review of Patients with Acanthamoeba Keratitis Who Have Received 0.8 Mg/ml Polihexanide As Part of a Compassionate Use Program: a Non-interventional Study with Secondary Use of Data; 2024	https://clinicaltrials.gov/study/NCT06641882?tab=results	Results not available
Parasitic Ulcer Treatment Trial; 2024	https://clinicaltrials.gov/study/NCT06213649	Results not available
A report of 10 patients with Acanthamoeba keratitis; 2018	https://www.sciencedirect.com/science/article/abs/pii/S0365669118301291?via%3Dihub	Article in Spanish. Data included in the abstract not sufficient for inclusion.
Excimer-Laser and mitomycin C 0.02% to treatment acanthamoeba keratitis; 2019	https://iovs.arvojournals.org/article.aspx?articleid=2741442#:~:text=Conclusions%20%3A%20The%20combination%20of%20100%C2%B5m%20PTK%20with,cysts%20at%20the%20depth%20of%20up%20to%20240%C2%B5m.	Conference abstract
Microbiological analysis in contact lens-associated keratitis; 2011	https://www.thieme-connect.de/products/ejournals/abstract/10.1055/s-0029-1245840	Article in German. Data included in the abstract not sufficient for inclusion.
Clinical management and prognosis in Acanthamoeba keratitis: a retrospective study of 25 cases; 2002	https://pubmed.ncbi.nlm.nih.gov/12527823/	Article in French. Data included in the abstract not sufficient for inclusion.
The German Acanthamoeba keratitis register: Initial results of a multicenter study; 2015	https://link.springer.com/article/10.1007/s00347-014-3225-7	Article in German. Data included in the abstract not sufficient for inclusion.
The Orphan Drug for Acanthamoeba Keratitis (ODAK) Trial: PHMB 0.08% (Polihexanide) and Placebo versus	NA	Reference excluded as duplicate. Therefore, PDF is not provided

PHMB 0.02% and Propamidine 0.1; 2023		since the ODAK trial met the criteria for inclusion in the SLR
Efficacy of chlorhexidine- versus phmb for acanthamoeba keratitis; 1999	https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00674599/full	Conference abstract
Clinical characteristics of microbial keratitis in a university hospital in Taiwan; 2004	https://linkinghub.elsevier.com/retrieve/pii/S0002939403010742	Conference abstract
Acanthamoeba keratitis – pKP versus conservative treatment in a 20-year follow-up study; 2017	https://onlinelibrary.wiley.com/doi/10.1111/j.1755-3768.2017.03553	Conference abstract
Acanthamoeba Keratitis in Residents' Clinic Compared with a Faculty Private Practice; 2018	https://ascrs.org/clinical-education/abstracts/2018/acanthamoeba-keratitis-in-residents-clinic-compared-with-a-faculty-private-practice	Conference abstract
Queratitis por Acanthamoeba. Análisis de casos en el Hospital Oftalmológico Santa Lucia (2009-2010); 2011	https://www oftalmologos.org.ar/catalogo/items/show/4703	Article in Spanish. Data included in the abstract not sufficient for inclusion. Full text not available.
Assessment of real-time polymerase chain reaction detection of Acanthamoeba and prognosis determinants of Acanthamoeba keratitis; 2012	https://www.aaojournal.org/article/S0161-6420(11)01191-2/ppt	Conference abstract
Topical application of polyhexamethylene biguanide on Acanthamoeba keratitis; 2015	https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000019739	Results not available
Should we be using polyhexamethylene biguanide to treat Acanthamoeba keratitis; 1997	https://onlinelibrary.wiley.com/doi/10.1111/j.1442-9071.1997.tb01288.x	Editorial
Systemic Miltefosine as an Adjunct Treatment of Progressive Acanthamoeba Keratitis; 2019	https://europepmc.org/article/MED/32469616	Conference abstract (Full text version of this conference abstract (Naranjo 2021, included in the reference

		package folder) excluded because outcomes not reported by treatment)
Prescribing trends in infectious keratitis: a survey of New Zealand ophthalmologists; 2003	https://onlinelibrary.wiley.com/doi/10.1046/j.1442-9071.2003.00708.x	Full text not available
Comment on: Rose Bengal Photodynamic Antimicrobial Therapy for Patients With Progressive Infectious Keratitis: A Pilot Clinical Study; 2020	https://linkinghub.elsevier.com/retrieve/pii/S0002939420300532	Comment on a primary publication
Rose Bengal Electromagnetic Activation With Green Light for Infection Reduction; 2021	https://clinicaltrials.gov/show/NCT05110001	Results not available
Parasitic Ulcer Treatment Trial Pilot; 2018	https://clinicaltrials.gov/show/NCT03484507	Results not available
Contact lens-related keratitis and purulent corneal ulcers; 2018	https://www.mediasphera.ru/issues/vestnik-oftalmologii/2018/4/downloads/ru/10042465X2018041017	Article in Russian. Data included in the abstract not sufficient for inclusion.
Orphan Drug for Acanthamoeba Keratitis (ODAK) project: results of a 10-Year retrospective study in Italy and in the United Kingdom; 2014	https://iovs.arvojournals.org/article.aspx?articleid=2271125	Conference abstract
The incidence of severe complications in acanthamoeba keratitis: Qualitative and quantitative systematic assessment; 2024	https://linkinghub.elsevier.com/retrieve/pii/S0039625724000699	Full text not available
Efficacy of Topical 2% Cyclosporine in Controlling the Inflammation and Improving the Treatment Outcomes in Patients with Acanthamoeba Keratitis; 2023	https://iovs.arvojournals.org/article.aspx?articleid=2790865	Conference abstract
Clinical features and outcome of Acanthamoeba keratitis; 1997	J Formos Med Assoc 1997;96(11):895-900	Full text not available, only abstract screened

C4. Section 2.3.3 mentioned *‘The median age of the polyhexanide 0.8mg/ml arm and the polyhexanide 0.2mg/ml with propamidine 1 mg/ml was 35.2 years and 38.3 years, respectively.’* However, these were mean values taken from CS, Table 6. Please clarify this discrepancy.

This was a typographical error in Section 2.3.3 of the CS. The corrected statement should read: “the mean age of the polyhexanide 0.8 mg/ml arm and the polyhexanide 0.2 mg/ml with propamidine 1 mg/ml was 35.2 years and 38.3 years, respectively” in line with the values reported in Table 6 of the CS.

C5. Section 2.6.7 mentioned ‘Only two (n=2/69; 2.9%) participants’, stating 69 patients while the accompanying table states 66 patients. Please clarify this discrepancy.

In Section 2.6.7 of the CS, the description of two (n=2/69; 2.9%) participants refers to the number of patients with AK requiring surgery, based on the safety analysis set in the polyhexanide 0.8 mg/ml arm (N=69). The accompanying table (Table 16 of the CS) reports the number of patients with AK requiring adjunctive therapy, based on the full analysis set in the polyhexanide 0.8 mg/ml arm (N=66). Therefore, these data refer to different endpoints and both are accurately reported from the ODAK CSR (see CSR Table 14.3.2.1 for the rate of patients with adjunctive therapy and Section 12.10 for the rate of subjects requiring surgery).

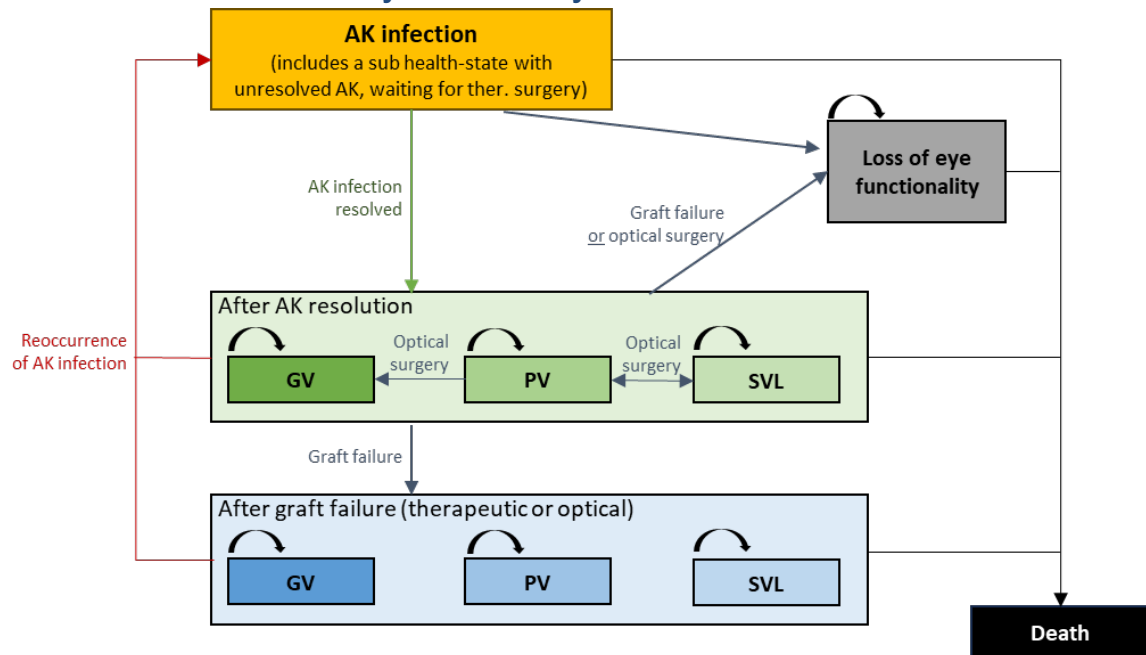
C6. Please can the company clarify if there should be a reoccurring arrow on the ‘Loss of eye functionality’ health state in the illustrative structure in the ‘Introduction’ worksheet as is in CS, Figure 5.

Loss of eye functionality is defined as the permanent inability to see due to these clinical scenarios. Enucleation, which involves the complete removal of the eyeball while preserving surrounding muscles and tissues, results in total loss of function. Similarly, evisceration (where the internal contents of the eyeball are removed while retaining the outer shell) also leads to full functional loss. Therefore, in both cases, it is assumed that all patients lose their eye functionality.

Within the model, the arrow indicating that patients who experience complete loss of eye functionality remain in the same health state has been added, ensuring the alignment with the CS (Figure 5). It is important to highlight that these patients do not experience a recurrence of infection. This outcome encompasses individuals with unresolved, severe AK, those undergoing surgical procedures such as enucleation or evisceration and patients who do not pursue additional interventions following graft failure. Last, patients in the loss of eye functionality health state can transit to death (as occurs for all the health states considered in the model).

Figure 5 describes the structure relating to the loss of eye functionality health state.

Figure 5: Clarification of loss of eye functionality health state



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Single Technology Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	[REDACTED]
2. Name of organisation	Fight for Sight
3. Job title or position	[REDACTED]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Fight for Sight is Funder of scientific research into all eye conditions and social change community interventions for blind and vision impaired people. We have 15,000 supporters on our database. Our funding comes from major donors, trusts and foundations, community and events, legacies and individual giving.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	None
4c. Do you have any direct or indirect links	None.

with, or funding from, the tobacco industry?	
5. How did you gather information about the experiences of patients and carers to include in your submission?	Fight for Sight is a member of the Global Alliance against Acanthamoeba Keratitis, as part of the alliance we contributed to the publication of a white paper to raise awareness of AK with a focus on prevention, diagnosis and treatment. The paper was published in October 2024. As part of this work, we gathered testimonials from patients living with the condition.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Patients have told us that AK is a physically painful disease which also causes a great deal of mental distress. Patients experience eye pain, light sensitivity, and blurred vision as well as psychological symptoms such as social anxiety and in extreme cases post-traumatic stress disorder due to traumatic surgical procedures meaning that this condition takes a toll on a person's mental wellbeing and quality of life. Testimonials of patients - <i>My Acanthamoeba keratitis (AK) diagnosis at age 15 meant my whole world was disrupted - no swimming, no reading, no travelling.</i> - <i>Every tiny light, sound and touch of my face is like a stabbing knife into my exploding eye and head. I feel desperate in a dark universe of endless, excruciating pain.</i> - <i>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.</i> - <i>Dealing with a disease like AK made me insecure, not only about my eye, but also about myself. With that, I developed social anxiety as well.</i>

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients find the current combination treatment regimen often comprising two types of drops which need to be initially applied on an hourly basis (with a 5-minute gap between each type of drop) extremely challenging and disruptive.
8. Is there an unmet need for patients with this condition?	Yes, at present there are no licensed treatments available for this condition.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The advantage of this technology is that patients will just use one set of disinfectant eye drops to treat their AK infection this will minimise some of the inconvenience patients experience

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	The fact that the treatment protocol still requires an 'intensive' phase with hourly drop instillation. However, patients recognise that this is not a true disadvantage since current treatment also follows an intensive treatment phase where two different types of drops are instilled on an hourly basis.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who experience drop toxicity and side effects from eye drops might still experience these. Patients who find it difficult to comply with the frequency of drop instillation and/ or have difficulties self-administering eye drops find it difficult to use eye drops are likely to not to benefit as those who are able to follow the regimen.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues

13. Are there any other issues that you would like the committee to consider?	None

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• AK is a physically and emotionally debilitating condition for which there exists no licenced treatments in the NHS. • Patients struggle with the high volume of drops that need to be used to treat AK especially in the early stages of treatment. Prescription of Akantior could potentially halve the number of drops that patients need to use. • •

Thank you for your time.

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Your privacy

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Please select YES if you would like to receive information about other NICE topics - YES or NO

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Single Technology Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	
2. Name of organisation	Royal College of Ophthalmologists (RCOphth)
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The Royal College of Ophthalmologists represents the ophthalmic profession in the United Kingdom and supports overseas members in low and middle income countries, building a global community to influence eye health policy and to share standards, training, professional learning and development.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	No
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The aim of this treatment is to treat and eradicate a type of parasitic corneal infection named Acanthamoeba keratitis (AK).
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Complete resolution of the corneal infection.
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, currently there is an unmet need for treating AK.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	AK is an uncommon but sight-threatening corneal infection which often poses significant therapeutic challenges. Currently, within NHS, it is treated as a corneal emergency and affected patients usually require intensive treatment every hourly for the first week, then every 6-8 times per day for the subsequent weeks-to-months. The average treatment course for this condition is usually 3-6 months.

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Currently, there is no standardised national clinical guideline for this particular condition. However, regional guidelines and recommended approach published in the literature (https://pubmed.ncbi.nlm.nih.gov/19660733/) are available.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care is relatively well-defined in terms of the intensive treatment regimen required for treating this condition. However, opinion about the choice of anti-amoebic treatment may vary considerably between institutes and regions.
9c. What impact would the technology have on the current pathway of care?	This technology would provide a valuable addition to the current therapeutic armamentarium of AK.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes, the technology will be used in the same way as current NHS care.
10a. How does healthcare resource use differ between the technology and current care?	Currently, patients affected by AK are commonly treated by two types of anti-amoebic treatment. The current technology is shown to exhibit comparable efficacy and safety to the current combination treatment, therefore a single treatment (instead of combination treatment) is likely to improve treatment compliance and reduce burden on the patients and healthcare resources (e.g. staff time for administering the treatment if patients are admitted to the hospital for intensive treatment).
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care and eye specialist clinics
10c. What investment is needed to introduce the technology? (For example,	No investment is required as similar treatment (with a lower concentration) is already being used in NHS settings

for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes
11a. Do you expect the technology to increase length of life more than current care?	No
11b. Do you expect the technology to increase health-related quality of life more than current care?	Possibly yes, due to less need for more than one treatment.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant	The technology will be easier to use for patients and healthcare professionals as it may be administered as a monotherapy instead of combination therapy.

treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional rule will be required. This technology will follow the same principles and rules that are applied to other anti-amoebic or anti-infective treatment for corneal infection.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes, currently there is no approved drug for treating AK. Having this drug approved for use in NHS by NICE would make a significant impact on health-related benefits for patients affected by AK.
16a. Is the technology a 'step-change' in the	Yes

management of the condition?	
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes, this technology would address an unmet need for patients affected by AK.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Similar to other types of anti-amoebic treatment, this technology may result in side effects or adverse effects such as red eye, ocular irritation, and inflammation, therefore monitoring of the treatment response (and potential side effects) is required during the treatment period.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
18a. If not, how could the results be extrapolated to the UK setting?	
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	The medical cure rate, which is measured in the trial.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A

18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. How do data on real-world experience compare with the trial data?	They were similar.

Equality

21a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
21b. Consider whether these issues are different from issues with current care and why.	N/A

Key messages

22. In up to 5 bullet points, please summarise the key messages of your submission.	• Acanthamoeba keratitis (AK) is an uncommon but sight-threatening corneal emergency. • Currently, there is no approved drug for treating AK, highlighting an unmet need for AK. • Polihexanide (0.08%) monotherapy provides a valuable addition to the current treatment of AK. • As polihexanide (0.08%) monotherapy demonstrates similar efficacy and safety to the current combination therapy (polyhexanide 0.02% + brolene), it could help improve treatment compliance and reduce burden on the patients and healthcare resources.

Thank you for your time.

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Single Technology Appraisal

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

Clinical expert statement

Information on completing this form

In [part 1](#) we are asking for your views on this technology. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted as '**confidential [CON]**' in turquoise, and all information submitted as '**depersonalised data [DPD]**' in pink. If confidential information is submitted, please also

Clinical expert statement

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

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send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm on Friday 22nd August 2025**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Part 1: Treating acanthamoeba keratitis and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Miss Lana Fu
2. Name of organisation	East Kent Hospitals University NHS Foundation Trust
3. Job title or position	Consultant Ophthalmologist (special interest Cornea)
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with acanthamoeba keratitis? ☒ A specialist in the clinical evidence base for acanthamoeba keratitis or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
8. What is the main aim of treatment for acanthamoeba keratitis? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To cure the condition, prevent loss of vision and/or the eye.

Clinical expert statement

9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Reduction of patient symptoms e.g. pain, improved or stabilised vision, resolution of ocular inflammation.
10. In your view, is there an unmet need for patients and healthcare professionals in acanthamoeba keratitis?	Yes
11. How is acanthamoeba keratitis currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	There is currently no licensed treatment for Acanthamoeba keratitis (AK). There is a lack of consensus/guidelines for the management of Acanthamoeba keratitis with variation within the UK and abroad. There is variation in the access to compounded drugs currently used to treat acanthamoeba keratitis, e.g. different formulations and concentrations of PHMB (polyhexanide). The pathway of care is not well defined, and there is a difference of opinion between professionals across the NHS, e.g. on the timing and indication of starting steroid treatment for the management of associated ocular inflammation and its sequelae. The introduction of a licensed drug for acanthamoeba keratitis will help to standardise the treatment pathway and reduce the risk of treatment delay or initiation.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The PHMB 0.08% should be used in secondary care on diagnosis or clinical suspicion of Acanthamoeba within ophthalmology services. There is no anticipated additional investment needed to introduce the therapy, as it can be stored at room temperature. Co-ordination with hospital pharmacy teams and the committee will be necessary to include it on the formulary. PHMB 0.08% has been used as part of clinical trials, in early access compassionate care programmes in Europe, and also in my NHS trust without any adverse outcomes.

Clinical expert statement

13. Do you expect the technology to provide clinically meaningful benefits compared with current care? - Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	I would expect the licensed medication to reduce the risk of treatment delay for acanthamoeba patients and also reduce the risk of complications associated with unlicensed specials, e.g. compounding errors/contamination. In acanthamoeba keratitis, early diagnosis and initiation of anti-amoebic therapy reduce adverse outcomes.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Easier, as it will be more accessible and able to be stocked with a longer shelf life than the current unlicensed specials.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Initiation is upon diagnosis or clinical suspicion of Acanthamoeba keratitis, based on clinical history, examination, imaging, e.g. confocal microscopy findings.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	The administration of a licensed PHMB 008% will allow the treatment to be more readily available and administered than the current standard of care, which currently relies on unlicensed specials that will need to be ordered.

Clinical expert statement

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	The licensed drug addresses the lack of a readily available, effective drug for treating Acanthamoeba keratitis. So, it will have a positive impact on the health-related benefits for patients who contract this rare infection.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are no additional side effects of the PHMB 0.08%. There could potentially be fewer side effects compared with unlicensed specials due to the risk of compounding errors, e.g. ocular toxicity.
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? - Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	The pivotal trial (ODAK) compared PHMB 0.08% monotherapy with PHMB 0.02% and Propamidine 0.1%. The use of the combined PHMB 0.02% and Propamidine 0.1% was reflective of UK practice at the time of the trial. The most important outcome is clinical cure, defined as the clinical elimination of AK, with an intact corneal epithelium and absence of signs or symptoms of ocular inflammation, after discontinuing anti-amoebic and anti-inflammatory treatments for 30 days. This is then confirmed at a 90-day end-of-study visit. In the ODAK trial, this primary outcome measure was the medical cure rate within 12 months, that is, the proportion of patients achieving clinical cure without needing surgery or a change in anti-amoebic therapy. Dart JKG, Papa V, Rama P, Knutsson KA, Ahmad S, Hau S, Sanchez S, Franch A, Birattari F, Leon P, Fasolo A, Kominek EM, Jadczyk-Sorek K, Carley F, Hossain P, Minassian DC. The Orphan Drug for Acanthamoeba Keratitis (ODAK) Trial: PHMB 0.08% (Polihexanide) and Placebo versus PHMB 0.02% and Propamidine 0.1. Ophthalmology. 2024 Mar;131(3):277-287. doi: 10.1016/j.ophtha.2023.09.031. Epub 2023 Oct 5. PMID: 37802392.

Clinical expert statement

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. NICE understands that some comparators in this appraisal are only available as unlicensed specials (with variability in pricing), specifically: • polihexanide 0.2 mg/ml • polihexanide 0.6 mg/ml • chlorhexidine 0.2 mg/ml Do you have any information on the prices for these comparators?	No, it will depend on where the unlicensed specials are made and their costs according to their manufacturers.
23. Could the fact that some comparators are only available as unlicensed specials impact patient outcomes? • For example, lack of standardised treatment protocols or delays in treatment	Yes, because there is always a risk of contamination with compounding unlicensed medication. This could lead to treatment delay and adversely impact patient care.
24. How do data on real-world experience compare with the trial data?	A recent patient-level indirect treatment comparison (ITC) using data from the ODAK trial and retrospective real-world study of current AK treatments was conducted (Papa et al). The clinical cure rate without surgery within 12 months was 84.8% for PHMB 0.08% (n = 66), 43.6% for any anti-amoebic treatment. 55% for PHMB 0.02% & a diamidine (n = 111), and 40% for chlorhexidine 0.02% with or without a diamidine (n = 35). A separate study by Dart et al comparing outcomes for treatment delivered using a protocol versus physicians' individualised treatment found a 1.59-fold improvement in the medical cure rate at 12 months for protocolized care. Papa V, Galeone C, De Francesco M, Bodicoat DH, Alves R, Spaepen E, Dart JKG, Arteaga C. Polihexanide (PHMB) 0.08% versus currently used treatments

Clinical expert statement

	for <i>Acanthamoeba</i> keratitis: indirect treatment comparisons. BMJ Open Ophthalmol. 2025 Jul 13;10(1):e002082. doi: 10.1136/bmjophth-2024-002082. PMID: 40659372; PMCID: PMC12258341. Dart JKG, Papa V, Rama P, Knutsson KA, Ahmad S, Hau S, Sanchez S, Franch A, Birattari F, Leon P, Fasolo A, Mrukwa-Kominek E, Jadczyk-Sorek K, Carley F, Parwez H, Minassian DC. Acanthamoeba keratitis treatment outcomes compared for drug delivery by protocol versus physician's individualised treatment. Ocul Surf. 2025 Apr 7;38:132-141. doi: 10.1016/j.jtos.2025.03.008. Epub ahead of print. PMID: 40204130.
25. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population	Acanthamoeba keratitis is a rare disease with no current licensed treatment available; this can potentially disadvantage patients who develop this condition. I do not believe this evaluation could exclude any people for whom this treatment is or will be licensed, but who are protected by the equality legislation. I do not believe the recommendations from this technology evaluation will have a different impact on people protected by the equality legislation than on the wider population, or have an adverse impact on disabled people.

Clinical expert statement

- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here](#).

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- There are no licensed therapies for treating Acanthamoeba keratitis in the UK, and there is variation in the treatment delivery and pathways for managing this rare disease.
- Recent clinical trial data provide evidence of similar clinical efficacy using PHMB 0.08% monotherapy compared with dual therapy using PHMB 0.02% + propamidine (widely used combination) when used with the trial treatment protocol.
- PHMB 0.08% monotherapy delivered with the recommended treatment protocol is significantly more effective than currently used treatments in achieving clinical cure without surgery for Acanthamoeba keratitis.

Click or tap here to enter text.

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Clinical expert statement

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

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Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In [part 1](#) we are asking you about living with acanthamoeba keratitis or caring for a patient with acanthamoeba keratitis. The text boxes will expand as you type.

In [part 2](#) we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our [hints and tips for patient experts](#). You can also refer to the [Patient Organisation submission guide](#). **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Patient expert statement

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Your response should not be longer than 15 pages.

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Patient expert statement

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

2 of 7

Part 1: Living with this condition or caring for a patient with acanthamoeba keratitis

Table 1 About you, acanthamoeba keratitis, current treatments and equality

1. Your name	Joe beer
2. Are you (please tick all that apply)	☐ A patient with acanthamoeba keratitis? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with acanthamoeba keratitis? ☐ A patient organisation employee or volunteer? ☒ Other (please specify): lost left eye to AK
3. Name of your nominating organisation	
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☒ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert engagement teleconference

Patient expert statement

	☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with acanthamoeba keratitis? If you are a carer (for someone with acanthamoeba keratitis) please share your experience of caring for them	I suffered from AK during the covid time, so my treatment was compromised & misdiagnosed (as most cases are), & after months of treatment, numerous eye drops I made the decision to have my eye removed, Eviseration
7a. What do you think of the current treatments and care available for acanthamoeba keratitis on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	I have no idea what the treatments are at this time but my main observations are that no one including doctors understand the pain & trauma the someone goes through! The light sensitivity, the pain from both the bug & the drops, both physical & mental. I lost 22kilos during the 6 or so months.
8. If there are disadvantages for patients of current NHS treatments for acanthamoeba keratitis (for example, how they are given or taken, side effects of treatment, and any others) please describe these	N/A
9a. If there are advantages of polihexanide eye drops (0.8mg/ml) over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does polihexanide eye drops (0.8mg/ml) help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	My main experience was of PHMB at 0.2 but was put on 0.8 for a while. At one point I was on so many different drops it was hard to tell which was the worst. Most were like putting tabasco sauce into yr eye, especially Cloro/nide (sorry can't remember name, probably my mind has erased it from my brain) which I couldn't bear at all. PHMB was more bearable but with my outcome I can't comment on its effectiveness. One of the worst was a vial of steroids, which along with all the others I had to put all of the vial in 4 times a day, it sounded easy when explained but was like torture. Every hour on the hour I had what seemed like an endless array of drops to put in, in a certain order!

Patient expert statement

10. If there are disadvantages of polihexanide eye drops (0.8mg/ml) over current treatments on the NHS please describe these. For example, are there any risks with polihexanide eye drops (0.8mg/ml)? If you are concerned about any potential side effects you have heard about, please describe them and explain why	As above the discomfort, pain, mental torture of any of the drops PHMB included, along with dwindling hope, light at the end of the tunnel ends up demoralising
11. Are there any groups of patients who might benefit more from polihexanide eye drops (0.8mg/ml) or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	N/A
12. Are there any potential equality issues that should be taken into account when considering acanthamoeba keratitis and polihexanide eye drops (0.8mg/ml)? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme	As above clinicians need to engage more in understanding the patients side of the story, understanding, understanding..... the team that treated me we on the whole fantastic but at times they were nonplussed with my cries of how painful things were! E.g. I had 2 amniotic membranes surgeries, when the 1st was completed the surgeon said, oh most people have no pain with this procedure but use paracetamol if & when. I woke in absolute agony & I know each person journey is different, from what I have gathered during & since. But I found the bug painful, the drops painful, the mental anguish painful & realise my case was what seemed an extreme case. I tried everything, every painkiller, from gabapentin down nothing really helped & one thing that will help people in the future is how our psyche & our reaction, positive mental attitude etc will enable us to get through with a better mental outcome. Doctors, clinicians need to understand this & help the patient, as I understand most AK sufferers have PTSD, I'm lucky I had help but not from NHS

Patient expert statement

[Find more general information about the Equality Act and equalities issues here.](#)

13. Are there any other issues that you would like the committee to consider?

In my last comment

Patient expert statement

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

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Quicker identification of AK
- More support & understanding for patients (honesty)
- Knowledge that patients will probably suffer from PTSD
- Losing yr eye isn't the end of the world but the treatment at times seems like it
- Every patient is individual

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Patient expert statement

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

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External Assessment Group (EAG) Report

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

Produced by

Centre for Evidence and Implementation Science, University of
Birmingham

Authors

Angela Mwape, Research Fellow in Evidence Synthesis

Christiana Anyebe, Research Associate in Health Economics

Mubarak Patel, Research Fellow in Medical Statistics

Mubarak Patel, Research Fellow in Evidence Synthesis

Rachel Court, Senior Information Specialist

Emma Loveman, Systematic review consultant, Effective
Evidence LLP

Jill Colquitt, Systematic review consultant, Effective Evidence
LLP

Peter Auguste, Assistant Professor in Health Economics &
Decision Modelling

¹Centre for Evidence and Implementation Science, Health
Services Management Centre, University of Birmingham,
Birmingham, B15 2RT

Correspondence to

Dr. Peter Auguste
Centre for Evidence and Implementation Science
Health Services Management Centre
University of Birmingham
Birmingham, B15 2RT

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None

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Rider on responsibility for report

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Contributions of authors

Angela Mwape conducted the review of the clinical effectiveness evidence
Christiana Anyebe conducted the review of the cost-effectiveness evidence and undertook additional analyses
Mubarak Patel conducted the review of the statistical analyses

Mubarak Patel conducted the review of the clinical effectiveness evidence

Rachel Court conducted the review of the literature searches and undertook additional searches

Emma Loveman conducted the review of the clinical effectiveness evidence

Jill Colquitt conducted the review of the clinical effectiveness evidence

Peter Auguste led the project and conducted the review of the cost-effectiveness evidence and undertook additional analyses

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Table of Abbreviations

Abbreviation	Definition
AAT	Anti-amoebic therapy
AE	Adverse event
AK	<i>Acanthamoeba</i> keratitis
BCVA	Best-corrected visual acuity
BNF	British National Formulary
CEM	Cost-effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organisations of Medical Sciences
COMP	Committee for Orphan Medicinal Products
CPI	Consume price inflation
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CUP	Compassionate use programme
DALK	Deep lamellar keratoplasty
DNA	Deoxyribonucleic acid
DSA	Deterministic sensitivity analysis
DSAEK	Descemet's Stripping Automated Endothelial Keratoplasty
DSU	Decision Support Unit
EEPRU	Policy Research Unit in Economic Evaluation of Health and Care Interventions
EMA	European Medicines Agency
EPAR	European public assessment report
ESA	Employment and Support Allowance
ESS	Effect sample size
FAS	Full analysis set
FDA	Food and Drug Administration
GBP	Great British Pounds
GMP	Good manufacturing practice
GV	Good vision
HCRU	Healthcare resource use
HRG	Healthcare resource group
HRQoL	Health-related quality of life
HSK	Herpes Simplex keratitis
HST	Highly specialised technology
HSUV	Health-state utility value
HSV	Herpes simplex virus
ICER	Incremental cost-effectiveness ratio
INHB	Incremental net health benefit
IPD	Individual patient data
IQR	Interquartile range
IRP	International recognition procedure
ISPOR-SMDM	International Society of Pharmacoeconomics and Outcomes Research and Society for Medical Decision Making
ITC	Indirect treatment comparison

Abbreviation	Definition
ITT	Intention-to-treat
IVCM	In vivo confocal microscopy
LogMAR	Logarithm of the minimum angle of resolution
LYG	Life years gained
MAIC	Matching-adjusted indirect comparison
MCR	Medical cure rate
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed model repeated measures
NA	Not applicable
NAS	New Active Substance
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSAID	Non-steroidal anti-inflammatory drug
ODAK	Orphan Drug for Acanthamoeba Keratitis
PAS	Patient access scheme
PCR	Polymerase chain reaction
PHMB	Polyhexamethylene biguanide
PIM	Promising Innovative Medicine
PIP	Personal Independence Payment
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PSM	Propensity scoring matching
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
PTSD	Post-traumatic stress disorder
PV	Poor vision
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
RWD	Real-world data
RWE	Real-world evidence
SAE	Serious adverse event
SAP	Statistical analysis plan
SLR	Systematic literature review
SMD	Standardised mean difference
SMDM	Society for Medical Decision Making
SOC	System organ class
STA	Single technology appraisal
SVL	Severe vision loss
TEAE	Treatment-emergent adverse events
Ther	Therapeutic
TSD	Technical support document
VAS	Visual analogue scale
VBA	Visual Basic for Applications
VFQ	Visual Functioning Questionnaire
VRQoL	Vision-related quality of life questionnaire
WHO	World Health Organisation
WTP	Willingness-to-pay threshold

1 Executive summary

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of EAG's key issues

In Table 1, we present a summary of the key issues identified by the EAG, along with the impact of each individual change/use and further details in the report of where these issues have been discussed.

Table 1: Summary of key issues

ID[6497]	Summary of issue	Impact on results	Report sections
Key issue 1	Inappropriate exclusion of the ODAK trial comparator Based on clinical advice to the EAG and from a methodological point of view the EAG consider that the ODAK trial comparator is relevant to the appraisal. The EAG treats ODAK as a randomised controlled trial (RCT) as its evidence is of value to the appraisal.	Large	Sections 3.2.1, 3.2.2, 3.3
Key issue 2	Exclusion of ODAK comparator in the ITC The company's economic analysis aligns to the economic analysis as set out in the NICE scope. However, the company excluded the ODAK comparator (polihexanide 0.2mg/ml + propamidine 1mg/ml) from the ITC, instead comparing ODAK	Unknown	Sections 3.5.8, 3.5.14 and 3.5.15

	intervention polihexanide 0.8mg/ml + placebo to the pooled/blended AAT from Papa et al. with distributions obtained from the Delphi panel, which used in the economic model.		
Key issue 3	Validity of the company's indirect treatment comparison The EAG identified factors, which questions the internal validity of the ITC and the robustness of the treatment effect estimates underpinning the cost-effectiveness results.	Unknown	Section 3.5
Key issue 4	Mean time-on-treatment used from Franch et al. 2024 The company used mean time-on-treatment from Franch et al. 2024 but used the median time to cure for the pooled AAT. However, the median time-to-cure information is available from the ODAK trial. Also, Franch study had a low number of participants, which may not be representative of the wider population of people with AK.	Large	Section 4.2.18
Key issue 5	██████████ in people treated with polihexanide 0.8mg/ml The company assumed that people who achieved AK resolution following treatment with polihexanide 0.8mg/ml ██████████ ██████████ AK recurrence but assumed that people would experience AK recurrence when treated with pooled AAT.	Medium	Section 5.2.2
Key issue 6	Inclusion of disutilities associated with long-term complications The company included additional disutilities for long-term conditions (e.g., pain, lacrimation, photophobia and anxiety and depression), which they argue might not have been captured because of the trial duration. The EAG argues that this could potentially lead to double counting as this information would have been captured from the patient reported outcomes during the trial	Medium	Section 4.2.14

	and are not likely to change over time.		
AAT, anti-amoebic therapy; AK, acanthamoeba keratitis; EAG, evidence assessment group; ITC, indirect treatment comparison; ODAK, Orphan Drug for Acanthamoeba Keratitis; RCT, randomised controlled trial			

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- Inclusion of the ODAK trial comparator polyhexanide 0.2mg/ml + 1mg/ml propamidine as the main comparator.
- Use the median time-to-cure for polyhexanide 0.8mg/ml rather than using the mean time-on-treatment from the Franch et al (2024)¹ retrospective study.
- [REDACTED] following treatment with polyhexanide 0.8mg/ml
- Exclusion of disutilities associated with long-term complications
- Patient and carers disutilities associated with the intensive treatment period with polyhexanide 0.8mg/ml.
- People treated with polyhexanide 0.8mg/ml may require hospitalisation during the intensive treatment phase.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Utility associated with AK infection and best corrected visual acuity
- Disutilities associated with events including intensive treatment phase, therapeutic surgery, graft failure and optical surgery
- Caregiver disutilities associated with intensive treatment phase, therapeutic surgery, graft failure, loss of eye functionality and severe vision loss and optical surgery

Overall, the technology is modelled to affect costs by:

- Drug acquisition costs, with the technology having a higher price compared to comparator treatments being given as a monotherapy, rather than dual therapy
- Hospitalisation costs. People treated with polihexanide 0.8mg/ml would not require hospitalisation compared to 26.60% of people treated with polihexanide 0.2mg/ml + propamidine 1mg/ml, who would require hospitalisation.
- Costs associated with therapeutic and optical surgeries, and resource use and costs associated with AK infection, visual acuity and loss of eye functionality

Based on the company's deterministic one-way sensitivity analysis, the modelling assumptions that have the greatest effect on the ICER are:

- Discount rate applied to outcomes by using lower and upper values of 1.5% and 6%, respectively.
- Relative risk for medical cure rate at 12 months by using lower and upper values of [REDACTED] and [REDACTED], respectively.
- Duration of treatment (days), polihexanide 0.8mg/ml, using lower and upper values of 72.14 and 129.86 days, respectively.

1.3 EAG's key issues

Summary of the EAG's key issues: In the decision problem

Key issue 1: Inappropriate exclusion of the ODAK trial comparator

Report section	Sections 3.2.1, 3.2.2, 3.3
Description of issue and why the EAG has identified it as important	The EAG considers that the ODAK trial comparator is relevant to the appraisal and the exclusion of the comparator from the main submission and treating ODAK as a single arm study is not appropriate. This is based on clinical advice to the EAG and from a methodological point of view that the randomised controlled trial (RCT) evidence is of value to the appraisal.
What alternative approach has the EAG suggested?	The EAG has treated the ODAK trial as an RCT and presented the ODAK comparator alongside the data from the intervention.
What is the expected effect on the cost-effectiveness estimates?	In the ODAK trial there was non-inferiority between the intervention and comparator. Given the results of the ODAK trial, we expect the ICER to increase by comparing polihexanide 0.8mg/ml versus polihexanide 0.2mg/ml + propamidine 1mg/ml. The EAG undertook this comparison, which resulted in an ICER of [REDACTED].

Could any additional evidence or analyses be provided to resolve this key issue?	Inclusion of the ODAK trial comparator into the model, either directly or from within the ITC would resolve this key issue.
EAG, evidence assessment group; ITC, indirect treatment comparison; ODAK, Orphan Drug for Acanthamoeba Keratitis; RCT, randomised controlled trial	

Summary of the EAG's key issues: Clinical effectiveness

Key issue 2: Exclusion of ODAK comparator in the ITC

Report section	Sections 3.2.1, 3.2.2, 3.3, 3.5, 3.5.8 and 3.5.14
Description of issue and why the EAG has identified it as important	The pooled comparator used in the company submission includes polihexanide 0.2mg/ml, polihexanide 0.6 mg/ml, chlorhexidine, propamidine and hexamidine used in different combinations. However, the company excluded the ODAK comparator (polihexanide 0.2mg/ml + propamidine 1mg/ml) from the indirect treatment comparison, instead comparing ODAK intervention polihexanide 0.8mg/ml + placebo to the pooled/blended anti-amoeba therapy from Papa et al. with distributions obtained from the Delphi panel. The company stated that the effectiveness of the comparator arm is not reflective of therapeutic approaches used in real-world practice and the results are not likely to be replicated in the real-world because, in practice, polihexanide 0.2mg/ml + propamidine requires compounding and this would lead to delays, and there were no delays in the ODAK trial. Additionally, ODAK followed a rigid protocol, compared to real-world practice which is dependent on physician discretion and less likely to result in consistent outcomes. The EAG disagrees with the choice to exclude the ODAK comparator and the focus only on the pooled comparator from Papa et al. A view which was supported by the EAG's clinical experts that polihexanide 0.2mg/ml + propamidine 1mg/ml is standard treatment in real world practice. Additionally, the company contradicts their position by excluding the active comparator arm from ODAK for not being representative but included it as a current treatment in their economic model with the UK Delphi panel stating that polihexanide 0.2mg/ml + propamidine 1mg/ml accounts for 52.3% of therapeutic approaches used to treat acanthamoeba keratitis. By excluding the ODAK comparator from the ITC, this is likely to lead to overestimating the effectiveness of

	polihexanide 0.8mg/ml compared to pooled anti-amoeba therapy, which is a key driver of the economic analysis.
What alternative approach has the EAG suggested?	To reflect this uncertainty, the EAG conducted additional analyses using the company's model by varying the medical cure rate hazard ratios between 0.95 and 1.65 in 0.10 increments, to understand the impact of treatment effect assumptions on cost-effectiveness outcomes. The EAG explored this range due to the lack of IPD available for the EAG to conduct their own analyses.
What is the expected effect on the cost-effectiveness estimates?	In the ODAK trial, it was found that treatment with polihexanide 0.2mg/ml + propamidine 1mg/ml was no less effective than treatment with polihexanide 0.8mg/ml + placebo, and it is likely that the inclusion of the comparator arm in an indirect treatment comparison is likely to reduce the treatment efficacy. Thus, including a reduced medical cure rate in the model is likely to reduce the incremental QALYs and; hence, leading to an increased ICER.
Could any additional evidence or analyses be provided to resolve this key issue?	Additional analyses that could potentially reduce this uncertainty is by including the results of the ODAK comparator arm (polihexanide 0.2mg/ml + propamidine 1mg/ml) in the indirect treatment comparison to see what impact it has on the medical cure rate risk ratio and the economic results. Given the unavailability of the company's individual patient data, we were unable to undertake this analysis.
EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; IPD; individual patient data; ODAK, Orphan Drug for Acanthamoeba Keratitis	

Issue 3: Validity of the company's indirect treatment comparison

Report section	Section 3.5
Description of issue and why the EAG has identified it as important	The EAG considers the company's ITC to be methodologically weak and at a high risk of bias. The company's base case relies on an ITC between the ODAK RCT and Papa et al. (2020), a retrospective cohort with a high risk of bias. The ITC excludes the ODAK comparator arm (polihexanide 0.2mg/ml + propamidine 1mg/ml), which is clinically relevant in the UK setting, and instead compares polihexanide 0.8mg/ml against a heterogeneous pooled comparator group. The EAG considers this approach methodologically weak due to differences in study design, lack of adjustment for important covariates (contact lens use), inconsistent handling of missing data and subsequent treatment, and reliance on a pooled comparator while a direct comparator which is used in clinical practice exists. These factors threaten the internal validity of the ITC and the robustness of the treatment effect estimates underpinning the cost-effectiveness results.
What alternative approach has the EAG suggested?	The EAG explored alternative scenarios, including incorporation of the ODAK comparator arm, and threshold

	analysis varying the risk ratio to reflect uncertainty around the relative effectiveness.
What is the expected effect on the cost-effectiveness estimates?	The expected impact is uncertain. The EAG cannot determine whether the company's ITC over- or underestimated the treatment effect of polihexanide 0.8mg/ml relative to active comparisons. For this reason, the EAG undertook threshold and scenario analyses to assess the consequence of varying treatment effectiveness.
Could any additional evidence or analyses be provided to resolve this key issue?	A new RCT comparison polihexanide 0.8mg/ml against active AATs.
AAT, anti-amoebic therapy; EAG, evidence assessment group; ITC, indirect treatment comparison; ODAK, Orphan Drug for Acanthamoeba Keratitis; RCT, randomised controlled trial	

Key issue 4: Mean time-on-treatment used from Franch et al. 2024

Report section	Section 3.3.1 and 4.2.18
Description of issue and why the EAG has identified it as important	There appears to be inconsistency by using the mean duration of treatment for polihexanide 0.8mg/ml but using the median time-to-cure for pooled AAT, which was obtained from Papa et al. This approach favours polihexanide 0.8mg/ml. The company used the mean time-on-treatment for polihexanide 0.8mg/ml from Franch et al. study rather than using the median time-to-cure information that is readily available from the ODAK trial for people randomised to polihexanide 0.8mg/ml.
What alternative approach has the EAG suggested?	For consistency, the EAG prefers using the median time-to-cure for both polihexanide 0.8mg/ml and pooled AAT. The Franch et al retrospective study included a small number of participants (n=11) and it is in the opinion of the EAG that this sample size would not be representative to determine the treatment duration for people with AK receiving polihexanide 0.8mg/ml. Additionally, there were other differences noted in the baseline characteristics in terms of age and prior topical corticosteroid treatment.
What is the expected effect on the cost-effectiveness estimates?	Using the median time-to-cure rather than mean duration of treatment impacts the base-case by increasing expected total mean costs associated with polihexanide 0.8mg/ml; thus, increasing the ICER by [REDACTED].
Could any additional evidence or analyses be provided to resolve this key issue?	No additional evidence or analyses required.
AAT, anti-amoebic therapy; AK, acanthamoeba keratitis; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio	

Summary of the EAG's key issues: Economic analysis

Key issue 5: [REDACTED] in people treated with polihexanide 0.8mg/ml

Report section	Section 5.2.2 (Table 54)
Description of issue and why the EAG has identified it as important	The company assumed that people who achieved AK resolution following treatment with polihexanide 0.8mg/ml [REDACTED] However, based on the Delphi panel supported by two case studies, the company assumed that people would experience AK recurrence when treated with pooled AAT. In the absence of robust evidence, excluding AK recurrence following treatment with polihexanide 0.8mg/ml is likely to favour this treatment, by underestimating costs and overestimating the benefits. Hence, for a more equitable economic analysis we assumed the same proportion of people would experience AK recurrence in both strategies.
What alternative approach has the EAG suggested?	Given the lack of long-term information, the EAG made a conservative assumption that the same proportion of people who experienced AK recurrence when treated with pooled AAT would experience AK recurrence when treated with polihexanide 0.8mg/ml.
What is the expected effect on the cost-effectiveness estimates?	[REDACTED] in people treated with polihexanide 0.8mg/ml, we expect there to be an increase to the expected mean costs and reduction to the expected QALYs yielded, which are generated from the additional costs associated with treating AK recurrence and QALY loss due to lower utility associated with AK recurrence. Overall, this should lead to an increase to the company's ICER.
Could any additional evidence or analyses be provided to resolve this key issue?	Additional evidence collected through a follow-up would provide evidence whether people treated with polihexanide 0.8mg/ml may experience AK recurrence.
AAT, anti-amoebic therapy; AK, acanthamoeba keratitis; CUP, compassionate use programme; EAG evidence assessment group; ICER, incremental cost-effectiveness ratio; ODAK, Orphan Drug for Acanthamoeba Keratitis; QALY, quality adjusted life year	

Key issue 6: Exclusion of disutilities associated with on-going long-term conditions

Report section	Section 4.2.14
Description of issue and why the EAG has identified it as important	There is the possibility of double counting disutilities associated with on-going long-term conditions of AK. The EAG considered that the ODAK trial already captures the impact of the disease and the associated complications from the HRQoL measure.
What alternative approach has the EAG suggested?	We propose excluding these additional disutilities from the economic analysis.

What is the expected effect on the cost-effectiveness estimates?	Excluding these additional disutilities should result in an increase to the expected QALYs yielded in both the intervention and comparator, and a decrease to the incremental QALYs. Additionally, we expect that that incremental difference between the costs to remain the same as this change should have no impact to the costs. Hence, we expect there to be an increase to the ICER. Making these changes resulted in a decrease to the incremental QALYs from 2.56 to 2.03 and an increase to the ICER by [REDACTED] %.
Could any additional evidence or analyses be provided to resolve this key issue?	No additional evidence or analyses required.
AK, acanthamoeba keratitis; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ODAK, Orphan Drug for Acanthamoeba Keratitis; QALY, quality adjusted life years	

1.4 Secondary issues identified by the EAG

Here, we highlight secondary issues, which are areas of uncertainty but have less impact on the company's base-case ICER.

Issue 7: Patient and carers disutilities associated with the intensive treatment period with polihexanide 0.8mg/ml

Report section	Section 4.2.16
Description of issue and why the EAG has identified it as important	The company excluded disutilities in the intensive phase during treatment with polihexanide 0.8mg/ml, but disutilities were included for treatment with pooled AAT even with treatment switching. This was justified on the basis that polihexanide is administered at daytime only and does not lead to sleep deprivation. Clinical advice to the EAG indicates would not treat AK with daytime only medication even with high concentration of polihexanide, despite the published treatment schedule in the MHRA and EMA SmPCs; in an exploratory analysis, patient and caregivers' disutility was applied to treatment with polihexanide 0.8mg/ml.
What alternative approach has the EAG suggested?	The EAG has considered the inclusion of intensive phase disutilities, for patients and carers, together and individually.
What is the expected effect on the cost-effectiveness estimates?	The effect on ICER was negligible for the 3 scenarios explored. The joint, patients and carers respectively resulted in increase of [REDACTED], [REDACTED] and [REDACTED] to the company base case ICER.
Could any additional evidence or analyses be provided to resolve this issue?	No additional evidence or analyses required.

AAT, anti-amoebic therapy; AK, acanthamoeba keratitis; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio

Issue 8: People treated with polyhexanide 0.8mg/ml may require hospitalisation

Report section	Section 4.2.20
Description of issue and why the EAG has identified it as important	The company claimed that treatment with polyhexanide 0.8mg/ml will be less burdensome to the patient because eyedrops would be administered during the daytime only. Hence, they assumed that there would be no costs associated with hospitalisation during the intensive treatment phase. The company assumed that 26.60% of people treated with pooled AAT would be hospitalised during the intensive treatment phase. In the opinion of our clinical experts some people commencing treatment with polyhexanide 0.8mg/ml are likely to be hospitalised because they will not treat AK with daytime only medication even with high concentration of polyhexanide, despite the published regulatory label of polyhexanide 0.8mg/ml and recommended daytime only posology.
What alternative approach has the EAG suggested?	In the absence of available information about the percentage of people requiring hospitalisation during the intensive treatment phase with polyhexanide 0.8mg/ml, we assumed that the same proportion of people (26.60%) as those requiring hospitalisation during the intensive treatment phase with pooled AAT would require hospitalisation.
What is the expected effect on the cost-effectiveness estimates?	We expect there to be a change to the expected mean cost of polyhexanide 0.8ml/ml, with no change to the comparator or difference in QALYs. Implementing this change resulted in an increase of [REDACTED] to the company's updated base-case ICER submitted at clarification stage.
Could any additional evidence or analyses be provided to resolve this issue?	This input is not a key driver of the economic analysis, even if we assumed that 100% of people commencing treatment with polyhexanide would require hospitalisation.
AAT, anti-amoeba therapy; EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio	

1.5 Company's modelling errors identified by the EAG

The EAG has not identified any modelling errors.

1.6 Summary of EAG's preferred assumptions and resulting ICER

Table 2: Summary of EAG preferred assumptions (pairwise comparison)

Scenario	Incremental cost (£)	Incremental QALYs	ICER (£) (change from company's base case)	INHB at £20K	INHB at £30K
Company's base case Company's deterministic results submitted at clarification stage.	[REDACTED]	2.56	[REDACTED]	[REDACTED]	[REDACTED]
EAG's corrected company base case (not applicable)	[REDACTED]	2.56	[REDACTED]	[REDACTED]	[REDACTED]
Key issue 1: Inappropriate exclusion of the ODAK trial comparator (Issue 2). These results are based on the comparison between polihexanide 0.8mg/ml versus polihexanide 0.2mg/ml + propamidine 1mg/ml	[REDACTED]	0.10	[REDACTED]	[REDACTED]	[REDACTED]
Key issue 3: Mean time-on-treatment used from Franch et al. 2024 (Issue 3)	[REDACTED]	2.54	[REDACTED]	[REDACTED]	[REDACTED]
Key issue 4: [REDACTED] in people treated with polihexanide 0.8mg/ml	[REDACTED]	1.71	[REDACTED]	[REDACTED]	[REDACTED]
Key issue 5: Exclusion of disutilities associated with on-going long-term conditions	[REDACTED]	2.03	[REDACTED]	[REDACTED]	[REDACTED]
Additional EAG preferred assumption: include disutilities (patients and caregivers) associated with the intensive treatment period with polihexanide 0.8mg/ml	[REDACTED]	2.54	[REDACTED]	[REDACTED]	[REDACTED]
Additional EAG preferred assumption: Assume that 26.60% of people treated with	[REDACTED]	2.56	[REDACTED]	[REDACTED]	[REDACTED]

polihexanide 0.8mg/ml would require hospitalisation					
EAG's preferred base- case deterministic		-0.11			
EAG's preferred base- case probabilistic		-0.20			
EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; ODAK, Orphan Drug for Acanthamoeba Keratitis; QALY, quality-adjusted life year					

1.7 Outline of confidential comparator or subsequent treatment prices

The EAG has not submitted a confidential appendix to the EAG report because there are no confidential comparator or subsequent treatment prices.

2 Background

This report critiques the company submission for polihexanide eye drops for acanthamoeba keratitis (AK) in people 12 years and over.

2.1 Critique of the company's description of underlying health problem

The company discusses the disease pathophysiology and risk factors for AK, symptoms of AK and burden of AK in CS sections 1.3.1 to 1.3.3. The EAG notes that many of the references cited by the company are secondary sources of evidence, such as overviews or websites. AK is described as a very rare, devastating, sight threatening disease. The incidence in England and Wales has been estimated at 2.41 per million per year.²

Disease pathology and risk factors

The pathophysiology of AK reported by the company in CS section 1.3.1 is as described in the cited reference,³ although the EAG notes this is a secondary reference. AK is caused by *Acanthamoeba*, unicellular protozoan parasite, which adheres to the surface of the cornea of the eye. This triggers phagocytosis and the release of enzymes and toxins, leading to epithelial destruction and apoptosis which allow invasion into the stroma and then into the cornea. Damage to the corneal nerve can occur, which causes severe pain. Intraocular infection is rare. The mechanism of action is depicted in CS Figure 1, which is reproduced from another source.⁴ There are two life-cycle stages of *Acanthamoeba*; the trophozoite stage is when they are active and mobile, causing damage and symptoms, and the dormant cyst phase is when they are passive, with a protective double-walled cell that allows them to survive in harsh environments for months to years.⁵ The cyst phase can occur due to exposure to treatments, and if treatment is stopped early or lacks effectiveness, the cysts can revert to active trophozoites. The EAG notes that one of the company's cited reference⁵ is a website by the AK Eye Foundation which does not provide citations for the primary sources. The other reference⁶ is also secondary reference but doesn't appear to discuss relapse occurring years after treatment as per the company's statement.

The company states that poor contact lens hygiene accounts for 87% of AK cases, and lists other risk factors as eye trauma, overnight wear, prolonged use and lens use during activities like swimming and showering. Three references are cited.^{2, 3, 7} The first is a recent UK study, which found that 87% of 124 AK cases were contact lens wearers, 2.4% of cases were related to trauma, and no etiological risk factors were identified in 10.5% of cases.² However, the study was unable to make any conclusions on potential risk factors due to missing data regarding specific contact lens care and products and hygiene practices, including exposure to tap water. The second reference³ is an overview, which cites the company's third reference.⁷ This is a UK study on cases presenting between 1997 to 1999 of 106 cases. It found the risk of AK was nine times greater among contact lens users in the south compared to the Midlands and north. In addition, hard water was significantly associated with a threefold increase in the risk of AK when compared with soft water. Data suggested that one to four weekly disposal lenses were associated with a significantly higher risk than daily disposable lenses. The study notes that 'although overnight wear has never been identified as a significant risk factor for *acanthamoeba* keratitis, the continuity of wear may increase the likelihood of the lenses being used while engaged in water sports'. One or more previously identified risk factors (swimming with contact lenses, irregular or omitted disinfection, and poor basic contact lens storage case hygiene) were identified for 91% of 55 participants who provided information. Showering with contact lenses wasn't assessed as a risk factor, but authors suggested it as a way contact lens users may contaminate their lenses with tap water. It is possible that advances have been made in the last 25 years in contacts lens solutions and advice to patients.

Symptoms of AK

The company describes three stages of AK, citing Dart 2024,⁸ the publication of the key trial. The three stages are described under 'Definitions used in the trial' of Dart 2024,⁸ but are not referenced. CS 1.3.2 also cites a number of other references when describing the stages,^{6, 9-14} but while one of these (Dart 2009⁶) describes typical clinical features according to duration of symptoms (not stated as 'stages'), and some of the other papers mention early and advanced AK, there doesn't seem to be an agreed standard definition of these stages. Nevertheless, the EAG clinical

advisors agreed that the 'stages' presented by the company do appear to be appropriate.

Vision loss is reported to occur in around a third of patients with AK, however this is only stated in the background section of the cited publication¹⁵ and is not an outcome of the study. This publication in turn cites another secondary source (Dart 2009⁶). Blindness (severe vision loss) is stated to occur in about 25% of cases, as reported by a UK study (Papa 2020¹⁶). Delayed treatment has been associated with poorer prognosis.^{17, 18}

The company asserts that cure of AK is essential for preventing long-term complications, preserving vision and alleviating symptoms, and states that definitions of clinical resolution/cure can vary in the literature. The EAG agrees with this, and notes that only 58% of the eligible studies in the company's literature review reported some form of resolution or cure as an outcome. The stringent definition cited, healed corneal epithelium and no signs of ocular inflammation, after one month off from any therapy (anti-amoebic or anti-inflammatory), was used in the company's key trial (ODAK⁸) and the selected comparator study (Papa 2020¹⁶), which have an overlap of authors. The company and EAG were unable to identify any other studies that have used this definition. Patients are often treated for several months with pharmacological and sometimes surgical interventions in the case of persistent infection. Therefore, reducing time to cure is important to reduce the risk of disease progression and severe complications, and is considered another measure of treatment success. Papa 2020¹⁶ found a median time to cure of 5 months (IQR 3.25 to 9.00 months). The CS states that >50% fail a cure at 12 months and cites the ODAK trial 2022 clinical study report (CSR) and the company's 2025 ITC report (both provided to the EAG as 'data on file' references), but it is unclear how these data were derived.

Burden of AK

The company describes the physical and mental burden of symptoms on Health-related quality of life (HRQoL) of patients, and the burden placed on caregivers due to ongoing care needs. Symptoms including extreme pain, photosensitivity, redness and swelling, deformation of the eyeball, intense and constant tearing and vision impairment. Vision impairment has a major impact on daily activities, social

interactions and working. Patients report anxiety and depression due to constant pain, sleep disturbances and isolation, and also frustration and anger due to uncertainties associated with delayed diagnosis, complex treatment regimens and the risk of vision loss. The sources of information cited include a qualitative study funded by the company, which involved interviews with [REDACTED] (report provided to the EAG, filename: 'SIFI. Data on File. Patient Journey of Acanthamoeba Keratitis Patients. 2022'), a White paper from the Global Alliance Against Acanthamoeba Keratitis,¹⁹ which includes quotes from patients, and a review article.²⁰ Although none of these studies have used a validated HRQoL measure, the company notes that the average baseline utility of their key trial is lower than that of the general population in the UK.²¹

Impact on health care resource use

Information on health care resource use (HCRU) is sourced from the qualitative study (SIFI. Data on File. Patient Journey of Acanthamoeba Keratitis Patients. 2022) and UK Delphi panel (report v3.0 provided to the EAG at clarification, filename: 'Technical report Delphi panel on acanthamoeba keratitis in the UK v3.0'), both funded by the company. Healthcare appointments are needed every 2-3 days, which can be decreased with response to treatment. An average of nineteen ([REDACTED]) ophthalmologist or optometrist visits per year are estimated to be needed for most people, and nurse (mean 7.2, [REDACTED]) and psychiatric (mean 1.1, [REDACTED]) visits may also be required. Disease monitoring appointments can involve an intraocular pressure check (16.1 times per year, [REDACTED]) and ophthalmoscopy (9.6 times per year). In addition, the Delphi panel estimated that about a quarter of patients are hospitalised during the initial intensive phase of treatments, for an average of 4 days ([REDACTED]).

2.2 Critique of the company's overview of current service provision

Prior to marketing authorisation of polihexanide 0.8mg/ml, there was no approved therapeutic treatment for AK in England and Wales, and there is currently no definitive standard of care (SoC). Management relies on unlicensed or off-label anti-amoebic therapies (AATs), typically used individually or in combination. Common agents include biguanides such as polihexanide (0.2mg/ml or 0.6mg/ml) which is a lower strength compared to that of the current appraisal (polihexanide 0.8mg/ml) and chlorhexidine and diamidines such as propamidine and hexamidine. In the UK, propamidine is often the first-choice diamidine, whereas hexamidine is more commonly used in Italy.²² The EAG clinical experts highlight that currently, in UK clinical practice, polihexanide or chlorohexanide, often combined with propamidine, are commonly used in the absence of robust randomised controlled trials (RCTs).

A UK Delphi panel commissioned by the company identified nine different combinations of AATs in clinical use, the most frequent being polihexanide combined with a diamidine (CS Section 1.3.5, Table 3). To assess the validity of these findings, the EAG requested additional details of the panel membership, the questions asked, and median and minimum-maximum values of responses (Clarification Question A7). In response the company provided a two-round survey report involving 13 UK ophthalmologists (10 completing both rounds) from NHS centres across multiple regions. The survey covered epidemiology, treatment patterns, surgery, recurrence, outcomes and HRQoL/resource use. Results were reported as means with minimum, maximum, and 90% CIs. The EAG notes that while the survey provides qualitative insight in the absence of epidemiological data, the small sample size, self-reported practice, and reliance on mean values (which may misrepresent skewed data) limit its generalisability.

The CS (Section 1.3.5) states that this heterogeneity in UK practice reflects the absence of a licensed product and the lack of nationally standardised treatment protocols. This creates variability in care, with prescribing ophthalmologists applying local protocols or clinical judgement, resulting in differing treatment combinations and potentially variable clinical outcomes. The EAG clinical experts agree with this,

although they report that the most commonly used treatment in the UK is polihexanide 0.2mg/ml with propamidine.

A further challenge is timely access: the CS (Section 2) reports a mean delay of 17.7 days from diagnosis to treatment initiation due to the short shelf life and compounding requirements of current biguanides. This value was calculated from the UK Delphi panel estimates, which ranged from [REDACTED] days. However, the EAG clinical experts suggested 48 hours is the maximum delay in their centres, with up to three to five days maximum as an exception. The EAG experts also noted that regional pharmacies can keep a stock of polihexanide to avoid treatment delays.

Existing regimens also impose a high treatment burden, often requiring hourly administration day and night, which can significantly disrupt sleep and reduce quality of life. Furthermore, the CS states that the initial phase of treatment may require patients to administer drops every 20 to 30 minutes during the night. The EAG clinical experts disagree, stating that drops may be administered every hour, day and night for two days in the initial phase.

The CS reports that in current practice those not cured with medical therapy may require surgery. There are two types of keratoplasty (corneal transplant from a donor), therapeutic keratoplasty and optical keratoplasty. Therapeutic keratoplasty is performed for corneal perforation, or for non-healing epithelial defects or to eradicate AK as a last resort, although this is less common.²³ Optical keratoplasty an elective procedure conducted when the infection is presumed to be eradicated, for visual rehabilitation of the eye.²³ Enucleation involves removal of the entire eyeball and optical nerve and may be required in severe cases. The company presented data from the UK Delphi panel suggesting 21.5% of patients not cured with medical therapy (including those who switched to another AAT after 12 months) underwent therapeutic surgery (range of responses [REDACTED]). The company does not state what proportion of patients would not be cured, but the EAG believes that in the Delphi report the estimates provided suggest that 41.9% of all AK patients would not be cured, and that 21.5% of these would need therapeutic keratoplasty. The EAG clinical experts considered the estimate to be high, unless it included optical surgery, which it does not appear to from the information provided.

Graft rejection can occur after keratoplasty. Other surgeries may be required once the AK infection has been eradicated (CS section 1.3.5).

The CS reports that these limitations in the current treatment pathway and lack of SOC as a clear unmet need. The company positions polihexanide 0.8mg/ml as the first licensed, targeted monotherapy for AK in adults and children from 12 years. According to the CS (Section 1.3.6), polihexanide 0.8mg/ml addresses an unmet need for a stable, good manufacturing practice (GMP)-quality treatment, offering reduced treatment burden via daytime-only dosing and improved access through longer shelf life and standardised manufacture. Advice to the EAG suggests that at the present time it is unlikely that centres would administer polihexanide during the daytime-only, even at the 0.8mg/ml dose, despite the published regulatory label of polihexanide 0.8mg/ml and recommended daytime only posology. The EAG clinical experts also highlight that this concentration has not been used in UK practice and caution that higher concentrations may cause corneal scarring and inflammation. In addition, the EMA noted that there was uncertainty regarding the proposed benefit of the higher dose of polihexanide compared to usually administered lower doses with no evidence of clinical benefit over lower doses established; the EMA approval was driven by the urgent clinical need and the clear improvement over no treatment.²² Further comments from the EMA are reported in Section 3.6.2.

The EAG notes that polihexanide 0.8mg/ml represents a novel, licensed option that could address issues of supply, stability, and manufacturing consistency. EAG expert opinion supports the need for a licensed treatment but raise concerns about potential safety implications of higher concentrations, and assumptions regarding treatment delays and burden reduction. The company's Phase I dose-escalation trial compared safety outcomes (dose-limiting events i.e. all SAEs and AEs that prompted interruption of the study drug) between polihexanide 0.2mg/ml, 0.4mg/ml and 0.8mg/ml. No SAEs occurred in any dose group. The safety profile of polihexanide 0.8mg/ml was also established in the Phase III ODAK clinical trial programme, in which the overall rates of AEs and severe AEs were similar between polihexanide 0.8mg/ml and polihexanide 0.2mg/ml + propamidine 1mg/ml and the majority of AEs were mild or moderate in severity."

2.3 Critique of the company's definition of decision problem

The decision problem in the CS has some differences to the final NICE scope. The key difference being the choice of comparator. The comparator in the company's decision problem is a blended group of treatments which were aligned with those stated in the NICE scope with one additional treatment, polihexanide 0.6mg/ml. This choice excludes any comparison with the most commonly used treatment and the EAG considers that a comparison with the individual treatments in the NICE scope, where data permit, should have been undertaken. This has a bearing on the economic analysis as described in detail in Table 3.

Table 3: Summary of decision problem

Item	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
Population	Adults and children from 12 years of age with AK	Adults and children from 12 years of age with AK	NA	The population in the decision problem matches the NICE scope and marketing authorisation. The characteristics of the population generally reflects the patient population in England and Wales eligible for treatment.
Intervention	Polihexanide 0.8mg/ml	Polihexanide 0.8mg/ml	NA	The intervention in the company's submission matches the intervention in the scope. Polihexanide 0.8mg/ml is a preservative-free biguanide with a dual mechanism of action to disrupt Acanthamoeba cell membranes and bind amoebal DNA to block Acanthamoeba replication. It has marketing authorisation from the European Medicines Agency (EMA) and the Medicines and Healthcare products Regulatory Agency (MHRA)
Comparators	Used individually or in combination: Polihexanide 0.2mg/ml Chlorhexidine Propamidine Hexamidine	A pooled AAT comparator in which the following are used individually or in combination: Polihexanide 0.2mg/ml Chlorhexidine Propamidine Hexamidine	The proposed comparator is in line with the NICE final scope, comprising compounded/off label polihexanide 0.2mg/ml, chlorhexidine and diamidines (propamidine and hexamidine) used individually or in	The pooled comparator used in the CS includes treatments stated in the scope (polihexanide 0.2mg/ml; chlorhexidine, propamidine and hexamidine) used in different combinations in different

Item	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
		Polihexanide 0.6mg/ml	combination. This reflects findings from a Delphi panel conducted in the UK, which informs the distribution of the comparator. Compounded polihexanide 0.6mg/ml is also included as part of the pooled AAT comparator as a small proportion of patients who had received this treatment were identified in a UK-based Delphi panel which is used to inform this submission. A pooled comparator is presented to reflect the heterogeneity of treatment classes and regimens received by patients in UK clinical practice in the absence of a SoC.	individuals. The pooled comparator group also includes individuals who were treated with polihexanide 0.6 mg/ml. These data were from a retrospective cohort study. The CS excludes their own comparator polihexanide 0.2mg/ml used in combination with propamidine 1mg/ml which was used in their registration trial, ODAK. The CS decision was based on concerns regarding the treatment protocols used to administer polihexanide 0.2mg/ml + propamidine 1mg/ml within the trial, which do not reflect how patients would receive this therapeutic approach in the real-world (discussed further in sections 3.5, 3.5.8 and 3.5.15). The CS also excludes data for each of the four treatment subgroups of the retrospective cohort study (polihexanide 0.2mg/ml monotherapy, polihexanide 0.2mg/ml and diamidine, diamidine monotherapy, combined AAT [polihexanide 0.2mg/ml and chlorhexidine and diamidine]).

Item	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				The EAG disagrees with the choice to exclude the ODAK comparator and the focus only on the pooled comparator from the retrospective cohort study. The EAG approach to the comparators is discussed in more detail in sections 3.5.8 and 3.5.15.
Outcomes	The outcome measures to be considered include: Clinical resolution rate Time-to-cure Visual acuity Reduction of symptoms (for example: pain, swelling, redness) Adverse effects of treatment Health-related quality of life	The outcome measures include: Clinical resolution rate Time-to-cure Visual acuity Reduction of symptoms (pain as captured in health-related quality of life measures, corneal scarring, ulceration severity and anterior chamber inflammation) Adverse effects of treatment Health-related quality of life	The outcomes presented are in line with the NICE final scope. Pain was not measured as a distinct outcome in the pivotal ODAK trial; however, the EQ-5D-5L includes a domain on pain/discomfort and the VFQ-25 includes a measure of ocular pain. Reduction of symptoms is also addressed in this submission through inclusion of data on corneal scarring, ulceration severity and anterior chamber inflammation from the ODAK trial.	The outcomes match the scope. Clinical resolution rate was defined as Medical Cure Rate (MCR) and the company based their definition on that used in the ODAK trial. The definition of MCR used in the retrospective cohort study was comparable. Pain is a key symptom of AK as noted in the scope. The CS does not have a direct measure of ocular pain, however, the EAG are satisfied that ocular pain is addressed through the health-related quality of life tools used in the ODAK trial.
Economic analysis	Cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.	Cost-effectiveness of polihexanide 0.8mg/ml is expressed in terms of incremental cost per quality-adjusted life year.	The results, time horizon and perspective of the economic analysis for polihexanide 0.8mg/ml are in line with the NICE reference case. ³ A simple PAS is proposed in this	The company's economic analysis aligns to the economic analysis as set out in the NICE scope. However, the company excluded the ODAK comparator (polihexanide 0.2mg/ml +

Item	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
	The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The cost effectiveness analysis should include consideration of benefit in best and worst seeing eyes.	A lifetime horizon is used in the model and the base case perspective is NHS and Personal Social Services. The cost-effectiveness model includes consideration of the worst seeing eye only.	submission (see Table 2 below). The pivotal source of efficacy data for polihexanide 0.8mg/ml is the ODAK trial, which reports outcomes only for the worst seeing eye. There are no data available to support a best seeing eye cost-effectiveness analysis of polihexanide 0.8mg/ml and this has therefore not been presented.	propamidine 1mg/ml) from the ITC, instead comparing ODAK intervention polihexanide 0.8mg/ml + placebo to the pooled/blended AAT from Papa et al. with distributions obtained from the Delphi panel, which used in the economic model. The company provided their rationale for excluding the ODAK comparator from the ITC: a) <i>'The effectiveness of the active comparator arm in the ODAK trial is not reflective of therapeutic approaches used in real-world practice and the results for this trial arm are not likely to be replicable in the real-world clinical setting.'</i> (CS, page 25) No compounding delays in the ODAK trial. In practice, polihexanide 0.2mg/ml + propamidine 1mg/ml) requires compounding, which leads to treatment delays, which

Item	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comment
				was not an issue in the trial. • ODAK followed a rigid protocol, compared to real-world practice which is dependent on physician discretion and less likely to result in consistent outcomes. The EAG consulted with their clinical experts and considers this as a major omission as highlighted in sections 3.5, 3.5.8 and 3.5.15.
AK, acanthamoeba keratitis; CS, company submission; EAG, evidence assessment group; EQ-5D-5L, EuroQol 5-dimension with five levels; MCR, medical cure rate; NA, not applicable; ODAK, Orphan Drug for Acanthamoeba Keratitis; SoC, standard of care; VFQ, visual function questionnaire				

3 Clinical effectiveness

This section presents a summary and critique of the clinical-effectiveness evidence included in the company's submission. Section 3.1 focuses on the company's review of clinical and safety evidence. Sections 3.2 to 3.3 provide a critique of the included studies and clinical-effectiveness analyses. Sections 3.4 to 3.5 critique any indirect comparisons presented by the company. Section 3.6 covers additional work undertaken by the EAG.

3.1 Critique of the methods of review

The company conducted a systematic literature review (SLR) to evaluate the efficacy and safety of therapeutic approaches used for AK. The SLR was conducted from a global perspective, therefore included comparators that were not specified on the NICE scope.

3.1.1 Search strategies

Searches sought data relevant to the SLR aim and eligibility criteria. Searches in an adequate set of bibliographic databases were undertaken on 25th and 26th July 2022 and updated on 24th March 2025. Database searches were limited to 1995 onwards, and reasonable justification is given. Suitable terms for AK and interventions / comparators were included. Overall, standard database searching retrieved low numbers (e.g. 221 in PubMed, 16 in CENTRAL) because AK is a rare disease and terms for outcomes were unnecessarily included in the searches (this is not good practice because article records do not reliably include all study outcomes). Positively, backwards and forwards citation searching of 48 eligible articles included in the SLR and 11 identified SLRs (Clarification question A1 response, table 1) was also performed, along with checks of relevant, recent conferences and trial registers. Additionally, a targeted literature review performed before the SLR was undertaken, was checked.

3.1.2 SLR methods

A full SLR report was submitted in the company's reference pack. A summary of the EAG's assessment of the SLR is presented in Table 4. The methods of the review

were generally appropriate, although it was unclear how many data extractions were not validated by a second reviewer, and risk of bias (ROB) assessments were undertaken by only one reviewer in the 2025 update, which is not best practice.

The eligibility criteria for the SLR were generally appropriate, although the EAG had a few concerns. The SLR included studies with an ophthalmic eye drop medication or oral miltefosine (which the EAG clinical experts confirmed is not used in the UK) in any concentration or combination, therefore interventions beyond the scope of the current appraisal were included. However, studies that reported treatment regimens with a combination of treatments were only eligible if all participants (or a subgroup with reported outcomes) received the same combination of treatments. Studies were excluded if outcomes were only reported for study populations where participants did not all receive the same treatment regime as each other. Given that the comparator selected by the company in the decision problem is a pooled AAT comparator, it is possible that some relevant studies may have been excluded. However, the EAG did not check further because the EAG preferred comparator was polihexanide 0.2mg/ml with propamidine (see Section 3.6 for EAG screening of studies identified in the SLR). Reduction of symptoms was not listed as an eligible outcome, but otherwise outcomes eligible for the SLR were in line with the NICE scope. Most of the included studies were not discussed further in the CS, other than tabulation of limited summary details CS (Appendix Tables 5 and 7, Clarification Table 22). The processes of the feasibility assessment for identifying studies for the matching-adjusted indirect comparison (MAIC) were not reported, despite the EAG requesting this (Clarification A6).

Table 4: Summary of SLR methods and EAG assessment of robustness

Systematic review step	EAG assessment of robustness of methods
Searches	Appropriate. Although the inclusion of outcome terms in the traditional database searches is likely to have reduced sensitivity and led to low numbers, other approaches (extensive citation searching, checking trial registers and recent conference proceedings) improved the overall search strategy.
Inclusion criteria CS Appendix Table 4	The SLR was conducted from a global perspective and included interventions not specified on the NICE scope. The EAG clinical expert's opinion on the additional interventions was that they are not widely used in UK practice.

	Studies that included treatment regimens with a combination of treatments remained eligible so long as all participants (or a subgroup with reported outcomes) received the same combination of treatments. Studies were excluded if outcomes were only reported for study populations where participants did not all receive the same treatment regime as each other. Given that the comparator selected by the company in the decision problem is a pooled AAT comparator, some relevant studies may have been excluded (see Section 3.6 for EAG screening of studies). The eligible outcomes listed in CS Table 4 were appropriate. However, studies that did not report cure rate were later excluded, making cure rate the only eligible outcome in the SLR. Only studies selected in the feasibility assessment were include in a narrative discussion. Date of publication was limited to the last 30 years. No justification was given for this, but this was considered appropriate by the EAG.
Screening B.1.2	Appropriate: screening by two independent reviewers, with the record proceeding to the next stage in cases of disagreement.
Selection of included studies CS Appendix B.1.2	Appropriate: Full text screening by two independent reviewers with consensus through a third reviewer if needed. In Appendix B Figure 1 PRISMA, the numbers in the flow diagram and text do not appear to be correct (2250 records minus 704 duplicates equals 1546, not 1539), however the company explained in Clarification C2 that additional duplicates were removed automatically on import into Covidence screening software. 48 studies were initially included; limited summary details of these were presented in CS Appendix Table 5. Details of the interventions and pdfs were provided in response to Clarification A27. A feasibility assessment was then undertaken to identify whether any of the 48 included studies reported clinical resolution rate using a definition that was 'sufficiently aligned' with that used in ODAK. The EAG asked for details of the process (e.g. were the criteria pre-stated, how many reviewers), but the company did not provide this as they said the feasibility assessment was separate to the SLR. (Clarification A6). The 20 studies that did not report cure were not discussed further in the CS. These were checked by the EAG, See Section 3.6. Definitions of cure reported by the remaining 28 studies were presented in Appendix Table 7. The company considered that only the Papa 2020¹⁶ study used a definition aligned with ODAK. The process for establishing that is unclear. The EAG checked these studies, see Section 3.6. A list of 133 studies excluded at full text with reason for exclusion was provided in CS Appendix Table 6, and pdfs were provided in response to Clarification C3. These were checked by the EAG (Section 3.6). The company selected a real-world evidence study of polihexanide 0.8mg/ml (Franch 2024¹) to support the results of the ITC (CS 2.13.1) and to provide alternative treatment effectiveness results in a scenario analysis (CS 3.3.2.1). The study was in the list of 28 studies reporting cure rate, but the process of selecting this study was not reported.

Data extraction	Data extraction was undertaken by one reviewer, with validation by a second reviewer for all studies in the 2022 SLR and for 50% of studies in the 2025 update, with disagreements resolved through discussion and a third reviewer if needed. The CS does not report how many studies were identified at the 2025 update so it is unclear how many study extractions were not validated Pre-planned requests for data from study authors for missing data on medical cure rate were made. Only 66.7% of authors were contacted due to lack of contact details in the remaining studies.
Tools for quality assessment	Risk of bias was assessed using National Heart, Lung and Blood Institute's Study Quality Assessment Tools by two reviewers in the 2022 SLR and by one reviewer in the 2025 update; this is not considered best practice. ODAK was assessed as an RCT, despite it being considered a single arm study for the appraisal. The EAG requested that the company assess it as a single arm trial for completeness, and this was provided in Clarification A16.
Evidence synthesis	Clinical and safety outcomes (other than cure rate in selected studies) of the 48 'included' studies were not reported or discussed in the CS. A narrative synthesis was presented in the separate SLR report provided to the EAG (SIFI. Data on File. Clinical and epidemiological evidence for treatments in Acanthamoeba keratitis: systematic literature review report. 2025).
AAT, anti-amoeba therapy; CS, company submission; EAG, evidence assessment group; HRQoL, health related quality of life; ITC, indirect treatment comparison; RCT, randomised-controlled trial; SLR, systematic literature review	

3.2 Critique of the methods of the trials of the technology of interest

The pivotal study providing safety and efficacy data for AK is the ODAK (Orphan Drug for AK) trial (NCT NCT03274895).²⁴ The ODAK study characteristics are described in the CS Section 2.3.1. The trial was a prospective, randomised, double-masked, active-controlled, multicentre phase 3 study. The trial compared polihexanide 0.8mg/ml (0.08%) and placebo with polihexanide 0.2mg/ml (0.02%) and propamidine 1mg/ml (0.01%) as an active comparator arm in people with AK.

3.2.1 ODAK study design

The EAG summary of the key characteristics of the ODAK trial, based on the company submitted information, is reported in Table 5. Table 5 combines data obtained and checked by the EAG from the CS with the available clinical study report (CSRs), NCT record,²⁴ company protocol version 2²⁴ and publication.⁸

ODAK was designed to evaluate the efficacy and safety of a polihexanide formulation for AK treatment (CS, section 2.3.1). Conducted across six European centres in Italy, Poland and the UK, the trial ran from August 17, 2017, to June 18, 2021. It was a pivotal clinical trial, aspects of which were designed following feedback from the European Medicines Agency (EMA).²² The trial was primarily designed as a superiority study but also included the possibility to test for non-inferiority if the superiority hypothesis was not met. This approach was used following feedback based on an EMA methodological guideline.²² A predefined non-inferiority margin was set at 20 percentage points. According to the ODAK statistical analysis plan (SAP), this margin was chosen to ensure the test treatment retained at least 50% of the standard treatment effect over placebo, based on historical data. Clinically, the margin was justified on the basis that a small delay in response from using a biguanide monotherapy would not be expected to lead to blindness or serious morbidity, given the slow progression of AK and the close monitoring of patients in practice. The study protocol also included safeguards typical of non-inferiority designs, such as minimising protocol deviations, requiring consistency across full analysis and per-protocol sets, and ensuring the comparator treatment demonstrated its usual level of efficacy.

Eligible participants were 12 years of age or older, with clinical findings consistent with AK (e.g., epithelial, stromal, extra corneal lesions) and in vivo confocal microscopy (IVCM) findings consistent with AK who were randomised 1:1 into two treatment groups. While the study protocol planned for 130 participants to be randomised, actual enrolment was a total of 135 participants. The trial involved comparing topical (eye drops) polihexanide 0.8mg/ml monotherapy (with placebo) against a combination therapy of topical polihexanide 0.2mg/ml and propamidine 1mg/ml. The placebo contained the preservative benzalkonium chloride (BAC) 0.05 mg/ml (0.005%), which was also present in the propamidine formulation obtained from the manufacturer Sanofi-Aventis, UK.⁸ The combination therapy was chosen as an active comparator based on its widespread use and to reflect current management approaches.⁸

As discussed in Table 3 the CS considered that the effectiveness data from the active comparator arm in ODAK was not appropriate for comparison. The Delphi panel was used to source the distribution in real-world UK clinical practice and inform the composition of a pooled AAT comparator, which the company suggests is more representative of the real-world effectiveness of current therapeutic approaches. The CS highlights that this was deemed necessary because the active comparator arm in the ODAK trial (polihexanide 0.2mg/ml and propamidine 1mg/ml combination therapy) was not considered reflective of real-world UK clinical practice, largely due to the absence of treatment delays common in the UK (where unlicensed treatments require compounding) and the trial's use of a detailed, standardised protocol (discussed in more detail in section 3.5.8). The company, therefore, chose an alternative comparator, as discussed in more detail in Section 3.5. The EAG consider that the comparator in ODAK is appropriate, as discussed in Section 2.3.

The ODAK trial followed an intensive 19-day AAT dosing protocol where participants received varying doses as follows:

- Days 0-5: Hourly drops during daytime (16 drops a day).
- Days 6-12: Every 2 hours during daytime (8 drops a day).
- Days 13-19: Every 3 hours during daytime (6 drops a day).
- From Day 20 until clinical resolution: Four times a day during daytime.

Maximal treatment duration was one year after randomisation. To provide the dual therapy in each arm, one drop of propamidine 1mg/ml or placebo (multi-use containers) was administered first, followed by polihexanide 0.8mg/ml or 0.2mg/ml (single-use vials) after a minimum of five minutes to prevent dilution and potential wash-out effects. The clinical data presented in this submission are based on a data cutoff of [REDACTED]. The key primary outcome relevant to the decision problem as assessed in the ODAK trial was the Medical Cure Rate (MCR), also referred to as Clinical Resolution Rate (CRR), within 12 months from randomisation.

A participant was considered to have achieved a medical cure if they met several criteria, specifically clinical evidence of the elimination of AK, indicated by an intact

(healed) corneal epithelium and the absence of any clinical signs or symptoms of ocular inflammation. This cure had to be confirmed 30 days after the discontinuation of all AAT and anti-inflammatory treatment, with no relapses occurring within 90 days of treatment cessation and within 11 months of randomisation. Furthermore, for the MCR classification, participants who discontinued the study without being classified as cured were regarded as not cured (CS Section 2.6.1).

Secondary efficacy outcomes included: Best-corrected visual acuity (BCVA), time-to-cure, symptom reduction and clinical signs such as corneal scarring, ulceration severity, and anterior chamber inflammation. Eye pain, a common symptom, was assessed using health-related quality of life (HRQoL) tools EQ-5D-5L and VFQ25 questionnaires. In response to why eye pain was not measured systematically as a trial outcome (Clarification A15), the company reiterated that pain was regularly and systematically captured using the aforementioned tools at multiple time points throughout the trial. These tools showed statistically significant improvements in pain scores from baseline to end-of-study, indicating that pain was effectively monitored as a component of patient-reported outcomes. The EAG's clinical experts agreed that, while the use of symptom-specific tools for pain assessment would have been preferable, the company's approach was justified given the absence of alternative validated tools specific to ocular pain in AK. Safety outcomes included adverse events (AEs), discontinuation due to AEs and systemic safety.

Table 5: Clinical effectiveness studies of technology of interest

ODAK Trial		Section(s) of CS of relevance or other source
Study details	ODAK trial (NCT03274895) Italy, Poland, United Kingdom Years of recruitment: August 17, 2017, to June 18, 2021 Primary database lock: [REDACTED] [REDACTED] [REDACTED]	CS Section 2.2, Table 4 Dart et al 2024 Protocol version 2, 8th October 2018 CSR section 10.1
	Prospective, randomised, double-masked, active-controlled, multicentre, parallel-group Phase 3 study. Randomisation: Participants were randomised 1:1 into two treatment groups using a computer-generated block size of 4. The study was initially designed as a superiority trial but included the possibility to test for non-inferiority if the superiority hypothesis was not met, as per EMA guidance.²² The primary hypothesis was that polihexanide 0.8mg/ml monotherapy would be superior or non-inferior to the comparator by a predefined 0.20 margin (Δ).	CS Section 2.2, Table 4 and 2.3, 2.3.2, Table 5 Dart et al 2024 Protocol version 2, 8th October 2018
Intervention and administration	Group 1: polihexanide 0.8mg/ml monotherapy plus placebo eye drops. Group 2 (Active Comparator): polihexanide 0.2mg/ml plus propamidine 1mg/ml eye drops. Dosing Protocol: An intensive 19-day anti-amoebic treatment (AAT) protocol was followed: Days 0-5: Hourly during daytime (16 drops per day)^a. Days 6-12: Every 2 hours during daytime (8 drops per day). Days 13-19: Every 3 hours during daytime (6 drops per day). From Day 20 until clinical resolution: Four times a day during daytime. Treatment Duration: Treatment could continue for up to one year. As two interventions were applied for each arm, a 5-minute interval between eye drop applications was mandated to prevent wash-out effects. Bilateral Disease: For participants with bilateral disease, the study treatment was allocated to the worst affected eye (or the right eye if equally severe), while the non-study eye was treated according to clinical practice at the centre.	CS Section 2.3.2, Table 5 Dart et al 2024 Protocol version 2, 8th October 2018
Sample size	Analysis Sets:	CS Section 2.3.2, Table 5

ODAK Trial		Section(s) of CS of relevance or other source
	Planned Enrolment: The study protocol planned for 130 participants to be randomised 1:1. Actual Enrolment: A total of 135 participants were randomised. Intention-to-treat: N = 135 Full-analysis subset (FAS): N = 127 Safety analysis subset: N = 134 Per-protocol analysis set (PPAS): N = 119	Dart et al 2024 Protocol version 2, 8 th October 2018
Population and eligibility criteria	Key inclusion Criteria: 12 years of age or older (with selected sites enrolling those under 18 years). Clinical findings consistent with AK (e.g., epithelial, stromal, extra corneal pathologic features) and in vivo confocal microscopy (IVCM) findings consistent with AK. Those with concurrent bacterial keratitis, or using topical steroids, antivirals, or antifungals were eligible if they met the above criteria A complete list of the population eligibility is reported in the CS, Section 2.3.2, Table 5.	CS Section 2.3.2, Table 5 Dart et al 2024 Protocol version 2, 8 th October 2018
Outcomes (primary and secondary)	The outcomes of relevance to the decision problem are listed below: Primary Efficacy outcome: MCR: Also referred to as CRR, the percentage of subjects cured 30 days after discontinuing all study therapies, within 12 months of randomisation. Secondary Efficacy Outcomes: Best-corrected visual acuity (BCVA). Assessed using LogMAR values. Time to cure: Defined as the number of days from randomisation to the visit where clinical resolution was first recorded. Corneal scarring rates: As identified by slit lamp examination (present or absent) Ulceration severity: as identified by slit lamp examination using a 2-grade scoring procedure (present or absent) Anterior chamber inflammation: As identified by ophthalmoscopy, using a 3-grade or 4-grade scoring procedure EuroQol 5 Dimension 5 Level (EQ-5D-5L): This addresses overall health status.	CS Section 2.2, Table 4 Dart et al 2024 Protocol version 2, 8 th October 2018

ODAK Trial		Section(s) of CS of relevance or other source
	25 Item Visual Function Questionnaire (VFQ25): This addresses visual function status. Secondary safety Outcomes: Adverse event (AE) rates	
^a The protocol in Section 5.2, states that on the first day, 16 drops might not be feasible but the treatment should be applied as many times as possible, not exceeding the hourly regimen. AE, adverse events; AK, acanthamoeba keratitis; BCVA, best corrected visual acuity; CS, company submission; EQ-5D-5L, EuroQoL five dimension and five levels; ODAK, Orphan Drug for Acanthamoeba Keratitis		

3.2.2 Critique of participants' baseline characteristics

Although the company treats ODAK as a single-arm study, it reports baseline characteristics in the CS for both the treatment and active comparator arms. In line with the discussion in the decision problem (Section 2.3) the EAG considers polihexanide 0.2mg/ml with propamidine 1mg/ml to be an appropriate comparator. As such the EAG adopts the same approach, summarising baseline characteristics for both the treatment and the active comparator arms, the EAG obtained data for both arms from the CS Section 2.3.3, Table 6, and validated against the submitted company CSR and publication.⁸ The EAG noted minor discrepancies between sources, for example, the prevalence of bilateral disease differed between the publication and the CS; the EAG considers there to be an error in the publication. Additionally, some data, such as baseline refractive error reported in the publication, differed slightly from those reported in the CSR (see Table 6).

An overview of the patient characteristics is summarised in Table 6 and key points discussed below.

The ODAK trial randomised 135 participants in the intention to treat population (ITT), with 127 in the full-analysis set (FAS) and 134 in the safety analysis subset. The CS and the Dart et al⁸ publication focus on the FAS, however, it is not clear why the focus was placed on the FAS. The EAG has also identified baseline characteristics for the ITT population from the supplement of the main publication⁸ and present

these for comparison (these were also provided to the EAG in response to clarification question A10).

In the FAS, the CS defines the baselines as the “*last valid evaluation prior to first dose of study medication*”. The EAG requested further details in Clarification A9. In response, the company stated that a “valid evaluation” was defined as the last non-missing value recorded before administration of the investigational medicinal product. They further clarified that baseline assessments and first dosing typically occurred on the same day (Day 0); however, the protocol permitted baseline assessments to take place up to two days prior to randomisation and dosing. However, the EAG notes that allowing baseline measurements to be taken up to two days prior to dosing may introduce systematic differences in individuals, especially for a condition with time-sensitive clinical features. Therefore, it is possible that there may be differences across study arms in baseline. Most baseline characteristics appeared broadly similar between groups, with contact lens wear being the predominant risk factor in both arms (97.0% vs. 95.1%), and comparable mean ages (35.2 vs. 38.3 years) there was a notable difference in age distribution. There was a higher proportion of younger patients (15–35 years) in the 0.8mg/ml + placebo group (54.6%) compared to the 0.2mg/ml + propamidine 1mg/ml group (45.9%). Given that age is a known prognostic factor in AK, this difference may have influenced the outcomes, although it may also reflect a chance effect.

Notable differences were also observed in prior corticosteroid use (47.0% vs. 32.8%) and the proportion of bilateral disease (15.2% vs. 6.6%), both of which are considered poor prognostic indicators by the EAG clinical experts. Disease staging at baseline also varied slightly: while most participants were stage II in both groups, there were differences in the proportion in the three stage categories between groups with fewer stage I and stage III cases and more stage II cases in the comparator arm (see Table 6).

The EAG notes that the company did not provide the racial distribution of the participants. The company stated in clarification question A11 that racial demographic data were not collected in the ODAK trial, and that race/ethnicity is not

a known risk factor or associated with outcomes in AK. The EAG reviewed the cited sources ^{25, 26} and agree that risk factors for AK include contact lens use, environmental exposures, corticosteroid use, and diagnostic delays, with no evidence that race or ethnicity influences risk or prognosis. However, the lack of racial demographic data is a limitation, as it prevents assessment of participant diversity and generalisability.

Baseline characteristics in the ITT population (n = 135) were largely consistent with those in the FAS (Table 7). Age, sex, baseline BCVA, and risk factors such as contact lens wear (97.0% vs. 95.2%) were similar across arms.

Table 6: Summary of patients' baseline characteristics of the included ODAK trial (full analysis set, n=127)

Characteristic	Polihexanide 0.8mg/ml + Placebo (N = 66) ^c	Polihexanide 0.2mg/ml + Propamidine 1mg/ml (N = 61) ^c
Age, years		
Mean (SD)	35.2 (13.2)	38.3 (14.4)
Median (min, max)	33.5 (15,73)	37 (17,71)
Age group (years), n (%)	-	-
15 - 35	36 (54.6)	28 (45.9)
36 - 73	30 (45.5)	33 (54.1)
Male Sex, n (%)	27 (40.9)	26 (42.6)
Race, n (%)	Not Reported	Not Reported
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)
Unknown	5	8
Risk factors for AK	-	-
CL wear, n (%)	64 (97.0)	58 (95.1)
Ocular trauma	3 (4.6)	2 (3.3)
Time from onset of symptoms (days)		
Mean (SD)	33.5 (39.2)	36.9 (55.0)
Median (min, max)	19 (8–42)	20 (8–37)
Time from first treatment for keratitis before baseline (days)	-	-
Mean (SD)	12.0 (22.2)	13.5 (22.3)
Median (interquartile range)	4 (0 – 17)	4 (0 – 20)

Characteristic	Polihexanide 0.8mg/ml + Placebo (N = 66) ^c	Polihexanide 0.2mg/ml + Propamidine 1mg/ml (N = 61) ^c
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)
Severe inflammatory disease: scleritis or hypopyon, n (%)	0 (0.0)	0 (0.0)
Bilateral disease, n (%) ^a	-	-
Absent	55 (83.3)	57 (93.4)
Present	10 (15.2)	4 (6.6)
Unknown	1 (1.5)	0 (0.0)
Refractive error at baseline, n (%) ^b	-	-
Myopia	55 (85.9)	49 (81.7)
Hyperopia	8 (12.5)	7 (11.7)
Emmetropia	1 (1.6)	4 (6.7)
Unknown	2	1
AK, acanthamoeba keratitis; BCVA, baseline best corrected visual acuity, CL, contact lens		
^a data source: Company CSR and CS. Data differs for the treatment arm reported by Dart et al. ⁸ were a wrong denominator was used (n =65 instead of n =66) to calculate the proportions. Therefore, values were 55 (84.6 %), 10 (15.4%), and 1 for absent, present, and unknown, respectively.		
^b data source. ⁸ Data differs from that in CSR Table 14.1.2.1 where they are described as entity rather than condition and the n's appear to be slightly different for myopia/myopes (CSR: Treatment 54 (81.8%), comparator: 47 (77.0%))		
^c Data source: CS, CSR and publication. ⁸		

Table 7: Summary of patients' baseline characteristics of the included ODAK trial (Intention to treat population, n=135)

Characteristic	Polihexanide 0.8mg/ml + Placebo (N = 69)	Polihexanide 0.2mg/ml + propamidine 1mg/ml (N = 66)
Age, years	-	-
Mean (SD)	35.1 (13.0)	37.8 (14.0)
Median (min, max)	33 (15 - 73)	36 (17 -71)
Age group (years), n (%)	-	-
15 - 35	38 (55.1)	31 (47.0)
36 - 73	31 (44.9)	35 (53.0)

Characteristic	Polihexanide 0.8mg/ml + Placebo (N = 69)	Polihexanide 0.2mg/ml + propamidine 1mg/ml (N = 66)
Male Sex, n (%)	28 (40.6)	29 (43.9)
Race, n (%)	Not Reported	Not Reported
BCVA, n (%)	-	-
≥ 6/6	60 (96.8)	49 (92.5)
< 6/6–6/12	1 (1.6)	3 (5.7)
6/15–6/30	1 (1.6)	1 (1.9)
Unknown	7	13
Risk factors for AK	-	-
CL wear, n (%)	65 (97.0)	59 (95.2)
Ocular trauma	3 (4.5)	2 (3.2)
Time from onset of symptoms (days)	-	-
Mean (SD)	33.6 (39.0)	36.7 (54.6)
Median (min, max)	20 (8 - 42)	20 (8 - 37)
Time from first treatment for keratitis before baseline (days)	-	-
Mean (SD)	11.5 (21.9)	12.7 (21.6)
Median (interquartile range)	4 (0 - 16)	3 (0 - 20)
Prior medications, n (%)	-	-
Antibiotics	58 (84.1)	53 (80.3)
Antivirals	18 (26.1)	19 (28.8)
Antifungals	1 (1.4)	0
Corticosteroids (any cause)	32 (46.4)	20 (30.3)
Disease stage at baseline, n (%)	-	-
Stage I	15 (21.7)	9 (13.6)
Stage II	43 (62.3)	49 (74.2)
Stage III	11 (15.9)	8 (12.1)
Severe inflammatory disease: scleritis or hypopyon, n (%)	0	0
Bilateral disease, n (%)	-	-
Absent	56 (84.8)	58 (93.5)
Present	10 (15.2)	4 (6.5)
Unknown	3	4
Refractive error at baseline, n (%)**	-	-
Myopia	56 (84.8)	54 (83.1)
Hyperopia	8 (12.1)	7 (10.8)
Emmetropia	2 (3.0)	4 (6.2)
Unknown	3	1

Characteristic	Polihexanide 0.8mg/ml + Placebo (N = 69)	Polihexanide 0.2mg/ml + propamidine 1mg/ml (N = 66)
Source: Dart et al 2024 ⁸ supplement table		

The company stated that the ODAK trial is generalisable to UK clinical practice, noting that the trial population reflects the real-world population affected by AK, particularly in terms of treatment approach (CS, Sections 2.2 and 2.3.3). The ODAK trial recruited patients from three UK centres (London, Southampton, and Manchester) as summarised in Table 8, which shows both the FAS and ITT populations. The EAG notes that from the 135 randomised patients, 70 were enrolled in the UK with 63 enrolled at Moorfields London, 3 at Manchester, and 4 at Southampton. No additional information on specific baseline characteristic of UK participants was provided in the CS.

Table 8: Recruitment of UK participants in the ODAK trial by site and treatment arm (FAS population n=127/ITT population n=135)

Site	Polihexanide 0.8mg/ml + placebo n=66 / n=69 n (%)	Polihexanide 0.2mg/ml + propamidine 1mg/ml n=61 / n=66 n (%)	Total UK Participants n=127 / n=135 n (%)
Moorfields Eye Hospital	28 (42.4)/ 29 (42.1)	30 (49.2)/ 34 (51.5)	58 (45.7)/ 63 (46.7)
Manchester Eye Hospital	1 (1.5)/ 2(2.9)	1 (1.6)/ 1 (1.5)	2 (1.6) 3 (2.2)
University Hospital Southampton	1 (1.5) / 1 (1.4)	3 (4.9) / 3 (4.5)	4 (3.1) / 4 (3.0)
Total	30 (45.5) / 32 (46.4)	34 (55.7) / 38 (57.6)	64 (50.4) / 70 (51.6)
Data source: CS, CSR and publication. ⁸			

UK participants in the ODAK trial where approximately half the sample of the total populations in both the ITT and FAS. The EAG clinical experts generally agreed that the ODAK trial was generalisable to UK clinical practice; however, they noted that it is rare for AK to be bilateral and that the rates of people with bilateral AK in the trial was high, particularly with a higher proportion in the polihexanide 0.8mg/ml and placebo arm.

Quality assessment of ODAK trial

The company assessed the ODAK trial using the quality assessment of controlled intervention studies and presented this as Table 9 in CS section 2.5. The ROB

questions were cited from National Heart, Lung and Blood institute using a critical appraisal checklist.²⁷ The EAG assessed the ODAK trial with these questions, Table 9, however, given the study's design (randomised, double-masked, active-controlled, parallel-group), the EAG also applied the Cochrane Risk of Bias- 2 (ROB2) tool (Table 10).²⁸

There are some differences between the EAG and the company's assessments (see Table 9 and Table 10). While the company rated the overall quality of the ODAK trial as good using the NHLBI checklist,²⁷ the EAG noted some concerns. When, applying the Cochrane RoB2 tool the EAG, also identified some concerns with respect to bias arising from the randomisation process, deviations from intended interventions, and selective reporting.

Table 9: Company's and EAGs quality assessment criteria of ODAK trial

Question	CS	EAG assessment
Was the study described as randomised, a randomised trial, a randomised clinical trial, or an RCT?	Yes	Yes, the study was described as randomised, double-masked, active-controlled parallel trial.
Was the method of randomisation adequate (i.e., use of randomly generated assignment)?	Yes	Yes, the randomisation was 1:1 using a computer-generated block size of 4.
Was the treatment allocation concealed (so that assignments could not be predicted)?	Yes	Yes, the ODAK trial used a computer-generated block randomisation schedule and a double-masked, double-dummy design with a unique randomisation code assigned by pharmacies.
Were study participants and providers blinded to treatment group assignment?	Yes	Yes. However, the EAG note that the bottle of the dummy (placebo) was "very similar" but "not identical" to the study product. The CS states that masking was maintained study subjects and the sponsor only had access to masked treatment assignment information on a "need to know basis" until the database was locked. measures were in place to mitigate potential unmasking, and the trial reported that no subjects were unmasked.

Question	CS	EAG assessment
Were the people assessing the outcomes blinded to the participants' group assignments?	Yes	Yes, efficacy assessments were performed by study personnel not having access to the study treatment, dispensing logs, accountability forms, the eCRF, or other sources of treatment assignment information. Specifically, records of unmasked subjects were not seen by the doctors carrying out the study.
Were the groups similar at baseline on important characteristics that could affect outcomes (e.g. demographics, risk factors, co-morbid conditions)?	Yes	No, notable differences for corticosteroid use prior to diagnosis in the treatment arm were observed. The EAG notes the lack of stratification factors especially with respect to identified imbalances (e.g. prior corticosteroid use). The EAG also note that while the mean ages between groups were similar, the distribution by age group differed, with a higher proportion of younger patients (15–35 years) in the treatment arm.
Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	Yes	Yes, a total of 135 patients were randomised. The FAS included 127 subjects (94.1% of randomised cohort). In the FAS, 17 subjects (13.4%) prematurely withdrew from the study (polihexanide 0.8mg/ml + placebo group: 10/66 (15.2%) and polihexanide 0.2mg/ml + propamidine group: 7/61 (11.5%)). The overall drop-out rate of 13.4% is below the 20% threshold.
Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	Yes	Yes, the difference in premature withdrawal rates between the two groups in the FAS was 15.2% - 11.5% = 3.7 percentage points. This is below the 15-percentage point threshold.
Was there high adherence to the intervention protocols for each treatment group?	Yes	Yes
Were other interventions avoided or similar in the groups (e.g. similar background treatments)?	Yes	Yes
Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	Yes	Yes

Question	CS	EAG assessment
Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	Yes	Yes, the study protocol planned for 130 participants to be randomised 1:1. This sample size was calculated to provide approximately 80% power to detect a 20-percentage point superiority for polihexanide 0.8mg/ml monotherapy for the primary outcome (MCR within 12 months), with a 2-sided alpha value of 0.10 (or 1-sided 0.05) and a predefined non-inferiority margin of 20 percentage points. This was based on retrospective data from a previous study.
Were outcomes reported or subgroups analysed prespecified (i.e. identified before analyses were conducted)?	Yes	Yes, the publication by Dart et al. ⁸ states that subgroup analysis was prespecified. A multivariable analysis, which included handling AK disease stage as a subgroup, was prespecified in the protocol to account for anticipated baseline imbalances.
Were all randomised participants analysed in the group to which they were originally assigned, i.e. did they use an intention-to-treat analysis?	Yes	Probably yes, ODAK protocol states that subjects will be analysed 'as randomised', however, seven randomised subjects were excluded in the FAS. The exclusion of seven randomised participants from the FAS due to unconfirmed diagnosis means that a strict, full intention-to-treat (ITT) analysis was not performed. However, the company provided data for the primary outcome from the safety population which the EAG considers as modified ITT.
Overall quality	Good	Some concerns
CS, company submission; EAG, evidence assessment group; FAS, final analysis set; ITT, intention-to-treat; MCR, medical cure rate; ODAK, Orphan Drug in Acanthamoeba Keratitis; RCT, randomised controlled trial		

Table 10: Cochrane Risk of Bias 2 appraisal for ODAK trial

Domain	Signalling question	Response	Comments
Bias arising from the randomisation process	1.1 Was the allocation sequence random?	Y	The randomisation was 1:1 using a computer-generated block size of 4. Eligible patients received a masked treatment assignment with a unique randomisation code
	1.2 Was the allocation sequence	Y	

Domain	Signalling question	Response	Comments
	concealed until participants were enrolled and assigned to interventions?		designed not to disclose treatment assignment.
	1.3 Did baseline differences between intervention groups suggest a problem with the randomisation process?	PN	Notable differences for corticosteroid use prior to diagnosis in the treatment arm were observed. The EAG note that while the ODAK trial employed an adequate randomisation method (computer-generated block randomisation with allocation concealment), the absence of stratification led to imbalances in key prognostic factors. The EAG also note while the mean ages between groups were similar, the distribution by age group differed, with a higher proportion of younger patients (15–35 years) in the treatment arm.
	Risk of bias judgement	Some concerns	There are concerns about potential bias arising from the randomisation process, due to baseline imbalance.
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?	N	The trial was double-masked and used a double-dummy design. This means both participants and personnel (including those delivering interventions) were unaware of the assigned treatment allocation. However, the placebo and propamidine bottles were noted to be "slightly different", the study by Dart et al. ⁸ states that masking was maintained throughout, as no unmasking occurred during the trial. The EAG note that while the trial aimed for successful masking, the acknowledged difference in bottle appearance for two of the study drugs introduces a potential risk of unintentional unblinding. This could lead to bias, especially in the assessment of subjective outcomes, if participants were able to infer their treatment allocation based on the
	2.2. Were carers and people delivering the interventions aware of participants assigned intervention during the trial?	PN	

Domain	Signalling question	Response	Comments
			appearance of the medication bottles.
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA	-
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	-
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	The company only focused on the full analysis set in the CS. While baseline data for the ITT population was available from Dart et al., ⁸ only AE ITT outcomes were reported. The EAG requested the ITT outcomes at clarification (CQ A13), in response the company stated that the efficacy outcomes for the full ITT population (N=135) were not available. The company explained that seven patients from the safety analysis set were excluded from the FAS because their AK diagnosis was unconfirmed. However, the EAG notes that the company did provide 12-month MCR results for both arms using the safety analysis set (n=134), which included all randomised patients who received at least one dose of study treatment which the EAG consider as a modified ITT analysis. Discontinued subjects were regarded as not cured in the primary analysis, and multiple imputation was performed for missing data (patients withdrawn/discontinued due to reasons other than treatment

Domain	Signalling question	Response	Comments
			failure) under MAR accounting for treatment group.
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?	NA	-
	Risk of bias judgement	Low	Despite the slight concern about the container difference, the masking efforts and provision of data for the modified ITT by the company was appropriate with robust handling of missing data thus suggesting no concerns regarding the risk of bias
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	PY	Of the 135 patients randomised, the full analysis set included 127 patients (5.9% excluded, primarily due to unconfirmed diagnosis). This indicates that outcome data were available for nearly randomised patients. For the primary analysis, discontinued patients were considered not cured, and multiple imputation was performed to account for missing data, suggesting that appropriate methods were used to minimise bias. Sensitivity analyses were also conducted to support the robustness of findings.
	3.1 Were data for this outcome available for all, or nearly all, participants randomised?	NA	-
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	-
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	-
	3.4 If Y/PY/NI to 3.3: Is it likely that	NA	-

Domain	Signalling question	Response	Comments
	missingness in the outcome depended on its true value?		
	Risk of bias judgement	Low	The volume of missing data was low (5.9%), and most exclusions were due to unconfirmed diagnosis prior to treatment. For the primary outcome, appropriate methods were used to handle missing data, including multiple imputation, and conservative assumptions (e.g. treating discontinued patients as not cured).
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	The primary outcome, MCR also referred to as Clinical Resolution Rate (CRR), was defined by clinical examination findings (intact corneal epithelium, no ocular inflammation, minimal staining). The EAG considers this outcome to be largely objective in nature and clinically relevant. Secondary outcomes are standard ocular assessments. Patient-reported outcomes (EQ-5D-5L, VFQ25) were also used. However, the EAG (Clarification A15) sought clarity on why pain, a key symptom of AK, was not measured directly using a symptom-specific scale. In response, the company reiterated that pain was assessed through the EQ-5D-5L (pain/discomfort domain) and the VFQ-25 (ocular pain subscale), both of which were administered at each scheduled visit throughout the trial. The EAG's clinical experts agreed that, while the use of symptom-specific tools for pain assessment would have been preferable, the company's approach was justified given the absence of alternative validated tools specific to ocular pain in AK.
	4.2 Could measurement or ascertainment of the outcome have	N	The measurement or ascertainment of the outcome is unlikely to have differed between the intervention groups because the ODAK study's outcome

Domain	Signalling question	Response	Comments
	differed between intervention groups?		measures were clearly defined and implemented consistently across all study participants.
	4.3 Were outcome assessors aware of the intervention received by study participants?	N	Outcome assessors were blinded. According to the protocol by Dart et al. ⁸ efficacy assessments were made by individuals who did not have access to the study treatment, dispensing logs, accountability forms, the eCRF, or other sources of treatment assignment information.
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	-
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	-
	Risk of bias judgement	Low	Appropriate and standardised outcome measures were used, and masking of outcome assessors was implemented through a double-masked, double-dummy design. These factors reduce the likelihood of differential outcome assessment between groups.
Bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis?	PN	The analyses generally followed the predefined statistical analysis plan included in the trial protocol. However, there was a notable deviation concerning the time-to-cure analysis. The company's analysis of "time-to-eventual-cure" differed from that described in the original phase 3 statistical analysis plan. Specifically, the pre-specified analysis defined time-to-cure for all patients (cured or not) as the timepoint assessed at the 30-day follow-up (or at 90 days) after discontinuation of trial drugs or within 12 months of

Domain	Signalling question	Response	Comments
			starting AAT, whichever came first. In contrast, the reported analysis included all trial failures at the point of final cure, rather than applying a fixed assessment point. This indicates that not all outcomes were analysed strictly in accordance with the pre-specified statistical analysis plan.
	5.2 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	The primary outcome, MCR was clearly prespecified in the protocol as the main endpoint and was consistently reported as such throughout the trial documentation and results (Dart et al., 2024; CS). However, the EAG note that secondary outcomes were not statistically analysed because “no meaningful differences” were observed which raises concern about potential bias. If results had favoured one arm, formal analysis may have been conducted and reported. This outcome-dependent decision-making introduces a risk of selective reporting. The EAG consider it unlikely that the numerical result for the primary outcome was selectively chosen from among multiple eligible outcome measurements.
	5.3 Is the numerical result being assessed likely to have been selected, on the basis of the results, from multiple eligible analyses of the data?	N	No evidence to suggest selective reporting of numerical results was found as all primary and secondary outcomes were prespecified.
	Risk of bias judgement	Some concerns	There are some concerns about deviation from pre-specified analyses. For secondary outcomes, statistical analysis was only conducted or reported when “meaningful differences” were observed.
Overall bias	Risk of bias judgement	Some concerns	The ODAK trial shows presents some concerns across a few domains.
AAT, anti-amoebea therapy; CS, company submission; EAG, evidence assessment group; ITT, intention-to-treat; NA, not applicable; ODAK, Orphan Drug for Acanthamoeba Keratitis			

3.3 Critique of the results of the trials of the technology of interest

3.3.1 Overview of efficacy results

Key results from the ODAK trial are summarised in Table 11. These are presented for the FAS (n = 127). The CS Section 2.6 only focused on outcomes for the FAS results in the treatment arm, polihexanide 0.8mg/ml + placebo (n = 66), while presenting results for the active comparator, polihexanide 0.2mg/ml + propamidine 1mg/ml (n = 61), in Appendix J. The company justified this approach by citing limitations of the comparator arm, arguing that it does not reflect current UK clinical practice, and therefore considers the ODAK trial be a pseudo single-arm study (section 2 of the CS). The EAG notes that this interpretation may be influenced by an EMA assessment of the ODAK trial.²² This report stated that, *“considering that the active arm as applied in the ODAK trial contained a medicinal product [polihexanide 0.2 mg/ml] manufactured to GMP quality, with immediate availability and a standardised treatment protocol, it could not be considered representative of current practice”*.²² The EMA statement is further discussed in Section 3.6.2. Furthermore, the company’s response to clarification question A8, stated that the EMA noted the *“the comparator used in the ODAK trial, a combination of polihexanide 0.2 mg/ml plus propamidine 1mg/ml, is an unlicensed regimen and does not constitute a standardised or licensed therapy for AK within the EU”*. However, while this may be true for EU clinical practice, the EAG clinical advisors unanimously disagreed with the company’s claim that *“the efficacy observed in the active comparator of the ODAK trial is unlikely to reflect current UK clinical practice”* (as stated in the CS) and emphasised that polihexanide 0.2mg/ml is the standard front-line treatment used in UK clinical practice. Therefore, while the EAG acknowledges the company’s position, the ODAK trial was designed and conducted as a randomised, double-masked, active-controlled trial, as discussed in Section 3.2.1 of this EAG report. Therefore, both the treatment and comparator arms were reported within this EAG report, in line with the EAG clinical advisors’ recommendation.

Table 11: Summary of the primary and secondary outcome results from the ODAK trial

Outcome	Polihexanide 0.8mg/ml + placebo (n = 66) ^{a,b,c,d,e}	Polihexanide 0.2mg/ml + propamidine 1mg/ml (n = 61) ^{a,c,d,e}	Polihexanide 0.8mg/ml + placebo vs Polihexanide 0.2mg/ml + propamidine 1mg/ml
Medical Cure Rate (MCR) % (n)	84.8 (56)	88.5 (54)	OR: 0.73 (95% CI: 0.26 to 2.04), P = 0.544
Median Time-to-Cure (days)	140	114	HR: 0.68 (90% CI: 0.49 to 0.94), P = 0.048
Mean change in BCVA (LogMAR) from baseline	-0.293 (SD 0.469) (n = 64) ^a	-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) ^f	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
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
EQ-5D-5L: Least squares (90% CI)	1.34 (1.20 to 1.48) ^a	1.38 (1.23 to 1.53)	P = 0.772

EQ-5D-5L: Pain/discomfort dimension n (%)	No pain or discomfort = 41 (63.1) ^a Slight pain or discomfort = 14 (21.5) ^a Moderate pain or discomfort = 3 (4.6) ^a Severe pain or discomfort = 0 (0) ^a Extreme pain or discomfort = 0 (0) ^a	No pain or discomfort = 37 (60.7) Slight pain or discomfort = 10 (16.4) Moderate pain or discomfort = 3 (4.9) Severe pain or discomfort = 1 (1.6) Extreme pain or discomfort = 0 (0)	Not reported
VFQ-25 Composite Score: Mean Change (n = number assessed/numb er missing)	23.5 (SD 19.4) (n = 60/5) ^a	23.7 (SD 19.7)(n = 55/6)	P = 0.655
VFQ-25 mean ocular pain score (SD)	86.8 (17) ^a	88.8 (19.5)	Not reported
BCVA, Best corrected visual acuity; CI, confidence intervals; HR, hazard ratio; MCR, medical cure rate; OR, odds ratio; VAS, Visual Analogue Scale Note: ^a Number of patients for each outcome and arm is polihexanide 0.8mg/ml (n = 66) and polihexanide 0.2mg/ml + propamidine (n = 61) unless otherwise stated. ^f For corneal scarring table presented data from CS Appendix J.1.5, however, different values appear in Dart et al. ⁸ VFQ-25 ocular pain scores out of 100 which represents the best possible outcome and 0 the worst. Data sources: ^b = CS, ^c = CS Appendix J, ^d = CSR and ^e = Dart et al. (2024) ⁸ CS Tables 10- 18; CS Appendix J Tables 28-36; CSR Tables 11.6, 14.2.2.1, 14.2.3.2, 14.2.4.10, 14.2.4.4, 14.3.2.1, 14.2.5.2, 14.2.5.9, 14.2.5.10, 14.2.6.1, 14.2.6.4; Dart et al. (2024) Table 4; Clarification question response Table 7 (0.8mg/ml only)			

The company presented ITT baseline data, reported in Section 3.2.2 above, and ITT adverse event data was provided in supplementary information by Dart et al. (2024).⁸ However, no ITT analysis of the results were presented. The EAG requested that the company (Clarification Question A13) provide the trial outcomes from both the study arms using the ITT population (all 135 randomised patients). The company responded by stating that “trial outcomes are not available for the ITT (n = 135) population.” The company stated that seven participants were removed from the ITT as the diagnosis of these participants was “unconfirmed upon expert review of in vitro confocal microscopy (IVCM) results and both culture and PCR were negative.” The company also state that the EMA recognised that the inclusion of these seven

participants may introduce bias into the efficacy results deeming the exclusion of these seven participants to be appropriate. The company did, however, provide ITT data for the primary outcome of MCR, for 134 participants, citing that all but one of the randomised participants received at least one dose of the study drug. The EAG considers this as a modified ITT analysis. Table 12 presents the modified ITT data for the primary outcome of MCR provided in the company's response to clarification questions. As can be seen the proportion resolved was higher in the polihexanide 0.2mg/ml + propamidine 1mg/ml arm but the difference was not statistically significant.

Table 12: Summary of the primary outcomes of the ODAK trial (modified ITT population n = 134)

population n = 134		
12-month MCR	Polihexanide 0.8mg/ml + placebo (n=69)	Polihexanide 0.2mg/ml + propamidine 1mg/ml (n=65)
Resolved, n (%)	58 (84.1)	58 (89.2)
Relative risk (95% CI)	0.94 (0.82, 1.08)	
p-value	0.452	
Source: Table 6 of the company's response to clarification question A13. Abbreviations: CI: confidence interval; MCR: medical cure rate.		

Primary outcome

The ODAK trial's primary outcome was MCR at 12-months, defined as resolution of symptoms and clinical signs of AK, including cessation of anti-Acanthamoeba and anti-inflammatory treatment for at least 30 days, without the need for surgery or a change in therapy. MCR was achieved in 84.8% of patients in the polihexanide 0.8mg/ml + placebo treatment arm, and 88.5% of patients in the polihexanide 0.2mg/ml + propamidine 1mg/ml comparator arm (Table 11). The odds ratio was 0.73 (95% CI: 0.26 to 2.04; P = 0.544), with a test for non-inferiority difference in MCR of -0.04 (95% CI: -0.16 to 0.09) which met the non-inferiority criterion. The company's SAP for ODAK specified a non-inferiority margin of $\Delta = 0.20$, justified on statistical grounds (ensuring $\geq 50\%$ retention of the standard treatment effect over placebo) and clinical grounds. The company argued that a true difference of ≤ 0.20 in cure rate would be clinically acceptable as it would, at worst, cause a short delay in

resolution without serious morbidity, while potentially offering practical benefits if monotherapy were at least as effective. While superiority of polihexanide 0.8mg/ml was not shown, the lower bound of the 95% confidence interval met the $\Delta = 0.20$ criterion. Therefore, polihexanide 0.8mg/ml was non-inferior to polihexanide 0.2mg/ml + propamidine 1mg/ml. The EAG notes the company's acknowledgment that there was no evidence of superiority in the results. Furthermore, the EAG notes that the company's interpretation does not comment on the fact that the observed point estimate for MCR was numerically higher in the comparator arm (88.5%) than in the treatment arm (84.8%). While this difference is not statistically significant and should not be over-interpreted, transparency around such numerical findings is important when discussing trial results. This is particularly relevant when considering methodological concerns raised by both the EMA and the EAG regarding the trial's hypothesis testing approach and the justification for the non-inferiority margin. In essence, these issues introduce uncertainty in the interpretation of the comparative effectiveness results.

While the MCR (84.8%) appears to represent a high rate of clinical success, the EAG notes that the MCR definition adopted by the company within the CS does not incorporate patient-reported outcomes, visual function, or structural sequelae such as corneal scarring. The EAG considers this important because AK commonly results in functional vision impairments.^{20, 29} Whilst, corneal scarring, which is a notable consequence of AK (highlighted within the CS), is also strongly linked to poorer visual acuity.³⁰ Furthermore, patient reported quality of life is significantly reduced in AK patients, notably in domains such as reading, mobility, and emotional well-being, and does not fully normalise with resolution of AK.³¹ Therefore, the EAG considers that this limits its interpretability as a standalone measure of patient benefit.

Secondary Outcomes

Several secondary outcomes were also reported within the CS and Appendix J of the CS, including time-to-cure, visual acuity, reduction of symptoms such as corneal scarring, ulceration, anterior chamber inflammation, and HRQoL outcomes, which are in line with the decision problem and NICE final scope. The company also included the use of adjunctive therapies as an additional secondary outcome. Finally,

the EAG requested clarification (Clarification Question A15) as to why pain was not a stand-alone outcome in the ODAK trial, this will be discussed in greater detail below.

Time-to-Cure

The median time-to-cure was 140 days in the polihexanide 0.8mg/ml + placebo arm compared to 114 days in the polihexanide 0.2mg/ml + propamidine 1mg/ml comparator arm. The median time-to-cure between group differences was statistically significant, favouring the active comparator (hazard ratio: 0.68, 90% CI: 0.49 – 0.94, $P = 0.048$) (Table 11). The time-to-cure for both arms as assessed by Kaplan-Meier analysis is illustrated in Figure 1. The polihexanide 0.2mg/ml + propamidine 1mg/ml arm had zero cures until around 56 days after which consistently had a higher proportion of cured patients compared to polihexanide 0.8mg/ml, except at around 150 days where the lines meet but then diverge again. This result suggests that patients treated with polihexanide 0.8mg/ml + placebo had a longer disease course, despite similar ultimate cure rates. Given the chronic and painful nature of AK, a delayed recovery period may have meaningful consequences for patient experience and quality of life.

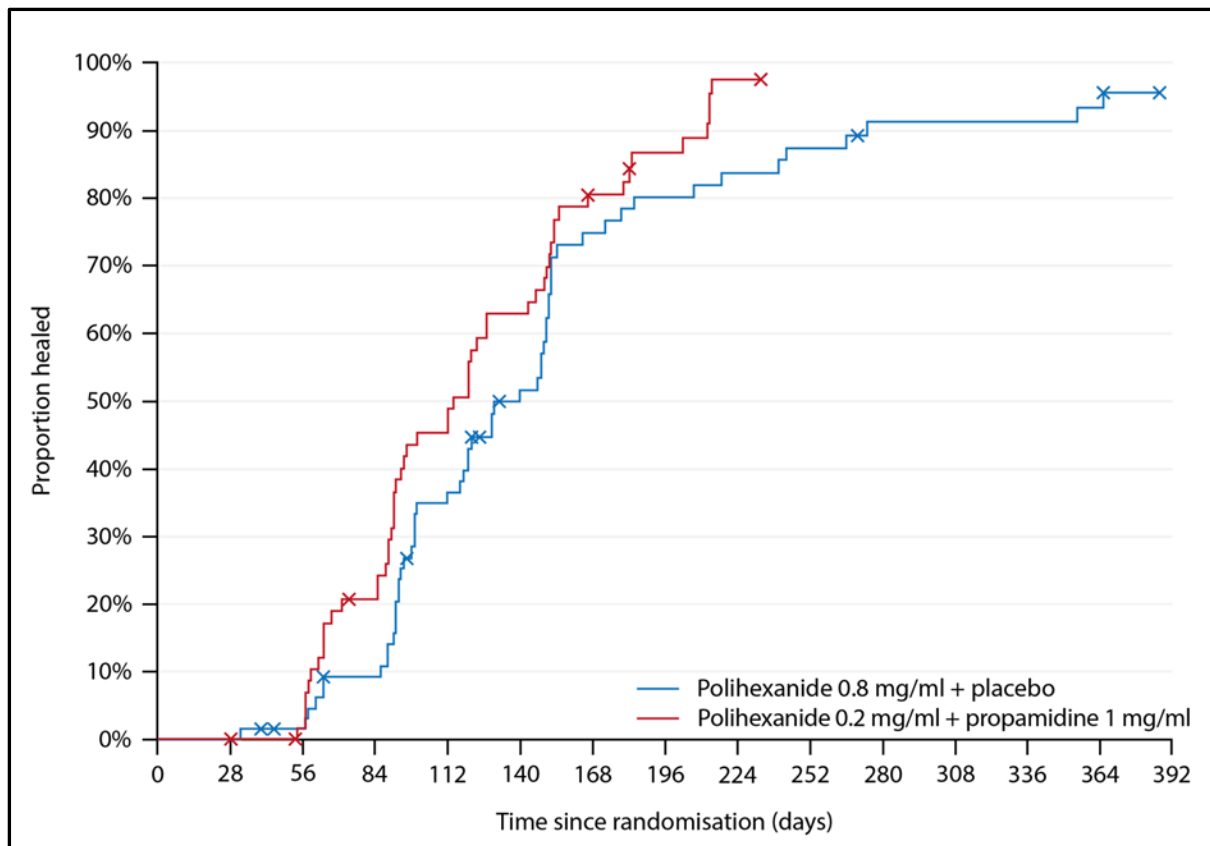


Figure 1: Kaplan-Meier plot for time-to-cure analysis (full analysis set) (taken from Figure 4 of CS Appendix J, with source: SIFI. Data on File. ODAK Trial CSR. 2022)

Best corrected vision acuity (BCVA)

In the polihexanide 0.8mg/ml arm, mean LogMAR improved from 0.47 to 0.19 (mean change: -0.293 SD 0.469), and in the polihexanide 0.2mg + propamidine 1mg/ml arm from 0.36 to 0.10 (mean change -0.251 SD 0.326) (Table 11), a statistically significant improvement in both arms (both $p < 0.0001$, CS Appendix Table 30).

Despite these statistically significant differences within groups, there were no statistically significant between groups (mean difference: 0.05 (90% CI: -0.06 to 0.16, $P = 0.444$). The EAG notes that this would imply comparable visual recovery between treatments. Furthermore, without stratifying BCVA by key clinical variables such as the presence or extent of corneal scarring, it is unclear to the EAG whether observed visual improvements were consistent across all patient subgroups or limited to those with less severe disease or fewer structural complications. Stratification of BCVA would aid in understanding whether visual outcomes are generalisable to patients with significant scarring or even advanced AK.

Corneal scarring

In the polihexanide 0.8mg/ml arm, 50% of patients presented corneal scarring at the end of the study, up from 0 patients at baseline. Whilst in the polihexanide 0.2mg/ml + propamidine 1mg/ml comparator arm 49.2% of patients presented corneal scarring at the culmination of the study, which was up from 3 patients who showed corneal scarring at baseline (Table 11). The odds ratio was 1.14 (95% CI: 0.55 to 2.36, P = 0.734), demonstrating no statistically significant difference between arms. The EAG notes that corneal scarring reported in Dart et al. (2024),⁸ was 51.6% in the polihexanide 0.8mg/ml arm, and 54.5% in the in the polihexanide 0.2mg/ml + propamidine 1mg/ml comparator arm, which is slightly different to those presented by the company in the CS and CS Appendix J. The EAG is unclear why this is. Given that corneal scarring has a strong effect on the quality of vision by diminishing visual acuity,³⁰ 50% corneal scarring observed in the ODAK trial perhaps undermines the high MCR results from the primary outcome and suggests that functional recovery may have been more limited than implied. The EAG clinical advisors were of the position that scarring is a consequence of late AK diagnosis and increased AK severity, irrespective of cure rates.

The CS does not provide any detailed analysis linking scarring to MCR and BCVA, and the EAG considers this to be a notable omission which limits the ability of the EAG to interpret these outcomes in an integrated manner. Therefore, at clarification questions (Clarification Question A19), the EAG requested that the company explain how this 50% corneal scarring result can be interpreted with regards to MCR and visual function outcomes. Furthermore, the EAG also requested (Clarification Question A20) the company to provide results of MCR and BCVA outcomes stratified by the presence and absence of corneal scarring at the culmination of the study. The company responded by attempting to combine their responses to A19 and A20. The company provided a “crude (unadjusted)” analysis of MCR and BCVA stratified by the presence of corneal scarring. This was done solely in the polihexanide 0.8mg/ml treatment arm. The company’s response suggested participants with corneal scarring had a higher MCR (93.9%) and better BCVA (LogMAR of 0.07) compared to participants without scarring (MCR of 77.4% and LogMAR of 0.31). However, the company did acknowledge that these results are potentially misleading and likely

reflect underlying baseline differences between groups. Particularly, the possibility that participants with more severe disease at baseline may have been more likely to develop scarring, but also more intensively treated and followed. This statement by the company was also supported by the EAG clinical advisors who, as previously stated, confirmed that greater disease severity at baseline would increase the chance of corneal scarring post treatment.

As previously mentioned, the company did not provide results for the polihexanide 0.2mg/ml + propamidine 1mg/ml comparator arm or conduct multivariable analyses to account for potential confounding variables, such as baseline severity, duration of symptoms, or adjunctive therapy use. The company stated that they were *“unable to complete this analysis within the clarification period timelines.”* Therefore, while clarification question A20 was answered at a basic level, the interpretation of this remains limited due to the absence of adjusted comparisons and the lack of complete data across trial arms. Therefore, as the company states, *“these data should be interpreted with caution.”*

With regards to clarification question A19, which sought clarity on how a high rate of corneal scarring (50% of participants in the treatments arm) can be interpreted in relation to MCR and BCVA, the company failed to directly address this question. No clinical interpretation or discussion was provided by the company to the EAG, on whether scarring may diminish the meaningfulness of positive MCR results or the effect on BCVA.

Ulceration severity

In the polihexanide 0.8mg/ml arm ulceration reduced from 27.3% at baseline to 6.1% by the end of the study, and in the polihexanide 0.2mg/ml + propamidine 1mg/ml comparator arm, ulceration reduced from 26.2% to 4.9% (Table 11), with no statistically significant differences observed between groups (OR: 1.09 (95% CI: 0.22 to 5.47, P = 0.917). These within group differences suggest that both treatments may contribute to improving corneal ulceration.

Anterior chamber inflammation

In the polihexanide 0.8mg/ml arm, the number of patients with no inflammation increased from 78.8% at baseline to 93.9% at the end of the study ($P = 0.0221$). In the active comparator arm, the number of patients with no inflammation increased from 72.1% to 82% ($P = 0.01$). However, no between group statistical differences were observed, odds ratio 0.65 (95% CI: 0.14 to 3.11, $P = 0.651$) (Table 11). Interpretation of this result could also be limited by higher missing data at the end of the study in the comparator arm, 13.1% in the comparator arm, compared to 3% in the treatment arm. This may bias the estimated proportion of patients without inflammation and reduces confidence in between group comparisons. Nevertheless, while the inflammation results appear encouraging, they are potentially confounded using adjunctive anti-inflammatory medications which must also be accounted for, discussed below.

Use of alternative treatment and surgery

The company defined adjunctive therapy as any new or escalated use of topical steroids or oral non-steroidal anti-inflammatory drugs (NSAIDs) after baseline. Adjunctive therapy use was reported in 45.5% of patients in the polihexanide 0.8mg/ml arm and 41% in the polihexanide 0.2mg/ml + propamidine 1mg/ml comparator arm (Table 11). Post randomisation steroid use was 16.7% (polihexanide 0.8mg/ml arm) and 21.3% respectively (polihexanide 0.2mg/ml + propamidine 1mg/ml arm). The company described adjunctive therapy use as “low” for the polihexanide 0.8mg/ml arm, which the EAG considers to be inconsistent with the actual reported adjunctive therapy use rates.

The company also reported a low surgery rate of 2.9% in the polihexanide 0.8mg/ml arm and this may indicate good disease control. However, the high use of adjunctive anti-inflammatory medication makes it harder to separate the independent treatment effect of polihexanide 0.8mg/ml from the impact of additional medications.

Particularly when interpreting other secondary outcomes such as, anterior chamber inflammation, ulceration severity and quality of life measures. Despite this, the company did not provide subgroup or adjusted analyses comparing outcomes in patients who did and did not receive adjunctive therapies, nor did they assess the potential confounding effect of steroids on inflammation-related outcomes or pain-

related quality of life measures. Therefore, the EAG requested the company (Clarification Question A18) to explain how adjunctive therapy use (45.5%) was accounted for in the interpretation of outcomes like inflammation, ulceration and quality of life. It was agreed that MCR stratified by adjunctive steroid use to be prioritised due to the company's insistence that time would be a limiting factor on multiple clarification questions. In response, the company provided data presented in the CSR (SIFI. Data on File. ODAK Trial CSR. 2022). The stratified analysis focused on patients without prior steroid use, comparing those who initiated steroid treatment after baseline to those who received no steroid therapy at all. Across both polihexanide 0.8mg/ml and 0.2mg/ml + propamidine 1mg/ml, the 12-month MCR was comparable between groups (95.8% vs. 92.9% and 81.8% vs. 76.9%, respectively), with no statistical significance between groups ($P = 1.0000$), for both stratifications.

The EAG notes that while cure is an important outcome, other clinical and patient reported outcomes, particularly those sensitive to inflammation may be influenced by adjunctive therapy, especially steroid use. Nevertheless, EAG clinical advisors emphasised that the use of adjunctive therapies, particularly anti-inflammatory corticosteroids, are a routine and necessary component of AK management. Therefore, clarifying the extent and impact of adjunctive treatment use within the trial is important to contextualise the results and assess their relevance to clinical practice.

Health related quality of life measures

EQ-5D-5L VAS scores increased by 17.9 (SD 19.6) in the polihexanide 0.8mg/ml arm and 18.8 (SD 20.0) in the polihexanide 0.2mg/ml + propamidine 1mg/ml arm, with no between group statistical difference reported ($P = 0.366$) (Table 11). Similarly, the VFQ-25 scores improved in the intervention arm (0.8mg/ml) by 23.5 and in the active comparator arm (0.2mg/ml) by 23.7, respectively, a result which was also exhibited no between group statistical significance ($P = 0.655$) (Table 11). The EAG notes that in section 3.4.2 of the CS, the company state that "*EQ-5D-5L index scores were converted to utilities for use in the model*". However, these "index scores", which are used in the economic model are not presented in the clinical effectiveness section and the EAG has been unable to check them at source.

The improvements reported across the EQ-5D-5L and VFQ-25, suggest a positive impact on perceived health and visual functioning for both arms, but not for the intervention over the comparator. However, as the EQ-5D is not condition specific and includes only a single pain domain, and the VFQ-25 primarily focuses on visual function, these tools may not fully capture symptom burden, particularly ocular pain, which as stated throughout Section 1.3 of the CS, is a hallmark of AK and was not directly assessed in the trial.

The absence of a direct measure of ocular pain is a notable limitation of the trial and results, especially given the known severity of pain associated with AK and the dense corneal innervation. Additionally, if adjunctive steroids were used to manage pain and inflammation, it becomes even more difficult for the EAG to assess the treatment effect of polihexanide 0.8mg/ml from that of supportive therapies.

Therefore, the company was asked (Clarification Question A15) to provide clarity as to why pain was not measured systematically as a trial outcome and to further explain how pain could be adequately captured through EQ-5D-5L (one item on pain/discomfort) or VFQ-25 (functional vision). The company responded by stating that “pain was adequately and regularly evaluated as a systematic trial outcome” through the EQ-5D, VFQ-25 tools and through monitoring adverse events. The company also stated that patient reported pain outcomes using both tools were assessed on “study Days 0, 7 (± 2), 14 (± 2), 21 (± 2), 30 (± 3), 60 (± 3) and every 30 days (± 5) until resolution, in addition to follow-up and end-of-study visits.” The company also provided data regarding pain domains for the EQ-5D-5L and VFQ-25 for the polihexanide 0.8mg/ml arm, whilst the CSR also provided the same data including the comparator arm of polihexanide 0.2mg/ml + propamidine 1mg/ml. Key results from the pain domain can be found in Table 11. In addition to this, the EAG clinical advisors stated that there is no universal or systematic tool to assess and quantify pain in AK patients, due to the inter-subject variability of pain experienced by patients, and it was advised that patient-reported outcomes are an acceptable way to measure pain in AK patients. Therefore, the EAG is satisfied that ocular pain has been addressed as best as it could have been in the ODAK trial.

Adverse Events and Compliance in the ODAK Trial

In this section, the EAG summarises the available data on treatment compliance, study discontinuation, and AEs reported in the ODAK trial. The focus is on key metrics from both treatment arms, drawn from the FAS (for compliance) and safety analysis set (SAS, for treatment discontinuation and AEs), with particular attention to the nature and frequency of adverse events, reasons for discontinuation, and the robustness of safety reporting.

Compliance

Compliance with study drug administration was assessed in the FAS, based on the number of full treatment days missed. Participants were classified as non-compliant if they missed one full day of treatment within the first five days or up to two full days after the initial five-day period (ODAK protocol). Additionally, investigators could withdraw participants if compliance was considered insufficient. Compliance was high in both the polihexanide 0.8mg/ml arm (93.9 % (62/66)) and polihexanide 0.2mg/ml + propamidine 1mg/ml arm (95.1% (58/61)) as noted in CS Section 2.1.

Study Discontinuation

According to CS Section 2.11.2 and Appendix D 15.9% (11/69) of participants in the polihexanide 0.8mg/ml arm and 10.8% (7/65) in the polihexanide 0.2mg/ml + propamidine 1mg/ml arm discontinued study treatment. The most common reason was adverse events, accounting for 63.6% (7/11) of discontinuations in the polihexanide 0.8mg/ml arm and 100% (7/7) in the polihexanide 0.2mg/ml + propamidine 1mg/ml arm. Two participants also discontinued due to “other” reasons in the polihexanide 0.8mg/ml arm and no such incidences occurred in the polihexanide 0.2mg/ml + propamidine 1mg/ml arm. The EAG notes that the reason “other” was not explicitly defined while those of “physician decision” were included in the CS (Section 2.11.2) and CSR. The EAG asked the company what the reasons were for discontinuation listed as “other” (Clarification Question A12b). The company responded by stating that, this included one participant who had a viral infection, which was part of the ODAK trial exclusion criteria, and another (one) participant *“who remained on study treatment after 12 months from randomisation (the maximum time frame of treatment), which was classed as a treatment failure.”*

The EAG notes that the CS table refers to these data as being for “discontinuations from the study,” while the CS narrative describes them as “discontinuations from study drug.” In the CS Appendix, the wording is limited to “discontinuations from the study.” Based on the data available, the EAG is unable to confirm whether these terms were applied consistently. The protocol definition appears to refer to study discontinuation, but it is known that there were some non-compliant participants (above).

The EAG notes that the study discontinuation rates reported in the CS and appendix are slightly higher in the polihexanide 0.8mg/ml arm than those reported in the CSR (Table 14.1.1.4), where results are presented for the FAS.

Adverse Events (AEs)

Across both treatment arms, 44.8% of participants experienced at least one adverse event (CS 2.11.1 and Appendix D 1.1.1); rates were similar between groups (44.9% and 44.6%) (see Table 13). No serious AEs (SAEs) were reported in either arm based on the original protocol definitions. However, following re-evaluation prompted by the EMA²² and using CIOMS (Council for International Organisations of Medical Sciences) criteria, four SAEs were identified in three patients, two in the polihexanide 0.8mg/ml arm and one in the polihexanide 0.2mg/ml + propamidine 1mg/ml arm. These included corneal perforation, corneal transplant, and visual impairment. The EAG notes that AEs were reclassified post hoc using CIOMS criteria at the request of the EMA, to align with their classification system, which designates a broader range of preferred terms as serious. The EAG considers that while this change reflects differences in classification approach rather than new safety signals, it highlights the potential for underestimation of serious harm depending on the criteria applied. Severe AEs (as initially reported in the ODAK protocol) occurred in 5.8% of participants in the polihexanide 0.8mg/ml arm and 7.7% in the polihexanide 0.2mg/ml + propamidine 1mg/ml arm. No AEs led to dose reductions in either arm, though dose increases occurred in 7.2% of patients (all in the polihexanide 0.8mg/ml arm). Treatment interruption due to AEs occurred in 15.9% of participants in the polihexanide 0.8mg/ml arm and 9.2% in the polihexanide 0.2mg/ml + propamidine 1mg/ml arm. No AEs were classified as “certainly related” to the study drug, but

30.4% of participants in the polihexanide 0.8mg/ml arm and 21.5% in the polihexanide 0.2mg/ml + propamidine 1mg/ml arm experienced AEs considered “possibly” or “probably” related to the study drug.

Table 13: Summary of adverse events across treatment arms (safety analysis set)

Adverse event outcome	Polihexanide 0.8mg/ml + placebo (n=69)	Polihexanide 0.2mg/ml + propamidine 1mg/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
Not applicable	6 (8.7), 12	5 (7.7), 6

AEs were coded using MedDRA® (Medical Dictionary for Regulatory Activities) version 20.0–24.0.

Source: Table 8 of CS Appendix D.1.1

Common AEs (>5%)

CS Section 2.11.2 and Appendix D.1.1 reports common AEs. The most frequently reported adverse events (≥5% of participants in any arm) were (reported as, polihexanide 0.8mg/ml vs. polihexanide 0.2mg/ml + propamidine 1mg/ml):

- Eye pain: 13.0% vs. 10.8%
- Ocular hyperaemia: 11.6% vs 10.8%
- Lacrimation increased: 8.7% vs. 3.1%

- Infections and infestations (SOC): 13.0% vs. 12.3%
- General disorders and administration site conditions (SOC): 5.8% vs. 7.7%

Adverse event severity

Data were not reported for adverse events by grade (e.g., using a standard grading system such as Common Terminology Criteria for Adverse Events [CTCAE]), but mild, moderate and severe AEs were described in CS Table 26 and CS Appendix Table 10. Moderate AEs were reported in 17.4% of participants in the polihexanide 0.8mg/ml arm and 16.9% in the polihexanide 0.2mg/ml + propamidine 1mg/ml arm. The ODAK protocol provided definitions for AE intensity and referred to these as Grade I–III, corresponding to mild, moderate, and severe. For moderate events (Grade II), the protocol defined intensity as: *minimal, local or non-invasive intervention indicated; limited age-appropriate instrumental activities of daily living*. The most reported moderate or severe events were eye disorders (including eye pain), with severe AEs such as corneal perforation and corneal transplant occurring in small numbers of participants.

The EAG clinical experts noted that the long-term effects of polihexanide 0.8mg/ml are unclear and that they would be unlikely to use polihexanide at this dose except in severe cases.

EAG Comment on the ODAK trial

In summary, the full randomised data results from the ODAK trial suggest that polihexanide 0.8mg/ml was not superior to polihexanide 0.2mg/ml + propamidine 1mg/ml but non-inferiority was demonstrated for the primary outcome. When analysing clinical and patient reported outcomes, no statistically significant advantages were observed favouring polihexanide 0.8mg/ml. Long time-to-cure, high rates of adjunctive therapy use, and sizable rates of corneal scarring, even among patients who were considered cured, raise concerns with regards to the clinical meaningfulness of the primary outcome of the trial, being medical cure rate. Adverse event rates were generally similar between the two treatments. The EAG has some concerns over the risk of bias which should be considered when interpreting the findings.

3.4 Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

The company states in sections 2.9 and 2.10 in the CS that a meta-analysis was not possible as ODAK was the only study identified by the company's SLR which evaluated the safety and efficacy of polihexanide 0.8mg/ml, and thus an indirect treatment comparison (ITC) was performed using the polihexanide 0.8mg/ml arm of ODAK and data from the Papa et al. 2020 publication which evaluated the time to cure for patients with AK using different AATs.

Due to the paucity of data for polihexanide 0.8mg/ml, the EAG agrees with the company that a conventional meta-analysis was not possible. The company did not mention the lack of feasibility for network meta-analyses (NMA) in the submission or appendices however, since the comparator arm of ODAK is reflective of UK clinical practice according to the EAG's clinical experts, it is likely studies that use polihexanide 0.2mg/ml plus propamidine 1mg/ml as a treatment option exist, so the EAG considers that an NMA may be feasible if the relevant studies are identified.

To generate the risk ratio needed for the economic model, the company conducted an ITC using individualised patient data (IPD) from both ODAK and the Papa et al. study to compare the 12-month MCR between polihexanide 0.8mg/ml versus pooled AAT. The company's ITC used IPD from both studies as the company owns polihexanide and retrieved the IPD for the pooled AAT group from the authors. The IPD was not submitted as part of the submission and is not a part of the EAG's critique.

3.4.1 Indirect treatment comparison data sources

The company's SLR identified the Papa et al. 2020 publication which was used as a source of evidence for the clinical effectiveness of the pooled AAT comparator.¹⁶ This pooled AAT cohort was used in the ITC to compare the effectiveness of polihexanide 0.8mg/ml from the ODAK study.

Though ODAK was a two-arm RCT, it was treated as a "pseudo-single-arm" study in the ITC where the MCR of the 66 patients who were allocated to the polihexanide

0.8mg/ml group were compared to the MCR of all 227 patients in the Papa et al. study.

3.4.2 Papa et al. 2020

The CS summarises the included comparator study, Papa et al. 2020¹⁶ in CS section 2.10.2. The study is a retrospective cohort study, including 227 people with AK from two sites (London, UK and Milan, Italy) who were treated between 1991 and 2012 and had retrievable medical records. The EAG asked in clarification A24 for justification of the use of a comparator dataset that predominantly predated 2012. In response to A24, the company justified this by stating that the core treatment pathway for AK has remained largely unchanged since it was first identified in the UK in 1974, while also acknowledging that diagnostic technologies and the understanding of AK has improved. Table 14 of the clarification question responses presents the treatment and management of AK pre- and post-2012, comparing the approaches in a study conducted in 2002,³² 2009,⁶ and 2015,³³ and also presented the guidelines from the College of Optometrists.¹⁷

The company provided additional sensitivity analyses for the ITC excluding patients prior to 2000 and 2005, in response to A25, and the results were consistent with the base case ITC (see section 3.5.13 and Figure 6).

The Papa study was funded by SIFI and was an expansion of an existing dataset to inform the design of the ODAK trial, it is unclear if this prior dataset was published. The corresponding author for the study was the same author of the ODAK trial publication. Inclusion and exclusion criteria are summarised in CS Table 20. The study only included people with AK who had data where the primary and secondary outcomes could be ascertained from complete data, no further details were reported on how this was assessed. In addition, people with concurrent bacterial keratitis and those who developed bacterial keratitis as a complication of AK were eligible. All participants received treatments with topical anti-amoebic therapy (AAT), which included biguanides (polihexanide 0.2mg/ml and chlorhexidine 0.2mg/ml) and diamidines (either propamidine 1mg/ml or hexamidine 1mg/ml, as one class) as monotherapy or in combination. As the aim of the Papa et al 2020 study was to

assess the outcomes from different AAT types, there were four groups of drugs analysed:

- polihexanide 0.2mg/ml monotherapy
- polihexanide 0.2mg/ml and diamidine
- diamidine monotherapy
- combined AAT (polihexanide 0.2mg/ml and chlorhexidine and diamidine in different combinations).

There were also two analyses, by baseline AAT (the AAT started at baseline) and by mutually exclusive AAT (patients in any one AAT treatment group must have been exposed to all the drugs in that group only for at least some time during their treatment (could be a few days). This was established at the end of treatment. The CS used the results from pooling all the four groups for their comparator (EAG assume from the 'by baseline AAT' group).

Cure was defined as having clinical evidence of elimination of AK (intact corneal epithelium, no clinical signs of ocular inflammation) after treatment had been discontinued for 30 days. The cure calculation included two people who required enucleation (surgical removal of the eye) to cure the AK. The primary outcome was MCR within 12 months, defined as cure without the need for surgery, independent of visual acuity including blindness (it is unclear if these two participants with enucleation were excluded from the primary outcome MCR). Secondary outcomes included time to cure and poor outcomes (visual acuity $\leq 6/24$ and/or surgical intervention). These were not included in the company ITC, as confirmed by the company in response to CQ A23.

232 patients met the inclusion criteria and had complete data for primary and secondary outcomes, however, five had follow-up of less than 31 days and were excluded. It is not clear whether this was pre-defined. It is unclear how many people were excluded for not having complete data for the primary and secondary outcomes overall but around 60% were excluded from the UK site. Of the 227 people included, 177 were from the UK (Moorfields, London). Although Papa et al¹⁶ state that the demographic data of those included at baseline were tabulated in the supplement, the participant characteristics at baseline were not reported except in the narrative which reported that none had concurrent fungal or herpes keratitis, 66%

of participants had concurrent or misdiagnosed bacterial keratitis and 'over' 34% had severe disease. The CS reports minimal baselines provided by the study author in Table 21 and reproduced in Table 14. The EAG has not been able to validate these data. At clarification A22, the EAG asked the company for any additional baseline characteristics available from Papa et al. 2020. The company provided two additional items: proportion of Caucasians, and prior use of antibiotics. The proportion of Caucasians in Papa et al. 2020 was 59.5%, and it was not reported in ODAK. Prior use of antibiotics was higher in the polihexanide 0.8mg/ml arm of ODAK compared to Papa et al. 2020 (84.8% vs 67.5%). In supplementary table 1 of Papa et al. 2020, ethnic group was reported as Caucasian, other, or unknown. Other variables presented were scleritis and/or hypopyon, presence of advanced or severe disease, and use of oral anti-fungal pre-AAT.

Data for use of 'potentially' adjunctive anti-amoebic treatments (oral voriconazole and itraconazole) and polihexanide 0.06% were recorded and it is apparent from the Papa et al 2020 publication¹⁶ that a small proportion of participants received adjunctive treatments as presented in Table 14. There was also a proportion (41%) of participants who switched treatment during the analysis period (also in Table 14). These were confounding factors for the analysis of the comparisons presented in the Papa et al 2020 publication, but it is unclear if these influence the comparison with the pooled AAT which was used in the CS ITC.

Table 14: Adjunctive and changes to treatment in the Papa sample n=227

n (%)	Treatment switching	Adjunctive oral immunosuppressants	Adjunctive polihexanide 0.6mg/ml	Adjunctive antifungal drugs
Pooled AAT, n=227	94 (41.1)	40 (17.62) ^a	14 (6.17)	20 (8.81)

^a Oral steroids 19 (8.37%); oral non-steroidals 4 (1.76%); both steroids and non-steroidals 17 (7.49%)

3.4.3 Comparison of study designs

The EAG qualitatively compares the various study features between the ODAK trial and the Papa et al. 2020 publication in Table 15. Of the study features compared, there were differences in study design, study setting, intervention, comparator, trial

start and end dates, sample size calculation, and the population used in the ITC analysis.

ODAK is a randomised, double-masked, active-controlled Phase III RCT, whereas Papa et al. is a retrospective observational cohort study. This is a fundamental difference in study designs. RCTs minimise confounding through randomisation, while observational studies rely on statistical adjustment for confounders. Therefore, the evidence generated by these studies differ in internal validity and susceptibility of bias, especially when conducting ITCs.

The ODAK trial prospectively enrolled and confirmed AK patients using standardised diagnostic criteria, whereas papa et al. included retrospectively identified patients with medical record completeness as the main criterion. This affects the consistency of baseline definitions, standard of diagnosis, and possibly disease severity as study entry. For instance, real-world practice in the earlier Papa cohort may have introduced heterogeneity in how AK was diagnosed or classified compared to that in ODAK.

The ODAK trial was a RCT comparing polihexanide 0.8mg/ml versus polihexanide 0.2mg/ml + propamidine 1mg/ml with the ITC using only one arm of ODAK, the single, precisely defined intervention: polihexanide 0.8mg/ml + placebo, while Papa et al. included a range of AAT regimens. This heterogeneity makes it difficult to establish a valid counterfactual to ODAK's fixed-dose monotherapy, especially since outcomes may differ between AAT types. Furthermore, ODAK also had a defined comparator, polihexanide 0.2mg/ml + propamidine 1mg/ml, selected to meet EMA ethical requirements rather than reflect UK standard of care. Papa et al. does not have a single intervention; instead, outcomes are reported across various AATs, with the different regimens analysed descriptively or via regression. These do not match the ODAK treatments directly and may represent different efficacy and safety profiles.

Of the 227 patients in Papa et al. study, 41.4% switched to an alternative AAT, compared to only two patients in the polihexanide 0.8mg/ml group (2.9%) who had surgery. Furthermore, subsequent use of AAT was not collected in ODAK. This highlights a potential difference in treatment exposure and escalation between

studies, with Papa et al. reflecting real-world switching and adjunctive treatment, while ODAK represents a controlled, fixed-treatment setting.

ODAK was conducted from 2017 to 2021, while Papa et al. spanned 1991 to 2012. There was no overlap between the trials, with ODAK starting 26 years after the start of Papa et al. and five years after the end of the Papa et al. study. This creates substantial concern around temporal bias as clinical practice, diagnostic technologies, treatment protocols, and patient monitoring have all evolved significantly, limiting the relevance of historical comparators to current practice. Nevertheless, the company provided sensitivity analyses excluding data from Papa et al. 2020 prior to 2000 or 2005, with results consistent with the base case ITC, indicating a robust and stable finding across time (see Section 3.5.13).

ODAK was powered a priori to detect a clinically meaningful difference in MCR with 80% power at a 10% significance level, while Papa et al. did not prespecify a sample size or statistical assumptions, given its retrospective design. This means the precision and interpretability of outcome estimates differ, especially for ITCs.

Only the polihexanide 0.8mg/ml arm from the ODAK study was used in the ITC, while the comparator was excluded as it did not reflect real-world practice. In contrast, all arms in Papa et al. were included in the analysis as a single combined arm. While this makes Papa et al. more representative, it introduces heterogeneity in treatment exposure and complicates the comparability with ODAK, where one intervention was isolated under trial conditions.

The EAG notes similarities between study locations, inclusion/exclusion criteria, primary and secondary outcomes, treatment switching, follow-up period, statistical analysis, and sample size.

While statistical adjustment successfully balanced the prognostic variables between ODAK and Papa et al. cohorts (CS Table 22), there remains structural differences between the two studies. These factors introduce a risk of residual confounding and non-comparability that cannot be fully mitigated through modelling or propensity scoring analysis. The ITC results may still provide useful evidence of relative treatment effects but should be interpreted with caution.

Table 15: Comparison of select study design and methodological features between ODAK and Papa et al. 2020

Feature	ODAK	Papa et al. 2020	Comparable	Notes
Study design	Randomised, double-masked, active-controlled, multicentre, parallel Phase III trial	Retrospective cohort	No	Fundamentally different study designs: RCT vs observational study
Study setting	Patients with clinical signs consistent with AK and positive confocal microscopy findings consistent with AK were eligible for randomization	Patients treated for AK at Moorfields Eye Hospital (London, UK) and San Raffaele Hospital (Milan, Italy)	Mostly no	Different recruitment methods and clinical workflows, one prospective, one retrospective
Locations	Six sites in 3 countries (Italy (2 sites), Poland (1 site), the UK (3 sites))	2 sites in 2 countries (Italy, the UK)	Yes	Same sites from UK and Italy recruited from, though ODAK does recruit from 4 further sites, including one from a different country (Poland)
Inclusion criteria	Patients aged ≥ 12 years of age with a diagnosis of AK. Participants with AK using the following previous treatments for keratitis (mis)diagnoses were also eligible: Antibiotics for a presumed or proven ocular bacterial infection at baseline. Antiviral and antifungal drugs given for a misdiagnosis and discontinued at baseline. Anti-inflammatory drugs, including those using topical steroids, oral nonsteroidal anti-inflammatory drugs, or both before baseline	Patients developing AK between 25th July 1991 and 10th August 2012, and with retrievable medical records. Patients with a diagnosis of AK, for whom the primary and secondary outcome measures could be ascertained from complete data. Patients with concurrent bacterial keratitis, as well as those developing bacterial keratitis as a complication of AK	Yes	Similar definitions, ODAK uses tight inclusion (for example diagnostic confirmation)

Feature	ODAK	Papa et al. 2020	Comparable	Notes
Exclusion criteria	Patients with a documented history or clinical signs of concomitant keratitis or both, caused by fungi or herpes simplex virus Treatment before baseline with anti-amoebic agents Participants using systemic IST Participants requiring urgent surgical intervention for AK	Patients with a diagnosis of other causes of chronic microbial keratitis, including fungal and herpes keratitis	Yes	Broadly aligned, ODAK excluded more proactively (for example prior AAT)
Intervention	Polihexanide 0.8mg/ml + placebo	Various anti-amoebic therapies (AAT): PHMB monotherapy PHMB+ diamidine Diamidine monotherapy Other combinations	No	No standardised intervention in Papa et al., not directly comparable to ODAK's single intervention
Comparator	Polihexanide 0.2mg/ml + propamidine 1mg/ml	Comparison made across AAT groups (noted above)	No	Papa et al. does not have a clear parallel group, differs significantly with ODAK.
Primary outcome	Medical cure rate at 12 months from randomisation without surgery	Medical cure rate at 12 months from randomisation without surgery*	Yes	Definitions and timeframes similar (see Table 17)

Feature	ODAK	Papa et al. 2020	Comparable	Notes
Secondary outcomes	Time to cure Best corrected visual acuity measured by Snellen feet Corneal scarring Ulceration severity Anterior chamber inflammation Use of alternative surgery Safety outcomes Treatment exposure Adverse events Patient-reported outcomes EQ-5D-5L VFQ-25	Proportion of patients with poor outcomes: Time to cure Snellen visual acuity $\leq 6/24$ and/or Surgery	Yes	Similar outcomes, ODAK includes more.
Subsequent treatment	Treatment failure rate occurred in 17 (13.4%) patients, with 8 (6.3%) undergoing keratoplasty. Two (3%) patients in polihexanide 0.8mg/ml group required corneal transplantation surgery	Switching of baseline ATT occurred in 41% of patients. Highest switching was from: - Diamidine monotherapy (88% switched) - Other/unclassified combinations (72%) - PHMB + diamidine (25%) - PHMB monotherapy (48%) Switching typically occurred within the first 31 days 42 (18.5%) patients underwent surgical intervention	No	Both report treatment modification and surgery; Papa shows more switching due to real-world setting.
Trial start and end dates	17 August 2017 to 18 June 2021	25 July 1991 to 10 August 2012	No	Conducted decades apart, with major differences in clinical practice and diagnostics.

Feature	ODAK	Papa et al. 2020	Comparable	Notes
Follow-up	Maximum: 12 months post-treatment	Minimum: 31 days Maximum: 26 months Median time to cure: 5 months IQR time to cure: 3.25 to 9.0 months	Mostly yes	Both studies capture long-term cure, though follow-up structure differs slightly.
Statistical analysis	Multivariable analysis: Poisson regression with robust variance was applied to estimate both unadjusted and adjusted risk differences in MCR. Covariates included in the model: Known prognostic factors: age, AK stage, delay in diagnosis, prior corticosteroid use, prior antiviral use Suspected prognostic factors: prior antibiotic use, study site (6 sites) A subgroup analysis was conducted for MCR by AK stage at baseline. Kaplan-Meier and Cox models were used to analyse time to cure, adjusting for covariates. Missing data were minimal. Dates with missing days or months were imputed as the 1st of the respective month or year.	Unadjusted bivariate analyses: Outcome proportions were estimated for each AAT using binomial exact method with 95% CI Associations between AAT type and outcomes assessed using Poisson regression with robust SEs, estimating risk ratio Associations between other baseline variables and outcomes explored using Fishers exact test Adjusted multivariate regression models: Multivariable Poisson regression with robust SEs and offsets was used to estimate adjusted risk ratios, for MCR and risk of poor visual outcome All covariates with $p < 0.2$ in unadjusted analyses included Known or suspected prognostic factors (identified a priori): age, disease severity at baseline (hypopyon, scleritis, or stage 3 disease), and prior corticosteroid use	Mostly yes	Both use adjusted models, but statistical methods and outcome modelling differ. Papa et al. used stepwise selection based on statistical thresholds.
Sample size	Total: n = 134 Intervention: n = 69 Control: n=65	Total: n=227	Yes	Sample sizes are different but both studies have sufficient size for comparative analysis.

Feature	ODAK	Papa et al. 2020	Comparable	Notes
Sample size calculation	Based on detecting a $\geq 20\%$ absolute difference in MCR, assuming a control group MCR of 67%, with 80% power and a two-sided alpha of 10%. This required 116 evaluable patients. To allow for 10% loss to follow-up, the required sample size was included to 130.	NA (Retrospective study; no prospective power calculation)	No	Only ODAK had a predefined sample size with power considerations.
ITC analysis	Only the polihexanide 0.8mg/ml group was included in the ITC. The comparator arm, propamidine 1mg/ml, included polihexanide 0.2mg/ml due to a request from the EMA to use an active comparator for ethical reasons. Hence, it is not reflective of options available in current real-world practice.	All patients included. Patients were treated with topical AAT, which included biguanides and diamidines, either as monotherapy or in combination.	Mostly no	Target arms differ; Papa includes more heterogeneous real-world treatment, while ODAK isolates one arm.
* Originally, discontinuation of baseline AAT was not treated as failure. The company contacted the corresponding author to provide the data so that the definition of MCR can be aligned to that used in ODAK. AAT, anti-amoebic treatment; AK, acanthamoeba keratitis; CI, confidence interval; EMA, European Medical Agency; EQ-5D, EuroQol 5-dimension; ITC, indirect treatment comparison; MCR, medical cure rate; PHMB, polyhexamethylene biguanide; SE, standard error; VFQ-25, visual function questionnaire 25-item				

3.4.4 Critical appraisal of studies

The quality of ODAK has been discussed in the EAG report section 3.2.2 (Table 9 and Table 10). While the company rated the overall quality of ODAK as good, the EAG had some concerns around imbalances in baseline characteristics, the exclusion of seven randomised patients from the FAS, and deviations from pre-specified outcomes. (see EAG report 3.2.2, Table 9 and Table 10).

The company assessed the quality of Papa et al. 2020 using the Quality Assessment Tool for Case Series Studies and rated the quality of this study as good overall (CS Table 10). The EAG assessment of the quality of the study can be seen in Table 16. The EAG differs from the company assessment on several factors, and the overall quality has been assessed as poor by the EAG. This is primarily because the study did not include consecutive cases and because minimal baseline characteristics were reported of the participants, particularly the omission of contact lens use. The EAG also notes that the objective of the study was to compare treatment options, and that the primary outcome data used by the company in the comparison to the ODAK population was not presented in the publication.

Table 16: Company and EAG risk of bias assessment of Papa et al. 2020

Question	CS assessment	EAG assessment	EAG Comments
Was the study question or objective clearly stated?	Yes	Yes	The objective was to compare treatment options
Was the study population clearly and fully described, including a case definition?	Yes	No	Minimal baseline characteristics were reported
Were the cases consecutive?	Yes	No	Cases were those who had retrievable medical records and where the outcomes could be ascertained, although no details of any exclusions on this basis this does not appear to be including consecutive cases. In addition, of the 227 participants, 177 were from the UK and this represented just 41% of the cases seen during the recruitment period.
Were the subjects comparable?	Yes	Unclear	No details were reported
Was the intervention clearly described?	Yes	Yes	

Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Unclear	Data were extracted from historical medical records; it is unclear if outcomes were assessed consistently
Was the length of follow-up adequate?	Yes	Yes	
Were the statistical methods well-described?	Yes	N/A	Well describe but not applicable to the current appraisal
Were the results well-described?	Yes	N/A	Well described but the data for the primary outcome of relevance to the present appraisal was not available in the publication and was obtained by the company (CS Table 23).
Overall quality	Good	Poor	At least one risk of bias question rated no
CS, company submission; EAG, evidence assessment group			

3.5 Critique of the indirect comparison or multiple treatment comparison

3.5.1 Indirect treatment comparison populations

In the company's ITC, the inputs of the MCR outcome for each study is informed by:

- ODAK: Full analysis set, polihexanide 0.8mg/ml group only (n=66; UK patients = 30 (45%))
- Papa et al. 2020:¹⁶ All patients regardless of whether baseline treatment was received, pooled AAT (n=227, UK patients = 177 (64%))

3.5.2 Selection of endpoints for the ITC analysis

Only one endpoint was of interest in the ITC, medical cure rate, which was the primary outcome of both studies, and the results of the ITC was used to inform the economic model. Table 17 compares the definition of MCR and cure in ODAK and Papa et al.¹⁶ Both studies defined MCR as being cured without the need of surgery, independent of visual acuity. Although the ODAK study also defined MCR as cure without a change of AAT and explicitly mentions that it is measured within 12 months of randomisation, both definitions of MCR are comparable.

Both studies also defined what cure means in the context of AK and MCR, which are also comparable. The only difference is that the ODAK study adds a requirement that anti-inflammatory treatment must be discontinued for 30 days, whereas Papa et al. requires only cessation of AAT.

The EAG asked the company during the CQ stage on whether any other outcomes were analysed in the ITC. The company responded that the key endpoint of interest was the cure of AK infection, defined as MCR as 12 months, therefore no other outcomes were analysed in the ITC.

Table 17: Definition of medical cure rate and cure in ODAK and Papa et al. 2020

Outcome included in ITC	Study	Time measured	Definition	Comparable?
Medical cure rate	ODAK	Within 12 months of randomisation	The rate cured (see below) by each treatment without the need for surgery or a change of AAT,	Yes. The definition used by the company for

Outcome included in ITC	Study	Time measured	Definition	Comparable?
			and independent of visual acuity.	the Papa et al. MCR was aligned to that of ODAK after contacting the Papa et al. authors.
	Papa et al.	Within 12 months	From publication: A cure (see below) without the need for surgery, independent of visual acuity (including blindness) For ITC: The company aligned this definition to that of ODAK by including changing AAT as a failure, originally this was not classed as a failure.	
Cure	ODAK	NA	Clinical evidence of elimination of Acanthamoeba, including an intact corneal epithelium with no clinical signs or symptoms of ocular inflammation after discontinuing AAT and anti-inflammatory treatment for 30 days	Mostly yes.
	Papa et al.	NA	Clinical evidence of elimination of Acanthamoeba—an intact corneal epithelium with no clinical signs of ocular inflammation after discontinuing AAT for 30 days	
AAT, anti-amoebic treatment; ITC, indirect treatment comparison; MCR, medical cure rate NA, not applicable				

3.5.3 Prognostic covariates chosen for the ITC

The company listed the six prognostic variables identified by clinical experts and included in the ITC in section 2.10.3 of the CS. These were: age, gender, AK disease stage, prior use of corticosteroids, prior use of antivirals, and delay in starting treatment.

The company states that these covariates were not reported consistently between studies and so cross-trial differences were limited to those factors which were available in each source. However, it is not clear if the company meant that one or more of these six prognostic variables were not reported, or if other variables outside of these six were dropped. Considering Table 22 of the CS which compared the six

prognostic variables before and after adjustment, it suggests that these six variables were reported in both studies, however it is not clear which variables the company were referring to. In the ITC Report 2025 (SIFI. Data on File. 2025), it states that only comparisons with the historical untreated AK cases data from the SLR (not relevant to the NICE scope) were adjusted for age and sex only since these patients were untreated and stage was not available. However, since this comparison was not presented in the CS, the above statement is likely irrelevant for the comparison with Papa et al. Nevertheless, the extent of this inconsistency, and its impact on the validity of the indirect comparison, was not fully explained. Unadjusted prognostic variables may lead to residual confounding.

Additionally, patients with missing covariates or outcome data were excluded from the ITC, except missing treatment delay data which was median-imputed, and age which was mean-imputed. There was an inconsistency in the way missing data were handled, with only two of the six variables imputed, while missing values in other covariates led to patient exclusion. Ideally, imputation should be consistent across all variables. Furthermore, the inconsistency in the imputation method used is a limitation. Mean and median imputation is a simplistic method which does not account for the uncertainty between variables, nor does it preserve the relationship between variables. A more robust and statistically appropriate method would have been multiple imputation, which preserves the multivariable structure of the data and yields more valid standard errors by reflecting the inherent uncertainty in the imputed values.

The EAG asked for clarity on why only two variables were imputed, why mean and median imputation were chosen, and if any other methods of imputation were considered. The company responded in response to CQ A32 with the following.

Firstly, missing data for the delay in starting treatment variable was minimal, and the company imputed the expected value of 30 days for the few cases of missing values. However, the claim of 30 days being the expected value was stated without explaining how this value was derived. If the median was used as the basis for imputing 30 days, this was not explicitly stated, and it could be reasonably assumed that 30 days could be the mean delay, or even a clinical assumption.

The EAG also asked why mean age was used to impute for missing age. The company did not respond to this question for age. Given the summary of baseline age from Table 6 in the CS, the age distribution in the polihexanide 0.8mg/ml arm appears positively skewed slightly, as indicated by the mean being higher than the median, and a long right tail extending up to 73 years. It is likely that median age would be a more appropriate value to impute given the likely skewed distribution of age in the polihexanide 0.8mg/ml arm.

However, more robust imputation methods exist, such as multiple imputation. The company did not state whether any alternative imputation methods were considered or explored. The response to A32 does not indicate that methods beyond single-value imputation were utilised.

The approach taken by the company was inconsistent, imputing data for age and treatment delay, but excluding cases with missing values for disease stage in the propensity score matching step. The hybrid approach of mixing imputation with complete-case analysis introduces a risk of selection bias, especially if missingness is not completely at random and if excluded patients differ from those retained in the ITC.

The company provided results of sensitivity analyses testing the robustness of this imputation strategy in response to CQ A30 and in the EAG report section 3.5.13.

The EAG's clinical advisors deemed the six covariates used by the company for the ITC adjustment to be clinically appropriate but questioned the lack of contact lens use. The company state that "*AK is most commonly acquired through contact lens misuse*" in section 1.3 of the CS, accounting for "*87% of cases*". Contact lens use is a major risk factor for AK, with different risk levels depending on lens type (e.g. daily vs monthly wear) and wearing habits (e.g. overnight use, improper hygiene, swimming or showering while wearing lenses). Inclusion of contact lens use, either as a binary (yes or no) or by frequency of wear, would likely improve the robustness of the adjustment.

Although the ODAK trial appears to have recorded contact lens wear (CS Table 6: Risk factors for keratitis contact lens wear), the Papa et al. 2020 study did not report

this information (Table 13 of CQ Responses A22). As a result, this variable could not be included in the propensity score model, which introduces potential residual confounding. Given the strong clinical relevance of contact lens use, this remains a limitation of the ITC.

3.5.4 Data analysis and weighting approaches

The company used propensity scoring matching (PSM) with overlap weighting (OW) as both sets of IPD were available to the company. PSM and OW allows one to compare patients fairly across the two studies using a method that gives more weight to patients who are similar between the studies and downweighting patients who are more different, making the indirect comparison more balanced than just a naïve comparison. After adjustment, weighted logistic regression was used to compare MCR, and the methodology aligns with guidance from NICE Decision Support Unit (DSU) technical support document (TSD) 17.³⁴

The company stated that overlap weight was calculated as one minus the propensity score for the corresponding treatment and were normalised to account for study sample size. Key prognostic and effect-modifying covariates included in the PSM model were age, sex, stage 3 disease, prior corticosteroid and antiviral use, and treatment delay. Following weighting, weighted logistic regression was used to estimate the comparative treatment effect on the outcome of interest, 12-month MCR.

The analysis targeted the average treatment effect (ATE) estimand, representing the expected treatment benefit in the broader patient population. The company states that this estimand allows for generalised to the full population of patients with AK.

The EAG requested the company provide the distribution of the propensity score and weights used in the ITC. The company provided the two tables and a histogram. The first table (Table 23 of CQ responses) compared the baseline characteristics of the polihexanide 0.8mg/ml group to the Papa et al. cohort before and after three methods of adjustment: overlap weighting, average treatment effect, and average treatment effect of treated. The company states that the PSM adjusted analysis with OW demonstrates more stable estimates and better covariate balance compared to the other two methods. The standardised mean differences (SMDs) for the

unweighted and weighted approaches are presented in Figure 2. All three adjustment methods result in small SMDs (less than 0.2 difference), though the OW adjustment performs the best, resulting in all SMDs equal to zero.

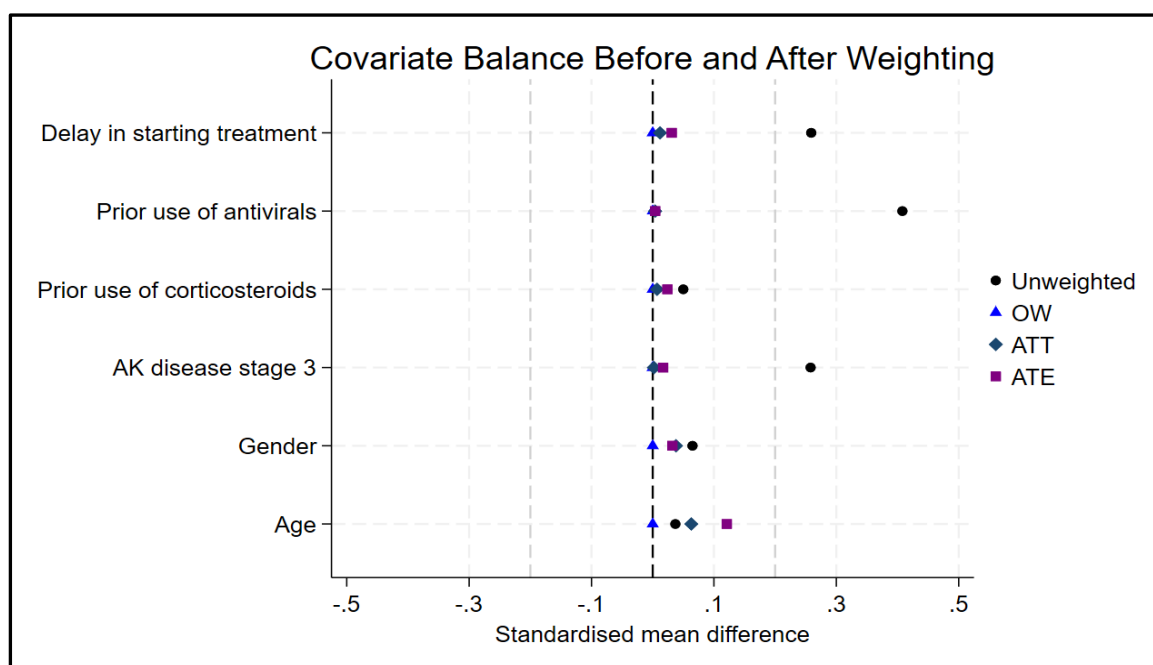


Figure 2. SMDs between prognostic factors at baseline from ODAK and Papa et al. before and after adjustment (ATE=average treatment effect, ATT = average treatment effect for the treated, OW=overlap weighting)

The second table (Table 24 of CQ responses) summarises the distribution of the propensity scores and weighting variables for the ODAK and Papa et al. cohorts. These were presented for each of the three methods used in the ITC: OW, ATE, ATT.

For the overlap weighting method, the mean propensity scores were 0.285 (SD = 0.099) in ODAK and 0.230 (SD = 0.097) in Papa et al., with the corresponding OWs being 0.715 and 0.230, respectively. These weights reflect the complement of the propensity score ($1 - \text{propensity score}$) for the treated and untreated groups and were designed to emphasise comparability between patients in the overlapping region of the PS distribution.

In contrast, ATE weights had a wider spread, with a mean of 4.108 (SD = 1.962) in ODAK compared to 1.322 (SD = 0.181) in Papa et al., indicating greater weight variability and suggesting a higher influence of outlier observations in the ODAK trial.

ATT weights were fixed at 1.000 in the treated (ODAK) group and variable in Papa et al., with a mean of 0.322 (SD = 0.181), consistent with reweighting the comparator population to resemble the treated cohort.

The histogram of weights provided the company (Figure 3) visually confirms that the overlap weighting method yields the most balanced and stable weighting scheme, minimising extreme weights and maximising comparability.

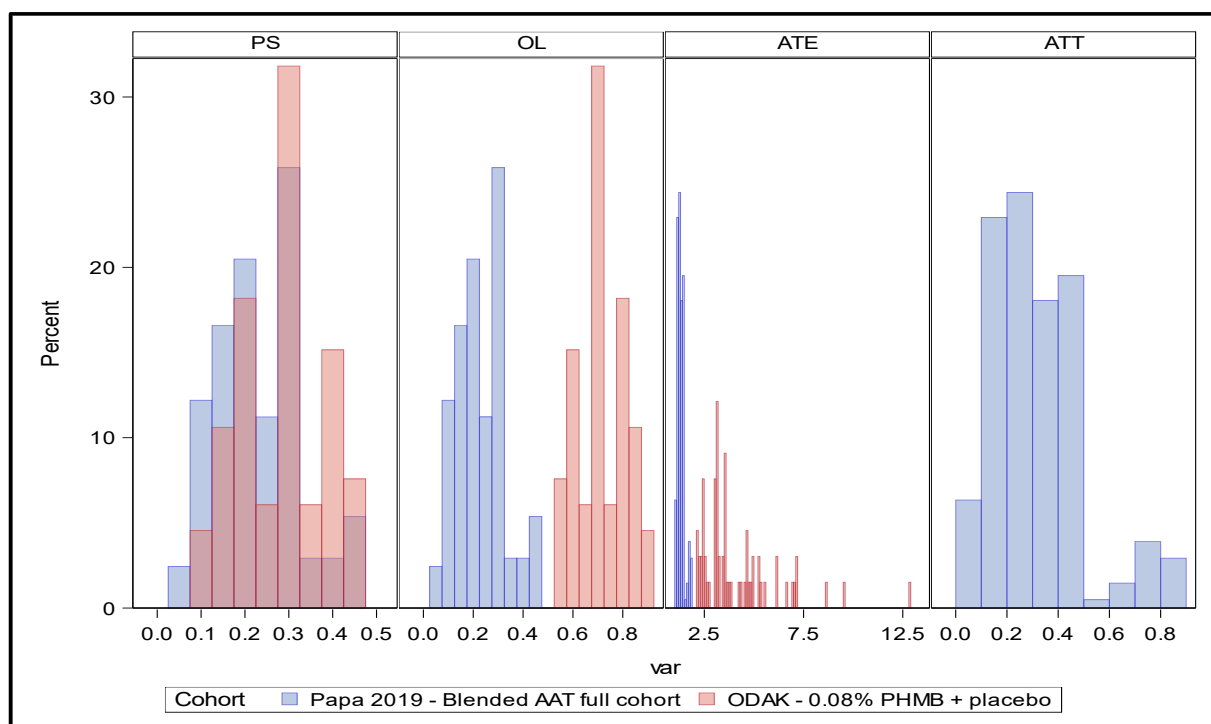


Figure 3. Distribution of propensity scores and derived weights (Figure 2 of CQ Responses)

3.5.5 Adjustment for switching to subsequent treatment

The company confirmed in section 2.7 of the CS that two patients in the polihexanide 0.8mg/ml group required corneal transplantation surgery in the OKAD trial, with only one of these being possibly related to the study treatment.

In Papa et al., substantial treatment switching occurred after baseline, especially in less effective regimens. From Table 1 of the Papa et al. 2020 publication, patients from the following switched to an alternative AAT:

- 28/114 (24.6%) of patients in the PHMB + diamidine group,
- 24/50 (48.0%) of patients in the PHMB monotherapy group,
- 22/25 (88.0%) of patients in the diamidine monotherapy group,

- 20/38 (52.6%) of patients in other AAT groups combined.

Furthermore, 40/227 patients (17.6%) were introduced to adjunctive oral immunosuppressants after baseline and ranged from 11% in the PHMB + diamidine group to 26% PHMB monotherapy group.

The large difference in subsequent treatments between ODAK and Papa et al. potentially biases the ITC results in favour of polihexanide 0.8mg/ml. The treatment switching and adjunctive therapy in Papa et al. may have diluted the apparent effect of any single AAT, as poor outcomes from initial therapies may have been mitigated by the subsequent therapies, and patients are still analysed by initial treatment. The MCR in ODAK reflects a clearer response to polihexanide 0.8mg/ml.

These differences were not accounted for in the ITC, which adjusted for six baseline prognostic variables only. The omission of these treatment-related factors may introduce post-baseline confounding and bias the treatment effect estimate in favour of ODAK. Therefore, the comparability of the MCR data between the studies is limited, and results should be interpreted with caution.

3.5.6 Covariates post-adjustment

Prognostic strength of covariates

The EAG requested that the company should test the prognostic strength of the covariates included in the adjustment process by fitting logistic regression models, adjusting for treatment and these prognostic variables (i) in bivariate analyses adjusting for only one of these factors, and (ii) in a multivariate model adjusting for all factors together. This analysis was intended to support the validity of the variables selected for the PSM. If the variables included are appropriate for the PSM, they should be statistically associated with MCR, even after adjusting for treatment. Additionally, if the treatment effect remains significant after adjusting for these variables, it would suggest that the observed treatment benefit is not fully explained by baseline differences between the groups, lending support to the robustness of the ITC findings. The results of these models are presented in Table 18.

In the bivariate models, all covariates except sex were statistically significantly associated with MCR at the 5% level, supporting their relevance for inclusion in the PSM. The treatment effect remained statistically significant across all bivariate models, suggesting that differences in individual covariates do not fully explain the observed treatment effect and that adjustment would result in more robust results.

In the multivariate model, age and disease stage remained statistically significant prognostic factors. Prior corticosteroids, prior antivirals, and sex were not statistically significant when adjusted for all covariates simultaneously, indicating possible collinearity or shared explanatory power with other variables. The treatment effect remained significant in the full model. Delay in starting treatment was not reported. It appears that due to a copying error in Table 25 of CQ Responses, age is presented twice at the expense of delay in starting treatment. Therefore, no clear conclusion on this covariate can be made.

Overall, the bivariate analyses support the selection of these variables as relevant prognostic factors for use in the PSM, while the multivariate model suggests that age and disease stage may be the strongest individual predictors of outcome. The persistence of a significant treatment effect in bivariate and multivariate models strengthens the case for a genuine treatment benefit beyond baseline imbalances.

Table 18. Prognostic strength of the six covariates used in the ITC when modelling MCR

Modeling MCR

Prognostic factor	Results of logistic regression (ODAK vs Papa et al.)			
	Bivariate		Multivariate	
	OR statistically significant	Treatment significant	OR statistically significant	Treatment significant
Age	Yes	Yes	Yes	Yes
Sex (male)	No	Yes	No	
Disease stage 3	Yes	Yes	Yes	
Prior corticosteroids	Yes	Yes	No	
Prior antivirals	Yes	Yes	No	
Delay in starting treatment	Yes	Yes	Not reported	
ITC, indirect treatment comparison; MCR, medical cure rate; OR, odds ratio				

Diagnostic balance of covariates

Prior to adjustment, three of the six variables had SMDs within ± 0.2 threshold. AK disease, antivirals, and delays in starting treatment had SMDs outside this threshold, justifying the need for population adjustment methods in the ITC and without adjustment any comparison will likely be confounded.

Following PSM and OW adjustment, the trials were balanced, with SMD = 0 in all cases (Table 19), suggesting that the adjustment method was effective. This is also shown in Figure 2. However, the initial imbalances highlight the potential for residual confounding due to unmeasured differences between studies, which should be considered when interpreting the results of the ITC.

Table 19. Comparison of baseline characteristics for patient populations from ODAK and Papa et al. pre- and post-weighting (adapted from Table 22 of CS)

	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						

3.5.7 Company's feasibility assessment

The company's feasibility assessment in the CS was conducted on whether it was feasible to compare ODAK to a relevant comparator study from the 48 that were identified; however, it was a brief assessment. A more detailed assessment was provided in section three of the ITC Report 2025 (SIFI. Data on File. 2025) which was provided in the reference pack of the submission.

The company discussed different ITC methods, including naïve comparisons, matching-adjusted indirect comparisons, network meta-analyses, and the PSM with OW approach that they ultimately went with. This was the chosen method since a connected network was not available and IPD were available for both ODAK and Papa et al.

The company's SLR identified 48 studies and only Papa et al. had a clinical resolution definition similar to that of ODAK to facilitate an ITC. Twenty-seven studies were excluded based on timing or outcome definition inconsistencies, and only two studies (Papa 2020 and Skarin 1996) reported clinical resolution at 12 months. Of these, Skarin 1996 was excluded due to a vague definition of cure.

Although the company stated that Papa et al. was the only study comparable to ODAK, key differences remained in population characteristics, disease severity, and subsequent treatments. The feasibility assessment concluded with the decision to apply PSM with OW using IPD from both ODAK and Papa et al., adjusting for six covariates identified as prognostic or effect modifying.

3.5.8 Company's choice of comparator

The company excluded the ODAK comparator arm (polihexanide 0.2mg/ml + propamidine 1mg/ml) from the ITC, instead comparing the polihexanide 0.8mg/ml + placebo group from ODAK to the pooled/blended AAT cohort from Papa et al. 2020, of which 48.90% of participants received polihexanide 0.2mg/ml + propamidine 1mg/ml. In the summary of CS section 2, the company states *“the effectiveness of the active comparator arm in the ODAK trial is not reflective of therapeutic approaches used in real-world practice and the results for this trial arm are not likely to be replicable in the real-world clinical setting”*.

The company argued that the ODAK comparator arm is not reflective of real-world practice, for two main reasons:

1. No compounding delays in the ODAK trial. In practice, polihexanide 0.2mg/ml + propamidine 1mg/ml) requires compounding, which leads to treatment delays. This was not an issue in the trial.
2. ODAK followed a rigid protocol, compared to real-world practice which is dependent on physician discretion and less likely to result in consistent outcomes.

Due to this, the company believes the comparator's effectiveness is overestimated in the trial. The above suggests that polihexanide 0.8mg/ml is more likely to reflect future practice, whereas the comparator is likely to remain unlicensed and heterogeneously administered.

However, the EAG's clinical experts disagree with the choice to exclude the comparator, stating that polihexanide 0.2mg/ml + propamidine 1mg/ml is a standard treatment in real-world practice. Furthermore, propamidine is a diamidine, and in Table 30 of the CS, polihexanide 0.2mg/ml + diamidine amounts to 52.3% of current therapeutic approaches used in UK clinical practice according to the UK Delphi Panel, and 48.9% from Papa et al. 2020 (CS Table 31). The company excludes the comparator arm data from the ODAK trial due to concerns around the real-world applicability of the treatment protocols used to administer this treatment within the trial, which do not reflect how patients would receive this treatment in the real-world for not being representative but then uses it. However, this treatment was used as a key component of the current treatment landscape in the economic model. The company also stated that the ODAK comparator was requested to be included, as opposed to a placebo control arm, due to 'ethical reasons'. The EAG's position, however, is that this comparator reflects standard care in the UK and should not have been excluded from the ITC.

Moreover, one could argue that if the comparator in ODAK is unrepresentative due to better trial conditions, the polihexanide 0.8mg/ml arm could be subject to the same criticism since it also benefits from early access and standardisation of protocol, though not the compounding issue. Another concern is of selective reporting. The

ODAK comparator showed slightly, though non-significant, higher medical cure rates (88.5% vs 84.8%). Choosing to exclude a more direct comparison with higher MCR, while retaining less robust indirect evidence, raises concerns about selective use of evidence.

3.5.9 Indirect treatment comparison results

3.5.10 Pooled/blended AAT

The results of the main ITC analysis for MCR are presented in Table 20. Results indicate that patients in the polihexanide 0.8mg/ml group of the ODAK study had a [REDACTED] relative risk of achieving a medical cure compared to the Papa et al. cohort, both before and after weighting.

Before adjustment, the MCR in ODAK was 41.2% higher than in the Papa et al. cohort (RR = [REDACTED]), Following population adjustment using overlap weighting, the difference [REDACTED] slightly to 36.4% (RR = [REDACTED]), though the difference was still [REDACTED].

Covariate balance was achieved post-weighting (all SMDs = 0), and effective sample sizes (ESSs) remained high in both studies, though the reduced overlap in the Papa cohort, given by the 23% decrease in ESS, may indicate residual population differences.

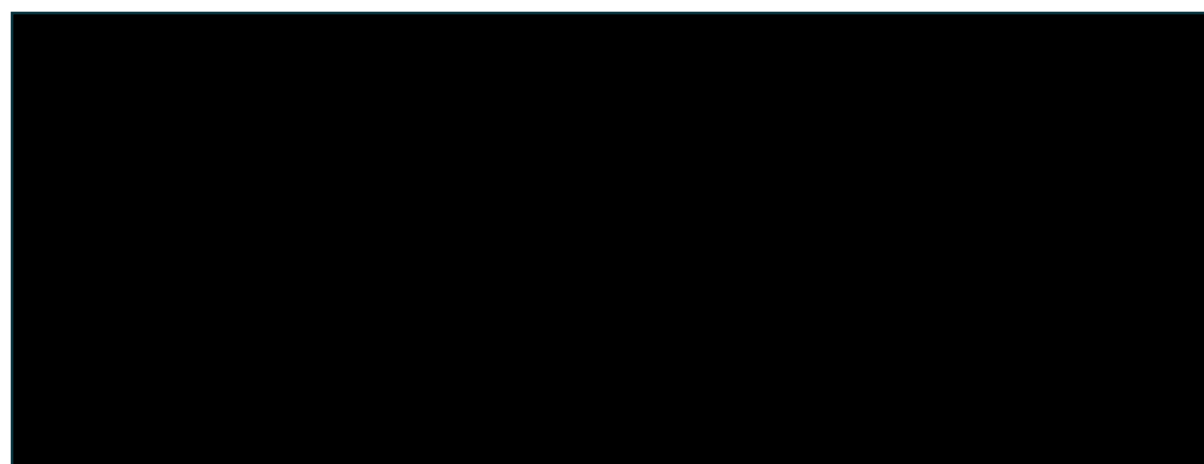
Table 20: Results of MCR comparison between ODAK and Papa et al. pre- and post-weighting

Study	Before weighting		After weighting	
	ODAK	Papa et al.	ODAK	Papa et al.
Effective sample size	66	227	64.8 (98.2%)	174 (76.7%)
Medical cure rate	-	-	-	-
Events	56 (84.8%)	99 (43.6%)	55.9 (84.7%)	109.7 (48.3%)
95% CI	73.9% to 95.5%	37.1% to 50.3%	76.1% to 93.4%	41.8% to 54.8%
Comparison				

Absolute difference	41.2% (28.8% to 51.2%)	36.4% (24.9% to 47.9%)
Relative risk		
CI, confidence interval; MCR, medical cure rate; ODAK, Orphan Drug for Acanthamoeba Keratitis		

3.5.11 Other comparisons

The company presented ITC results for the comparison to the polihexanide 0.2mg/ml plus diamidine and the chlorhexidine 0.2mg/ml $\pm$ propamidine subgroups of Papa et al. 2000s and to a cohort of untreated AK patients from the Untreated AK cases SLR in the ITC Report 2025 (not relevant to the NICE scope). The EAG produced a forest plot with these results as well as the base case ITC and the RR from ODAK, comparison of polihexanide 0.8mg/ml to polihexanide 0.2mg/ml plus 1mg/ml propamidine in Figure 4. Both the unadjusted and adjusted comparisons to the polihexanide + diamidine and chlorhexidine 0.2mg/ml $\pm$ propamidine subgroups of Papa et al. resulted in [REDACTED] in [REDACTED] of the polihexanide 0.8mg/ml group of ODAK, with RRs ranging from [REDACTED]. Compared to the cohort of untreated AK patients, the polihexanide 0.8mg/ml RR was [REDACTED] (RR = [REDACTED] in the adjusted comparison), providing evidence for its [REDACTED] versus being untreated. The company also performed a tipping point analysis to test the robustness of this comparison which is mentioned in the next section of this report. Only the within-ODAK comparison



results in a RR which numerically favoured the comparator, polihexanide + propamidine.

Figure 4: Results of company's ITC on Papa subgroups and untreated AK SLR

3.5.12 Tipping point analysis for untreated AK comparison

To demonstrate that the observed advantage of polihexanide 0.8mg/ml over untreated patients is robust to missing data in the untreated comparator group (for the comparison to untreated AK), the company performed a tipping point sensitivity analysis. Tipping point analyses simulate hypothetical scenarios where additional favourable outcomes are added to the untreated AK arm, to see at what point the observed treatment effect would no longer be statistically or clinically significant.

In this scenario, the company adds 20 hypothetical patients who were untreated and cured without surgery, doing so 30 times to show at which point there is no difference between the polihexanide 0.8mg/ml arm and the untreated AK group after running the propensity score analysis with overlap weighting.

The original mean RR different was 64.7% after adjustment, with only 11 of 56 patients achieving cure without surgery in the untreated AK arm compared to 56/66 patients in the polihexanide 0.8mg/ml arm. After adding 20 patients to the untreated AK arm, there are now 31 out of 76 patients cured in the untreated AK arm, decreasing the clinical resolution rate (CRR) difference to 43.9%. When 240 hypothetical patients who achieved cure in the untreated AK arm (251 cured out of 296 total patients), then there was no difference in CRR. The full tipping point analysis is presented in section 4.2.4 and Table 6 of the ITC Report 2025.

This analysis suggests that the result is robust. Unless there are hundreds of missing, untreated, successfully cure cases, the conclusion that polihexanide 0.8mg/ml is more effective than no AAT holds.

3.5.13 Indirect treatment comparison scenario analyses

The EAG asked the company in CQ A30 if any sensitivity analyses were conducted for the ITC since none were presented in the original submission. In response to question A30, the company presented sensitivity analyses using alternative weighting methods or with alternative model specifications, and in A24, analysing specific time periods from Papa et al. 2020.

Alternative adjustment methods

The company compared their primary method of adjustment, propensity score matching with overlap weighting, against two alternative methods average treatment effect (ATE), and average treatment effect on the treated (ATT):

OW checks for comparability and balance in the overlapping region of the propensity score distributions, providing stable estimates where both groups are most similar.

ATE estimates the average treatment effect across the entire study population, checking what would happen if everyone were treated versus not treated.

ATT estimates the average treatment effect for those who received the treatment, checking how effective the treatment was specifically for the treated group.

All three methods resulted in

[REDACTED], [REDACTED]
[REDACTED]

[REDACTED] (Figure 5). While the ATE method reduced the ESS of polihexanide the most (18% decrease), it also reduced the ESS of the Papa et al. full cohort the least (11% decrease) and resulted in the largest RR. The ATT method reduced the Papa ESS the most (31% decrease) but kept the same ESS for polihexanide as the unadjusted since all patients were given a weight of one. The OW method struck a balance between the other two methods while matching both study's patient characteristics the best, resulting in SMD = 0 for all covariates.

Alternative imputation methods

Due to the EAG's concerns surrounding the inconsistent imputation of age and treatment delay, the company conducted the following sensitivity analyses:

- Excluding disease stage from the adjustment
- Complete case analysis
- No imputation for AK disease stage 3
- Excluding treatment delay from the adjustment
- Excluding both disease stage and treatment delay
- Complete case analysis and excluding treatment delay

Results of these sensitivity ITCs follow a similar pattern to the sensitivity analysis based on adjustment method and resulted in [REDACTED] across the different sensitivity for adjustment method and covariates (Figure 5).

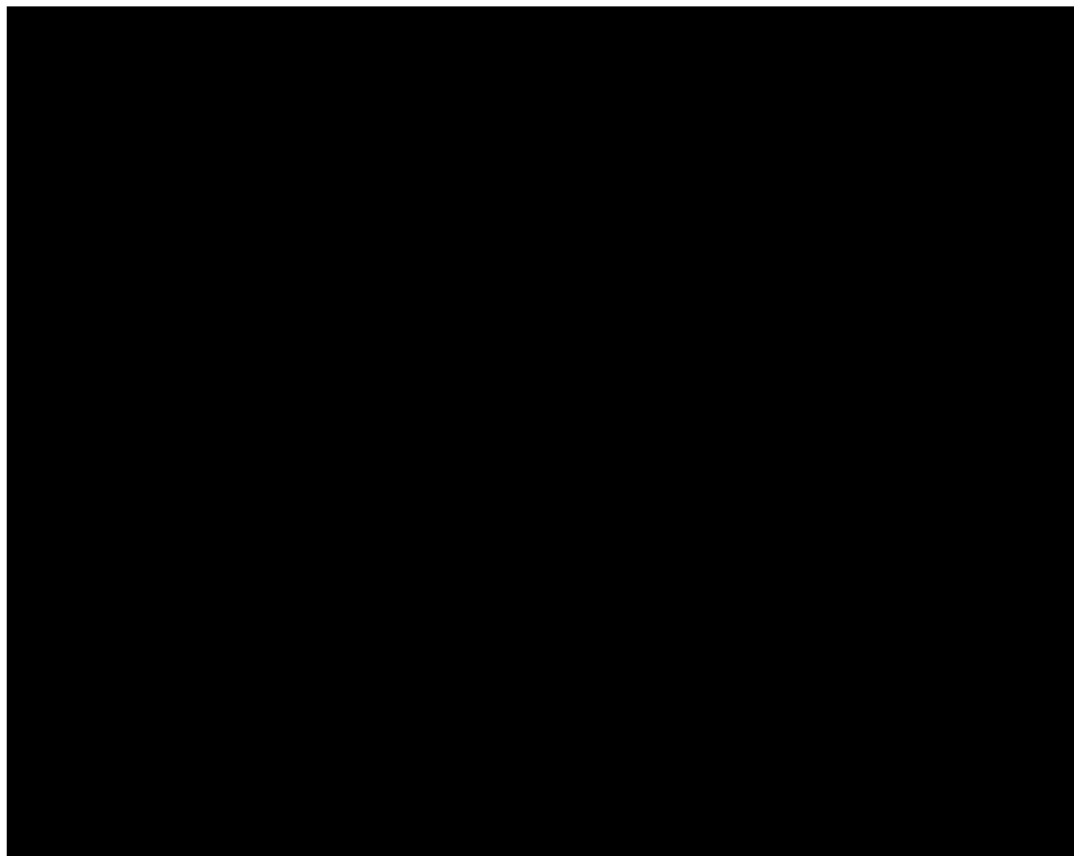


Figure 5: Sensitivity ITC results using different weighting methods and imputations

Papa et al. 2020 by year

The EAG asked the company in CQ A24 to justify the use of the Papa et al. 2000 study which predominantly predates 2012. The company justified the use of the Papa study by arguing that while diagnostic technologies and understanding of AK has evolved, the core treatment approach largely has not. The company state that since that 1980s, traditional AATs have remained the mainstay of therapy and highlight that real-world treatment still often involves unlicensed non-GMP compounds, leading to variabilities and delays in treatment. They further justify their use of the Papa study was that clinical practice in this study was consistent across time periods, and that observed treatment distributions align closely with those from the UK Delphi panel.

The EAG requested the company perform sensitivity analyses excluding data from Papa et al. 2020 prior to 2000 or 2005, and the company provided the results of two ITCs in response to CQ A25, one excluding data from Papa prior to 2005, and another prior to 2000. The results of these are shown in Table 15 of CQ Responses and presented in a forest plot in Figure 6. Results of the two sensitivity ITCs were consistent with base case ITC, regardless of weighting method used, indicating a robust and stable finding across time.

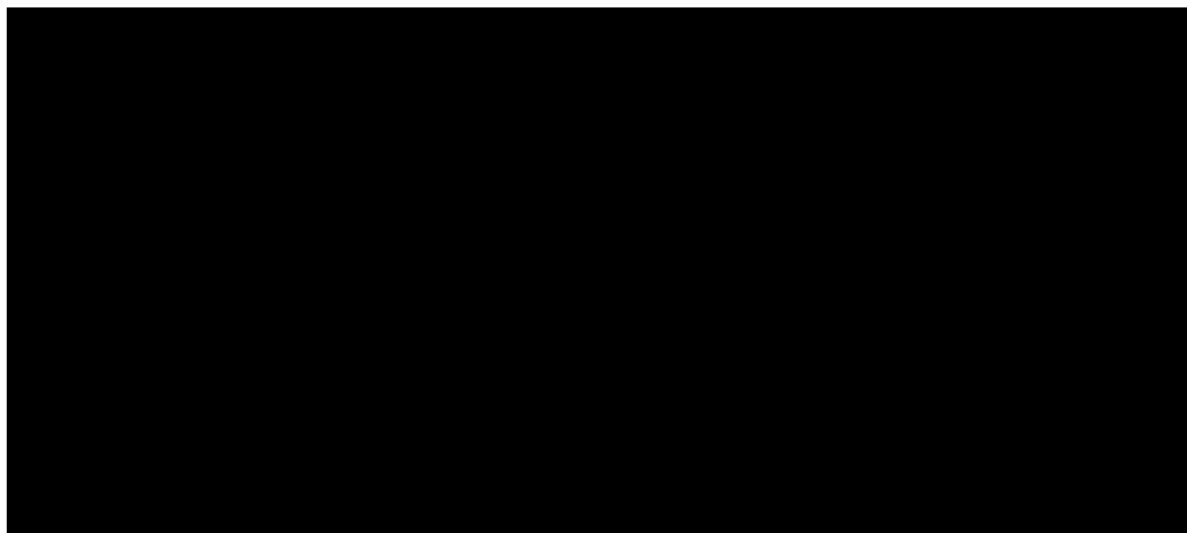


Figure 6: Sensitivity ITC results for the comparison to Papa full cohort, subjects since 2005, and subjects since 2000

3.5.14 EAG's critique of the company's ITC

Key issues surrounding ITC validity

The ODAK trial is a prospective RCT with some concerns of bias as judged by the EAG, whereas the Papa et al. 2020 study is a retrospective observational study with substantial methodological limitations, including heterogeneous treatment regimens, analysing based on initial treatment, and incomplete data capture. These differences in study design mean that combining evidence across two studies is liable to bias. The ROB assessment of the two studies highlights a few concerns for ODAK but serious concerns for Papa, further undermining the appropriateness of relying on Papa as the primary comparator dataset.

The company excluded the ODAK comparator arm, polihexanide 0.2mg/ml + propamidine 1mg/ml, arguing that the way it was used in ODAK was not reflective of its use in UK practice. However, this regimen (biguanide + diamidine) accounted for almost half of the therapies in Papa et al and more than half of the therapies

according to the Delphi panel, which was used as the source of current clinical landscape of AK therapies in the company's economic model.

In ODAK, MCRs were similar between polihexanide 0.8mg/ml and polihexanide 0.2mg/ml + propamidine 1mg/ml. The company instead shifted focus to an ITC against a weaker comparator source by excluding this direct, head-to-head evidence showing no added benefit of the higher concentration of polihexanide, omitting it from the ITC when results did not favour polihexanide 0.8mg/ml. This selective exclusion undermines the internal consistency and credibility of the company's ITC.

The company's chosen comparator group, pooled/blended AAT from Papa et al., combines a heterogeneous set of therapies. These regimens differ in mechanism, effectiveness, and frequency of use in UK practice. While Papa et al. (2020) reflects the overall distribution of therapeutic approaches in practice, pooling them masks clinically relevant variation, diluting the contribution of the most common regimen (PHMB + diamidine), and creates an artificial comparator arm that is not reflective of specific treatments used in practice.

Methodological weaknesses of the ITC

Contact lens use is a well-established prognostic factor in AK. Although OKAK recorded contact lens wear as a risk factor, Papa et al. did not, so this could not be included in the weighting model. The absence of this adjustment represents a limitation and a potential source of residual confounding.

The company noted that missing baseline data were imputed differently across variables. For some, complete case analysis was used, while others were imputed using the mean or median. Such inconsistency may introduce bias, particularly in a small dataset.

In both ODAK and Papa et al, patients could receive multiple or sequential therapies. The company's ITC only considered the first recorded treatment and did not adjust for treatment switching or subsequent additions. These risks overestimating the effect of the index treatment, since many "monotherapy" patients may in fact have received combination regimens later.

Minor issue

The multivariate model found only age and disease stage 3 to be statistically significant predictors of outcome. Sex was non-significant in both bivariate and multivariate analyses, yet it was still included as an adjustment factor. This raises questions about whether the model was over-fitted, particularly given the small patient numbers relative to the number of covariates adjusted for.

Positives

Both ODAK and Papa reported MCR as the primary outcome. Despite differences in study design, the outcome definitions were broadly consistent. The company contacted the authors of Papa and were able to align the definition of MCR, providing a common basis for comparison.

The company employed propensity score matching with overlap weighting, which is recognised in the literature as a valid method when anchored ITCs are not feasible. This is methodologically preferable to naïve comparisons or unadjusted indirect estimates and resulted in near-perfect alignment of arms in the ITC (SMD=0 for all factors).

The company presented additional analyses using alternative weighting schemes. Although effect sizes varied slightly, the results remained broadly consistent with the base case, suggesting a degree of robustness in directionality of the treatment effect.

Recently published ITC

The company's ITC was published in the BMJ Open Ophthalmology by Papa et al. 2025.³⁵ This paper was accepted by the journal three days after the company's submission to the EAG and reproduces the company's ITC methodology and results. However, it does not address the key concerns raised by the EAG regarding the validity and applicability for decision-making.

The paper presented the results as though the ODAK comparator arm was irrelevant, not acknowledging its clinical importance in the UK or explaining its exclusion from the ITC. The RCT itself was not even referred to by its acronym "ODAK", limiting transparency. The article provides little discussion of the validity of

combining a prospective RCT with a retrospective, non-randomised observational cohort, with no risk of bias assessment. Furthermore, the absence of contact lens use as a prognostic covariate, despite its clinical relevance.

The EAG considers that the Papa et al. 2025 publication does not strengthen the evidence base for the company's ITC. Instead, it replicates the weaknesses identified in the CS while failing to discuss them further.

3.5.15 Alternative ITC approaches

The EAG disagrees with the company's decision to exclude the ODAK comparator group from the ITC analyses. This regimen represents a substantial proportion of current UK clinical practice (around or more than a half according to the UK Delphi panel and Papa et al., 2020) and is supported by RCT evidence. Excluding this arm in favour of an unanchored comparison with an observational dataset introduces avoidable uncertainty.

The EAG considers the following approaches (in the absence of IPD) to be more appropriate methods in obtaining a comparator RR:

- **Inclusion of the ODAK comparator arm directly and excluding Papa et al. 2020:** Including the polihexanide 0.2mg/ml + propamidine 1mg/ml arm enables a direct head-to-head comparison with polihexanide 0.8mg/ml and avoids the methodological limitations of the Papa dataset comparison (section 3.5.4). While the ODAK comparator does not cover all regimens used in UK clinical practice (around or just under a half), it reflects a major component of standard care (the majority according to EAG's experts) and provides the most internally valid estimate of relative treatment effect.
- **Inclusion of the ODAK comparator as a link to the PHMB + diamidine subgroup from Papa et al. 2020:** The ODAK comparator regimen is similar to the PHMB + diamidine subgroup in Papa et al. 2020 as they both combine a biguanide and a diamidine and could permit an "anchored" comparison (see Figure 7) of polihexanide 0.8mg/ml versus the other regimens in Papa. This approach still inherits the limitations of Papa but may be less biased than a purely unanchored comparison, and differences between biguanide and

diamidine types would also need to be acknowledged. The analysis would be in three steps: first, to estimate the relative risk of 12-month MCR within ODAK; second, estimate the relative risk of 12-month MCR for PHMB + diamidine versus the other groups in Papa; third, combine the estimates using the Bucher method for anchored ITCs.³⁶ This method resulted in the same RRs as the naïve comparison.

- **Testing a range of RRs:** Conduct naïve comparisons between subgroups in Papa et al. 2020 against polihexanide 0.8mg/ml to find a plausible range for the treatment effect. This would be improved with IPD to conduct adjusted comparisons but is still caveated by the limitations of the Papa study.

Of the three approaches, the EAG favours the direct comparison of polihexanide 0.2mg/ml + propamidine 1mg/ml versus polihexanide 0.8mg/ml + placebo.

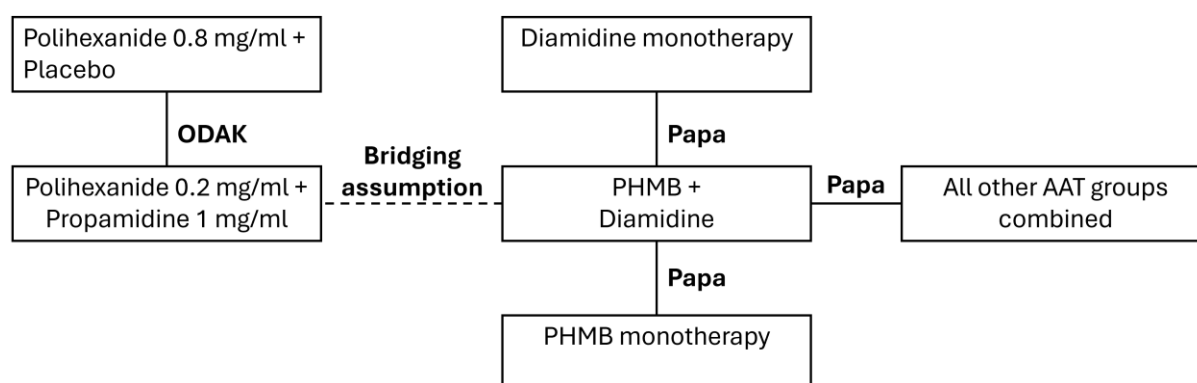


Figure 7. Connected network between ODAK and Papa assuming similarity between ODAK comparator and PHMB + diamidine from Papa et al. 2020

Another potential approach is to combine the relative risks from Papa and ODAK, a meta-analysis of aggregate RRs (ODAK: poli 0.8mg/ml vs poli 0.2mg/ml, Papa vs similar arms) which could provide a weighted average treatment effect. The drawback of this method is that the studies are too heterogenous, so pooling would not be statistically valid.

3.5.16 Choice of comparator and RR

In the absence of readily available IPD, the EAG were unable to replicate the company's PSM with OW analyses with the ODAK comparator included or conduct any other adjusted analyses.

The EAG explored alternative naïve comparison between polihexanide 0.8mg/ml and other relevant comparator arms. These included the ODAK comparator (polihexanide 0.2mg/ml + propamidine), as well as subgroups within Papa et al. 2020 reflecting real-world clinical practice.

The EAG then conducted exploratory scenario economic analyses using the unadjusted RRs derived from these comparisons. To assess the uncertainty around treatment effect, a threshold analysis was performed varying the RR in increments of 0.10 from 0.95 to 1.75, and the resulting ICERs were calculated at each value (Table 54).

The lowest observed RR of 0.96 (0.84, 1.09) was from the comparison of polihexanide 0.8mg/ml versus the ODAK comparator arm (polihexanide 0.2mg/ml + propamidine). While this is a clinically relevant comparator, it only represents around half of current therapeutic approaches based on both the UK Delphi panel and the Papa et al. dataset. As such, it would be unreasonable to assume that this subgroup alone reflects the full comparator landscape. Conversely, the company's adjusted RR of 1.75, derived via a PSM with overlap weighting comparing polihexanide 0.8mg/ml to a blended AAT cohort from Papa et al., may overestimate treatment benefit due to concerns around ITC, including residual confounding, selective comparator inclusion, and potential biases inherent in the unanchored ITC approach. The true treatment effect is therefore likely to lie somewhere between these two extremes. To reflect this uncertainty, the EAG conducted an exploratory threshold analysis varying the RR between 0.95 and 1.65 in 0.10 increments, to understand the impact of treatment effect assumptions on cost-effectiveness outcomes.

This approach allows the EAG to understand the impact of comparator selection and treatment effect assumptions on the ICER in the absence of a robust, reproducible ITC. It also supports transparency and reflects the clinical reality of current AK management more accurately than the company's preferred comparator. The EAG

considers these naïve estimates, while unadjusted, a useful sensitivity test to assess the robustness of the cost-effectiveness results given the uncertainty in the ITC.

Table 21 presents the naïve and company's ITC-adjusted RRs for MCR comparison polihexanide 0.8mg/ml from ODAK with a range of comparator regimens drawn from ODAK and Papa et al. 2020. The ODAK comparator group (polihexanide 0.2mg/ml + propamidine 1mg/ml) showed the highest cure rate, slightly higher than polihexanide 0.8mg/ml (88.5% vs 84.8%), resulting in a naïve RR of 0.96, suggesting a slightly lower, but not statistically significant, probability of cure in the 0.8mg/ml arm compared to the 0.2mg/ml + propamidine 1mg/ml group.

The Papa subgroups, using the numbers provided in Table 2 of the Papa et al. 2020 publication using their own definition of cure and not the company's slightly different definition, had consistently lower rates of cure compared to the polihexanide 0.8mg/ml group from ODAK, resulting in unadjusted RRs ranging from 1.34 to 1.46. When using the company's adjusted numbers for Papa et al., the RRs range from 1.54 to 2.12. When pooling the PHMB + diamidine subgroup of Papa to the comparator arm of ODAK, the unadjusted RR is 1.20.

These large RRs reflect the comparatively poorer outcomes in the observational Papa dataset, and the risk of confounding and bias in those data. The fact that RRs increase across Papa et al. subgroups, especially using the company's adjusted number of events, highlights the influence of case mix and potential for overestimation when relying on unanchored indirect comparisons with historical, retrospective data.

Table 21: 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 0.8mg/ml)

Study	Arm	Sample size	Cured	%	Naïve RR	Adjusted RR
ODAK	Polihexanide 0.8mg/ml	66	56	84.8%	Ref	Ref
ODAK	Polihexanide 0.2mg/ml + propamidine	61	54	88.5%	0.96	NC
ODAK/Papa groups pooled	PHMB + diamidine pooled	175	124	70.9%	1.20*	NC
Papa et al. (publication)	Other combined	38	24	63.2%	1.34*	NC

Papa et al. (publication)	Blended AAT	227	138	60.8%	1.40*	NC
Papa et al. (publication)	PHMB + diamidine	114	70	61.4%	1.38*	NC
Papa et al. (publication)	Diamidine monotherapy	25	15	60.0%	1.41*	NC
Papa et al. (publication)	PHMB monotherapy	50	29	58.0%	1.46*	NC
Papa et al. (company adjusted)	PHMB + diamidine	111	61	55.0%	1.54*	1.40*
Papa et al. (company adjusted)	Blended AAT	227	99	43.6%		
Papa et al. (company adjusted)	Chlorhexidine 0.2mg/ml ± propamidine	35	14	40.0%	2.12*	1.79*
*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; NC = not calculable; PHMB, polihexamethylene biguanide; RR, relative risk						

The EAG acknowledges that naïve, unadjusted comparisons may not fully account for baseline imbalances, and adjusted estimates would typically be expected to attenuate bias and the risk ratio. However, given that the unadjusted comparisons already suggest similar or slightly better outcomes for polihexanide 0.8mg/ml, it is reasonable to expect that adjusted risk ratios would still favour polihexanide 0.8mg/ml but with a smaller magnitude than the company's estimate of . This implies that even under conservative assumptions, polihexanide 0.8mg/ml is likely to remain at least non-inferior to existing therapies.

3.6 Additional work on clinical effectiveness done by the EAG

Screening of included and excluded studies

Of the 48 studies included by the company, only one was selected as a comparator for the MAIC. Twenty of the studies were not considered further by the company as they did not report cure. The EAG checked these studies and while three were identified as reporting an outcome similar to cure, none reported an intervention suitable for inclusion in a MAIC.

The company listed 28 studies in CS Appendix Table 7 that reported cure. One of these, Franch 2024,¹ was used by the company in a scenario analysis (see section 4.2.8). The EAG checked the definitions of cure and the relevance of the

interventions of the remaining studies and considered that no others were suitable for inclusion in a MAIC.

The EAG also checked the 133 studies excluded at full text and confirmed none were eligible.

In addition, the EAG notes that CS p62 cites a study, Di Zazzo 2024,³⁷ in support of the ODAK and ITC results. This study does not appear in any of the included or excluded studies lists, however the EAG notes that the publication reports outcomes for just two cases.

3.6.1 EAG targeted searches

The EAG undertook targeted update searches for polihexanide (any concentration) and AK in Embase and MEDLINE via Ovid. The searches were limited to records added to the databases in 2025.

Two reviewers independently screened the 13 identified references and three were retrieved for full text inspection. Of these, two were excluded by two independent EAG reviewers as they were duplicates and one study was included. This was the publication of the ITC,³⁵ as discussed in section 3.5.

The EAG also searched ongoing trial registers. One ongoing study of relevance was identified.³⁸ This is a retrospective cohort study of individuals given polihexanide 0.8mg/ml as part of a compassionate use program in Italy and is sponsored by SIFI SpA. Study completion is anticipated in October 2025.

3.6.2 EMA issues

The European Medicines Agency (EMA) Public Assessment Report²² provides a detailed discussion of the dossier submitted for the marketing authorisation of polihexanide. The EAG has listed here some of the key points relevant to the current appraisal, but with the caveat that a full summary and discussion of all the issues is not possible due to resource constraints.

The applied non-inferiority margin (i.e., 0.2) for the comparison between the arms in ODAK cannot be justified on either clinical or on statistical grounds.

There was uncertainty regarding the proposed benefit of the higher dose of polihexanide compared to usually administered lower doses, as no evidence of clinical benefit over lower doses was established.

Apparent differences between the finished product used in clinical trials and the commercial finished product that cannot be resolved were noted.

For bilateral disease, no data on treatment and outcome of fellow eye was recorded in ODAK, and no measures were taken to prevent treatment mistakes.

It was concluded that polihexanide 0.8mg/ml cannot be called non-inferior to the active comparator in the ODAK trial.

There was some discussion of Papa 2020 in terms of establishing a 'trial effect', but an indirect comparison with Papa 2020 was not provided in the EMA submission.

Treatment benefit of polihexanide was established using an external control group of 'untreated' patients ('untreated' was defined as not receiving treatment with an anti-amoebic treatment, i.e., polihexanide, chlorhexidine, propamidine, hexamidine).

The external control group was established by simple pooling of 56 'untreated' patients from 37 case reports and case series published between 1970 and 1995, identified by an SLR performed by the company. The approach was considered valid but was graded as low certainty of evidence with inherent bias.

It was concluded that polihexanide 0.8mg/ml performs better than no anti-amoebic treatment (when compared with historical data of 'untreated' patients).

The EAG asked the company to provide a summary of the points of critique made by the EMA about the ODAK trial (Clarification A8). The company states that *'the EMA acknowledged that ... the difference in treatment effect with polihexanide 0.8 mg/ml and the AAT comparator was sufficiently large to support that the treatment provides a beneficial effect compared to treatment with the AAT comparator'*. The EAG is unable to find this statement in the EMA report.

3.7 Conclusions of the clinical-effectiveness section

The CS presents evidence from the ODAK trial, a double-blind phase 3 randomised controlled trial, but focused on one arm treating ODAK as a single arm cohort study by the company. Participants from Italy, Poland and the UK who were aged at least 12 years old were included if they had clinical findings consistent with AK. While the CS focussed on the results of the polihexanide 0.8mg/ml arm (with placebo) the EAG also considered those from the comparator, polihexanide 0.2mg/ml + propamidine 1mg/ml. This was based on clinical advice that polihexanide 0.2mg/ml with propamidine 1mg/ml is the standard front-line treatment used in the UK. There were some notable differences in some baseline characteristics known to be prognostic factors between the two arms but it is not clear if this is a chance effect. The study was adequately powered but the EAG assessment of the risk of bias was that there are some concerns.

The primary efficacy outcome medical cure rate at 12 months for polihexanide 0.8mg/ml was not statistically significantly superior to polihexanide 0.2mg/ml + propamidine but was non-inferior. Although the EAG notes the rates were numerically lower in the polihexanide 0.8mg/ml arm. Time-to-cure was longer in the polihexanide 0.8mg/ml group. Other secondary outcomes were generally not statistically significantly different between groups. Both treatments had a positive impact on HRQoL. Adverse event rates were generally similar between groups, although treatment interruption owing to adverse events occurred more in participants in the polihexanide 0.8mg/ml group than the comparator. While no serious adverse events were initially reported, a re-evaluation using CIOMS criteria identified four serious adverse events in three patients, including corneal perforation, corneal transplant, and visual impairment, suggesting potential underestimation of serious harm at the time of original analysis.

The EAG clinical experts considered that the population of ODAK trial to be generalisable to UK clinical practice for people with AK infection. However, it was noted that there were more people with bilateral infection than would be expected. The EAG clinical experts also noted that they were unlikely to use polihexanide 0.8mg/ml as a first line treatment, due to the strength of the dose. However, the EAG

clinical experts did acknowledge that they would consider this stronger polihexanide 0.8mg/ml dose in patients with very severe cases of AK infection.

As the company's SLR identified no head-to-head trials, the company conducted indirect treatment comparisons to estimate the relative effectiveness of polihexanide 0.8mg/ml plus placebo with alternative anti-amoebic treatment using propensity score matching with overlapping weights. The company's ITC was based on the intervention arm of the ODAK trial and Papa et al. 2020, a retrospective cohort study at high risk of bias according to the EAG. The EAG considers this approach methodologically weak due to the fundamental differences in study design and quality.

The company's ITC excluded the clinically relevant ODAK comparator arm (polihexanide 0.2mg/ml plus propamidine 1mg/ml) and instead used a heterogeneous pooled comparator group derived from Papa et al. 2020. The EAG disagrees with this choice of comparator, given that the ODAK comparator reflects standard clinical practice in the UK, backed up by the EAG's clinical experts and the current therapeutic landscape of AK treatments using in the company's economic model.

The adjusted ITC results suggested a substantial benefit of polihexanide 0.8mg/ml relative to pooled AATs (risk ratio = [REDACTED], 95% CI = [REDACTED]). However, these results are highly uncertain, as they rely on assumptions about interchangeability between the ODAK and Papa cohorts which are unlikely to hold.

The EAG's assessment highlighted additional weaknesses in the ITC, included:

- Omission of a key covariate in the adjustment (contact lens use)
- Inconsistent imputation of missing data
- No adjustments for subsequent treatments
- Reliance on a pooled comparator group with heterogeneous treatment regimens
- The EAG's risk of bias assessment judged the OKAK trial to be at a low-to-moderate risk of bias, but Papa et al. 2020 to be a high risk of bias, further undermining confidence in the pooled analysis.

Overall, the EAG concludes that the company's ITC cannot be considered reliable evidence of comparative clinical effectiveness. The effect estimate of MCR underpinning the company's economic model is therefore subject to major uncertainty. The EAG prefers estimates based directly on the ODAK trial, supplemented only by cautious exploratory analyses where justified.

4 Cost effectiveness

This section focuses on the economic evidence submitted by SIFI and, additional information received in response to the EAG's clarification questions. The EAG critically appraised the evidence submitted and examined the company's electronic model. We provide a summary and critique of the company's economic evidence, including the company's systematic review(s), methods, and results (base-case, sensitivity and scenario analyses) as reported in the company submission using frameworks on best practices for reporting economic evaluation and economic modelling to assess the overall reporting quality and validity of these analyses. In the subsequent section, where possible, the EAG have addressed these concerns raised in the form of additional exploratory analyses undertaken, which concludes with the EAG base-case.

The submission received by the EAG included:

- A systematic review of the economic evidence
- Methods used to undertake the economic analysis, the company's base-case and sensitivity analysis results
- Electronic version of the *de novo* Markov model built in Microsoft Excel

4.1 Critique of the review of cost-effectiveness evidence

Search strategy

Searches for the cost-effectiveness studies SLR, HRQoL SLR and HCRU SLR were conducted together on 25th July 2022 and updated on 14th April 2025. Bibliographic database searches combined appropriate terms for AK/MK and intervention/comparators with a broad cost-effectiveness/HRQoL/HCRU search filter. No date limits were applied to the database searches.

Ideally, searches would have been conducted without intervention/comparator terms, to seek data on the conditions in general. The final line of the Cochrane Library search appears to be incorrectly reported, using the Boolean 'OR' instead of 'AND'. Sources are adequate, but ideally others, such as the freely available CEA Registry and a RePEC database, would have been included, as would a multidisciplinary database such as Scopus or Science Citation Index. Positively, backwards and

forwards citation searching of eligible articles included in the SLR and 11 identified SLRs (Clarification question A1 response, table 1) was also performed, along with checks of relevant, recent conferences and trial registers.

4.2 Critique of the submitted economic evaluation

The EAG reviewed SIFI's economic evaluation against the NICE reference case. Based on the findings from the company's systematic review, no previous economic models were identified; hence, a *de novo* model was built to assess the cost-effectiveness of polihexanide 0.8mg/ml compared to pooled AAT in treating people >12 years living with acanthamoeba keratitis, in line with the patient population, licence and decision problem for this submission. The EAG summarised the model schematic and the inputs required (e.g., the clinical evidence and the economic evidence), assumptions and company's analyses.

4.2.1 NICE reference case checklist

The EAG assessed the company's economic evaluation against the NICE reference standard, with the findings reported in Table 22.

Table 22: NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Defining the decision problem	The scope developed by NICE	Decision problem clearly stated, and it aligns with the scope developed by NICE.
Comparator(s)	As listed in the NICE scope	The pooled comparator used in the CS includes treatments stated in the scope (polihexanide 0.2mg/ml; chlorhexidine, propamidine and hexamidine) used in different combinations in different individuals. The pooled comparator group also includes individuals who were treated with polihexanide 0.6 mg/ml. These data were from a retrospective cohort study. The company excluded ODAK comparator polihexanide 0.2mg/ml + propamidine 1mg/ml. The CS decision was based on the outcome from

Element of health technology assessment	Reference case	EAG comment on company's submission
		their UK-based Delphi panel which considered that the ODAK comparator was not reflective of therapeutic approaches used in real-world practice (discussed further in sections 3.5, 3.5.8, 3.5.14 and 3.5.15). The CS also excludes data for each of the four treatment subgroups of the retrospective cohort study (polihexanide 0.2mg/ml monotherapy, polihexanide 0.2mg/ml and diamidine, diamidine monotherapy, combined AAT [polihexanide 0.2mg/ml and chlorhexidine and diamidine]). As indicated in the clinical effectiveness section 3.5.8, the EAG disagrees with the choice to exclude the ODAK comparator and the focus only on the pooled comparator from Papa et al. A view which was supported by the EAG's clinical experts that polihexanide 0.2mg/ml + propamidine 1mg/ml is standard treatment in real world practice. The EAG's approach to the comparators is discussed in more detail in sections 3.5.8 and 3.5.15.
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	All relevant health effects that occur following treatment have been considered in the economic analysis.
Perspective on costs	NHS and Personal Social Services	All relevant costs following treatment have been considered in the economic analysis, and it is in good keeping with the NHS and PSS viewpoint.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Company reported results in terms of cost per QALY
Time horizon	Long enough to reflect all important differences in costs or	Lifetime horizon of 63 years considered in the model, which is long enough to capture all

Element of health technology assessment	Reference case	EAG comment on company's submission
	outcomes between the technologies being compared	costs incurred and benefits accrued between the technologies being compared.
Synthesis of evidence on health effects	Based on systematic review	The company undertook a systematic review, then performed an ITC.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The company's preferred measure is in line with the NICE final scope.
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	EQ-5D-5L utility data were collected from participants in the ODAK trial.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The EQ-5D-5L health utility values were cross-walked to the EQ-5D-3L using the algorithm described by Hernández-Alava et al. ³⁹
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances	The company has not incorporated a QALY weighting in the analysis.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource use clearly reported and valued appropriately using current prices and is in line with the NHS and PSS perspective.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Discount rate based on a 3.5% per annum for both costs and benefits used.
EQ-5D-5L, EuroQoL five dimension five levels; NHS, National Health Service; PSS, Personal Social Services; QALY, quality adjusted life years		

4.2.2 Model structure

The company used a hybrid model comprising two phases to assess the cost-effectiveness of the technologies being compared. The first phase uses a decision tree structure to capture the treatment pathway people would expect to follow within the first year. The second phase uses a semi-Markov model structure to reflect the health states that people could occupy exiting the decision tree structure

characterised by whether they AK remained unresolved, visual acuity following resolution and loss of eye functionality.

The decision tree was used to represent the clinical pathway following treatment with polihexanide 0.8mg/ml versus pooled AAT within the first 12 months. At the end of the first year, people achieved a medical resolution of AK infection, changed in AAT or undergone therapeutic surgery or not cured. People cured within the first 12 months or those who received therapeutic surgery could occupy health states based on visual acuity. Following therapeutic surgery, people may experience a loss of functionality in the affected eye. Figure 8 depicts the decision tree structure for both strategies being compared.

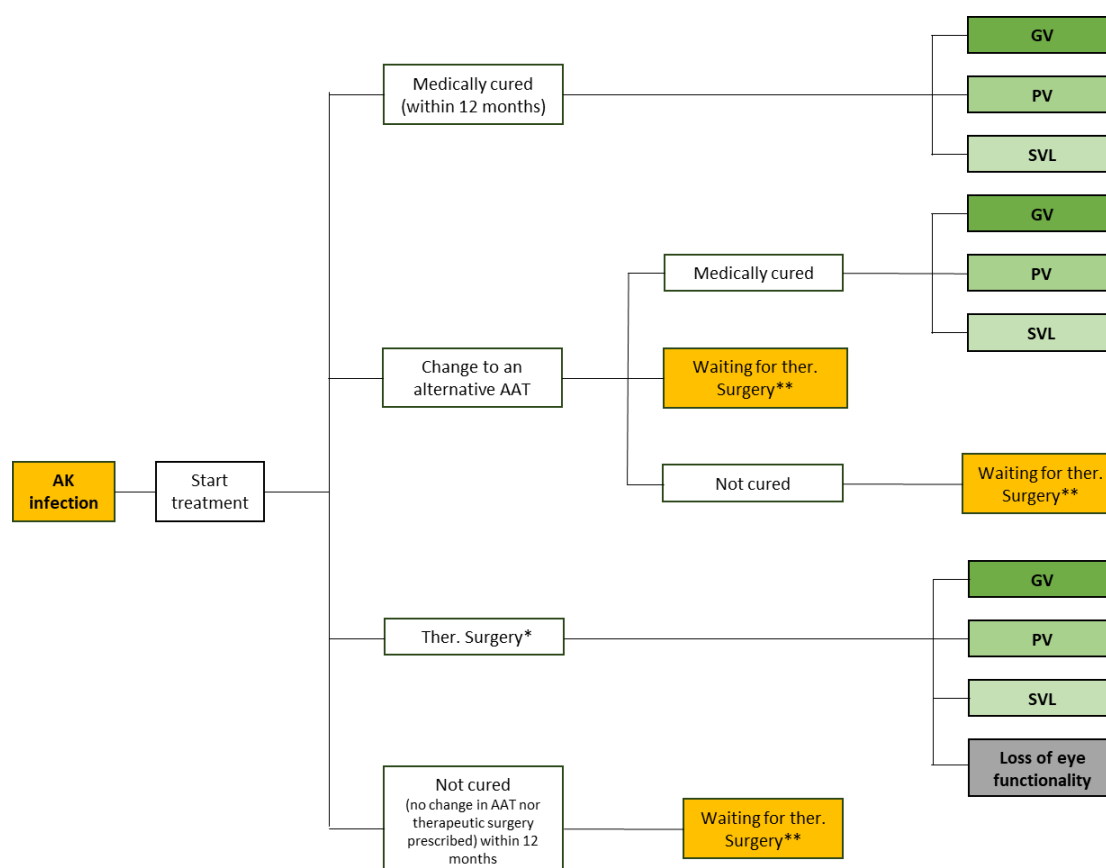


Figure 8: Decision tree structure

The proportion of people exiting the decision tree informs the starting distribution in the second phase, the semi-Markov model (see Figure 9). People occupied the health states based on if AK infection was still present, visual acuity (good vision, poor vision, severe vision loss) following AK resolution, or whether they had lost

functionality in the affected eye. Following resolution, people could remain in the same health state or until requiring optical surgery, graft failure or recurrence of AK infection or death.

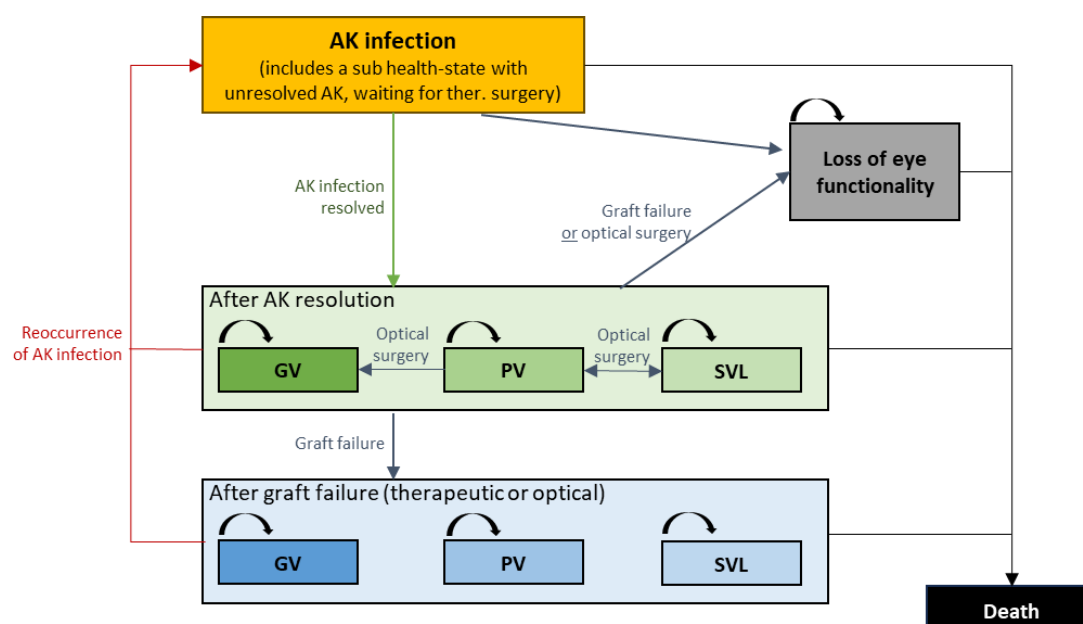


Figure 9: Semi-Markov model schematic

The company built a *de novo* model structured against two phases, which is a reasonable approach given the decision problem, treatment pathway and condition. The structure captures all important health states associated with AK infection.

4.2.3 Perspective, time horizon and discounting

The perspective/viewpoint of the analysis is that of the NHS and PSS, which aligns to the NICE Guide to the Methods of Technology Appraisal.⁴⁰ The model assumes a 63-year time horizon, which is long enough to capture the long-term costs incurred and benefits accrued, any differences between the technologies being compared. In the base-case, both costs and benefits were discounted at a rate of 3.5% per annum. The company's approach to implementing the discount rate from Year 1 onward is appropriate. Several one-way sensitivity analyses (OWSAs) were undertaken, with the results showing that the discount rate applied to outcomes had the greatest impact to the ICER. Taking an upper bound of 6% increased the ICER

to approximately [REDACTED] per QALY and the lower bound of 1.5% decreased the ICER to [REDACTED] per QALY.

4.2.4 Population

The population of interest is people diagnosed with AK. The population modelled represents the participants included in the ODAK trial (see Table 23).

Table 23: Baseline characteristics of the population modelled (obtained from CS, Table 32)

Baseline characteristic	Model Input	Source
Mean initial age (years)	36.70	Dart et al. 2024.
Male (%)	41.73	Dart et al. 2024.
Mean body weight (kg)	76.04	NHS Digital 2022. (Table 6, corrected value).

The EAG considers that the patient characteristics modelled are representative, but there are other characteristics that are more important (e.g., contact lenses wearers) compared to others (e.g., body weight).

4.2.5 Interventions and comparators

4.2.6 Intervention

The intervention included in the company's economic evaluation is polihexanide 0.8mg/ml eye drops administered as one drop in the affected eye, with a dosing regimen of:

Intensive 19-day treatment phase

- Day 0–5: 1-hourly drops (16 drops in a day) for 5 days
- Day 6–12: 2-hourly drops (8 drops in a day) for 7 days
- Day 13–19: 3-hourly drops (6 drops in a day) for 7 days

Continuation treatment phase

- Day 20 onwards: 4 drops in a day until resolution (maximum 12 months)

This schedule was in line with the drug regimen used in the Phase III ODAK trial. The EAG confirms that this regimen has been correctly implemented in company's the economic model.

4.2.7 Comparator

The company's approach to compare standard of care to polihexanide 0.8mg/ml was to use a pooled AAT to reflect current practice in the UK, comprising polihexanide 0.2mg/ml, chlorhexidine, propamidine, hexamidine, polihexanide 0.6mg/ml. Based on a Delphi panel comprising 10 clinical experts, the company claimed that the pooled AAT represents the range of treatment options and regimens used in the absence of a recognised standard of care. In Table 24, we report the pooled AAT, and their distribution obtained from the Delphi panel in comparison to the distribution from the Papa et al. study.¹⁶

Table 24: AAT distribution obtained from the Delphi panel and Papa et al. ¹⁶

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

The EAG's clinical experts consider the AAT distribution based on the Delphi panel appears to be reasonable. However, given that polihexanide 0.8mg/ml was compared to polihexanide 0.2mg/ml + propamidine 1mg/ml in the ODAK trial and it is in line with the NICE scope, the EAG considers that it would have been appropriate to at least include this comparison in a scenario analysis. The company undertook a scenario analysis based on the distribution from Papa et al.¹⁶

For details about the EAG's critique of the company's exclusion of the ODAK comparator arm (polihexanide 0.2mg/ml + propamidine 1mg/ml) from the ITC, please refer to Sections 3.5.8 and 3.5.15. This critique point is subsequently explored in the EAG's exploratory analyses in Sections 5.2.2. In the absence of IPD to re-run the

indirect treatment comparison, we explored a range of relative risks of medical cure rate at 12 months, then assessed their impact on the company's base-case ICER.

4.2.8 Treatment effectiveness and extrapolation

The company used 12-month MCR as the key measure of treatment effectiveness in the economic model. For polihexanide 0.8mg/ml, the company took the 12-month MCR directly from the ODAK trial (84.85%). The 12-month MCR data for the pooled AAT comparator was derived from the ITC comparing polihexanide 0.8mg/ml versus pooled AAT from Papa et al. 2020. The ITC conducted using PSM with OW and produced a risk ratio of [REDACTED] in favour of polihexanide 0.8mg/ml. The company took the MCR of polihexanide and divided it by [REDACTED] to estimate the comparator's MCR as [REDACTED].

The company also explored two scenario analyses using real-world data from Franch et al. 2024, which reported outcomes for 11 patients (12 eyes) treated with polihexanide 0.8mg/ml. These scenarios repeated the ITC with the Franch data in place of the ODAK data:

- Scenario 1: RR = [REDACTED] (95% CI: [REDACTED] to [REDACTED]), adjusting for all covariates in the base case (age, sex, disease stage, prior corticosteroid use, prior antiviral use, treatment delay).
- Scenario 2: RR = [REDACTED] (95% CI: [REDACTED] to [REDACTED]), without adjusting for age or sex.

4.2.9 Mortality

Mortality rates were required in the model to estimate the proportion of people who died within each model cycle and over the model time horizon. Mortality is accounted for in the model by using age- and gender-specific mortality risks and adjusted with different relative risks based on visual acuity. Age- and gender-specific mortality for the general population were obtained from the UK ONS 2025,⁴¹ which is based on data collected between 2021-2023. The company applied an increased risk (see Table 25) of mortality for people who were cured with poor vision, cured with severe vision loss and people who loss functionality in the affected eye. These increased risks were obtained from a study by Christ et al., (2008).⁴²

Table 25: Mortality rates

Health states	HR versus general population (95% CI)
Cured with poor vision	1.23 (1.16, 1.31)
Cured with severe vision loss	1.54 (1.28, 1.86)
Loss of eye functionality	
CI, confidence interval; HR, hazard ratio;	

Though not stated, there is no direct effect on mortality associated with treatment; there is indirect treatment effect on mortality from less people with AK infection and more people with better visual acuity for those treated with polihexanide 0.8mg/ml.

Applying an increase mortality risk showed that there were modest gains of 0.28 LY (discounted) when polihexanide 0.8mg/ml is compared to pooled AAT. The company undertook a scenario analysis that assumes there is no increased risk of mortality poor vision, severe vision loss or loss of eye functionality, i.e., same as general population mortality. As expected, taking this approach results in no difference in LYs.

4.2.10 Adverse events

In the absence of adverse events from the Papa et al. 2020 study, the authors used safety data from the ODAK trial, which showed that there was little difference between trial arms, in terms of frequency of events. Based on this finding, the company excluded resource use and costs for the treatment of, and disutilities associated with adverse effects from the economic analysis.

Despite little differences in the frequency of adverse events between participants in the trial arms, the EAG considers that these should have been included for a more accurate ICER, by capturing these costs associated with treating adverse events as well as their disutilities. The model does not include functionality to undertake such a scenario analysis.

4.2.11 Health-related quality of life

The company's economic model captured health-related quality of life by considering utility associated with AK infection and BCVA, disutilities associated with long-term complications of AK, disutilities associated with events, and caregiver disutilities.

4.2.12 Health-related quality of life studies identified in the review

The company performed systematic literature review (SLR) to identify cost-effectiveness and health state utility values that are associated with AK and MK. The SLR search found only one study that reported EQ-5D outcomes in AK patients (ODAK trial). The search identified three studies that reported on VFQ-25: two in patients with AK and one in patients with MK.

A detailed critique of the search strategy is provided in Section 4.1.

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

The primary source of utilities used in the cost-effectiveness model (CEM) is the EQ-5D-5L data collected from the ODAK trial mapped to the EQ-5D-3L UK value set using the DSU mapping function, based on the Policy Research Unit Economic Evaluation of Health and Care interventions (EEPRU) dataset.⁴³ The mapped EQ-5D-3L data from the ODAK trial was used in a mixed-model repeated measures (MMRM) analysis to obtain the disutility values for the health states poor vision and severe vision loss with good vision as the reference category (intercept). At clarification (question B13), the EAG requested the company to provide the output of the MMRM analysis to understand what variables were included as independent variables and to validate the coefficients obtained from the analysis. In their response, they explained how the analysis was performed, and the coefficients obtained from the analysis were provided in a table (clarification Table 44) but did not provide the EAG with the regression output obtained as it were from the software used. Therefore, the EAG were unable to validate the estimates of the MMRM provided by the company.

In the CEM, all patients enter the model with a utility same as that of the general population, adjusted for age and sex (0.902). The utility of the other health states in the model was obtained by applying the health state specific disutilities obtained from the MMRM analysis (Table 26). Disutility for AK infection state was obtained by subtracting the average baseline utility from all participants in the ODAK trial (██████)

from the intercept (██████) obtained from the MMRM analysis (utility for good vision).

The CS stated the disutility for loss of eye functionality health state was obtained from published literature⁴⁴ because no patient experienced this outcome in the ODAK trial. In response to clarification question B13, they further explained the disutility for loss of eye functionality was obtained as a two-fifths (2/5) of the difference between the utility in good vision from Rentz et al (0.8835) and the utility of the complete loss of eye function (0.264).⁴⁴ They applied the 2/5 factor to reflect the relative QoL impact of unilateral versus bilateral blindness. In the CEM, patients who were cured with good vision were assumed to have the same utility with the general population (0.902), with no disutility applied. The disutility of each health state was applied relative to the time patients were in those states. A constraint was applied in the model so that the utility of a patient at any time does not exceed the utility of the general population of same age and sex.

The CS indicates evidence from literature suggests that the EQ-5D may not fully reflect how ophthalmological conditions impact patients,^{45, 46} therefore an additional bolt-on dimensions for patients with vision problems was used. An additional bolt-on utility decrement of -0.0378 and -0.130 was further applied to the PV and SVL health states and the impact assessed in a scenario analysis.

Table 26: Health state disutilities used in the base case analysis (Source: CS, Table 50)

Health state	Disutility	Source
AK infection	██████	Assumption based on utility value in good vision (MMRM on ODAK data; ██████) population minus the average baseline utility from the ODAK trial (██████)
Cured with poor vision	██████	MMRM using GV as an intercept based on the ODAK trial data
Cured with severe vision loss	██████	MMRM using GV as an intercept based on the ODAK trial data
Loss of eye functionality	-0.248	Rentz et al. ⁴⁴
AK, Acanthamoeba keratitis; MMRN, mixed model repeated measures; GV, good vision; ODAK, Orphan Drug for Acanthamoeba Keratitis		

4.2.14 Disutilities associated with long-term complications

Disutilities were also applied to health states to account for the impact of long-term complications following AK resolution. The CS stated the ODAK trial EQ-5D was

unable to capture the effects of long-term complications due to the short trial duration (12 month). Therefore, disutilities were derived from a comprehensive catalogue of EQ-5D utility decrements associated with chronic disorders published by Van et al, 2019⁴⁷ and from Ara and Brazier et al, 2011.⁴⁸ The disutilities were combined for patients with multiple conditions via a multiplicative approach based on prevalence of each condition, then applied to the health states based on UK Delphi panel reported proportion of patients experiencing each complication. The EAG considers that application of long-term disutilities in the model is double counting the effect of AK on patients, noting that the EQ-5D measured in the ODAK trial already captures the impact of complications of AK. Patients with good vision were initially assumed to have the same utility as the general population, so no disutility was applied to them, but the company applied disutilities associated with long-term complications to those good vision patients. The EAG views this as not logical and could potentially be double counting. This critique is subsequently explored in the EAG's exploratory analyses of the company's base-case in Section 5.2, by company's base-case assumption from including disutilities association with long-term complications to excluding these disutilities'.

Table 27 presents the disutilities associated with long-term complications and Table 28 presents the health state disutilities from multiple long-term complications applied in the model.

Table 27: Disutilities associated with long-term complications (Source: CS, Table 51)

Long-term effects	Disutility	Source/Assumption
Intense and constant lacrimation/ Photophobia/ Pain	-0.0647	Average between -0.03 (Lacrimal system disorder, GBR, Van Wilder et al, 2019), -0.053 (Other eye complaints difference between 0.794 and 0.741, Ara and Brazier, 2011), -0.111 (migraine/headaches; difference between 0.888 and 0.777; Ara and Brazier, 2011)
Depression/ Anxiety	-0.1910	Average between -0.1120 (depressive disorders, Van Wilder et al, 2019) and -0.272 (mental illness/anxiety/depression; difference between 0.878 and 0.606; Ara and Brazier, 2011)
GBR, Great Britain		

Table 28: Health state disutilities associated with long-term complications applied in the model (Source: CS, Table 52)

Health state	Disutility
Cured with good vision	-0.031
Cured with poor vision	-0.079

Cured with severe vision loss	-0.125
Loss of eye functionality	-0.136

4.2.15 Disutilities associated with events

A one-off disutility associated with insomnia in the intensive treatment phase, therapeutic surgery, graft rejection and optical surgery was estimated for the duration that patients were assumed to be experiencing the events and applied in the model (Table 29). The company assumed that patients in the polihexanide 0.8mg/ml arm did not experience any disutility associated with insomnia because the intensive phase of polihexanide 0.8mg/ml administration does not result in sleep deprivation as it is applied in the daytime. Disutility was assigned to pooled AAT arm patients because of the burden of administration at night, which could impair quality of life by disrupting sleep.

The company performed a scenario analysis considering the disutility of insomnia in the intensive treatment phase for polihexanide 0.8mg/ml arm for a duration of 19 days (based on intensive phase protocol). This resulted in a minimal increase in the ICER.

Table 29: One-off disutilities associated with events (Source: CS, Table 53)

Event	Disutility	Durations	Source/assumptions
Insomnia associated with the intensive treatment phase	-0.280	24.00	Disutility associated with the intensive treatment schedule was assumed to be the same as the UK EQ-5D-3L disutility associated with sleep deprivation due to a treatment schedule which requires day and night administration as reported in Van Wilder et al The duration is assumed to be 24 days associated with the intensive treatment phase, reflecting current AAT use as per clinical expert opinion.
Therapeutic surgery	-0.140	121.75	Assumed to be same as the disutility reported for cataracts in NICE HST11 ⁴⁹ The duration is assumed to be between two weeks and four months, assuming that patients can return to work after two to three weeks if job does not involve physical strain, and three to four months if job involves manual labour. Therefore, the maximum duration of 4 months was applied in the model.
Graft rejection	-0.248	141.70	Assumed to be the same as the disutility associated with loss of eye functionality.

Event	Disutility	Durations	Source/assumptions
			The duration is assumed to be the same as waiting time to therapeutic surgery, in line with the procedures reported after graft failure (SIFI. Data on File. 2023. Technical Report. Results from two-round Delphi panel on acanthamoeba keratitis in the United Kingdom).
Optical surgery	-0.140	121.75	Assumed the same as therapeutic surgery.
HST, highly specialised technology; NICE: National Institute for Health and Care Excellence; UK, United Kingdom			

4.2.16 Caregiver disutilities

In the CEM, caregivers' disutility (-0.04) was applied to all cohorts in the intensive treatment phase (except for polihexanide 0.8mg/ml initial treatment), to all patients undergoing therapeutic surgery/optical surgery and to patients in the severe vision loss and loss of eye functionality health states. For graft failure, the caregiver disutility was adjusted by the proportion of patients receiving further procedures after a graft failure based on data reported by the Delphi panel (-0.014). The utility decrement associated with each event was estimated by multiplying the disutility by the proportion of patients for a certain duration. The caregiver disutility for the events was obtained from NICE HST11 of voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations⁴⁹ (Table 6). This was justified by the similarity in both AK and retinal dystrophies having a disease burden associated with managing chronic visual impairment. The EAG deems the assumption appropriate.

Table 30: Caregivers 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	—

The EAG considers the source of utilities, and its use in the CEM to be suitable. A few concerns are:

- Double counting of utilities in the CEM: Applying disutilities associated with long-term complications of AK was thought to be double counting considering that the ODAK trial already captures the impact of the disease and the associated complications from the HRQoL measure. This was excluded from the EAG base-case.
- The company stated that caregiver disutilities were applied to all patients in the intensive treatment phase, but in the model caregiver disutility was not applied during the intensive treatment phase with polihexanide 0.8mg/ml. This was applied only to the pooled AAT treatment, which includes patients that switched treatment to pooled AAT after initial treatment with polihexanide 0.8mg/ml. Clinical advice to the EAG indicates they will not treat AK with daytime only medication even with high concentration of polihexanide, despite the published treatment schedule in the MHRA and EMA SmPCs; in an exploratory analysis, a caregivers' disutility was applied to treatment with polihexanide 0.8mg/ml. The EAG notes the function to include/exclude caregiver disutility in the intensive treatment period for polihexanide 0.8mg/ml is the same as including/excluding disutility of patients in the intensive phase, as the two (patients and caregivers) set of disutilities were summed in calculating the utility decrement for intensive phase in the model. Therefore, using the function provided by the company, any scenario excluding the patient disutility during the intensive phase will also exclude the caregivers' disutility during the intensive phase with polihexanide 0.8mg/ml (the company performed this scenario). This critique is explored in the EAG's exploratory analyses in Section 5.2.2, where the EAG changed the company's base-case assumption to include caregiver disutility to the polihexanide 0.8mg/ml treatment. The results were found to have a negligible impact to the company's base-case ICER.

4.2.17 Resources and costs

Costs assessment was based on assigning resource use and costs associated with the intervention and comparator, concomitant costs, hospitalisation costs, therapeutic and optical surgery costs and adverse events treatment costs.

Resource use identification, measurement and valuation studies

The CS stated a SLR, and subsequent update was performed to identify costs and resource use data that might be relevant to the treatment of AK or microbial keratitis (MK). The initial and updated SLR identified 2,014 studies; two of these studies reported costs and resource use in the UK^{50, 51} and just one study involved a population that included individuals with AK.⁵⁰

Detailed critique of the search strategy can be found in section 4.1.

4.2.18 Intervention and comparators costs

The main costs categories included in the CEM are as follows: Drug acquisition and concomitant costs for povidone iodine 0.8mg/ml intervention and pooled AAT comparator, hospitalisation costs, surgery (therapeutic and optical) costs, healthcare resource use and costs.

Drug acquisition costs

The dosing regimen of povidone iodine 0.8mg/ml used in the CEM is consistent with the protocol of the ODAK study (SIFI. Data on File. ODAK Trial CSR. 2022).

Povidone iodine eye drop is administered only at daytime based on the protocol. The pooled AAT was costed using the dosing regimen of the therapies in the basket as given by UK clinical experts consulted by the company (Table 31). The eye drops in the pooled AAT are administered both at day and nighttime during the intensive treatment phase.

Table 31: Dosing regimen for Povidone iodine 0.8mg/ml and Pooled (Source: CS table 55)

Treatment phase	Days	Dose frequency, hour interval	Number of drops per day
Povidone iodine 0.8mg/ml			
Intensive phase	0-5	1	16
	6-12	2	8
	13-19	3	6
Maintenance	20+	4	4
Pooled AAT			
Intensive	0-3	1	24
	4-10	1	16
	11-24	2	8
Maintenance	25+	4	4

Polihexanide 0.8mg/ml cost was estimated for a duration of 101 days of treatment. This value was sourced from recent real-world evidence ¹ which reported the mean duration of treatment with polihexanide 0.8mg/ml. The costs of the pooled AAT basket were estimated for a duration of 152.19 days which is the median time-to-cure data obtained from the Papa et al retrospective study undertaken in the UK from 1990-2012.¹⁶

The EAG questioned the company's approach for not using the median time-to-cure for the polihexanide 0.8mg/ml arm like they did for the pooled AAT arm, since the ODAK trial provided this data. In question B15, for clarification, the EAG also asked why the mean treatment duration from Franch et al¹ was used instead of the median time-to-cure from ODAK trial. In their response, they indicated the mean duration from Franch et al represents the period during which patients are exposed to polihexanide 0.8mg/ml in real-world clinical practice. The EAG views the approach as unsuitable for some reasons: First, the sample size in the Franch et al 2024 study is too small (n=11) to be generalisable to determine the treatment duration required to treat AK with polihexanide 0.8mg/ml in practice. Although, AK is a very rare disease and so large sample sizes for a real-world compassionate use programme are likely unfeasible. Second, the baseline characteristics of patients recruited for the retrospective study in Franch et al differs in some ways to ODAK trial. For example, the mean age of patients in Franch et al is 41.4 compares to 35.2 in ODAK trial and previous topical corticosteroid treatment was received by 91% of patients in Franch et al compared to 47% in ODAK trial. Also, the EAG considers that it will be appropriate for consistency between the two arms to use the median time-to-cure reported in the ODAK study. Consequently, this critique is explored in the EAG's exploratory analyses in section 5.2.2, when the EAG changed the company's base-case assumption from using the mean time on treatment (101days) to median time-to-cure obtained from ODAK trial for polihexanide 0.8mg/ml (SIFI. Data on File. ODAK Trial CSR. 2022) to assess the impact of the duration of treatment assumption used in the model.

The unit costs of polihexanide 0.8mg/ml and the therapies in the pooled AAT comparator arm and their formulations are presented on Table 32.

Table 32: Drug acquisition costs

Drug	Volume per bottle (mls)	Cost per bottle/sachet (£)	Number of bottles	Expiry once opened (days)	Source
Polihexanide 0.8mg/ml	0.3	5,960	30	28	List price, company (SIFI)-determined
Polihexanide 0.2mg/ml	10	45.00	200	7	2023 Policy Matters, Market Intelligence Report (SIFI. Data on File)
Polihexanide 0.6mg/ml	10	50.00	200	7	2023 Policy Matters, Market Intelligence Report (SIFI. Data on File)
Chlorhexidine	10	23.00	200	7	2023 Policy Matters, Market Intelligence Report (SIFI. Data on File)
Propamidine 1mg/ml*	10	4.05	200	28	BNF 2025 ⁵²
* Hexamidine was assumed to have the cost as propamidine since the BNF did not separately report the cost of hexamidine. BNF, British National Formulary					

In the CEM, the costs per treatment course (Table 33) were estimated considering the number of bottles required for the intervention and pooled AAT comparator therapies over the treatment durations, considering the period of expiration of the therapies after sachet/bottles are opened; 17 bottles for polihexanide 0.8mg/ml, 22 bottles for the biguanides that are part of the pooled AAT comparator and 6 bottles for propamidine. To estimate the costs of the pooled AAT, the cost of treatment course was calculated considering the distribution of patients taking each of the therapies or combination of therapies as indicated by the UK Delphi panel consulted by the company (SIFI. Data on File. 2023). A PAS price of [REDACTED] % was applied to estimate the total cost of treatment for polihexanide 0.8mg/ml.

In a scenario analysis, the company estimated the treatment costs of the pooled AAT using distributions obtained from the Papa et al 2020¹⁶ (see Section 5.1.5)

The costs of treatment switch after initial therapy in both arms was assumed to be same as the pooled AAT treatment costs, given that patients will usually use one of the treatments in the blended AAT. The EAG is satisfied with this assumption.

Table 33: Intervention and comparator costs per treatment course (Source: CS, Table 58)

Therapy	Costs per treatment course (£) with PAS
Polihexanide 0.8mg/ml (intervention)	
Pooled AAT (comparator)	938.98
AAT, anti-amoebic therapy	

4.2.19 Concomitant medication costs

The cost of concomitant medication £31.38 (updated cost after clarification) was applied as a one-off cost to both arms when patients started one of the initial therapies or changed to an alternative AAT. The concomitant medications (ongoing medications or medications stopped on or after baseline) (Table 34) that were used by more than 10% of patients in the polihexanide 0.8mg/ml treatment arm of the ODAK trial (SIFI. Data on File. CSR. 2022) was used to inform the model. These includes various types of ophthalmological medications, anti-inflammatory and antirheumatic products, analgesics and antivirals. The CS stated this approach was taken because of the lack of standard of care, heterogeneity in the types and duration of concomitant therapeutic approaches used. While the EAG recons with the company that this is a conservative assumption, it notes that the costs of concomitant medications applied in the model were underestimated because costs were estimated for number of drops/tablets required while in real world practice this are only available to purchase and use in bottles or pack sizes. During clarification (question B16), the EAG asked the company to provide the costs of concomitant medications for presentations that can be obtained in real world clinical practice. The company implemented the EAG request and provided an updated table for the costs of concomitant medications (Table 34).

Table 34: Concomitant medication used in at least 10% of patients in the polihexanide 0.8mg/ml treatment arm of the ODAK trial (Source: CS, Table 59)

Concomitant medications	Proportion of patients (%)
Ophthalmological	
Fluoroquinolones	51
Corticosteroids, plain	36
Other ophthalmological	29
Anticholinergics	14
Antibiotics	16
Other anti-infective	17
Anti-inflammatory and antirheumatic products	

Concomitant medications	Proportion of patients (%)
Acetic acid derivatives and related substances	32
Propionic acid derivatives	16
Analgesics	
Anilides	16
Antivirals for systematic use	
Nucleosides and nucleotides excluding reverse transcriptase inhibitors.	13
ODAK, orphan drug for acanthamoeba keratitis	

Table 35: Updated unit costs of concomitant medications (Source: Clarification response, Table 47)

Concomitant medication (>10%)	Name and dose	Volume per pack (ml)	Pack cost	Number of drops per pack	Number of drops required	Cost, £	Cost source
Ophthalmological (eye drops)							
Fluoroquinolones	Levofloxacin 5mg/ml: 1 or 2 drops into affected eye(s) every 2 hours up to eight times daily while awake for first 2 days, then four times daily on days 3 to 5.	5	10.03	100	56	10.03	BNF 2025 ⁵³
Corticosteroids, plain	Dexamethasone phosphate 1mg/ml: 1 drop into affected eye(s) four to six times daily. If necessary, initiate with 1 drop hourly and reduce to 1 drop every 4 hours when inflammation subsides. Maximum duration 14 days.	0.4	9.7	30	84	29.10	BNF 2025 ⁵⁴
Other ophthalmological	Carmellose sodium 0.5%: 1 or 2 drops into affected eye(s) as required.	10	1.68	200	42	1.68	BNF 2025 ⁵⁵
Anticholinergics	Atropine sulphate 1%: 1 drop as required	10	70.01	200	42	70.01	BNF 2025 ⁵⁶
Antibiotics	Chloramphenicol 0.5%: 1 or 2 drops into affected eye(s) up to 6 times daily, or more frequently if required. Continue for 48 hours after cure.	10	3.37	200	84	3.37	BNF 2025 ⁵⁷
Other anti-infective	Propamidine 0.1%: 1 or 2 drops into affected eye(s) four times daily.	10	4.05	200	56	4.05	BNF 2025 ⁵²
Anti-inflammatory and anti-rheumatic products (tablets)		Quantity per pack (mg)	Pack cost	Number of tablets per pack	Number of tablets required	Cost, £	Cost source
Acetic acid derivatives and related substances	Aspirin: 300–900mg every 4–6 hours as required with food; maximum 4g daily.	300	7.09	100	56	7.09	BNF 2025 ⁵⁸
Propionic acid derivatives	Ibuprofen: 1.2–1.8g daily in divided doses with food; maximum 2.4g daily.	200	2.31	84	42	2.31	BNF 2025 ⁵⁹

Concomitant medication (>10%)	Name and dose	Volume per pack (ml)	Pack cost	Number of drops per pack	Number of drops required	Cost, £	Cost source
Analgesics							
Anilides	Paracetamol: 500mg–1 g every four to six hours as required; max 4g daily.	500	2.09	100	42	2.09	BNF 2025 ⁶⁰
Antivirals for systemic use							
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	Aciclovir: Varicella or herpes zoster: 800 mg five times daily at four-hourly intervals, omitting the nighttime dose, for 7 days. Start treatment as soon as possible after onset of rash.	200	1.16	25	140	6.96	BNF 2025 ⁶¹
BNF, British National Formulary; ml, millilitres; mg, milligrams, g, gram							

4.2.20 Hospitalisation costs

Hospitalisation costs were applied in the model for patients in the pooled AAT arm. The CS stated the costs was only applied to the pooled AAT and not the polihexinaide 0.8mg/ml arm because the later requires administration during the daytime in the intensive phase which can be administered by patients at home. At clarification (question B9 & B10), the EAG sought further justification as to why these costs should only be allocated to the pooled AAT arm and asked the company to provide reasons why patients are hospitalised during the intensive phase. In their response, they reiterated on the demand of care associated with current therapeutic approaches because of the overnight treatment regimen and polytherapy of ophthalmics which necessitates hospital admissions to improve compliance and better patient outcomes.

Clinical advice to the EAG indicates they will never commence treatment for AK with daytime only regimen in the intensive phase even with a higher dose of polihexanide, Despite the published regulatory label of polihexanide 0.8mg/ml and recommended daytime only posology. And so, it is thought that even patients who might receive polihexanide 0.8mg/ml will be hospitalised. This critique point is explored in the EAG's exploratory analyses in Section 5.2.2, where the EAG changed the company's base-case assumption from people would not require hospitalisation to people would require hospitalisation for treatment with polihexanide 0.8mg/ml in the intensive treatment phase. Conservatively, we assumed the same percentage (26.60%) of people who require hospitalisation when treated with pooled AAT would require hospitalisation when treated with polihexanide 0.8mg/ml. The results show a minimal increase to the ICER (see Table 54).

Table 36 presents the proportion of patients, number of hospitalisation days and total cost of hospitalisation during the intensive phase applied in the model. The number of patients estimated to require hospitalisation, and the number of hospitalisation days were based on data from the UK Delphi panel (SIFI. Data on File. 2023). A unit cost of £484 per hospitalisation day sourced from the National Schedule of NHS costs 2023/24 was multiplied with the number of hospitalisation days and the

proportion of patients requiring hospitalisation to obtain the total cost of hospitalisation during the intensive treatment period.

Table 36: Toal cost, number of hospitalisation days and the proportion of patients requiring hospitalisation.

Treatment	Patients requiring hospitalisation (%)	Number of hospitalisation days	Total cost of hospitalisation
Polihexanide 0.8mg/ml	0.00	0.00	0.00
Pooled AAT	26.60	4.20	540.72
AAT,anti-amoebic therapy			

4.2.21 Costs associated with therapeutic surgery

A one-off cost of £11,681.69 (updated cost after clarification) for therapeutic surgery was incorporated into the model for both arms. This includes pre-surgery costs, costs associated with the different types of therapeutic surgery and the overall costs for post-surgery patient management, including treatment of surgical complications and post-surgical adjuvant systemic and immunosuppressive therapies. The one-off cost was calculated as the total cost of therapeutic surgery multiplied by the average number of therapeutic surgeries (1.2) as reported in the UK Delphi panel (SIFI. Data on File. 2023).

Pre-therapeutic surgery costs

A pre-therapeutic surgery cost (one-off) was applied to account for the management of patients before therapeutic surgery. This cost was calculated from the average NHS outpatient expenses related to ophthalmology, anaesthetic and pain management services (see Table 37).

Table 37: Pre-therapeutic surgery costs (Source: CS, Table 63)

Pre-operation consultation	Cost, £	Source
Ophthalmology service	140.01	National Schedule of NHS Costs 2023/24, Summary: Outpatient Attendances, Code 130
Anaesthetic service	141.42	National Schedule of NHS Costs 2023/24, Summary: Outpatient Attendances, Code 190
Pain management service	228.49	National Schedule of NHS Costs 2023/24, Summary: Outpatient Attendances, Code 191
Total pre-therapeutic surgery cost (one-off)	169.97	Average of pre-operation consultation services

Therapeutic surgery costs

The different types of therapeutic surgeries and their unit cost obtained from the National Schedule of NHS costs 2023/24 are presented on Table 38. The distribution of patients receiving therapeutic surgery (Table 37) as obtained from the UK Delphi panel (SIFI. Data on File. 2023) were accounted for in the total one-off cost.

Table 38: Unit cost of the different types of therapeutic surgeries applied in the model (Source: CS, Table 64)

Therapeutic surgery	Costs, £	Source
Therapeutic keratoplasty	5,123.25	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of the costs for following codes: BZ60A, BZ60B, BZ62A, BZ62B ⁶²
Enucleation	5,690.33	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ50Z, BZ53A, BZ53B ⁶²
Deep lamellar keratoplasty	5,123.25	Assumed to be the same cost as therapeutic keratoplasty
Evisceration	3,538.25	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ61A, BZ61B, BZ63A, BZ63B ⁶²
Amniotic membrane	5,347.00	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ51A, BZ51B, BZ54A, BZ54B ⁶²
Amniotic membrane and penetrating keratoplasty	10,470.25	Assumed to be the sum of the costs for two procedures
Conjunctival flap	1,597.50	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average costs for the following codes: BZ64A and BZ64B ⁶²

Table 39: Distribution of patients receiving therapeutic surgery (Source: CS, Table 39)

Therapeutic surgery	Distribution (%)
Therapeutic keratoplasty	60.40
Enucleation	2.60
Deep lamellar keratoplasty	16.90
Evisceration	4.20
Other*	15.90
* Amniotic membrane, amniotic membrane + penetrating keratoplasty and conjunctival flap were grouped as other type of therapeutic surgery.	

Post-therapeutic surgery costs

Complications after therapeutic surgery

This consist of the costs of resolving complications that patients experience during or following therapeutic surgery. The unit costs and the proportion of patients estimated to experience the complications of therapeutic surgery according to the UK Delphi panel are presented on Table 40. A one of cost of £2,291.88 was applied in the model estimated as the sum of the product of unit costs and proportions. Any costs indicated that was not in the current financial year was inflated to 2024/25 using the ONS, consumer price inflation (CPI) index.

Table 40: Costs and proportion of patients associated with complications of therapeutic surgery (Source: CS, Table 65 & 66)

Complications	Proportions (%)	Costs, £	Source
Glaucoma	42.6	3,633.11	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average costs for the following codes: BZ90Z, BZ91A, BZ91B, BZ92A, BZ92B, BZ93A, BZ93B, BZ94A, BZ94B, BZ95Z ⁶²
Scleritis	11.2	2,113.28	Brolucizumab for treating diabetic macular oedema [TA820]. Assumed the same as the cost for endophthalmitis (Table 45) ⁶³
Corneal melt	5.9	3,092.34	Assumed as the average of intermediate corneal procedures (National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Code BZ64A) ⁶²
Neurotrophic keratopathy	4.7	948.65	Brolucizumab for treating diabetic macular oedema [TA820]. Assumed the same cost as 'visual acuity reduced' in Table 45 ⁶³
Perforation, wound leak	1.5	1,256.00	UH Bristol NHS Foundation Trust Private Patient Tariff 2014-15 Version 1. Assumed same as Descemet's Stripping Automated Endothelial Keratoplasty (DSAEK) Corneal Transplant costs (C4640) ⁶⁴
Re-suturing	1.8	1,597.50	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ64A and BZ64B ⁶²
Corneal vascularisation	12.0	948.65	Brolucizumab for treating diabetic macular oedema [TA820]. Assumed the same cost as 'visual acuity reduced' in Table 45 ⁶³
Optic atrophy	1.8	948.65	Brolucizumab for treating diabetic macular oedema [TA820]. Assumed the same cost as 'visual acuity reduced' in Table 45 ⁶³
Total cost to treat surgical complications (one-off)		2,291.88	-

HRG, Health Resource Group; TA, technology appraisal

Systemic therapies

The costs of adjuvant systemic therapies and systemic immunosuppressants used by patients after therapeutic surgery to reduce the risk of rejection and other complications were included in the model. A one-off-cost of £1637.36 and £463.92 for systemic immunotherapies and adjuvant systemic therapies respectively were applied (updated costs after clarification). This were obtained as a sum of product of the cost per treatment (product of cost per mg, dose per administration, number of administrations per day and the mean duration of treatment) and proportion of patients requiring these therapies based on UK Delphi panel (SIFI. Data on File. 2023). The company adjusted weight-dependent drugs based on the average weight of the patient population (76.04kg) to calculate the dose per administration.

At clarification, the company provided an updated table of costs associated with systemic therapies following EAG request to clarify the values reported in column 6, table 68 of the CS (question B18). Costs based on number of packets required for specified dose of the therapies were provided to align with what was done for the concomitant medications. Table 41 presents the proportion of patients and mean treatment duration, post-therapeutic surgery. The updated costs associated with systemic therapies are presented on Table 42.

Table 41: Proportion and Mean treatment duration of systemic therapies (Source: CS, Table 67)

Table 67)			
Systemic therapies	Proportions (%)	Mean treatment duration (days)	Source
Systemic immunosuppressive			UK Delphi panel 2023 (SIFI. Data on File. 2023)
Cyclosporine	17	217.5	
Azathioprine	1	23.4	
Mycophenolate	26	309.4	
Steroids	25	27.5	
Tacrolimus	14	284.5	
Adjuvant systemic therapies			
Miltefosine	1	9.7	
Voriconazole	20	37.3	
Prednisolone	52	54.2	
Polihexanide 0.6 mg/ml	26	79.4	
Doxycycline	15	76.5	

Table 42: Updated costs associated with systemic therapies (Source: Clarification response, Table 48)

Systemic therapies	Quantity unit (mg)	Units per pack	Pack cost, £	Cost per mg, £	Dose per administration, mg	Number of administrations per day	Costs per treatment, £	Source
Systemic immunosuppressive								
Cyclosporine	50	30	25.5	0.0170	1,140.64*	1	4,233.00	BNF 2025 ⁶⁵
Azathioprine	50	56	1.33	0.0005	114.06*	1	1.33	BNF 2025 ⁶⁶
Mycophenolate	500	50	5.78	0.0002	1,000.00	2	144.50	BNF 2025 ⁶⁷
Steroids	10	28	9.70	0.0346	40.00	1	38.80	BNF 2025 ⁶⁸
Tacrolimus	1	50	71.59	1.4318	7.60*	2	6,228.33	BNF 2025 ⁶⁹
Total one-off cost							1,645.20	
Adjuvant systemic therapies								
Voriconazole	50	28	193.53	0.1382	200	2	2,128.83	BNF 2025 ⁷⁰
Prednisolone	10	28	9.70	0.0346	40	1	77.60	BNF 2025 ⁶⁸
Polihexanide 0.6 mg/ml	-	200	50.00	0.2500	1	4	150.00	2023 Policy Matters, Market Intelligence Report (SIFI. Data on File)
Doxycycline	50	28	1.44	0.0010	200	1	15.84	BNF 2025 ⁷¹
Total one-off cost							496.25	
*Estimated based on mean weight of patient population BNF, British National Formulary;								

4.2.22 Costs associated with optical surgery

Pre-optical surgery costs

The company applied a one-off pre-optical surgery cost in the model to account for the management of patients before optical surgery as seen with therapeutic surgery. This was calculated as the average of NHS outpatient expenses related to ophthalmology, anaesthetic and pain management services (see Section 4.2.21, Table 37).

Optical surgery costs

A total one-off cost of £4,205.99 was incorporated into the model to account for costs associated with optical surgery. This was estimated as the sum of the product of unit costs and the proportion of patients undergoing each type of optical surgery based on UK Delphi panel (SIFI. Data on File. 2023) (Table 43). The pre-optical surgery (£169.97) was added up to obtain the total one-off cost associated with optical surgery stated above.

Table 43: Unit costs of by type of optical surgery and the proportion of patients (Source: CS, Tables 43 & 69)

Optical surgery	Proportion of patients (%)	Costs, £	Source
Optical keratoplasty	41.48	5,123.25	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of the costs for following codes: BZ60A, BZ60B, BZ62A, BZ62B ⁶²
Evisceration	3.70	3,538.25	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ61A, BZ61B, BZ63A, BZ63B ⁶²
Cataract	43.70	3,025.80	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ30A, BZ30B, BZ31A, BZ31B, BZ32A, BZ32B, BZ33Z, BZ34A, BZ34B, BZ34C ⁶²
Deep anterior lamellar keratoplasty	5.78	5,123.25	Assumed the same cost as optical keratoplasty

Surgical correction for astigmatism	5.33	3,025.80	Assumed the same cost as cataract given that refractive lens exchange is the same procedure as cataract surgery ⁷²
Total one-off costs associated with optical surgery		4,205.99	
HRG, Healthcare Resource Group; NHS, National Health Service			

As optical surgeries are mainly for rehabilitation and not usually associated with subsequent ongoing treatments with systemic therapies as seen with therapeutic surgeries, no post-surgical costs were applied to optical surgery. The CS stated that this was confirmed during their elicitation process with UK Delphi panel.

4.2.23 Graft failure

After a graft failure some patients undergo some procedures. A one-off cost of £899.60 was applied in the model. This was obtained by summing the product of the proportion of patients undergoing procedures after graft failure with the unit costs of the procedures (see Table 44). Costs were inflated to 2024/25 where necessary using the consumer price inflation (CPI) index.

Table 44: Unit costs of procedures after graft failure

Procedures after graft failure	Proportion of patients (%)	Cost, £	Source
Endothelial keratoplasty	24.41	1,256.00	UH Bristol NHS Foundation Trust Private Patient Tariff 2014-15 Version 1. Assumed same as Descemet's Stripping Automated Endothelial Keratoplasty (DSAEK) Corneal Transplant costs (C4640; includes day case rate) ⁶⁴
Enucleation	5.25	5,690.33	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ50Z, BZ53A, BZ53B ⁶²
Evisceration	5.38	3,538.25	National Schedule of NHS Costs 2023/24, Summary: HRG – Elective. Average of costs for the following codes: BZ61A, BZ61B, BZ63A, BZ63B ⁶²
No further procedures	64.96	0.00	If a patient does not undergo any further procedures after a graft failure, no further costs are assumed.
Total one-off costs associated with graft failure		899.60	

4.2.24 Health states resource use and costs

Health care resource use (HCRU) and costs associated with monitoring and follow-up of patients in the health states were incorporated into the model. The frequency of HCRU and the proportion of patients using the resources in the different health states was informed by the UK Delphi panel (SIFI. Data on File. 2023) by Table 45 and Table 46.

Table 45: Health state resource use (Source: CS, Table 72)

Resource	AK infection	Frequency of resource use (times/year)						
		AK infection resolved with pharmacological treatment			AK infection resolved with surgical treatment			Loss of eye functionality
		GV	PV	SVL	GV	PV	SVL	
Ophthalmologist/Optometrist visit	19	4.3	9	10.2	9.4	11.8	12	7.3
Psychiatrist visits	1.1	0.1	0.9	1.4	0.2	1.9	1.4	1.7
Nurse visits	7.2	1.7	7	3.7	2.9	4.4	4.2	3
Intraocular pressure check	16.1	4	8.5	9.8	9.2	11.5	11.8	7.3
Scraping of the eye	1.6	0.3	0.6	0.7	0.7	0.6	0.6	0.6
Ophthalmoscopy	9.6	2.7	5.7	8.2	4.9	6	7.4	4.3
Low vision rehabilitation sessions	1.9	0	1.4	2.6	0.1	1.7	1.8	1.3
Visual aids – magnifiers	1.4	0	0.8	1.4	0	1	0.9	0
In vivo confocal microscopy	1.6	0.5	0	0	0	0	0	0
Visual aids – contact lens clinic (rigid gas permeable contact lens)	0	0	0	0	0	1.9	1.3	0
AK, Acanthamoeba keratitis; GV, good vision; PV, poor vision; SVL, severe vision loss								

Table 46: Patient distribution of health state resource use (Source: CS, Table 73)

Resource	AK infection	Proportion of patients (%)						
		AK infection resolved with pharmacological treatment			AK infection resolved with surgical treatment			Loss of eye functionality
		GV	PV	SVL	GV	PV	SVL	
Ophthalmologist/Optometrist visit	86.60	77.10	72.80	78.80	83.20	82.60	80.80	62.20
Psychiatrist visits	9.90	17.60	18.20	26.90	7.10	23.20	25.10	25.20

Nurse visits	24.20	33.80	35.30	32.50	41.60	43.60	41	33.30
Intraocular pressure check	79.40	82.30	74.70	78.50	87.30	85.30	83.50	66.40
Scraping of the eye	72.10	19.50	49.10	41.10	22.60	30.50	32.70	21.50
Ophthalmoscopy	58.50	68.30	63.50	56.20	52.90	53.80	57	45.90
Low vision rehabilitation sessions	8	13.50	27.50	50	15.10	25.30	33.60	18.20
Visual aids – magnifiers	5.40	0	14.10	23.40	0	7.10	9.70	0
In vivo confocal microscopy	32	48.50	0	0	0	0	0	0
Visual aids – contact lens clinic (rigid gas permeable contact lens)	5.40	0	14.10	23.40	0	17.80	17.80	0
AK, Acanthamoeba keratitis; GV, good vision; PV, poor vision; SVL, severe vision loss								

The unit costs of the resource use items were sourced from the PSSRU unit costs of health and social care ⁷³ and from literature (Table 47). Where necessary costs were inflated to 2024/25 using the CPI index.

Table 47: Unit cost of resource use

Resource	Cost, £	Source
Ophthalmologist/Optometrists visit	103.00	PSSRU 2024. Cost per working hour (including qualifications) of a consultant (medical) as per Table 11.3.2 ⁷³
Psychiatrist visits	289.00	PSSRU 2024. Cost of general psychiatry service as per Table 2.1.1 ⁷³
Nurse visits	64.00	PSSRU 2024. Cost per working hour (including qualifications) for Band 6 as per Table 9.2.1 ⁷³
Intraocular pressure check	73.00	NHS Payment Scheme. Outpatient attendances – unit prices, 2024/25. (WF01A Follow Up Attendance – Single Professional) 130 – Ophthalmology Service ⁷⁴
Scraping of the eye	73.00	NHS Payment Scheme. Outpatient attendances – unit prices, 2024/25. (WF01A Follow Up Attendance – Single Professional) 130 – Ophthalmology Service ⁷⁴
Ophthalmoscopy	73.00	NHS Payment Scheme. Outpatient attendances – unit prices, 2024/25. (WF01A Follow Up Attendance – Single Professional) 130 – Ophthalmology Service ⁷⁴
Low vision rehabilitation sessions	323.30	NICE Macular degeneration Appendix J: Health Economics ⁷⁵
Visual aids – magnifiers	214.69	NICE Macular degeneration Appendix J: Health Economics ⁷⁵
In vivo confocal microscopy	123.34	Gov.UK: Hospital eye service maximum charges ⁷⁶
Visual aids – contact lens clinic (rigid gas permeable contact lens)	61.77	Gov.UK, Annex A: Contact lenses for which a prescription is given in consequences of a sight test by an NHS trust or NHS foundation trust ⁷⁶
PSSRU, Personal social services research unit; NHS, National Health Service; NICE, National Institute for Health and Care Excellence.		

The healthcare resource use per cycle in each health state (Table 48) was evaluated as a product of frequency of resource use, proportion of patients using the resource and the unit cost of the resource use.

[ID6497 EAG report for polihexanide eyedrops for treating acanthamoeba keratitis in people 12 year and over; 28/08/2025]

Table 48: Health state resource use cost per cycle

Health state	Cost per cycle, £
AK infection	3,415.80
Good vision after medical resolution of AK infection	792.45
Poor vision after medical resolution of AK infection	1,828.67
Severe vision loss after medical resolution of AK infection	2,587.37
Good vision after surgical resolution of AK infection	1,680.47
Poor vision after surgical resolution of AK infection	2,446.68
Severe vision loss after surgical resolution of AK infection	2,553.16
Loss of eye functionality	1,265.19
AK, Acanthamoeba keratitis	

4.2.25 Adverse event resource use and costs

The CS did not include costs associated with treating AE in the model. This was justified with a rationale that in the ODAK study, AEs occurred at a similar frequency in both arms (44.9% in the polyhexanide 0.8mg/ml arm and 44.6% in the active comparator arm), hence the impact of AEs on result is negligible.

EAG comments

The EAG deems that resource use and costs values were appropriate and are satisfied with their implementation within the economic model but had some concerns.

- The cost of hospitalisation was included only in the pooled AAT arm because the eye drops are administered day and night in the intensive treatment phase. Clinical advice to the EAG notes that AK patients are hospitalised for increase compliance with their nighttime administration of eye drops which could be patients in either arm as they (clinicians) will never commence treatment with daytime regimen only.

- A caregiver disutility was applied to patients in the pooled AAT during the intensive phase to account for the effect of taking care of patients in the intensive phase to administer eye drops at night. The EAG considers that there is potential double counting on the effect of nighttime administration on outcomes for patients in the pooled AAT arm. As noted above, hospitalisation costs have been applied to proportion of patients in the pooled AAT with same justification.
- The company used mean treatment duration from a real-world study (Franch et al 2024) and used median time-to-cure for the comparator arm in estimating the drug treatment costs. With the availability of median-time to cure from the ODAK study, the EAG considers such data will be more consistent with data for the comparator used in the company base case analysis.

4.2.26 Severity modifier

The indication (AK) in this appraisal does not meet criteria for a severity modifier.

5 Cost-effectiveness results

Section 5.1 summarises the company's cost-effectiveness results, Section 5.2 presents the EAG's additional work and preferred assumptions.

5.1 Company's cost-effectiveness results

The company reported deterministic, sensitivity and scenario analysis results for the comparison between polihexanide 0.8mg/ml versus pooled AAT. Main outcomes are reported in terms of expected mean costs, expected mean life-years, QALYs, with the overall results presented in the form of an incremental cost-effectiveness ratio expressed as cost per QALY.

Here, all results have been reported based on applying the PAS price for polihexanide 0.8mg/ml.

5.1.1 Company's deterministic base-case results

In Table 49, we report the results of the company's deterministic base-case analysis, which shows that treatment with polihexanide 0.8mg/ml is [REDACTED] more expensive than treatment with pooled AAT and expected to yield an additional 0.28 LYs and 2.56 QALYs, which equates to an ICER of [REDACTED] per QALY gained. These results also show that at a willingness-to-pay thresholds of £20,000 and £30,000K the incremental net health benefit is [REDACTED] and [REDACTED], respectively.

Table 49: Company's deterministic base-case results, using list prices

Strategy	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB at £20K	INHB at £30K
Pooled AAT	[REDACTED]	22.37	14.76	-	-	-	-	-	-
Polihexanide 0.8mg/ml	[REDACTED]	22.65	17.31	[REDACTED]	0.28	2.56	[REDACTED]	[REDACTED]	[REDACTED]

5.1.2 Company's sensitivity analyses results

The company explored uncertainty in key parameters by undertaking sensitivity analysis (see CS, Section 3.11), including probabilistic sensitivity analysis and scenario analyses.

5.1.3 Company's probabilistic sensitivity analysis results

Probabilistic sensitivity analysis (PSA) was undertaken for the outcome cost per QALY. In PSA, each parameter is assigned a distribution to reflect the pattern of its variation and the ICERs are calculated based on randomly selecting variables from each distribution. Probability distributions were applied to key model input parameters. The PSA results were reported in tabular form (see Table 50), and iterations/scatterplots presented on an incremental cost-effectiveness plane (see Figure 10) and their corresponding cost-effectiveness acceptability curves (CEACs) in

Figure 11.

In Table 50, these results show that while considering joint parameter uncertainty, treatment with polihexanide 0.8mg/ml is expected to be [REDACTED] more expensive than treatment with pooled AAT and expected to yield 2.50 more QALYs, resulting in an ICER of [REDACTED]. This slight overestimate in the PSA is likely to be caused by the slight underestimate in the expected mean costs for treatment with pooled AAT and overestimate in expected mean costs for treatment with polihexanide.

In Figure 10, all the iterations are in the northeast quadrant indicating that treatment with polihexanide 0.8mg/ml is likely to be more expensive and more effective when compared to pooled AAT. There was a good spread of the iterations across the costs and effects. The results from the CEAC show that at a willingness-to-pay threshold of £30,000 per QALY, treatment with polihexanide 0.8mg/ml has a [REDACTED] probability of being cost-effective when compared to pooled AAT.

Table 50: Company's probabilistic sensitivity analysis results, using the PAS

Strategy	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB at £20K	INHB at £30K
Pooled AAT	[REDACTED]	22.37	14.81	-	-	-	-	-	-
Polihexanide 0.8mg/ml	[REDACTED]	22.65	17.31	[REDACTED]	0.27	2.50	[REDACTED]	[REDACTED]	[REDACTED]

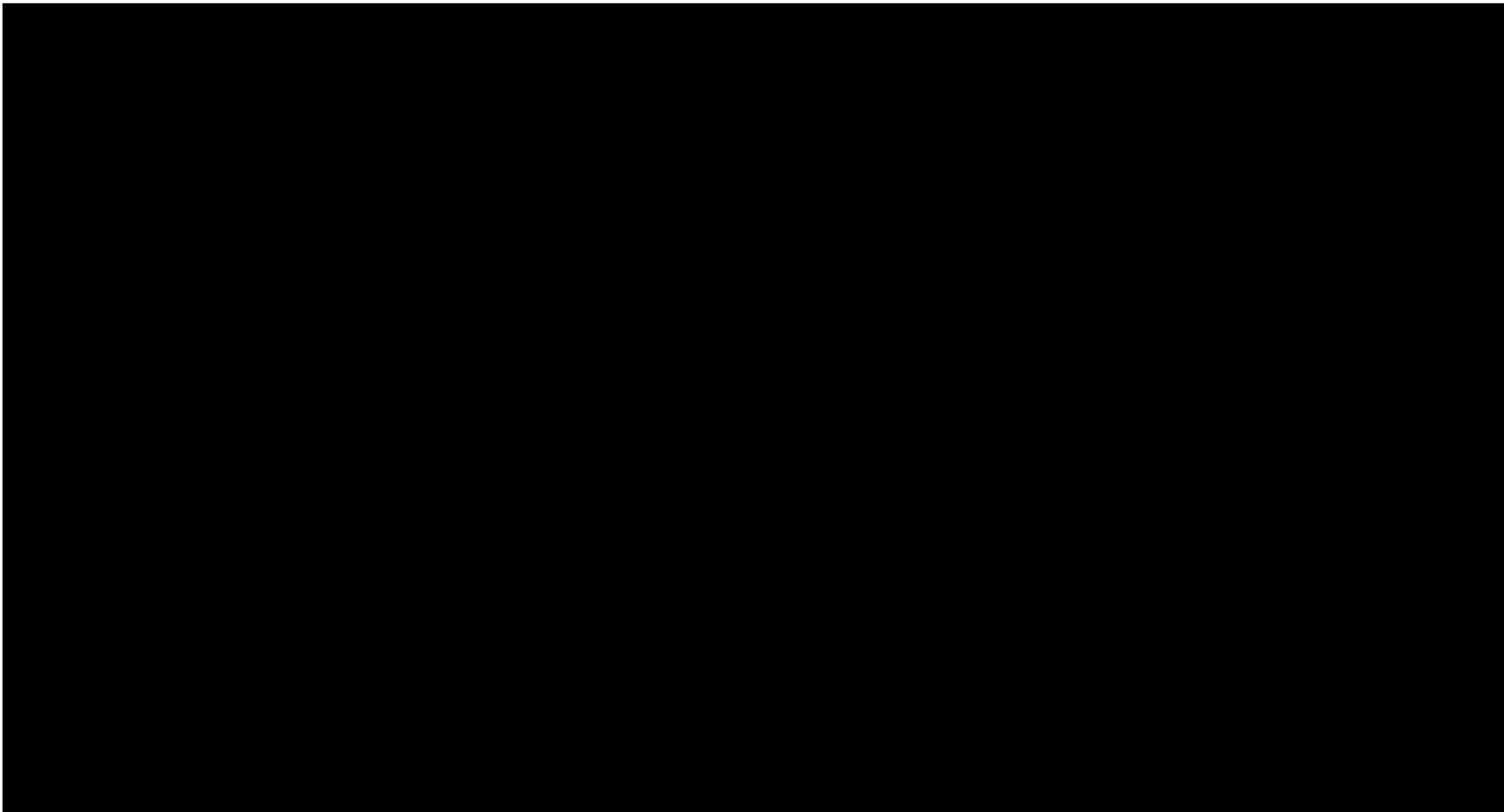


Figure 10: Cost-effectiveness scatterplot for the comparison between polihexanide 0.8mg/ml vs. pooled AAT

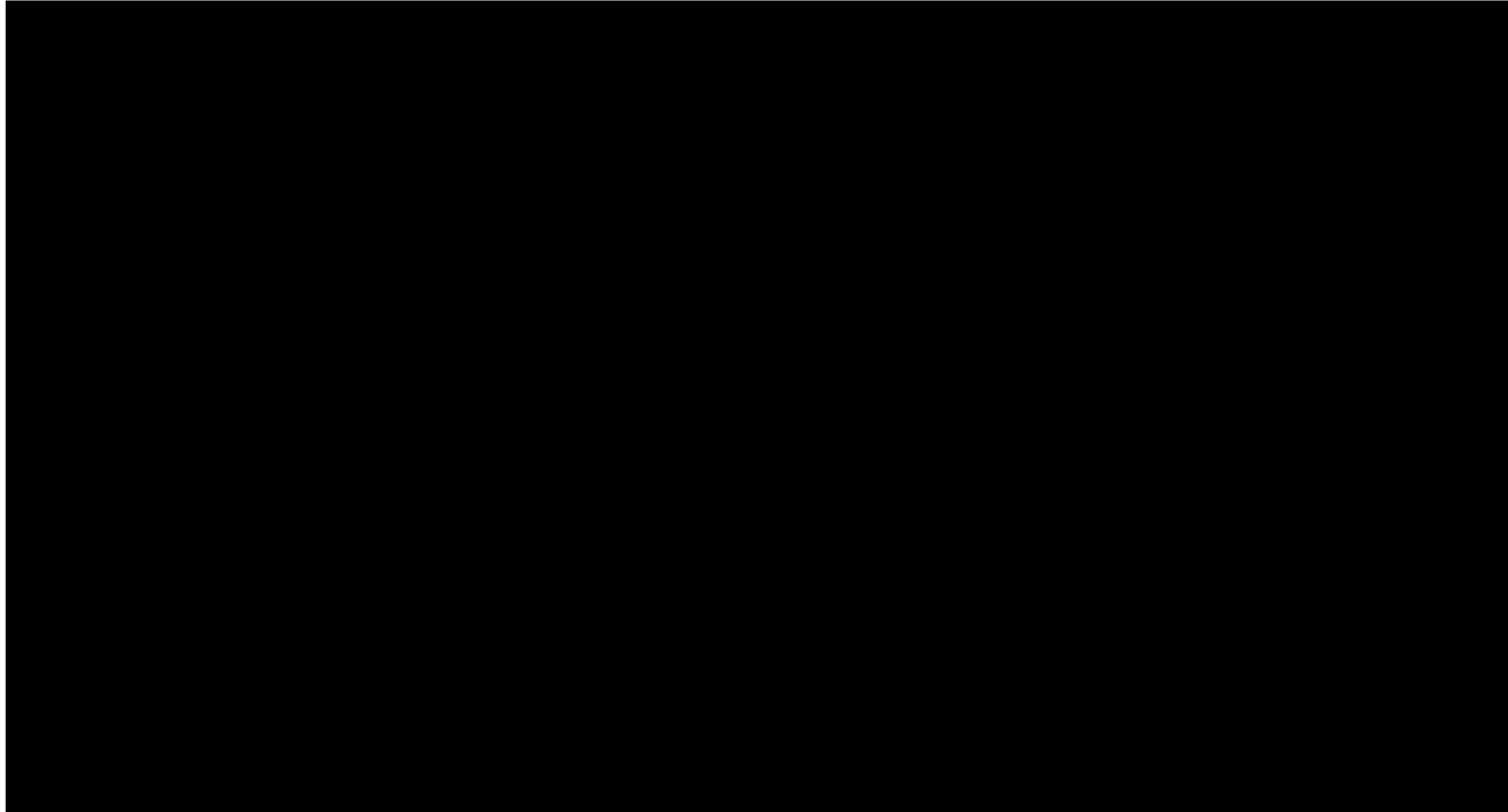


Figure 11: Cost-effectiveness acceptability curve (CEAC)

5.1.4 One-way sensitivity analysis

Numerous inputs were varied in the company's OWSA, with the company presenting the 10 most impactful on a tornado diagram (see

Figure 12). These results show that discount rate applied to outcomes and RR for MCR at 12 months appeared to be key input parameters. Using a lower (1.5%) and upper (6.0%) values for discounting outcomes results in a decrease of the base-case ICER to [REDACTED] and [REDACTED] [REDACTED] per QALY, respectively. With regards to the RR for MCR, using the lower and upper limits resulted in ICERs of [REDACTED] and [REDACTED] [REDACTED] per QALY, respectively.

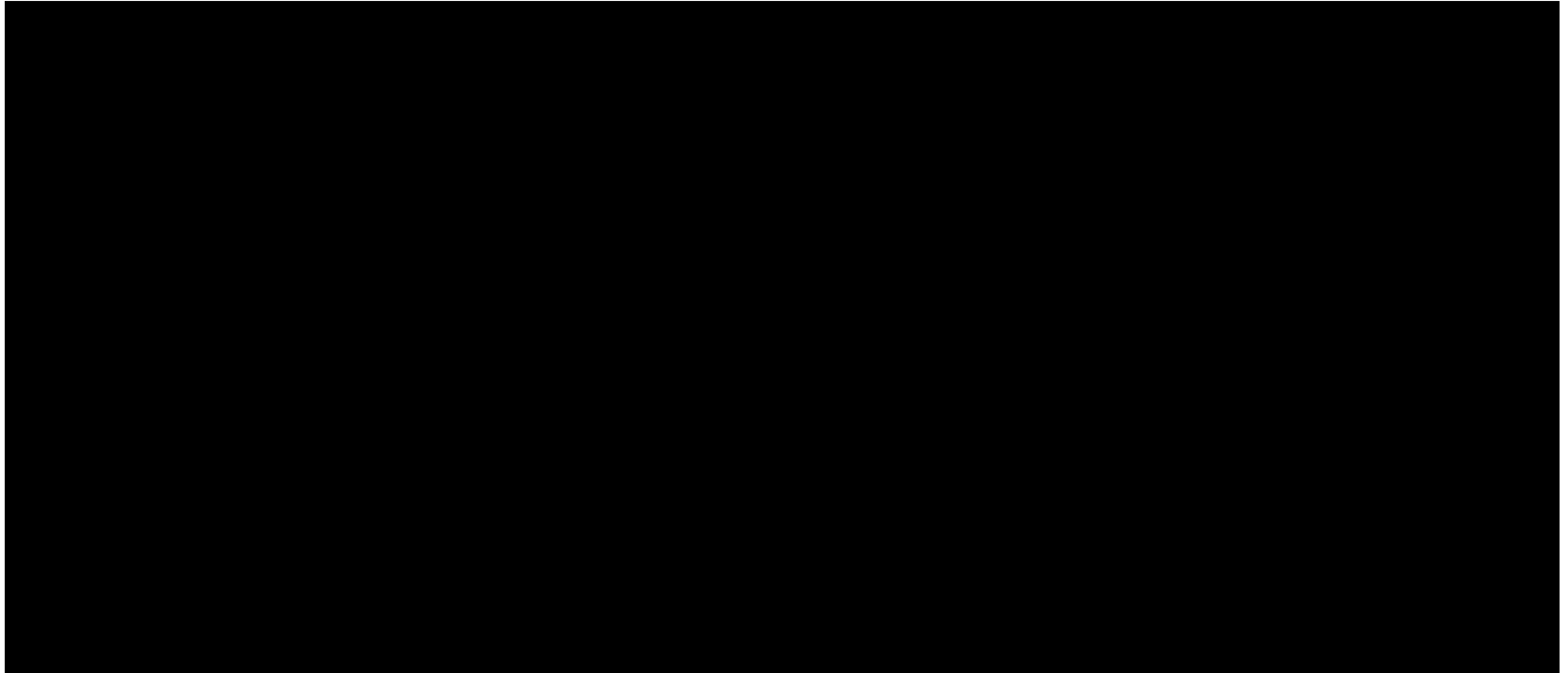


Figure 12: Company's OWSA results

5.1.5 Company's scenario analysis results

The company undertook several scenario analyses to assess the impact to their deterministic base-case results. Details of the scenario analyses along with the rationale was presented. In Table 51, we present a critique of the company's analyses, then report their results in Table 52.

Table 51: Scenario analyses undertaken by the company

Scenario	Scenario detail	Rationale	EAG critique
Pooled comparator distribution	Distribution of AATs in pooled comparator arm sourced from Papa et al. (2020)	To explore an alternative distribution of therapeutic approaches derived from the published Papa et al. (2020) study instead of the UK Delphi panel,	This scenario analysis is reasonable.
Treatment effectiveness inputs	12-month MCR for pooled AAT comparator sourced from ITC of polihexanide 0.8mg/ml RWD (Franch et al. 2024) and pooled AAT (Papa et al. 2020), imputing age and % males, based on average values reported for the entire cohort	To explore the impact of using treatment effectiveness inputs from available RWD for polihexanide 0.8mg/ml versus from the ODAK trial	These scenario analyses appear reasonable; however, the company could have undertaken a scenario analysis, which included the results from the comparator arm (polihexanide 0.2mg/ml + propamidine 1mg/ml) of ODAK in their ITC to show the impact on their base-case results. Additionally, the company should have undertaken an economic analysis that compared polihexanide 0.8mg/ml versus polihexanide 0.2mg/ml + propamidine 1mg/ml based on the clinical effectiveness from the ODAK trial.
	12-month MCR for pooled AAT comparator sourced from ITC of polihexanide 0.8mg/ml RWD (Franch et al. 2024) and pooled AAT (Papa et al. 2020), not adjusted for age or sex		
Mortality	General population mortality applied to all health states	This scenario was explored to model a conservative approach to mortality risk for the GV, SVL and loss of eye functionality	The EAG considers this to be a plausible scenario analysis.

Scenario	Scenario detail	Rationale	EAG critique
		health states, instead of applying mortality HRs derived from the published literature, associated with direct and indirect effects of visual impairment on mortality	
Utility data inputs	Inclusion of disutility associated with intensive treatment phase in polihexanide 0.8mg/ml arm	This scenario explores the impact of applying disutilities associated with insomnia in the intensive treatment phase to patients treated with polihexanide 0.8mg/ml, although the intervention does not require administration during the night hours (in Section). This scenario therefore models a conservative approach to disutilities.	These scenario analyses are reasonable.
	Utility for PV and SVL health states informed by MMRM using cured GV as intercept, from ODAK trial with vision bolt-on disutilities	This scenario explores the use of a vision 'bolt-on' utility decrement for the PV and SVL health states, as the published literature suggests the EQ-5D may not capture all the impacts of ophthalmological conditions.	
AAT, anti-amoebic therapy; AK, Acanthamoeba keratitis; BCVA, best corrected visual acuity; EAG, evidence assessment group; GV, good vision; HR, hazard ration; ICER, incremental cost-effectiveness ratio; ITC: indirect treatment comparison; MCR: medical cure rate; MMRM, mixed-models repeated measures; ODAK, Orphan Drug for Acanthamoeba Keratitis; PV, poor vision; QALY, quality-adjusted life year; RR, relative risk; SVL, severe vision loss; TA, technology assessment.			

Table 52: Company's scenario analyses results, using PAS

Scenario	Incremental costs, £	Incremental QALYs	ICER (£/QALY)	Absolute % Change in ICER	INHB at £20k	INHB at £30k
Base-case	██████████	2.56	██████████	NA	██████████	██████████
Distribution of AATs in pooled comparator arm sourced from Papa et al. (2020)	██████████	2.56	██████████	██████████	██████████	██████████
12-month MCR for pooled AAT comparator sourced from ITC of polihexanide 0.8mg/ml RWD (Franch et al. 2024) and pooled AAT (Papa et al. 2020), imputing age and % males	██████████	3.36	██████████	██████████	██████████	██████████
12-month MCR for pooled AAT comparator sourced from ITC of polihexanide 0.8mg/ml RWD (Franch et al. 2024) and pooled AAT (Papa et al. 2020), not adjusted for age or sex	██████████	3.29	██████████	██████████	██████████	██████████
General population mortality applied to	██████████	2.46	██████████	██████████	██████████	██████████

Scenario	Incremental costs, £	Incremental QALYs	ICER (£/QALY)	Absolute % Change in ICER	INHB at £20k	INHB at £30k
all health states						
Inclusion of disutility associated with intensive treatment phase in polihexanide 0.8mg/ml arm		2.54				
Utility for PV and SVL health states informed by MMRM using cured GV as intercept, from ODAK trial with vision bolt-on disutilities		2.67				
AAT, anti-amoebic therapy; GV, good vision; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; ITC, indirect treatment comparison; MMRM, mixed model repeated measures; NA, not applicable; ODAK, Orphan Drug for Acanthamoeba Keratitis; PV, poor vision; QALY, quality adjusted life years; RWD, real-world data; SVL, severe vision loss						

In summary, the company included appropriate model inputs in the PSA, along with their plausible distributions to assess the impact of joint parameter uncertainty. In OWSA and scenario analysis, a range of model inputs were varied to show the impact to the company's base-case ICER. The EAG were able to replicate the company's scenario analyses. However, we consider that there could have been other scenario analyses that could have been undertaken by the company. At clarification, the EAG requested a scenario analysis that relaxed the assumption that people treated with polihexanide pooled AATs would not experience recurrent AK infection (clarification

question B7). The company stated *‘this scenario is not clinically plausible’* as it is well documented that AK infection can re-occur following medical or surgical cure. Nevertheless, the company undertook the scenario analysis where the results show [REDACTED] to the ICER ([REDACTED] per QALY).

5.2 EAG’s additional analyses

5.2.1 Model validation and face validity check

The company’s validation checks comprised clinical and technical methods. The company reported the Delphi panel methods used and clinical expert opinion to provide model inputs to support existing evidence or in the absence of evidence. The company stated that technical validation included checking formulae, equations and Excel developed Visual Basic Macros, and that results were consistent with the model inputs and robust to extreme values. These validation checks appear to be appropriate, but it was not clear to the EAG if clinical expert opinion was sought on the outputs of the economic evaluation.

The EAG undertook technical checks and used extreme values, and it appears that the model generated the expected results when key model inputs (e.g., MCR RR, disutilities, recurrent AK infection) were changed. No model corrections were made to the company’s economic model; however, changes were made to the preferred assumptions as discussed in Section 5.2.3.

5.2.2 EAG’s exploratory analyses using company’s base-case

Based on our critique of the company’s clinical and cost-effectiveness evidence, the EAG undertook analyses to explore the impact of using alternative assumptions to assess the impact to the company’s base-case results. In Table 53 we present a summary table with some of the company’s

base-case assumptions, along with the EAG's assumptions used in exploratory analyses.

These analyses are based on the company model (Copy of ID6497 polihexanide SIFI SpA Clarification CEM v1.0 07082025 JE [CON]) submitted during the clarification period.

Table 53: Summary of EAG's exploratory analyses using company's base-case

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
1.	AK recurrence after cure occurs only in people treated with pooled AAT. AK Recurrence after Y1: 11.50%; Y2+: 3% and Y3-15: 9.50%	No AK recurrence after cure in people treated with pooled AAT.	Due to the uncertainty around these inputs, the EAG explored the impact to the company's base-case results by making changes to these values.	Section 5.1.5
2.	AK recurrence after cure occurs only in people treated with pooled AAT. AK Recurrence after Y1: 11.50%; Y2+: 3% and Y3-15: 9.50%	Same AK recurrence after cure in people treated with polihexanide 0.8mg/ml as people who received a cure following treatment with pooled AAT.		Section 5.2.2
3.	The company excluded the ODAK comparator arm (polihexanide 0.2mg/ml + propamidine 1 mg/ml) from the ITC, instead comparing the polihexanide 0.8mg/ml + placebo group from ODAK to the pooled/blended AAT cohort from Papa et al. ¹⁶	Include polihexanide 0.2mg/ml + propamidine. To assess the uncertainty around treatment effect, we undertook scenario analyses by varying the RR in increments of 0.10 from 0.95 to 1.75.	The EAG's clinical experts confirmed that polihexanide 0.2mg/ml + propamidine 1mg/ml is a relevant treatment used within the NHS.	Section 3.5.14
4.	Inclusion of disutilities associated with on-going long-term conditions (e.g., pain, lacrimation,	Exclusion of disutilities associated with on-going long-term conditions	Potentially double counting disutilities associated long-term conditions.	Section 4.2.14

	photophobia and anxiety and depression).			
5.	Using mean time on treatment from Franch et al 2024 to calculate treatment cost for polihexanide and median time-to cure from Papa et al 2020 to calculate the treatment cost for the pooled AAT.	Using median time-to-cure from ODAK trial to calculate the treatment cost for polihexanide but maintaining the company's approach for pooled AAT.	Franch et al 2024 might not be generalisable to treat AK in practice and to maintain consistency between the two arms in using median time-to-cure in estimating cost of treatment course.	Section 4.2.18
6.	The company stated that people treated with polihexanide 0.8mg/ml would not require hospitalisation during the intensive treatment phase.	Assume that 26.60% of people treated with polihexanide 0.8mg/ml required hospitalisation during the intensive treatment phase.	The EAG's clinical expert stated that it is likely that people commencing treatment with polihexanide would require hospitalisation during the intensive treatment phase.	Section 4.2.20
7.	The company excluded disutilities associated with intensive phase from their base case analysis during treatment with polihexanide 0.8mg/ml because it is administered at daytime only and will not cause sleep deprivation.	Included intensive phase disutilities for polihexanide 0.8mg/ml treatment, jointly for patients and carers and independently.	Clinical advice to the EAG indicates they will not commence treatment for AK with only daytime administration even with a higher concentration of polihexanide.	Sections 2.2 and 4.2.16
AAT, Anti-amoebic therapy; AK, acanthamoeba keratitis; EAG, evidence assessment group; ITC, indirect treatment comparison; NHS, National Health Service; ODAK, Orphan Drug for Acanthamoeba Keratitis; Y, year				

In Table 54, we present the deterministic results of the EAG's exploratory analyses, which uses the company's model submitted at clarification stage (ID6497 polihexanide SIFI SpA Clarification CEM v1.0 07082025 JE [CON]) and PAS price for polihexanide 0.8mg/ml.

Table 54: Deterministic results of EAG's exploratory analyses using company's base case model and PAS price

Exploratory analysis number	Scenario applied to company's base case	Incremental costs (£)		Incremental QALYs	ICER £/QALY	Impact to the ICER (%)
	Company's base-case					
1.	No AK recurrence after cure in people treated with pooled AAT					
2.	Same AK recurrence after cure in people treated with polihexanide 0.8mg/ml as people who received a cure following treatment with pooled AAT					
3.	Comparison between polihexanide 0.8mg/ml versus polihexanide 0.2mg/ml + propamidine 1mg/ml					
4.	Include polihexanide 0.2mg/ml + propamidine. To assess the uncertainty around treatment effect, we undertook scenario analyses by varying the RR in increments of 0.10 from 0.95 to 1.65.	0.95				
5.		1.05				
6.		1.15				
7.		1.25				
8.		1.35				

9.		1.45	██████	██████	██████	██████
10.		1.55	██████	██████	██████	██████
11.		1.65	██████	██████	██████	██████
12.	Exclusion of disutilities associated with on-going long-term conditions	██████████████		██████	██████	██████
13.	Using median time-to-cure from ODAK trial to calculate the treatment cost for polihexanide but maintaining the company’s approach for pooled AAT.	██████████████		██████	██████	██████
14.	Assume that 26.60% of people treated with polihexanide 0.8mg/ml required hospitalisation during the intensive treatment phase.		██████	██████	██████	██████
15.	Inclusion of intensive phase disutilities, jointly, patients and carers.		██████	██████	██████	██████
16.			██████	██████	██████	██████
17.			██████	██████	██████	██████
AAT, anti-amoebe therapy; AK, acanthamoeba keratitis; ICER, incremental cost-effectiveness ratio; ODAK, Odak Drug for Acanthamoeba Keratitis; QALY, quality adjusted life year; RR, relative risk						

5.2.3 EAG's preferred assumptions

The EAG's base-case compares polihexanide 0.8mg/ml versus polihexanide 0.2mg/ml + propamidine 1mg/ml using the PAS agreements in place for polihexanide 0.8mg/ml and list prices for the comparator.

The EAG's base-case includes making the following changes simultaneously:

- Include the results of the comparator (polihexanide 0.2mg/ml + propamidine 1mg/ml) of ODAK.
- Using median time-to-cure from ODAK trial to calculate the treatment cost for polihexanide 0.8mg/ml but maintaining the company's approach for pooled AAT.
- AK [REDACTED] following treatment with polihexanide 0.8mg/ml.
- Exclusion of disutilities associated with on-going long-term conditions.
- Patient and carers disutilities associated with the intensive treatment period with polihexanide 0.8mg/ml.
- People treated with polihexanide 0.8mg/ml may require hospitalisation during the intensive treatment phase.

In Table 55, we report the results of the EAG's preferred assumptions by considering the impact of each change, then making all changes simultaneously. Results show that using the results for the direct comparison between polihexanide 0.8mg/ml versus polihexanide 0.2mg/ml + propamidine 1mg/ml had the greatest impact to the company's ICER, increasing from [REDACTED] per QALY to [REDACTED] per QALY. Considering all EAG assumptions resulted in [REDACTED] [REDACTED] [REDACTED] [REDACTED] (see Table 56).

Table 55: Results using EAG's preferred model assumptions

EAG preferred assumption	Exploratory analysis number	Incremental cost (£)	Incremental QALYs	ICER (£) (change from company's base case)	Cumulative ICER (£/QALY)	INHB at £20K	INHB at £30K
Company's base case Company's deterministic results submitted at clarification stage.	N/A	██████████	2.56	██████████	██████████	██████████	██████████
EAG's corrected company base case (not applicable)	N/A	██████████	2.56	██████████	██████████	██████████	██████████
Inappropriate exclusion of the ODAK trial comparator. These results are based on the comparison between polihexanide 0.8mg/ml versus polihexanide 0.2mg/ml + propamidine 1mg/ml	3	██████████	0.10	██████████	██████████	██████████	██████████
Mean time-on-treatment used from Franch et al. 2024	13	██████████	2.54	██████████	██████████	██████████	██████████
██████████ in people treated with polihexanide 0.8mg/ml	2	██████████	1.71	██████████	██████████	██████████	██████████

Exclusion of disutilities associated with on-going long-term conditions	12		2.03				
Additional EAG preferred assumption: include disutilities (patients and caregivers) associated with the intensive treatment period with polihexanide 0.8mg/ml	15		2.54				
Additional EAG preferred assumption: Assume that 26.60% of people treated with polihexanide 0.8mg/ml would require hospitalisation	14		2.56				
EAG's preferred base-case deterministic	-		-0.11				
EAG's preferred base-case probabilistic	-		-0.24				
EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; ODAK, Orphan Drug for Acanthamoeba Keratitis; QALY, quality-adjusted life year							

Table 56: EAG's deterministic base-case results, using PAS price

Strategy	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB at £20K	INHB at £30K
Polihexanide 0.2mg/ml + propamidine 1mg/ml		22.66	18.34	-	-	-	-	-	-
Polihexanide 0.8mg/ml		22.64	18.23		-0.02	-0.11			
ICER, incremental quality adjusted life-year; INHB, incremental net health benefit; LYG, life-year gained; QALY, quality adjusted life-year									

Table 57: EAG's probabilistic sensitivity analysis results, using PAS price

Strategy	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB at £20K	INHB at £30K
Polihexanide 0.2mg/ml + propamidine 1mg/ml		22.88	18.51	-	-	-	-	-	-
Polihexanide 0.8mg/ml		22.70	18.27		-0.19	-0.24			
ICER, incremental quality adjusted life-year; INHB, incremental net health benefit; LYG, life-year gained; QALY, quality adjusted life-year									

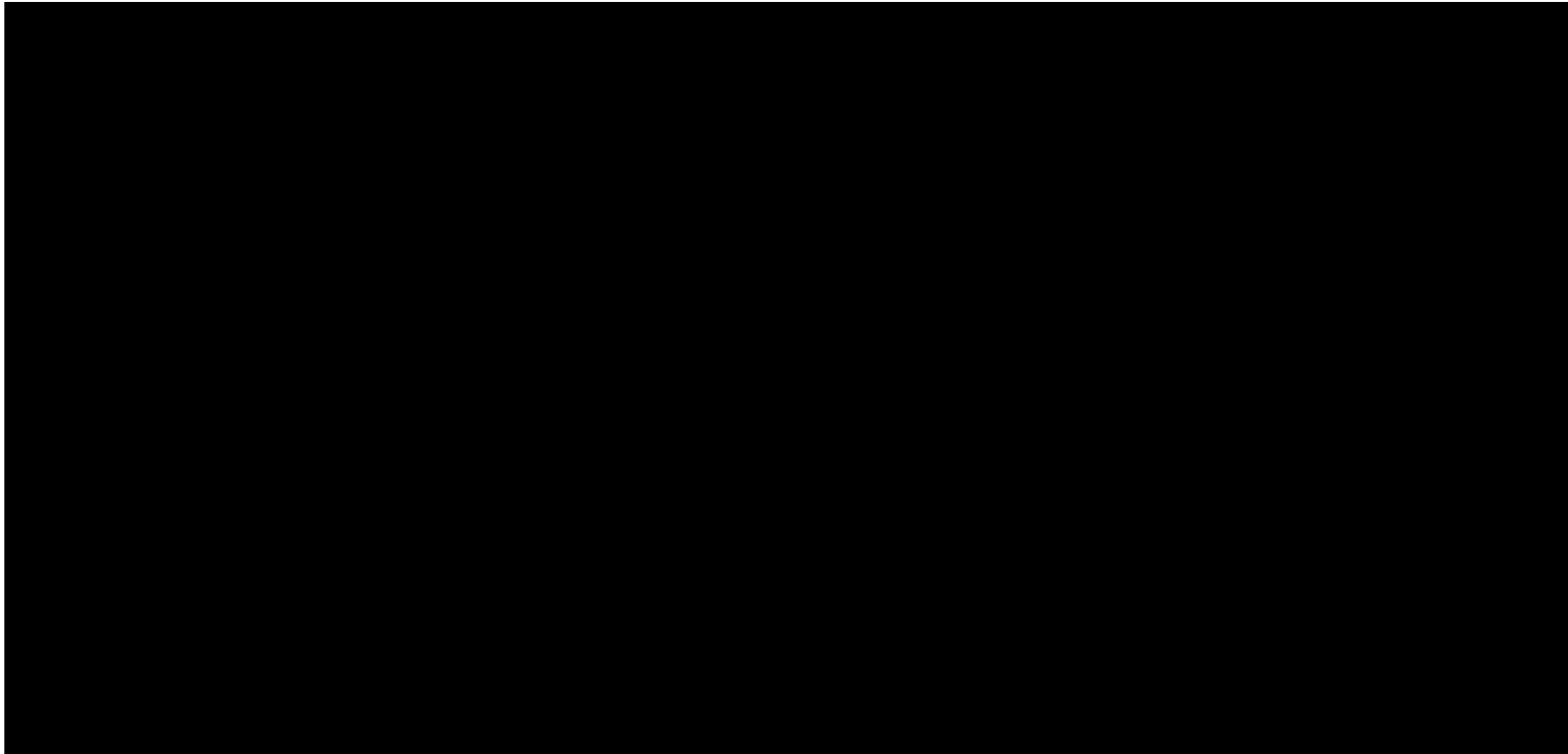


Figure 13: EAG probabilistic sensitivity results

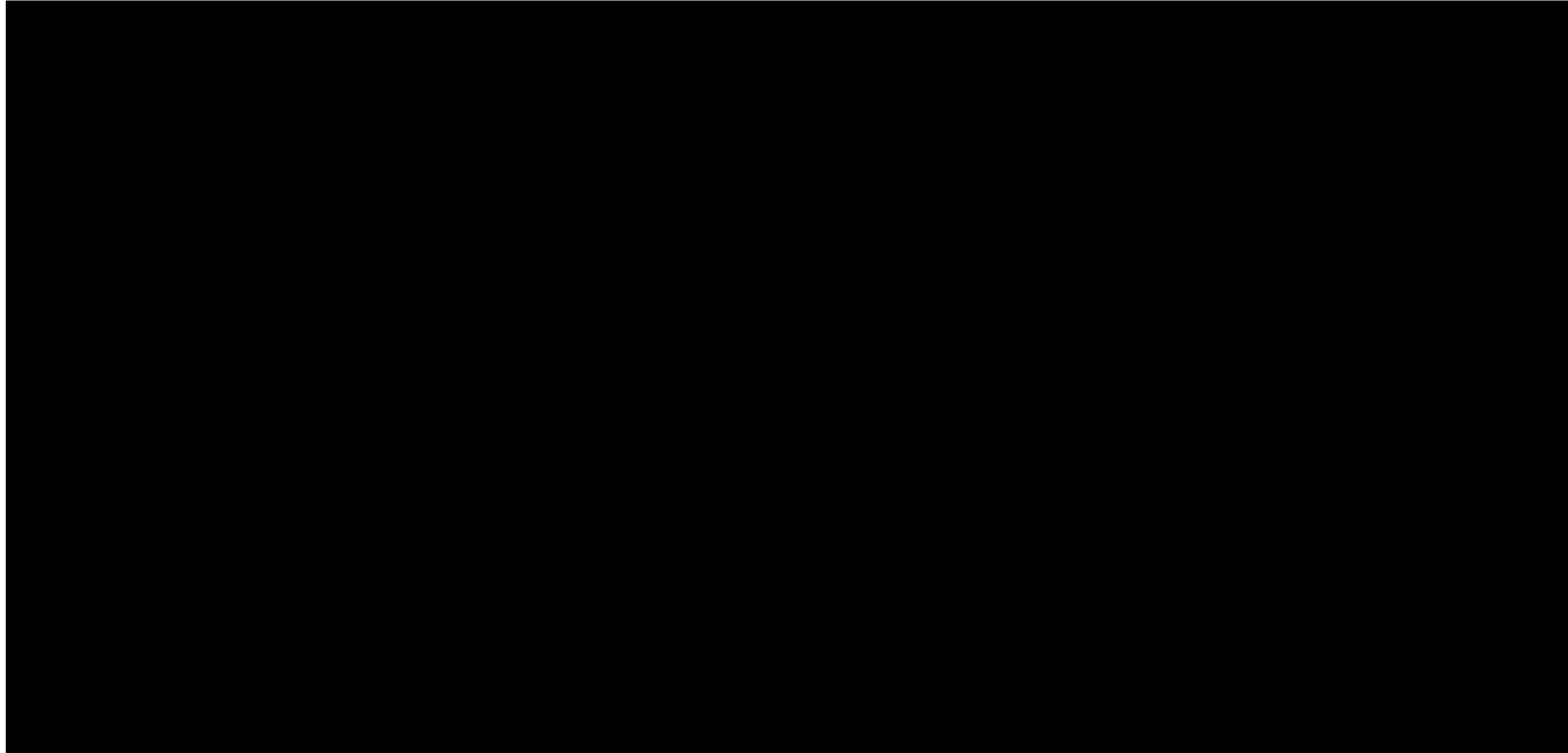


Figure 14: EAG cost-effectiveness acceptability curve

The EAG undertook a re-run of the PSA to obtain results that reflect our preferred assumptions. The EAG's PSA results show the joint distribution of cost and QALY estimates for each strategy generated through 1000 iterations are depicted incrementally in the form a scatterplot plotted on a cost-effectiveness plane and the cost-effectiveness acceptability curve, presented in Figure 13 and Figure 14, respectively. PSA results are reported in Table 55 and Table 57, showing that considering joint parameter uncertainty [REDACTED]

[REDACTED]. Results plotted on the scatterplot (see Figure 13) show that majority of the iterations were spread across the northwest and northeast quadrants, with majority in the northwest quadrant, which is consistent with the deterministic results. Figure 14 shows the PSA results in the form of a CEAC. The curve shows the proportion of the iterations in which polihexanide 0.8mg/ml is cost-effective at different willingness-to-pay thresholds for a QALY. These results show that at a willingness-to-pay threshold up to £100,000 per QALY when polihexanide 0.8mg/ml is compared to polihexanide 0.2mg/ml + propamidine 1mg/ml has a probability of [REDACTED] of being cost-effective.

5.2.4 Scenario analyses using EAG's preferred assumptions

Table 58 provides a summary of scenario analyses undertaken using the EAG's preferred assumptions/model. Given the EAG's choice of comparator (polihexanide 0.8mg/ml + propamidine 1mg/ml) using the clinical results from the ODAK trial, this limited the EAG to apply majority of the company's scenarios.

Table 58: Summary of EAG's scenario analyses using EAG's preferred assumptions

Exploratory analysis number	EAG's base-case assumption	EAG's scenario
1.	Increased mortality due to living with poor vision, severe vision loss and loss of eye functionality.	General population mortality applied to all health states, as undertaken in the company's scenario analyses
2.	Inclusion of disutility associated with the intensive treatment phase in polihexanide 0.8mg/ml.	Exclusion of disutility associated with the intensive treatment phase in polihexanide 0.8mg/ml, as done in the company's base-case analysis.
3.	Exclude disutilities associated with on-going long-term conditions (e.g., pain/lacrimation/photophobia and anxiety/depression).	Include disutilities associated with on-going long-term conditions. Cured with good vision (-0.031), cured with poor vision (-0.079), cured with severe vision loss (-0.125) and loss of eye functionality (-0.136).
EAG, evidence assessment group		

In Table 59, we present the EAG's deterministic scenario analysis results using the EAG's model with our preferred assumptions. These scenarios are based on the comparison of polihexanide 0.8mg/ml versus polihexanide 0.2mg/ml + propamidine 1mg/ml.

Table 59: Deterministic results of EAG's scenario analyses

Exploratory analysis number	Scenario applied to EAG's base-case	Incremental costs (£)	Incremental QALYs	ICER £/QALY	Impact to the ICER (%)	INHB at £20K/QALY)	INHB at £30K/QALY)
EAG's base-case		██████████	-0.11	██████████	█	██████████	██████████
1.	General population mortality applied to all health states, as undertaken in the company's scenario analyses	██████████	██████████	██████████	█	██████████	██████████
2.	Exclusion of disutility associated with the intensive treatment phase in polihexanide 0.8mg/ml	██████████	██████████	██████████	██████████	██████████	██████████
3.	Include disutilities associated with on-going long-term conditions. Cured with good vision (-0.031), cured with poor vision (-0.079), cured with sever vision loss (-0.125) and loss of eye functionality (-0.136)	██████████	██████████	██████████	██████████	██████████	██████████
EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; QALY, quality adjusted life year							

5.3 Decision modifiers

5.3.1 QALY weighting for severity

The company stated that polihexanide 0.8mg/ml did not meet the criteria for a severity modifier, which the EAG agrees.

6 Uncaptured benefits

The company provided other benefits for people with AK treated with polihexanide 0.8mg/ml, which they claimed are not captured within the economic assessment. First, anxiety while waiting for therapeutic surgery following failed pharmacological treatment and further anxiety in terms of the uncertainty in the outcomes following surgery. Based on the company's Delphi panel, there is likely to be a 141.7 day wait until receiving surgical treatment and, to capture the psychological impact may be difficult to capture in the QALY analysis. Though the EAG agrees with the company, we agree for a different reason, that is, it may be difficult to capture using the current model. It might be more accurate to use a patient-level model with the availability of time-to-therapeutic surgery data. The EAG considers that the EQ-5D questionnaire should be appropriate to capture people's health - related quality of life as it contains both pain and anxiety domains. The company included disutilities associated with AK infection, visual acuity and therapeutic surgery in both the decision tree and the Markov components of the model, so the psychological impact is being captured within the QALY analysis.

Second, the company acknowledged that the economic analysis was undertaken from the NHS and PSS perspective, which aligns to the NICE reference case. The company stated that AK infection may lead to isolation, and impacts to the working environment resulting in loss of productivity. Additionally, people with severe vision loss or blindness may be eligible for disability allowance, which they argue are not captured within the economic evaluation framework. The EAG views capturing productivity losses/costs in

this context would not be in line to the reference case. The economic evaluation captures the impact of AK on carers' HRQoL.

Third, the company argues that AK treatment is provided at specialist centres and people need to travel long distances incurring travel costs. Additionally, due to the lack of standardised treatment protocol, management and treatment outcomes will differ between centres, so the company suggested that there is a need for standardised treatment protocol to improve these outcomes- a view which the EAG's clinical experts agreed to, that there is a need for a standardised treatment protocol. However, they suggested that it would be their preference to start by using polihexanide 0.2mg/ml + propamidine 1mg/ml before using a higher concentration, as this is what is done in clinical practice.

6.1.1 Health inequalities

The company argues that in the absence of a standardised treatment protocol for AK, the treatment strategies currently being used across specialist centres are heterogeneous, a consequence of which is increased variability in patient care and could lead to different patient outcomes. The EAG agrees with the company that there is a need for a standardised treatment protocol, a view which is shared with our clinical experts, but we have reservations about how reimbursement of polihexanide 0.8mg/ml would result in a 'rapid treatment approach'. Our clinical experts stated that the 17.7-day delay between AK diagnosis and treatment initiation reported by the company is an overestimate, as people are likely to receive treatment within a few days once diagnosed. Also, we suggest that rapid diagnosis is as important as the availability of standardised treatment to improve patient outcomes. There is also limited evidence of increased variability in patient care, the EAG clinical experts and the evidence provided by the company, supported the view that polihexanide 0.2mg/ml with propamidine 1mg/ml is the most commonly used treatment in UK practice.

6.2 Confidential comparator and subsequent treatment prices

The EAG has not submitted a confidential appendix to the EAG report because there are no confidential comparator or subsequent treatment prices.

6.3 Conclusions of the cost-effectiveness section

The company's hybrid economic model structure was appropriate to simulate the pathway for a hypothetical cohort of people receiving treatment for AK infection and to assess the long-term costs and benefits associated with the technologies being compared. The company's model was driven by the costs associated with the technologies, surgical procedures and hospitalisation and benefits in terms of QALYs by capturing utilities associated with AK infection and BCVA, disutilities associated with long-term complications of AK, disutilities associated with events, and caregiver disutilities. The effectiveness in terms of medical cure rate at 12 months between the technologies was based on the company's ITC between the polihexanide 0.8mg/ml arm of the ODAK trial and a pooled AAT the Papa et al. study. Several key assumptions were made by the company, with support from their Delphi panel and additional clinical expert opinion. Despite there being no major concerns/errors with the company's model, we identified several concerns with the company's ITC methods, which potentially biased the effectiveness results in favour of polihexanide 0.8mg/ml, which impacts the economic results as it was deemed by the EAG to be a key model input. The key concerns identified:

- Company's base-case is centred on the ITC between the ODAK RCT and a retrospective cohort with a high risk of bias. This approach is methodologically weak due to differences in study design, lack of adjustment for important covariates (e.g., contact lens use), inconsistent handling of missing data and subsequent treatment.

- The ITC excluded the ODAK comparator arm (polihexanide 0.2mg/ml + propamidine 1mg/ml), which is clinically relevant in the UK setting, and instead compared polihexanide 0.8mg/ml against a heterogeneous pooled comparator group.

We amended the company's economic model based on our preferred assumptions, which formed the basis of the EAG's model. These changes resulted in differences between the company's and EAG's base-case results. Based on the concerns raised, the following changes were made:

- Included the results of the comparator (polihexanide 0.2mg/ml + propamidine 1mg/ml) of ODAK.
- Using median time-to-cure from ODAK trial to calculate the treatment cost for polihexanide 0.8mg/ml but maintaining the company's approach for pooled AAT.
- AK recurrence may occur following treatment with polihexanide 0.8mg/ml.
- Exclusion of disutilities associated with on-going long-term conditions.
- Patient and carers disutilities associated with the intensive treatment period with polihexanide 0.8mg/ml.
- People treated with polihexanide 0.8mg/ml may require hospitalisation during the intensive treatment phase.

Making all changes resulted in a change to the ICER from [REDACTED] for the comparison between polihexanide 0.8mg/ml versus pooled AAT to polihexanide 0.8mg/ml being [REDACTED] polihexanide 0.2mg/ml + propamidine 1mg/ml.

Despite the EAG's amendments to the company's model, important uncertainties remain regarding the reliability of the cost-effectiveness evidence:

- Comparisons with pooled AATs: in a trial setting, the relative effectiveness of polihexanide 0.8mg/ml compared to pooled AATs could be more modest than estimated in the company's ITC, suggesting that cost-effectiveness may have been biased in favour of polihexanide 0.8mg/ml.
- Comparator uncertainty: while the EAG preferred the ODAK comparator arm as clinically relevant for the UK, the absence of head-to-head evidence versus pooled AATs means that the ranking of the treatments remain uncertain.
- Uncaptured sources of bias: the omission of contact lens use and inconsistent handling of subsequent treatment and missing data in the ITC likely favour polihexanide 0.8mg/ml, but the magnitude of this bias cannot be measured.
- Generalisability: the ODAK study was a well-conducted RCT but represents a trial population under closely monitored conditions. Effectiveness in real-world clinical practice may be lower, which could further reduce the cost-effectiveness of polihexanide 0.8mg/ml.

Overall, the EAG considers that the direction of bias is more likely to favour polihexanide 0.8mg/ml given the uncertainties outlined above. The true cost-effectiveness of polihexanide 0.8mg/ml is therefore likely to be less favourable than suggested by the company's base-case.

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8 Appendices

8.1 EAG changes to the company's model

In Table 60, we present details of the changes made to the company's model that formed the basis of the EAG's base-case.

Table 60: Technical details of changes made to the company's model

EAG preferred assumption based on issues	Technical report of changes in the company's model
Key issue 1: Inappropriate exclusion of the ODAK trial comparator These results are based on the comparison between polihexanide 0.8mg/ml versus polihexanide 0.2mg/ml + propamidine 1mg/ml	"Drug usage and costs" worksheet, Cell D7 has changed to 100.00%, Cells in Range D8:D15 has changed to 0.00% "Clinical Data" worksheet, Cell B20 has changed to 0.96
Key issue 4: Mean time-on-treatment used from Franch et al. 2024	"Costs" worksheet, Cell E45 has changed to 140.00
Key issue 5: [REDACTED] in people treated with polihexanide 0.8mg/ml	"Clinical" worksheet, Cell E201 has changed to 0.1150 and Cell E206 has changed to 0.0300
Key issue 6: Inclusion of disutilities associated with on-going long-term conditions	"HRQoL" worksheet, Cells in Range D22:D25 has changed to 0
Additional EAG preferred assumption: include disutilities (patients and caregivers) associated with the intensive treatment period with polihexanide 0.8mg/ml	"Lookups" worksheet, Cell G42: choice has changed to "2"
Additional EAG preferred assumption: Assume that 26.60% of people treated with polihexanide 0.8mg/ml would require hospitalisation	"HCRU data&costs" worksheet, Cell B6 has changed to 26.60%

8.2 EAG re-run of the company's analyses, using eMIT prices

The EAG undertook a re-run of the company's deterministic and probability results using the electronic market information tool (eMIT) prices available. The deterministic results are reported in Table 61, which shows that using the eMIT prices made no difference to the company's base-case ICER. The company's probabilistic results are reported in Table 62 and

corresponding results in the form of a scatterplot and a CEAC are presented in Figure 15 and

Figure 16, respectively. Using, the eMIT prices for had no impact to the company's probabilistic results.

Table 61: Company's deterministic base-case analysis results, using the PAS and eMIT prices

Strategy	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB at £20K	INHB at £30K
Pooled AAT	[REDACTED]	22.37	14.76	-	-	-	-	-	-
Polihexanide 0.8mg/ml	[REDACTED]	22.65	17.31	[REDACTED]	0.28	2.56	[REDACTED]	[REDACTED]	[REDACTED]

Table 62: Company's probabilistic sensitivity analysis results, using the PAS and eMIT prices

Strategy	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB at £20K	INHB at £30K
Pooled AAT	[REDACTED]	22.38	14.83	-	-	-	-	-	-
Polihexanide 0.8mg/ml	[REDACTED]	22.65	17.30	[REDACTED]	0.27	2.47	[REDACTED]	[REDACTED]	[REDACTED]



Figure 15: Cost-effectiveness scatterplot for the comparison between polihexanide 0.8mg/ml vs. pooled AAT

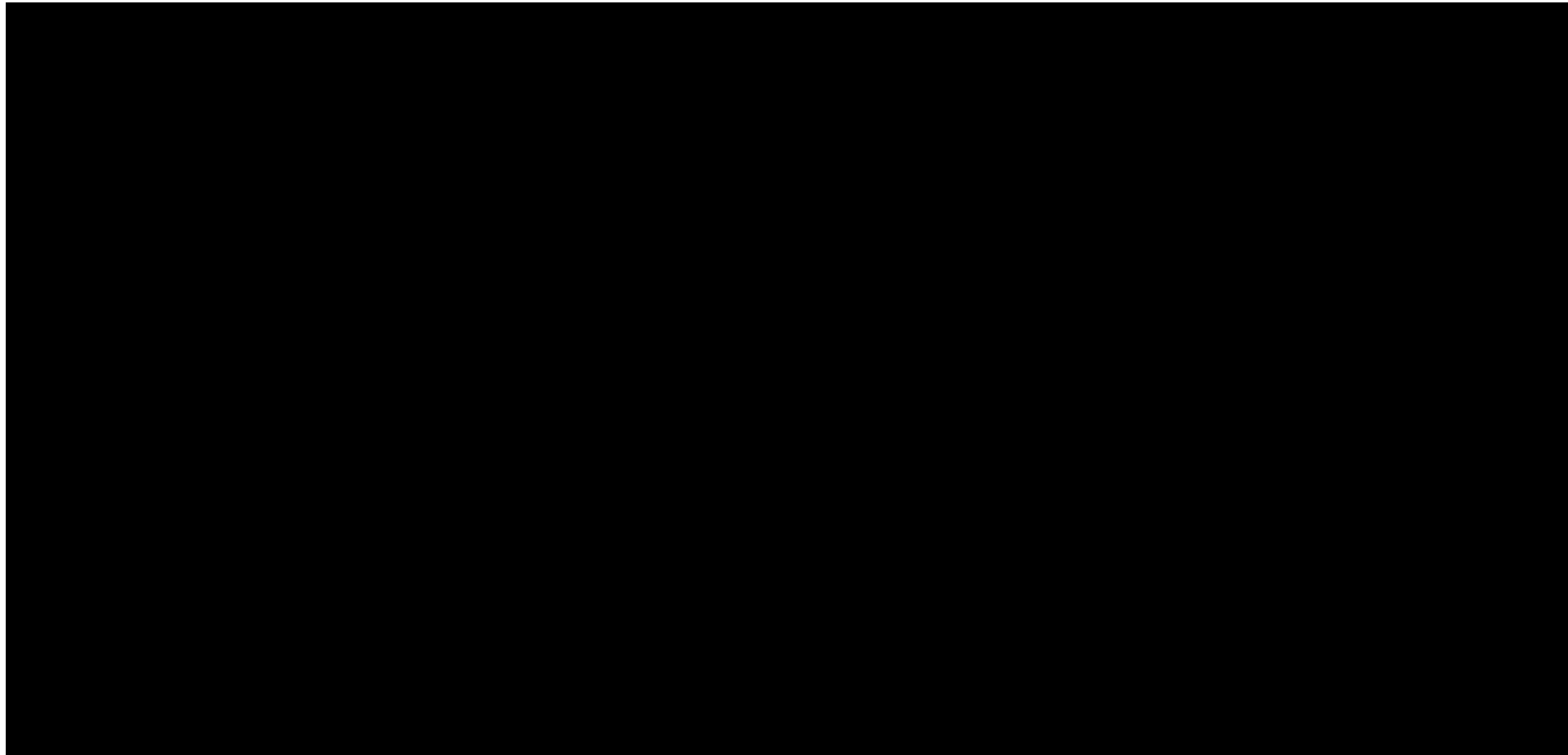


Figure 16: Cost-effectiveness acceptability curve (CEAC)

External Assessment Group (EAG) Report

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

Produced by

Centre for Evidence and Implementation Science, University of
Birmingham

Authors

Angela Mwape, Research Fellow in Evidence Synthesis

Christiana Anyebe, Research Associate in Health Economics

Mubarak Patel, Research Fellow in Medical Statistics

Mubarak Patel, Research Fellow in Evidence Synthesis

Rachel Court, Senior Information Specialist

Emma Loveman, Systematic review consultant, Effective
Evidence LLP

Jill Colquitt, Systematic review consultant, Effective Evidence
LLP

Peter Auguste, Assistant Professor in Health Economics &
Decision Modelling

¹Centre for Evidence and Implementation Science, Health
Services Management Centre, University of Birmingham,
Birmingham, B15 2RT

Correspondence to

Dr. Peter Auguste
Centre for Evidence and Implementation Science
Health Services Management Centre
University of Birmingham
Birmingham, B15 2RT

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Declared competing interests of the authors

None

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Angela Mwape conducted the review of the clinical effectiveness evidence
Christiana Anyebe conducted the review of the cost-effectiveness evidence

and undertook additional analyses

Mubarak Patel conducted the review of the statistical analyses

Mubarak Patel conducted the review of the clinical effectiveness evidence

Rachel Court conducted the review of the literature searches and undertook additional searches

Emma Loveman conducted the review of the clinical effectiveness evidence

Jill Colquitt conducted the review of the clinical effectiveness evidence

Peter Auguste led the project and conducted the review of the cost-effectiveness evidence and undertook additional analyses

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Table of Abbreviations

Abbreviation	Definition
AK	Acanthamoeba keratitis
EAG	Evidence assessment group
eMIT	Drugs and pharmaceutical electronic market information tool
HST	Highly Specialised Technology
INHB	Incremental net health benefit
LYG	Life-year gained
QALY	Quality adjusted life year
SmPC	Summary of product characteristics

1 Addendum

In this addendum, we provide additional analyses and responses to queries requested by the NICE technical team on 22 December 2025. In this addendum, all analyses include using Drugs and pharmaceutical electronic market information tool (eMIT) that are in place, and list prices where there are no commercial agreements. The addendum is structured as follows:

- *The technical team noted that the company based their inclusion of caregiver disutilities for AK on HST11 (inherited retinal dystrophies). However, the condition in HST 11 seems much more severe than AK as it inevitably leads to near-total blindness in both eyes. For this reason, we thought it might be useful to provide committee with some scenarios on the EAG base case that exclude caregiver utilities?*
- We noted that your clinical experts suggested that:
 - polihexanide 0.8 mg/ml would only be used for severe cases of AK. This does not align with the licence or clinical trial data (~17% polihexanide 0.8 mg/ml arm and 12 % of the comparator arm had stage 3 AK at baseline in ODAK). Is this something you considered exploring further with clinical experts or in any exploratory scenarios we could present to committee?
 - Polihexanide 0.8 mg/ml would be given at night during the intensive phase, despite daytime only administration being specified in the SmPC: could you possibly expand on this in terms of:
 - how many clinical experts provided this advice and whether you expect it to reflect clinical practice throughout the UK?
 - whether the experts anticipated that the frequency of drops in the intensive phase would align with the SmPC (e.g. hourly for the first 5 days, etc..)? Polyhexanide 0.8mg is costed assuming

daytime administration only with a maximum of 16 drops per day. If your clinical experts suggested otherwise, could you possibly provide a scenario increasing the number of drops per day during the intensive phase.

- The company's market intelligence report that establishes the costs for off-label treatments states that 'Recommendations are made regarding values which might be appropriate to use in the assumptions for economic modelling. However, Policy Matters strongly advise that these values are used for initial modelling purposes only and that during the HTA submission development the assumptions are validated with experts from Trusts covering a variety of areas across England (e.g. via an advisory board).' This does not appear to have been conducted by the company, so we consider the costs for off label treatments to be quite uncertain. Could you possibly provide some sensitivity analyses varying the costs of Polihexanide 0.2mg/ml, 0.6 mg/ml and Chlorhexidine, using highest/lowest plausible values, to assess the impact of this uncertainty on the cost effectiveness analyses.
- Could you also provide a scenario using the EAG's base case assumptions but applying the median time-to-cure from ODAK for both the intervention and comparator arm? Given that the ODAK trial provides direct time-to cure data for your preferred comparator, it would be helpful to better understand your rationale for using the median time-to-cure from Papa et al. for pooled AATs for the comparator arm in your base case?

2 Cost-effectiveness results

In this section we summarise the results of the additional analyses requested by NICE.

2.1 NICE's scenario analysis results

Several scenario analyses were undertaken around the EAG base-case, with the results presented in Table 1. Across all scenarios, the overall results

[REDACTED]

Table 1: Scenario analyses requested by NICE

Strategy	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)	INHB at £20K	INHB at £30K
EAG base-case									
Polihexanide 0.2mg/ml + propamidine 1mg/ml	██████	22.66	18.34	-	-	-	-	-	-
Polihexanide 0.8mg/ml	██████	22.64	18.23	██████	-0.02	-0.11	██████	██████	██████
Exclusion of caregiver disutilities									
Polihexanide 0.2mg/ml + propamidine 1mg/ml	██████	22.66	18.34	-	-	-	-	-	-
Polihexanide 0.8mg/ml	██████	22.64	18.23	██████	-0.02	-0.09	██████	██████	██████
Increase to number of polihexanide 0.8mg/ml drops per day to 24 for duration of 2 days									
Polihexanide 0.2mg/ml + propamidine 1mg/ml	██████	22.66	18.34	-	-	-	-	-	-
Polihexanide 0.8mg/ml	██████	22.64	18.23	██████	-0.02	-0.11	██████	██████	██████
Increase to number of polihexanide 0.8mg/ml drops per day to 24 for duration of 3 days									
Polihexanide 0.2mg/ml + propamidine 1mg/ml	██████	22.66	18.34	-	-	-	-	-	-
Polihexanide 0.8mg/ml	██████	22.64	18.23	██████	-0.02	-0.11	██████	██████	██████

[ID6497 EAG report for polihexanide eyedrops for treating acanthamoeba keratitis in people 12 year and over; 28/08/2025]

Increase to number of polihexanide 0.8mg/ml drops per day to 24 for duration of 4 days									
Polihexanide 0.2mg/ml + propamidine 1mg/ml	██████	22.66	18.34	-	-	-	-	-	-
Polihexanide 0.8mg/ml	██████	22.64	18.23	██████	-0.02	-0.11	██████	██████	██████
Increase to number of polihexanide 0.8mg/ml drops per day to 24 for duration of 5 days									
Polihexanide 0.2mg/ml + propamidine 1mg/ml	██████	22.66	18.34	-	-	-	-	-	-
Polihexanide 0.8mg/ml	██████	22.64	18.23	██████	-0.02	-0.11	██████	██████	██████
X3 increase in costs to polihexanide 0.2mg/ml, polihexanide 0.6mg/ml and chlorhexidine 0.2mg/ml									
Polihexanide 0.2mg/ml + propamidine 1mg/ml	██████	22.66	18.34	-	-	-	-	-	-
Polihexanide 0.8mg/ml	██████	22.64	18.23	██████	-0.02	-0.11	██████	██████	██████
X2 increase in costs to polihexanide 0.2mg/ml, polihexanide 0.6mg/ml and chlorhexidine 0.2mg/ml									
Polihexanide 0.2mg/ml + propamidine 1mg/ml	██████	22.66	18.34	-	-	-	-	-	-
Polihexanide 0.8mg/ml	██████	22.64	18.23	██████	-0.02	-0.11	██████	██████	██████
½ decrease in costs to polihexanide 0.2mg/ml, polihexanide 0.6mg/ml and chlorhexidine 0.2mg/ml									

Polihexanide 0.2mg/ml + propamidine 1mg/ml	██████	22.66	18.34	-	-	-	-	-	-
Polihexanide 0.8mg/ml	██████	22.64	18.23	██████	-0.02	-0.11	██████	██████	██████
1/3 decrease in costs to polihexanide 0.2mg/ml, polihexanide 0.6mg/ml and chlorhexidine 0.2mg/ml									
Polihexanide 0.2mg/ml + propamidine 1mg/ml	██████	22.66	18.34	-	-	-	-	-	-
Polihexanide 0.8mg/ml	██████	22.64	18.23	██████	-0.02	-0.11	██████	██████	██████
Median time-to-cure from ODAK									
Polihexanide 0.2mg/ml + propamidine 1mg/ml	██████	22.66	18.37	-	-	-	-	-	-
Polihexanide 0.8mg/ml	██████	22.64	18.24	██████	-0.02	-0.13	██████	██████	██████
EAG, evidence assessment group; ICER, incremental cost-effectiveness ratio; INHB, incremental net health benefit; QALY, quality adjusted life year									

3 Response to NICE queries

- *Polihexanide 0.8 mg/ml would only be used for severe cases of AK. This does not align with the licence or clinical trial data (~17% polihexanide 0.8 mg/ml arm and 12 % of the comparator arm had stage 3 AK at baseline in ODAK). Is this something you considered exploring further with clinical experts or in any exploratory scenarios we could present to committee?*

We received a response from one of our clinical advisors who stated that ‘a higher concentration is most likely to cause more ocular surface side effects. So i think as per previous publications from Dart et al, it has been recommended to start on lower concentration and upscale if severity increases. Starting a higher concentration right away, goes in a completely different direction to protocols proposed for the last 2-3 decades.’

- *Polihexanide 0.8 mg/ml would be given at night during the intensive phase, despite daytime only administration being specified in the SmPC: could you possibly expand on this in terms of:*
- *how many clinical experts provided this advice and whether you expect it to reflect clinical practice throughout the UK?*

Ahead of writing the EAG report, two of our clinical advisors stated that polihexanide would be given at night during the intensive phase. However, one expert stated that this would be given hourly for the first two days and the other expert stated that hourly for the first five days.

Our clinical advisors re-iterated that intensive day and night therapy has been the standard operating procedure for decades and they will not be changing that especially in moderate-to-severe disease.

- *Whether the experts anticipated that the frequency of drops in the intensive phase would align with the SmPC (e.g. hourly for the first 5 days, etc..)? Polyhexanide 0.8mg is costed assuming daytime administration only with a maximum of 16 drops per day. If your clinical experts suggested otherwise, could you possibly provide a scenario increasing the number of drops per day during the intensive phase.*

Clinical feedback suggested that the maximum number of drops during the intensive phase is 1-2 drops every hour day and night, which is around 24 instillations for 3-5 days based on the severity at time of commencement of therapy. Then, 18 installations (0700-0000) for 5-7 days, tapering of regime based on response. One of our clinical advisors stated that they cannot define the whole treatment period, but this will continue for at least 4-9 months or more based on response.

Another clinical advisor stated that because of the types of infection means usual practice is to continue overnight, so they would treat for a minimum of 48hrs day and night, with a maximum of 24 drops.

- *Given that the ODAK trial provides direct time-to cure data for your preferred comparator, it would be helpful to better understand your rationale for using the median time-to-cure from Papa et al. for pooled AATs for the comparator arm in your base case?*

Our preference would have been to use the median time-to-cure reported in the ODAK study for polyhexanide 0.8mg/ml and polyhexanide 0.2mg/ml + propamidine 1mg/ml for consistency as stated in our report. A scenario analysis, which is based on median time-to-cure obtained from the ODAK trial has now been undertaken with the results reported in Table 1. These results show that there was [REDACTED]

[REDACTED]

4 Appendices

4.1 EAG changes to the company's model

In Table 2, we present details of the changes made to the EAG's model that formed the addendum of the EAG's base-case.

Table 2: Technical details of changes made to the company's model

Analyses	Changes
Exclusion of caregivers disutilities	In QoL Data worksheet, change cell B88 to zero.
Increase to number of polihexanide 0.8mg/ml drops per day to 24 for duration of 2-5 days	In the Costs worksheet, change cell E26 to 24 and F26 to 2, 3, 4 and 5
High/low costs for polihexanide 0.6mg/ml, polihexanide 0.2mg/ml and chlorhexidine 0.2mg/ml	In the Costs worksheet, change cell F55-F57 to reflect the high and low costs
Median time-to-cure from ODAK	In the Costs worksheet, change cells E46 and E47 to 114.

Single Technology Appraisal

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

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by the end of **11th September 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [REDACTED] should be highlighted in turquoise and all information submitted as '[REDACTED]' in pink.

Section 1: Factual inaccuracies related to EAG's key issues

Issue 1 "Inappropriate exclusion of the ODAK trial comparator"

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 101, Sections 3.5.8: The EAG has misrepresented the company's rationale for excluding the ODAK comparator arm data from the CS. It is strongly recommended that the language around the rationale is changed throughout the EAG report to reflect the company's actual position. This applies throughout the full report but one instance includes: "However, the EAG's clinical experts disagree with the choice to exclude the comparator, stating that polihexanide 0.2mg/ml + propamidine 1mg/ml is a standard treatment in real-world practice. [...] The company excludes this comparator for not being representative but then uses it as a key component of the current treatment landscape in the economic model. The	Please amend the text as follows: "However, the EAG's clinical experts disagree with the choice to exclude the comparator arm data from the ODAK trial, stating that polihexanide 0.2mg/ml + propamidine 1mg/ml is a standard treatment in real-world practice. [...] The company excludes this the comparator arm data from the ODAK trial for not being representative, due to concerns around the real-world applicability of the treatment protocols used to administer polihexanide 0.2mg/ml + propamidine 1mg/ml within the trial, which do not reflect how patients would receive this therapeutic approach in the real-world. The company acknowledges that, whilst it is unlicensed in AK, polihexanide 0.2mg/ml + propamidine 1mg/ml is a commonly used therapeutic approach, by describing the results of the Delphi Panel exercise (Table 3, CS), the distribution of therapeutic approaches from the Papa et al. 2020 study (Table 31, CS) but then uses and by using it as a key component of the current treatment	Throughout the EAG report, the company's rationale for treating the ODAK trial of polihexanide 0.8 mg/ml as a single-arm trial has been misinterpreted. It is implied throughout that the company's position is that polihexanide 0.2 mg/ml + propamidine 1 mg/ml is not used in UK clinical practice, which is not the case. Polihexanide 0.2 mg/ml + propamidine 1 mg/ml was selected as the active comparator for the ODAK clinical trial, despite its lack of licensing in the AK indication, because it represents one of several therapeutic approaches used in UK clinical practice. At no point in the CS does the company challenge this and, throughout the CS and cost-effectiveness model, polihexanide 0.2 mg/ml + propamidine 1 mg/ml is represented in the key evidence sources used to inform the clinical and economic analyses (i.e. Papa et al. 2020 and	Not a factual error. The EAG does not change its position on the issue but acknowledges the company's points about wording. The following amendment has been made on page 101, section 3.5.8: "The company excludes the comparator arm data from the ODAK trial due to concerns around the real-world applicability of the treatment protocols used to administer this treatment within the trial, which do not reflect how patients would receive this treatment in the real-world for not being representative but then uses it. However, this treatment was used as a key component of the current treatment

company also stated that the ODAK comparator was requested to be included due to 'ethical reasons', but it reflects standard care."	landscape in the economic model. The company also stated that the ODAK active comparator arm, as opposed to a placebo control arm , was requested to be included in the ODAK protocol by the EMA due to 'ethical reasons', but it is the EAG's position that it reflects standard care."	the Delphi panel results). The EAG suggests that this represents a contradiction in the company's approach, but this is a misinterpretation of the company's position. As noted in the CS (see Section entitled 'Suitability of the evidence base' at the top of Section 2), the company's position is that the results from the active comparator arm are not likely to be reflective of the effectiveness of therapeutic options in real-world practice, not that the comparator itself is not used in real-world practice. As noted by the EMA in its European Public Assessment Report <i>"Considering that the active arm as applied in trial 043 [ODAK] contained a medicinal product manufactured to GMP quality, immediate availability and a standardised treatment protocol, it could not be considered a control representative of current practice."</i>	landscape in the economic model. The company also stated that the ODAK comparator was requested to be included, as opposed to a placebo control arm, due to 'ethical reasons'. The EAG's position, however, is that this comparator reflects standard care in the UK and should not have been excluded from the ITC."
Page 33, Section 2.3: The EAG's description of the reason the ODAK active comparator arm data was not included is inaccurate and should be amended: "The CS decision was based on the outcome from their UK-based Delphi panel which considered that the ODAK comparator was not reflective of therapeutic approaches used in real-world practice..."	Please amend the text as follows: "The CS decision was based on concerns regarding the treatment protocols used to administer polihexanide 0.2mg/ml + propamidine 1mg/ml within the trial, which do not reflect how patients would receive this therapeutic approach in the real-world. ~~regarding the the outcome from their UK-based Delphi panel which considered that the ODAK comparator was not reflective of therapeutic approaches used in real-world practice...~~ "	The ODAK active comparator arm used a detailed and standardised treatment protocol which patients were required to adhere to, which is in contrast to the current real-world clinical setting, where the lack of	The EAG has amended as requested to, "The CS decision was based on concerns regarding the treatment protocols used to administer polihexanide 0.2mg/ml + propamidine 1mg/ml within the trial, which do not reflect how patients would receive this therapeutic approach in the real-world."
Page 61, Section 3.3.1: The EAG clinical advisors statement misinterprets the company's position with regard	Please amend the text as follows: "...the EAG clinical advisors unanimously disagreed with the company's claim that the comparator arm "the efficacy observed in		We have amended to "...the EAG clinical advisors unanimously disagreed with the company's claim that "the

to the ODAK comparator and misquotes the CS: “...the EAG clinical advisors unanimously disagreed with the company's claim that the comparator arm “is unlikely to reflect current UK clinical practice” (as stated in the CS) and emphasised that polihexanide 0.2mg/ml is the standard front-line treatment used in UK clinical practice.”	the active comparator arm of the ODAK trial is unlikely to reflect current UK clinical practice is unlikely to reflect current UK clinical practice” (as stated in the CS) and emphasised that polihexanide 0.2mg/ml is the standard front-line treatment used in UK clinical practice.”	AK-specific summary of product characteristics (SmPCs) associated with unlicensed and off-label eye drops means that treatment regimens are determined by physician discretion and previous experience. This leads to heterogeneity in the care received by patients and therefore varying clinical outcomes. This undermines the generalisability of the ODAK trial as a source of evidence for the efficacy of polihexanide 0.2 mg/ml + propamidine 1 mg/ml in current clinical practice, given that the active comparator arm likely demonstrated artificially improved efficacy compared to if the same treatment were used in a real-world setting. The company would like to restate that none of the therapeutic approaches included in the company's proposed pooled AAT arm are licensed for use in AK specifically in the UK and several are compounded on demand, creating concerns with regards to manufacturing quality, supply and patient safety. Given its relevance to this appraisal, SIFI would like to bring to the EAG's attention that, recently, a	efficacy observed in the active comparator arm of the ODAK trial is unlikely to reflect current UK clinical practice (as stated in the CS) and emphasised that polihexanide 0.2mg/ml is the standard front-line treatment used in UK clinical practice.”

		major UK manufacturer of two of the therapeutic approaches currently used to treat AK (polihexanide [0.2 mg/ml and 0.6 mg/ml] and chlorhexidine) has recently had its license revoked, further calling into question the stability and quality of manufacturing processes for currently used therapeutic approaches in the UK. Currently no hospital or Healthcare Professional can source 0.2 mg/ml polihexanide, 0.6 mg/ml polihexanide or chlorhexidine and this looks to be likely for the foreseeable future. As 0.8 mg/ml polihexanide would be manufactured and supplied by SIFI, this is likely to be the only viable option for patients with AK. The company would be grateful if the EAG could confirm whether their position on the appropriate comparator for the evaluation of polihexanide 0.8 mg/ml still stands, given the current situation in which polihexanide 0.2 mg/ml + propamidine is neither licensed for use in AK or commercially available to centres across the UK. Finally, the company would like to note that the EAG's chosen	

		comparator is narrower in scope than the group defined by NICE as relevant to the evaluation. NICE's scope lists polihexanide 0.2mg/ml, chlorhexidine, propamidine and hexamidine, used individually or in combination. Therefore, we would argue that the pooled AAT comparator, comprising real-world effectiveness data for all comparators set out by NICE, is better aligned with the scope of the evaluation. To date, in all written and verbal and engagements with NICE and the EAG, the company have echoed NICE's chosen comparators and have regularly described the heterogenous picture of therapeutic approaches used in clinical practice. For instance: • Company's draft scope response (dated 18th February): "While there is no current standard of care in the UK, SIFI is in agreement with the comparators listed by NICE, although would highlight that not all listed treatments are used to the same degree."	

		Decision problem form (dated 19th March): “In the absence of products authorised in AK, current therapeutic options consist of unstandardised prescription of biguanides (chlorhexidine and polihexanide 0.2 mg/ml [as a compounded formulation made to order]) and diamidines (propamidine and hexamidine), which can be used as monotherapies or in combination.” As such, we strongly recommend the EAG’s wording on the rationale for the company’s approach to using a pooled AAT comparator, as opposed to the active comparator arm of ODAK, is revised throughout.	
Page 101, Section 3.5.8: The EAG’s interpretation of the comparability of a standardised, licensed treatment with an SmPC and an unlicensed treatment with no standard protocols is misleading: “Moreover, one could argue that if the comparator in ODAK is	Please amend the text as follows: “Moreover, one could argue that if the comparator in ODAK is unrepresentative due to better trial conditions, the polihexanide 0.8mg/ml arm ~~should~~ could be subject to the same criticism ~~since it also benefits from early access and standardisation of protocol~~, though not the compounding issue.”	Polihexanide 0.8 mg/ml is a licensed treatment, indicated to be used as a monotherapy, manufactured to GMP standards and guided by a SmPC and a standardised protocol. Therefore, the context surrounding the use of polihexanide 0.8 mg/ml in real-world practice would be more similar to the ODAK trial setting,	We do not consider there to be a factual error. The EAG acknowledges the company’s point (polihexanide 0.8 mg/ml will be licensed and manufactures to GMP standards), but licensing does not make trial and real-world conditions

unrepresentative due to better trial conditions, the polihexanide 0.8mg/ml arm should be subject to the same criticism since it also benefits from early access and standardisation of protocol, though not the compounding issue.”		although the company acknowledges that use of an intervention in a clinical trial setting will never be the same as in real-world practice. In contrast, the issues associated with use of unlicensed comparators in a real-world setting described above would be removed in the context of a clinical trial, and therefore efficaciousness of these therapeutic approaches would be overrepresented compared to their use in routine clinical practice. The concerns around the generalisability of the effectiveness data for the active comparator arm and polihexanide 0.8 mg/ml are not comparable, as polihexanide 0.8 mg/ml will be the first readily available licensed treatment in this indication.	identical, both arms benefitted from trial conditions. The EAG has amended the sentence, which now reads, “Moreover, one could argue that if the comparator in ODAK is unrepresentative due to better trial conditions, the polihexanide 0.8mg/ml arm could be subject to the same criticism since it also benefits from early access and standardisation of protocol, though not the compounding issue.”
Page 41, Section 3.2.1: The EAG’s description of the reasons for selection a pooled AAT comparator is not accurate and should be revised: “...the CS considered that the active comparator in ODAK was not appropriate, this was informed by findings from a Delphi panel and survey	Please amend the text as follows: “...the CS considered that the effectiveness data from the active comparator arm in ODAK was not appropriate for comparison, ~~this was informed by findings from a Delphi panel and survey conducted in the UK.~~ The Delphi panel was used to source the distribution of treatments used in real-world UK clinical practice and inform the	The Delphi panel did not determine that the pooled AAT was more relevant for the current submission. The Delphi panel was an evidence-generation exercise that, among other topics, was used to determine the distribution of therapeutic approaches currently used in UK clinical practice.	The EAG amended the text to, “the CS considered that the effectiveness data from the active comparator arm in ODAK was not appropriate for comparison. The Delphi panel was used to source the distribution of treatments used in real-world UK clinical practice and inform the composition

conducted in the UK. The Delphi panel considered that a pooled AAT comparator was more relevant for the current submission."	composition of ~~considered that a pooled AAT comparator,~~ which the Company suggests is more relevant representative of the real-world effectiveness of current therapeutic approaches ~~for the current submission."~~	The effectiveness data from the active comparator arm of the ODAK trial were considered inappropriate on the basis of misalignment of treatment protocols used in the trial and how the therapeutic approach is delivered in practice, which likely led to inflated efficacy estimates within the trial, as described above.	of a pooled AAT comparator, which the company suggests is more representative of the real-world effectiveness of current therapeutic approaches."

Issue 2 "Exclusion of ODAK comparator in the ITC"

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 100, Section 3.5.8: The statement describing the comparator included in the ITC is misleading and suggests that polihexanide 0.2 mg/ml + propamidine 1 mg/ml was explicitly not included and/or removed from the pooled AAT comparator chosen. "The company excluded the ODAK comparator arm (polihexanide 0.2mg/ml + propamidine 1 mg/ml) from the ITC, instead comparing the polihexanide 0.8mg/ml + placebo group from ODAK to	Please amend the text as follows: ~~"The company excluded~~ Data from the ODAK comparator arm (polihexanide 0.2mg/ml + propamidine 1 mg/ml) were not considered in ~~from the ITC. Instead comparing the~~ polihexanide 0.8mg/ml + placebo group ~~from ODAK~~ was compared to the pooled/blended AAT cohort from Papa et al. 2020, of which 48.90% of participants received polihexanide 0.2 mg/ml + propamidine 1 mg/ml."	The current statements are not accurate and are misleading, as they imply that polihexanide 0.2 mg/ml + propamidine 1 mg/ml, which the EAG correctly identify as a therapeutic approach used in UK clinical practice (as described in the CS, see Table 3 for Delphi Panel results on the distribution of approaches used in the UK), has been deliberately excluded from the comparative efficacy assessment. This is factually inaccurate, as data for this	We do not consider there to be a factual error. The EAG's position remains that the ODAK comparator was excluded from the ITC, as no efficacy data from this arm were used to inform the company's analysis. Whilst patients receiving polihexanide 0.2 mg/ml + propamidine were included within the pooled AAT cohort from Papa et al. (2020), this does not mitigate the exclusion of the randomised ODAK comparator arm, which is clinically relevant

the pooled/blended AAT cohort from Papa et al. 2020.”		comparator was included as part of the Papa et al. 2020 dataset. A pooled AAT comparator was selected to represent the range of different therapeutic approaches used in UK clinical practice. In Section 4.2.7 (pg. 127), the EAG notes that their “clinical experts consider the AAT distribution based on the Delphi panel appears to be reasonable”, confirming that a range of therapeutic approaches are used in clinical practice. Selecting only polihexanide 0.2 mg/ml + propamidine 1 mg/ml as the relevant comparator is also associated with generalisability concerns (as approximately half of patients receive an alternative intervention, in practice), which are in part addressed by using effectiveness data for all treatment approaches used in UK clinical practice.	and methodologically preferable to retrospective evidence. The EAG amends the sentence to include the proportion of patients in Papa et al. receiving the same regimen. “...Papa et al. 2020, of which 48.90% of participants received polihexanide 0.2 mg/ml + propamidine 1 mg/ml.”
Page 17, Section 1.3: As above, the statement on the comparator included in the ITC is misleading and suggests that polihexanide 0.2 mg/ml + propamidine 1 mg/ml was explicitly not included and/or removed from the pooled AAT comparator chosen: “Additionally, the company contradicts their position by excluding this comparator for not being representative but included it as a current treatment in their economic model with the UK Delphi panel stating that polihexanide 0.2mg/ml + propamidine 1mg/ml	Please amend the text as follows: ~~“Additionally, the company contradicts their position by excluding this comparator for not being representative but included it as a current treatment in their economic model with the UK Delphi panel stating that polihexanide 0.2mg/ml + propamidine 1mg/ml accounts for 52.3% of therapeutic approaches used to treat acanthamoeba keratitis.”~~ “Additionally, the company excludes the active comparator arm data from the ODAK trial, on the basis of the efficacy data this comparator for not being representative of real-world practice. But The company included polihexanide 0.2 mg/ml + propamidine 1 mg/ml as a current treatment in their economic model with the UK Delphi panel stating that polihexanide 0.2mg/ml + propamidine 1mg/ml accounts for 52.3% of therapeutic approaches used to treat acanthamoeba keratitis.”		Not a factual error. However, the EAG clarifies the exclusion being for the ODAK comparator only. “Additionally, the company contradicts their position by excluding the active comparator arm from ODAK for not being representative but included it as a current treatment in their economic model with the UK Delphi panel stating that polihexanide 0.2mg/ml + propamidine 1mg/ml accounts for 52.3% of therapeutic approaches

accounts for 52.3% of therapeutic approaches used to treat acanthamoeba keratitis.”			used to treat acanthamoeba keratitis.”

Issue 3 “Validity of the company’s indirect treatment comparison”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 109, Section 3.5.14: The statement implies the publication was provided to the EAG to provide clarification/new analyses, which was not the case: “The publication introduced no substantive new analyses beyond those provided in the CS, and while a few limitations were discussed, some key issues were not”.	Please remove this sentence from the report.	The ITC publication was provided as a published reference to accompany the ITC results presented in the CS. The intention was not to provide further analyses or to address previous requests; removal of this sentence would remove the implication that a request from the EAG was ignored.	As requested, we have removed this sentence.
Page 82, Section 3.4: The EAG’s concern described below does not consider the results from company-provided sensitivity analyses stated in a later section: “This creates substantial concern around temporal bias as clinical practice, diagnostic	Please amend the text as follows: “This creates substantial concern around temporal bias as clinical practice, diagnostic technologies, treatment protocols, and patient monitoring have all evolved significantly, limiting the relevance of historical comparators to current practice. Nevertheless, the company provided sensitivity analyses excluding data from Papa et al. 2020 prior to 2000 or 2005,	The amendment is justified as the EAG’s comment does not appear proportionate with the conclusion of the analyses provided on this issue and the EAG’s own assertions reported later in the report, in Section 3.5.13.	The EAG amended the text, which now reads, “This creates substantial concern around temporal bias as clinical practice, diagnostic technologies, treatment protocols, and patient monitoring have all evolved significantly, limiting the relevance of historical

technologies, treatment protocols, and patient monitoring have all evolved significantly, limiting the relevance of historical comparators to current practice.”	with results consistent with the base case ITC, indicating a robust and stable finding across time (see Section 3.5.13).”		comparators to current practice. Nevertheless, the company provided sensitivity analyses excluding data from Papa et al. 2020 prior to 2000 or 2005, with results consistent with the base case ITC, indicating a robust and stable finding across time (see Section 3.5.13).”
Page 108, Section 3.5.14: The EAG’s assertion that the distribution of therapeutic approaches in Papa et al. 2020 is not reflective of current practice is misleading: “Pooling them masks clinically relevant variation, diluting the contribution of the most common regimen (PHMB + diamidine), and creates an artificial comparator arm that is not reflective of specific treatments used in practice.”	Please remove the sentence.	Papa et al. 2020 represents the largest observational study of clinical outcomes in AK to date, with N=227 patients, over half of whom were from the UK (n=177). For a very rare disease, with an estimated incidence of 0.1175 cases per 50,000 people per year, Papa et al. 2020 represents a valuable real-world dataset, including participants from the UK. Therefore, the assertion that the study is “not reflective of specific treatments used in practice” is not founded. While the company acknowledges that data from Papa et al. 2020 were collected during an earlier time period than the ODAK trial, the distribution of therapeutic approaches reported in the study was similar to that reported in current UK clinical	Not a factual error. However, to avoid the impression that Papa is not representative, the EAG added the following sentence to the beginning of this paragraph: “While Papa et al. (2020) reflects the overall distribution of therapeutic approaches in practice, pooling...”

		practice by ophthalmologists in the SIFI-conducted 2023 Delphi panel.	

Issue 4 “Mean time-on-treatment used from Franch et al. 2024”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 137, Section 4.2.18: “First, the sample size in the Franch et al 2024 study is too small (n=11) to be generalisable to determine the treatment duration required to treat AK with polihexanide 0.8mg/ml in practice.”	Please amend the text as follows: “First, the sample size in the Franch et al 2024 study is too small (n=11) to be generalisable to determine the treatment duration required to treat AK with polihexanide 0.8mg/ml in practice. Although, AK is a very rare disease and so large sample sizes for a real-world compassionate use programme are likely unfeasible.”	The company acknowledges that the sample size of the Franch et al. 2024 is small but believe that the context of AK being a very rare disease is critical for a fair assessment of the evidence.	The EAG do not consider this to be an inaccuracy, but we have amended to provide further context. The text now reads, “First, the sample size in the Franch et al 2024 study is too small (n=11) to be generalisable to determine the treatment duration required to treat AK with polihexanide 0.8mg/ml in practice. Although, AK is a very rare disease and so large sample sizes for a real-world compassionate use programme are likely unfeasible.”

Issue 5 “AK recurrence may occur in people treated with polihexanide 0.8mg/ml”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 20, 1.1: The EAG’s assumptions are not supported by currently available evidence of polihexanide 0.8 mg/ml and other AATs: “...the EAG made a conservative assumption that the same proportion of people who experienced AK recurrence when treated with pooled AAT would experience AK recurrence when treated with polihexanide 0.8mg/ml.”	“...the EAG made a conservative assumption that the same proportion of people who experienced AK recurrence when treated with pooled AAT would experience AK recurrence when treated with polihexanide 0.8mg/ml. However, no evidence is currently available to support that recurrence occurs in individual treatment with polihexanide 0.8 mg/ml”	The company understand that the EAG conducts exploratory scenario analyses to look at the impact of different inputs, however, for clarity we feel it is important to add the caveat that there is no evidence currently available to support recurrence occurring in patients treated with polihexanide 0.8 mg/ml, while there is evidence to show this does occur in patients treated with other AATs.	The EAG does not consider there to be a factual inaccuracy. In the report, we stated that ‘Given the lack of long-term information, the EAG made a conservative assumption...’

Issue 7 “Patient and carers disutilities associated with the intensive treatment period with polihexanide 0.8mg/ml”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 21, Section 1.1: The EAG’s comment about the daytime only treatment regimen is speculative and does not align with the posology of	Please amend the text as follows: “...on the basis that polihexanide is administered at daytime only and does not lead to sleep deprivation. Clinical advice to the EAG indicates would not treat AK with daytime only medication even with high	According to the MHRA and EMA SmPC’s, the posology for polihexanide 0.8 mg/ml in the intensive phase is as follows: “Intensive 19-day treatment phase:	The EAG amended the text to include regulatory label. The text now reads, “...on the basis that polihexanide is administered at daytime only and does not lead to sleep deprivation. Clinical advice

polihexanide 0.8 mg/ml, as stated in the MHRA SmPC: “...on the basis that polihexanide is administered at daytime only and does not lead to sleep deprivation. Clinical advice to the EAG indicates would not treat AK with daytime only medication even with high concentration of polihexanide, implying patient and caregivers’ disutility should be applied to treatment with polihexanide 0.8mg/ml.”	concentration of polihexanide, despite the published treatment schedule in the MHRA and EMA SmPCs, implying; in an exploratory analysis, patient and caregivers’ disutility ~~should be~~ was applied to treatment with polihexanide 0.8mg/ml.”	• 16 times a day at 1-hour intervals, daytime only, for five days • 8 times a day at 2-hour intervals, daytime only, for further seven days • 6 times a day at 3-hour intervals, daytime only, for further seven days” The clinical advice appears to be speculative and in direct contradiction to the regulatory label for polihexanide 0.8 mg/ml, which was developed based on evidence from the clinical development programme for polihexanide 0.8 mg/ml.	to the EAG indicates would not treat AK with daytime only medication even with high concentration of polihexanide, despite the published treatment schedule in the MHRA and EMA SmPCs; in an exploratory analysis, patient and caregivers’ disutility was applied to treatment with polihexanide 0.8mg/ml.”
Page 135, Section 4.2.17: As above, the EAG’s comment does not align with the posology of polihexanide 0.8 mg/ml, as stated in the MHRA SmPC: “Clinical advice to the EAG indicates they will not treat AK with daytime only medication even with high concentration of polihexanide, implying a caregivers’ disutility should be applied to treatment with polihexanide 0.8mg/ml.”	Please amend the text as follows: “Clinical advice to the EAG indicates they will not treat AK with daytime only medication even with high concentration of polihexanide, despite the published treatment schedule in the MHRA and EMA SmPCs; implying in an exploratory analysis, a caregivers’ disutility ~~should be~~ was applied to treatment with polihexanide 0.8mg/ml.”		The text has been amended as requested.

Issue 8 “People treated with polihexanide 0.8mg/ml may require hospitalisation”

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 22, Section 1.4: The EAG’s comment with regards to the daytime only treatment regimen is speculative and does not align with the posology of polihexanide 0.8 mg/ml, as stated in the MHRA SmPC: “In the opinion of our clinical experts some people commencing treatment with polihexanide 0.8mg/ml are likely to be hospitalised because they will not treat AK with daytime only medication even with high concentration of polihexanide.”	Please amend the text as follows: “In the opinion of our clinical experts some people commencing treatment with polihexanide 0.8mg/ml are likely to be hospitalised because they will not treat AK with daytime only medication even with high concentration of polihexanide, despite the published regulatory label of polihexanide 0.8 mg/ml and recommended daytime only posology.” When discussing hospitalisation requirements for polihexanide 0.8mg/ml, please include all relevant details, such as treatment recommendations included in the SmPC, clinical trial protocol, and current use of polihexanide 0.8mg/ml in clinical practice.	The current phrasing in the EAG report disregards the fact that nighttime treatment (and therefore hospitalisation associated with nighttime treatment) during the intensive phase of treatment with polihexanide 0.8 mg/ml goes against recommendations detailed in the SmPC. Section 4.2 of the SmPC explicitly states all administrations in the intensive phase should be during daytime only (as noted for Key Issue 7). Further, the ODAK trial protocol stipulated daytime administration only. This protocol has subsequently been supported by the use of polihexanide 0.8mg/ml in clinical practice, reported by Franch et al. 2024, which notes “no administration during the night was required”. Further, in NICE’s resource impact assessment, the assumption of hospitalisation for pooled AAT but not for polihexanide 0.8 mg/ml was supported.	The EAG do not consider this a factual inaccuracy but have amended the text for further clarity. The text now reads, “In the opinion of our clinical experts some people commencing treatment with polihexanide 0.8mg/ml are likely to be hospitalised because they will not treat AK with daytime only medication even with high concentration of polihexanide, despite the published regulatory label of polihexanide 0.8 mg/ml and recommended daytime only posology.”
Page 31, Section 2.2: As above, the EAG’s comment does not align with the posology of polihexanide 0.8 mg/ml, as stated in the MHRA SmPC: “Advice to the EAG suggests that at the present time it is	Please amend the text as follows: “Advice to the EAG suggests that at the present time it is unlikely that centres would administer polihexanide during the daytime-only, even at the 0.8mg/ml dose, despite the published regulatory label of polihexanide 0.8 mg/ml and recommended daytime only posology.”		The text has been amended as requested.

unlikely that centres would administer polihexanide during the daytime-only, even at the 0.8mg/ml dose."			
Page 42, Section 4.2.20: As above, the EAG's comment does not align with the posology of polihexanide 0.8 mg/ml, as stated in the MHRA SmPC: "Clinical advice to the EAG indicates they will never commence treatment for AK with daytime only regimen in the intensive phase even with a higher dose of polihexanide. And so, it is thought that even patients who might receive polihexanide 0.8mg/ml will be hospitalised."	Please amend the text as follows: "Clinical advice to the EAG indicates they will never commence treatment for AK with daytime only regimen in the intensive phase even with a higher dose of polihexanide, despite the published regulatory label of polihexanide 0.8 mg/ml and recommended daytime only posology. And so, it is thought that even patients who might receive polihexanide 0.8mg/ml will may be hospitalised."		The text has been amended as requested on page 142, Section 4.2.20.

Section 2: Other factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 29 and 30, Section 2.2: The EAG clinical expert's position is not representative of	We would suggest the sentence in removed from the report, given its inaccuracy relative to the current availability of therapeutic approaches in the UK.	As described in response to Key Issue 1 above, the company would like to restate that a major UK manufacturer of two of the therapeutic approaches currently	This is the opinion of the EAG's experts and not a factual inaccuracy.

the current position in UK clinical practice: “However, the EAG clinical experts suggested 48 hours is the maximum delay in their centres, with up to three to five days maximum as an exception. The EAG experts also noted that regional pharmacies can keep a stock of polihexanide to avoid treatment delays.”		used to treat AK (polihexanide [0.2 mg/ml and 0.6 mg/ml] and chlorhexidine) has recently had its license revoked. Information received by SIFI from centres in the UK, suggests that availability of these therapeutic approaches has been severely impacted, meaning that the EAG clinical expert’s comments on regional pharmacies keeping a stock, is no longer accurate. This recent update further questions the stability and quality of manufacturing processes for currently used therapeutic approaches in the UK. As 0.8 mg/ml polihexanide would be manufactured and supplied by SIFI, this is likely to be the only viable option for patients with AK for the foreseeable future. The company would be grateful if the EAG could confirm whether their position on the appropriate comparator for the evaluation of polihexanide 0.8 mg/ml still stands, given the current situation in which polihexanide 0.2 mg/ml + propamidine is neither licensed for use in AK or commercially available to centres across the UK.	

Page 32, Section 2.2: The EAG's statement is factually inaccurate and does not reflect the currently available evidence for polihexanide 0.8 mg/ml: "The EAG clinical experts also highlight that this concentration has not been used in UK practice and caution that higher concentrations may cause corneal scarring and inflammation. [...]"	Please amend the text as follows: "The EAG clinical experts also highlight that this concentration has not been used in UK practice and caution that higher concentrations may cause corneal scarring and inflammation. The company notes that polihexanide 0.8 mg/ml has been used in routine clinical practice in the context of the compassionate use programme in the UK, presented within the CS. [...]	The EAG's statement that polihexanide 0.8 mg/ml has not been used in UK clinical practice is factually inaccurate and disregards the fact that some patients in the UK have received polihexanide 0.8 mg/ml in routine clinical care, as part of the company's compassionate use programme.	Not a factual inaccuracy. This is the opinion of the EAG clinical experts, additionally there is no supporting evidence in the CS to confirm compassionate use in UK clinical practice. The CS cites two publications of data from the CUP (discussed in EAG sections 3.6 and 4.2.18 respectively) and these are not from the UK. Additionally, the CS states in Section 2.12 that "A full dataset from the CUP is only available for a small number of cases currently and therefore has not been described in detail here "
Page 32, Section 2.2: The EAG's comment ignores the available evidence on the safety of polihexanide 0.8 mg/ml from the Phase I dose-escalation study and Phase III ODAK trial: "EAG expert opinion supports the need for a licensed treatment but raise concerns	Please amend the text as follows: "EAG expert opinion supports the need for a licensed treatment but raise concerns about potential safety implications of higher concentrations, and assumptions regarding treatment delays and burden reduction. The company's Phase I dose-escalation trial compared safety outcomes (dose-limiting events i.e. all SAEs and AEs that prompted interruption of the study drug)	The safety profile of polihexanide 0.8 mg/ml has been studied in the Phase I dose-escalation study and the multinational Phase III ODAK trial, the results of which are presented in the CS and in further detail in the CSR provided to the EAG. As such, the "potential safety implications" are known and have been described by the company in its reporting.	This is not a factual inaccuracy as this accurately reports the opinions of the EAG clinical experts, who expressed concerns about potential safety implications of higher concentrations. However, the company is correct that Phase I and ODAK trial data did not identify major safety

about potential safety implications of higher concentrations, and assumptions regarding treatment delays and burden reduction.”	between polihexanide 0.2 mg/ml, 0.4 mg/ml and 0.8 mg/ml. No SAEs occurred in any dose group. The safety profile of polihexanide 0.8 mg/ml was also established in the Phase III ODAK clinical trial programme, in which the overall rates of Aes and severe Aes were similar between polihexanide 0.8 mg/ml and polihexanide 0.2 mg/ml + propamidine 1 mg/ml and the majority of Aes were mild or moderate in severity.”	Given the importance of patient safety, statements on the safety of polihexanide 0.8 mg/ml should be informed by available trial evidence as opposed to expert opinion, which is typically considered to be a less robust form of evidence. The company would also like to note a contradiction in the clinical expert opinion with regards to the treatment schedule and safety of higher concentrations of polihexanide. On one hand, the experts report that they would “never commence treatment for AK with daytime only regimen in the intensive phase even with a higher dose of polihexanide” and therefore they assume patients would be hospitalised. On the other hand, they express concern about the “potential safety implications” of polihexanide 0.8 mg/ml. Administering polihexanide 0.8 mg/ml during the nighttime (against the daytime-only posology noted in the MHRA and EMA regulatory labels), as suggested by the EAG’s experts, would necessarily mean increasing the recommended	concerns with 0.8 mg/ml. To ensure balance the EAG has added the company’s amended text.

		dose, which by the same logic would increase safety concerns. The company's view is that polihexanide 0.8 mg/ml should be assessed based on the thorough safety data collected in the Phase III multinational trial and the administration schedule should align to those approved by the European and UK medicines regulators.	
Page 74, Section 3.3.1: The EAG's suggestion is speculative and does not reflect the reasons that the SAEs were categorized: "The EAG notes that the retrospective reclassification of SAEs using CIOMS criteria may suggest that some serious harm may have been underestimated at the time of analysis"	The company suggests that this sentence is removed from the report.	SAEs were reclassified using the CIOMS criteria, following a request from EMA to align to their preferred classification system, which considers a greater number of preferred terms as SAEs. The reclassification of Aes led to four severe Aes being reclassified as serious; no further Aes from ODAK would be categorised as serious under the classification used in the ODAK trial SAP or using the CIOMS. Therefore, we would request that the speculative sentence about why this reclassification was performed, is removed or updated to reflect that this was simply a result of a request from EMA, for their assessment.	The EAG has reworded this to state... "The EAG notes that AEs were reclassified post hoc using CIOMS criteria at the request of the EMA, in order to align with their classification system, which designates a broader range of preferred terms as serious. The EAG considers that while this change reflects differences in classification approach rather than new safety signals, it highlights the potential for underestimation of serious harm depending on the criteria applied."

Section 3: typographical and data errors

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 62, Section 3.3.1, Table 11 “EQ-5D-5L VAS: Mean change (n = number assessed/number missing)”	17.9 (SD 19.6) (n = 60/ ~~65~~) ^a	Data error	Thank you, we have amended.
Page 62, Section 3.3.1, Table 11 “EQ-5D-5L VAS: Mean change (n = number assessed/number missing)”	18.8 (SD 20.0) (~~n=52/9~~)	Addition of missing data to align to the reporting style of the intervention arm data	Thank you, we have included the additional information.
Page 67, Section 3.3.1	In the polihexanide 0.8mg/ml arm, mean LogMAR improved from 0.47 to 0.19 (mean change: -0.293 SD ~~0.326~~ ~~0.469~~), and in the polihexande 0.2mg + propamidine 1mg/ml arm from ~~0.47~~ ~~0.36~~ to ~~0.22~~ ~~0.10~~ (mean change -0.251 SD 0.326)	Data error	Thank you, we have amended.
Page 69, Section 3.3.1	In the polihexanide 0.8mg/ml arm ulceration reduced from 27.3% at baseline to 6.1% by the end of the study, and in the polihexanide 0.2mg/ml + propamidine 1mg/ml comparator arm, ulceration reduced from ~~24.3~~ ~~26.2~~ % to 4.9% (Table 11), with no statistically significant differences observed between groups (OR: 1.09 (95% CI: 0.22 to 5.47, P = 0.917).	Data error	

Page 70, Section 3.3.1	In the active comparator arm, the number of patients ~~of~~ with no inflammation increased from 72.1% to 82% (P = ~~0.004~~ 0.01).	Data and typographical error	
Page 85, Section 3.4.3, Table 15	- PHMB + diamidine (~~42%~~ 25%) - PHMB monotherapy (~~28%~~ 48%)	Data error	
Page 97, Section 3.5.5	Furthermore, 40/227 patients (17.6%) were introduced to adjunctive oral immunosuppressants after baseline and ranged from ~~4%~~ 11% in the PHMB monotherapy + diamidine group to ~~15.8%~~ 26% in the other AAT groups combined PHMB monotherapy group.	Data error	
Page 99, Section 3.5.6	~~33.2~~ 33.5 (15.0, 73.0)	Data error	
Page 137, Section 4.2.18	~~110days~~ 101 days	Data error	We have accepted these amendments and updated in the EAG report.
Page 150, Section 4.2.23	After a graft failure some patients undergo some procedures. A one-off cost of ~~£888.60~~ £899.60 was applied in the model.	Data error	
Page 155, Section 4.2.25	This was justified with a rationale that in the ODAK study, AEs occurred at a similar frequency in both arms (~~49%~~ 44.9% in the polihexanide 0.8mg/ml arm and 44.6% in the active comparator arm), hence the impact of AEs on result is negligible.	Data error	

Page 160, Section 5.1.3, Table 50	~~47.30~~ 17.31	Data error	
Page 167, Section 5.1.5, Table 52	██████	Data error	

Section 4: Incorrect confidentiality marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Page 30, Section 2.2	“The company does not state what proportion of patients would not be cured, but the EAG believes that in the Delphi report the estimates provided suggest that ██████ of all AK patients would not be cured,”	“The company does not state what proportion of patients would not be cured, but the EAG believes that in the Delphi report the estimates provided suggest that 41.9% of all AK patients would not be cured,”	As recommended by the company, the EAG has amended the confidentiality marking.
Page 62–63, Section 3.3.1, Table 11 “EQ-5D-5L: Least squares (90% CI)” & “EQ-5D-5L: Pain/discomfort dimension n (%)”	████████████████████ No pain or discomfort = ██████^a Slight pain or discomfort = ██████^a Moderate pain or discomfort = ██████^a Severe pain or discomfort = ██████^a Extreme pain or discomfort = ██████^a	Please remove confidentiality highlighting:	

		1.34 (1.20 to 1.48) ^a No pain or discomfort = 41 (63.1) ^a Slight pain or discomfort = 14 (21.5) ^a Moderate pain or discomfort = 3 (4.6) ^a Severe pain or discomfort = 0 (0) ^a Extreme pain or discomfort = 0 (0) ^a	
Page 62–63, Section 3.3.1, Table 11 “EQ-5D-5L: Least squares (90% CI)” & “EQ-5D-5L: Pain/discomfort dimension n (%)”	No pain or discomfort = Slight pain or discomfort = Moderate pain or discomfort = Severe pain or discomfort = Extreme pain or discomfort =	Please remove confidentiality highlighting: 1.38 (1.23 to 1.53) No pain or discomfort = 37 (60.7) Slight pain or discomfort = 10 (16.4) Moderate pain or discomfort = 3 (4.9) Severe pain or discomfort = 1 (1.6) Extreme pain or discomfort = 0 (0)	
Page 63, Section 3.3.1, Table 11 “VFQ-25 mean ocular pain score (SD)”		Please remove confidentiality highlighting:	

		86.8 (17) ^a	
Page 63, Section 3.3.1, Table 11 “VFQ-25 mean ocular pain score (SD)”	██████████	Please remove confidentiality highlighting: 88.8 (19.5)	
Page 129, Section 4.2.9, Table 25 “Mortality rates HR vs general population”	██████████	Please remove confidentiality highlighting: 1.23 (1.16, 1.31)	
Page 129, Section 4.2.9, Table 25 “Mortality rates HR vs general population”	██████████	Please remove confidentiality highlighting: 1.54 (1.28, 1.86)	
Page 131, Section 4.2.13, Table 26 “Health state disutility for loss of eye functionality”	████	Please remove confidentiality highlighting: -0.248	
Page 159, Section 5.1.3	The results from the CEAC show that at a willingness-to-pay threshold of £30,000 per QALY, treatment with polihexanide 0.8mg/ml has a █████ probability of being cost-effective when compared to pooled AAT.	Please add confidentiality highlighting: The results from the CEAC show that at a willingness-to-pay threshold of £30,000 per QALY, treatment with polihexanide 0.8mg/ml has a █████ probability of being cost-effective when compared to pooled AAT.	