Medicinrådet

Bilag til Medicinrådets vurdering af polihexanid til behandling af akanthamøbe keratitis

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. polihexanid
2. Forhandlingsnotat fra Amgros vedr. polihexanid
3. Ansøgers endelige ansøgning vedr. polihexanid

31 March 2026

Avanzanite Bioscience's comments on the draft assessment by the DMC regarding polihexanide (AKANTIOR) for the treatment of *Acanthamoeba* Keratitis

Avanzanite Bioscience appreciates the opportunity to comment on the draft assessment (Draft) by the Danish Medicines Council (DMC) of polihexanide (AKANTIOR), an orphan medicinal product, for the treatment of *Acanthamoeba* keratitis (AK) in adults and children from 12 years of age. AKANTIOR is the first and only medicinal product authorised for AK. AK is an ultra-rare and severe parasitic eye infection which – if not treated effectively and promptly – leads to irreversible visual loss, repeated corneal transplantations and even removal of the eye.

While we have broader comments on the draft assessment, we have intentionally limited our response to the critical issues with the greatest relevance to patient access, cost-effectiveness, and budget impact. In the same spirit of constructive engagement, and with the shared objective of securing patient access on responsible terms, we also refer to our confidential financial proposal to AMGROS submitted via email on 24 March 2026, which includes:

- a confidential rebate on the list price (net price); and
- an annual budget cap designed to provide financial predictability at regional level.

1. Ensuring access to the only authorized medicine for AK

As stated in the Draft, following the decision by the Danish Medicines Agency (DKMA) dated 7 November 2025, propamidine no longer qualifies for a compassionate use permit. In addition, the DKMA pointed out that the Court of Justice of the European Union has a strict line of case law regarding hospital pharmacies preparing and using magistral medicinal products such as chlorhexidine when a marketed alternative, such as AKANTIOR, exists. In practical terms, this means that if AKANTIOR is not recommended, Danish patients would be left without any authorised medical treatment for AK. The only remaining pathway would be therapeutic corneal transplantation, with half of the transplants failing within two years (Veugen et al. 2023). To the extent that individual compassionate use permits might be granted on a case-by-case basis, this would inevitably lead to fragmented and unequal access across regions, with the additional cost and complexity associated with sourcing unlicensed products through intermediaries.

Importantly, the Draft itself recognises two key points:

1. AKANTIOR effectively cures Acanthamoeba infection in 85% of patients within one year.
2. The draft assumes that more patients, if relying on therapeutic corneal transplantation to eradicate the pathogen, will experience significant vision loss in the affected eye compared to patients cured with AKANTIOR.

These points go to the heart of the decision. This is not a case in which the Council is being asked to fund a marginal innovation in a crowded treatment landscape. It is a case in which Denmark now can have access to the only authorised medicinal product for a rare, severe and sight-threatening infection, and the relevant alternative is, in essence, reliance on surgery which is associated with a high failure rate, significant vision loss and impact on patients' life. A recommendation that ensures access to AKANTIOR is therefore in the interest of patients, the DMC, Danish regions, DKMA, and the healthcare system.

2. Cost-effectiveness analysis: the remaining uncertainty can be resolved in a practical way

We recognise and respect the DMC's responsibility to address uncertainty conservatively. It is in that same spirit that Avanzanite has sought to engage pragmatically with both the DMC and AMGROS, focusing on the assumptions that matter most and proposing concrete financial mechanisms to

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mitigate residual uncertainty. To remain focused, our request for reconsideration is limited to two assumptions that are particularly important and for which there is support in the available evidence.

3. Requested revisions of DMC's cost effectiveness analysis (CEA)
Avanzanite is confident that, in real-world clinical practice, patients treated with AKANTIOR will require no more than an average of 17 packs. While we acknowledge the DMC's rationale for referencing the ODAK study and applying a more conservative assumption of 21 packs, we believe this likely overestimate actual usage. The original Avanzanite cost-effectiveness analysis applied an average of 17 packs, consistent with published real-world evidence, including Franch et al 2024. Building on this evidence, and in line with the Financial Proposal submitted to AMGROS, we propose that decision-making should be anchored in this validated real-world estimate.

Furthermore, the Draft base case applies a 3% relapse rate after cure with AKANTIOR in year 1. However, as the Draft itself notes, that assumption is not supported by direct clinical data for AKANTIOR. By contrast, available evidence supports an assumption of no relapse after cure with AKANTIOR.
First, no relapse was recorded in any of the AKANTIOR-treated patients in the ODAK trial within 90 days after stopping treatment with AKANTIOR as clearly described in the Ophthalmology Journal (Dart et al. 2024). Second, the same paper does not report relapses within longer follow-up. Thirdly, no confirmed relapses have been reported in patients treated with AKANTIOR in real-world practice.

We therefore request that the DMC revises its CEA by applying the following in the new base case used for DMC decision-making:

- a 0% relapse rate in year 1 for patients cured with AKANTIOR
- 17 packs per patient needed for the treatment with AKANTIOR
- the confidential net price proposed to AMGROS

This would not remove all uncertainty, but it would align the decision with the best available evidence while incorporating concrete financial mechanisms to protect the healthcare system. Avanzanite has deliberately structured its proposal to give the DMC and the regions the tools to manage any residual risk.

4. Budget impact
Avanzanite is confident, based on the review of epidemiological data and clinician input, that it is highly unlikely that in any given year there will be more than 15 patients requiring AKANTIOR for AK. The Draft assumes 35 patients, which very likely overestimates actual annual prevalence. The estimate of the budget impact should consider the reduced net price, the 17 packs per patient and the annual prevalence of 15 patients with AK per year. In fact, the proposed budget cap submitted in the Financial Proposal to AMGROS uses exactly these inputs to define the annual budget cap above which Avanzanite will supply any additional packs free of charge. This structure has been developed in close dialogue with AMGROS and is designed to provide the regions with a high degree of budget certainty.

Conclusion
Patients with AK have relied for too long on unlicensed and off-label treatment options with uncertain efficacy, uncharacterised safety, uncertain product quality and burdensome administration. A negative recommendation would not eliminate the need for treatment; it would simply return Danish patients to a fragmented landscape of compassionate use permits, with unequal access across regions and the attendant costs and risks that entails. We recognise the DMC's responsibility to address uncertainty prudently. Avanzanite has gone to considerable lengths to accommodate the concerns of both the DMC and AMGROS – through price reductions, pack caps, patient caps and an annual budget cap – because we share the conviction that making AKANTIOR available to Danish patients on sustainable terms is in the interest of all parties. For these reasons, we respectfully ask the DMC to revise its decision-making base case in line with the best available evidence and the financial safeguards proposed, and to support a positive recommendation for AKANTIOR – ensuring that Danish patients have equal and timely access to the only authorised treatment for this severe condition.

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31.03.2026

MBA/LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.04.2026
Leverandør	Avanzanite Bioscience B.V.
Lægemiddel	Akantior (polihexanide)
Ansøgt indikation	Polihexanid er indiceret til behandling af Akanthamøbe-keratitis hos voksne og børn i alderen fra 12 år.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende priser på Akantior (polihexanide):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Alternativ aftale SAIP (DKK) Tilbud 1	Betinget, flad rabat SAIP (DKK) Tilbud 2	Ubetinget, flad rabat SAIP (DKK) Tilbud 3
Akantior	0,8 mg/ml, 30x0,3 ml	96.689,89	[redacted]	[redacted]	[redacted]
Forhandlet rabat ift. AIP			[redacted]	[redacted]	[redacted]

Prisen, for tilbud 1 og tilbud 2, er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Akantior, indkøbes lægemidlet til prisen i tilbud 3.

Aftaleforhold

Amgros vil indgå en aftale på Akantior som tidligst kan gælde fra [redacted]
Leverandøren har mulighed for at sætte prisen ned i hele aftaleperioden.

Leverandøren har tilbudt tre forskellige pristilbud, som beskrives nedenfor. Aftaleperioden vil være den samme uanset hvilket pristilbud der vælges.

Pristilbud 1 – betinget, alternativ aftale:

Leverandøren tilbyder en rabatteret pris [redacted]

Prisen er betinget af en anbefaling af Medicinrådet.

Pristilbud 2 – betinget, flad rabat:

Leverandøren tilbyder en pris med en flad rabat på [redacted] Prisen er betinget af en anbefaling af Medicinrådet.

Pristilbud 3 – ubetinget, flad rabat:

Leverandøren tilbyder en pris med en flad rabat på [redacted] Prisen er ikke betinget af en anbefaling af Medicinrådet.

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Der findes ingen anbefalet standardbehandling for akantamøbe keratitis i Danmark. Der har tidligere i dansk klinisk praksis været anvendt 0,02 % klorhexidin i kombination med 0,1 % propamidin som behandling. Patienter, der ikke modtager medicinsk behandling vil blive tilbudt hornhindetransplantation, for at redde øjet fra akanthamøbe infektionen.

Tabel 2 viser lægemiddeludgiften for Akantior for et behandlingsforløb for hvert af de tre pristilbud. I følge produktresumeet doseres Akantior således:

- 16 gange dagligt med 1 times intervaller, kun i dagtimerne, i fem dage.
- 8 gange dagligt med 2 timers intervaller, i yderligere syv dage.
- 6 gange dagligt med 3 timers intervaller, i yderligere syv dage.
- Vedligeholdelsesbehandling af 4 doseringer dagligt med 4 timers interval

Behandlingslængden af et behandlingsforløb er 126 dage svarende til 18 ugers behandling, jf. Medicinrådets vurdering af polihexanid til behandling af akanthamøbe keratitis. Akantior gives som øjendråber.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient pr. behandlingsforløb

Pristilbud	Lægemiddel	Styrke (pakning s-størrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandlingsforløb (SAIP, DKK)
1	Akantior	0,8 mg/ml, 0,3 ml x 30 stk.	Doseres som beskrevet ovenfor, [redacted]	[redacted]	[redacted]
2	Akantior	0,8 mg/ml, 0,3 ml x 30 stk.	Doseres som beskrevet ovenfor, et behandlingsforløb er 126 dage	[redacted]	[redacted]
3	Akantior	0,8 mg/ml, 0,3 ml x 30 stk.	Doseres som beskrevet ovenfor, et behandlingsforløb er 126 dage	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Ikke ansøgt	-
England	Under vurdering	Link til status
Sverige	Under vurdering	Link ikke tilgængeligt

Opsummering

Leverandøren har tilbudt en alternativ aftale der adresserer nogen af de væsentligste usikkerheder i vurderingsrapporten.

[redacted]

[redacted]

Medicinrådet

Instructions for companies

This is the template for submitting evidence to the Danish Medicines Council (DMC) as part of the appraisal process for a new medicinal product or a new indication for an existing medicine. The template is not exhaustive.

Please note the following requirements:

- When preparing their application, companies must adhere to the current version of the DMC's methods guide.
- Always use the current (latest updated) version of this template downloaded from the DMC's website.
- Headings, subheadings and appendices must not be removed. Tables must not be deleted or edited, unless it is explicitly stated in the text.
- Text in grey and [in brackets] is only for example purposes and must be deleted.
- All sections in the template must be filled in. If a section or an appendix is not applicable, state "not applicable" (N/A) and explain why.
- The main body of the application must not be longer than 100 pages (including the title page, contact information and references – excluding appendices).
- The formatting is not to be altered and all cross-references must work.
- All applications must comply with the general data protection regulations, find more information on DMC's data policy here.
- Submissions in either Danish or English are accepted.

The assessment process cannot be initiated before all the requirements are met.

Documentation to be submitted

The following documentation must be sent to the DMC's email medicinraadet@medicinraadet.dk:

- Application in word format*
- Application in PDF format*
- Health economic model including budget impact model in one Excel file, with full access to the programming code. The model must include relevant sheets from the DMC Excel template 'Key figures including general mortality' available on the DMC's website.
- The European Public Assessment Report (EPAR) should be submitted. Send a draft version if the final one is not published at the time of submission, and send the final version as soon as possible.

Confidential information and blinding

The Danish Medicine Council publishes the application (including attachments) on the website together with the recommendation.

The applicant has the option to blind any confidential information in the application incl. appendices.

The application and paper/appendices

If there is confidential information in the application or note/appendices, the company must submit two versions of both the application and note/appendices:

- a version for the DMC's case processing, where the confidential information is marked with yellow marking.

- a version for publication on the DMC's website, where the confidential information is blinded with black marking. The DMC publishes this version.

It is the pharmaceutical companies that must ensure that the blinding is sufficient, so that the confidential information cannot be read when the document is edited.

Therefore, the applicant must ensure that the confidential information is sufficiently redacted blinded for publication on the DMC's website. This can be done, for example, by covering the text/information to be redacted with a black marker simultaneously replacing the underlying text with crosses ("XXX"), so that the text/information cannot be read when editing the document.

Read about redaction of confidential information on the DMC's website.

About macros in Excel

Due to IT security requirements, Excel files containing macros must be authorized and signed by the applicant before being submitted to the DMC. Find more information here.

Version log

Version log		
Version	**Date**	**Change**
2.5	10 September 2024	Section 3.4 and 3.4.1: new information regarding ATMP (Advanced Therapy Medicinal Products). Section 6.1.1 and 8.1: Updated text regarding data-cut. Section 4, 8, 10 and 12: Clarification regarding cost-minimization analysis.
2.4	5 July 2024	Section 11: Clarification in the text regarding costs and changes in the tables 26 and 30.
2.3	1 June 2024	Clarification regarding redaction of confidential information, clarification regarding EPAR, clarification regarding literature search and changes in the text regarding costs. New information about Joint Nordic assessments has been added.
2.2	3 November 2023	'Pharmaceutical' is exchanged with 'medicine'. Tabel 26 is new.
2.1	1 September 2023	Section 4.2: Updated information about discount rate (The DMC applies a discount rate of 3.5 % for all years) Section 10.1.3: Clarification regarding EQ-5D-5L and Danish preference weights Section 11.1: Updated information about Excel sheet 'Key Figures'
2.0	15 June 2023	New application template
1.3	6 December 2022	Clarification regarding new IT security requirements concerning macros in Excel files has been added, see page 1.
1.2	20 June 2022	Clarification of the introduction, including instructions on how to complete the form.
1.1	9 February 2022	Appendix K and onwards have been deleted (company-specific appendices)

Version log		
		Color scheme for text highlighting table added after table of contents Section 6: Specific requirements for literature search Section 7: Stated it explicitly that statistical methods used need to be described Section 8.3.1: Listed the standard parametric models Section 8.4.1: Added the need for description of quality of life mapping Appendix A: Specified that the literature search needs to be specific for the Danish context and the application Appendices B and D: Stated it explicitly that statistical methods need to be described in the tables in the appendices
1.0	27 November 2020	Application form for assessment made available on the website of the Danish Medicines Council.

Application for the assessment of Akantior for Acanthamoeba keratitis

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

Contact information	
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Tables and Figures

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Tables

Abbreviations

Abbreviation	Definition
AAT	Anti-amoebic therapies
AE	Adverse event
AIC	Akaike information criterion
AK	Acanthamoeba keratitis
ATC	Anatomical Therapeutic Chemical
ATE	Inverse weighting average treatment effect
ATT	Inverse weighting effect of treated
BCVA	Best-corrected visual acuity
CDC	Centers for Disease Control and Prevention
BIC	Bayesian information criterion
BL	Baseline
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEM	Cost effectiveness model
CHX	Chlorhexidine
CI	Confidence interval
cTTO	Composite time trade-off
COMP	Committee for Orphan Medicinal Products
DCE	Discrete-choice experiment
DKK	Danish krone
DMA	Danish Medicines Agency
DMC	Danish Medicines Council
DRGs	Diagnosis-Related Groups
EMA	European Medicine Agency
EPAR	European public assessment report
EQ-5D-3L	EuroQol 5 Dimension 3 Level health related quality of life
EQ-5D-5L	EuroQol 5 Dimension 5 Level health related quality of life
ERG	Evidence Review Group
EU	European union
EUR	Euro
FAS	Full analysis set
FDA	Food and Drug Administration
GBR	Great Britain
GLM	Generalized linear model
GMP	Good manufacturing price
GV	Good vision
HCRU	Health care resource use
HR	Hazard ratio
HRQoL	Health-related quality of life
HST	Highly Specialized Technology
HSUVs	Health state utility values
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IPD	Individual Patient Data
IRT	Item response theory
ITC	Indirect treatment comparison
IVCM	*In vivo* confocal microscopy
JNHB	Joint Nordic assessment
KM	Kaplan-Meier

LY	Life-year
MAIC	Matching-adjusted indirect comparison
MCR	Medical cure rate
MCR_12m	Medical cure rate within 12 months
Mg	Milligram
MMRM	Mixed model repeated measures
NG	NICE guideline
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit
ODAK	Orphan Drug for Acanthamoeba keratitis
OS	Overall survival
OW	Overlap weighting
OWSA	One-way sensitivity analysis
PCR	Polymerase chain reaction
PFS	Progression-free survival
PSA	Probabilistic Sensitivity Analysis
PSM	Propensity score matching
PSSRU	Personal Social Services Research Unit
PV	Poor vision
QALY	Quality-Adjusted Life Year
QoL	Quality of life
RCT	Randomized control trial
RWE	Real world evidence
RR	Relative risk
SE	Standard error
SmPC Akantior	Summary of product characteristics, Akantior, 2024
SLR	Systematic literature review
SVL	Severe vision loss
Therap	Therapeutic surgery
TTO	Time trade-off
USA	United States of America
UK	United Kingdom
VA	Visual acuity
VAS	Visual Analog Scale:
VFQ-25	National Eye Institute Visual Function Questionnaire-25
WHO	World Health Organization
WTP	Willingness to pay

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Akantior
Generic name	Polihexanide 0.8 mg/ml (0.08% w/w)
Therapeutic indication as defined by EMA	Akantior is indicated for the treatment of acanthamoeba keratitis in adults and children from 12 years of age. [1]
Marketing authorization holder in Denmark	SIFI S.p.A. Via Ercole Patti 3695025 Aci Sant'Antonio (CT), Italy
ATC code	ATC code: S01AX24
Combination therapy and/or co-medication	No
Date of EC approval	22 August 2024
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes, 14th of November 2007
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? Yes, to certain degree. Is the product suitable for a joint Nordic assessment? No If no, why not? The current dossier represents a revised dossier following a change of the comparator. The initial submission to Denmark was prioritized and sequenced earlier due to Danish Medicines Agency (DMA) grant of national license (Generel Udleveringstilladelse) prior to market authorization. Patients have already been treated with Akantior in Denmark prior to marketing authorisation.

Overview of the medicine	
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Akantior is contained in single-dose containers filled with 0.3 ml solution. Each ml of solution contains 0.8 mg polihexanide (0.08% w/w). The single-dose containers are moulded in 5-unit sealed strips which in turn are wrapped in a sachet and packaged inside a carton box. Each carton box contains 6 sachets/30 single-dose containers. [1] The finished product, Akantior, contains polihexanide in a novel, patented, preservative-free, eye drop solution formulation. [32]

2. Summary table

Summary	
Indication relevant for the assessment	Treatment of acanthamoeba keratitis (AK) in adults and children from 12 years of age. AK is an ultra-rare very painful and sight-threatening eye infection.
Dosage regiment and administration	The recommended dose is 1 drop in the affected eye according to a two-part regimen that consists of a 19-day intensive phase and a continuation phase from day 20 until cure, or up to 12 months (only daytime dosing). [1] No other anti-amoebic agents are added to Akantior (monotherapy). RWE data shows that patients use Akantior for a median time of 100 days and a mean time of 101 days. [2]
Choice of comparator	'No antiamoebic treatment' or placebo (referenced as "EMA comparator – no AAT" arm in the current dossier). The DMA informed the holders of dispensing permits for Brolene (propamidine 0.1%) eye drops and their hospital pharmacies that the treatment of AK is no longer covered by the issued dispensing permits. Furthermore, the DMA also drew attention to the fact that the European Court of Justice applies strict legal practice regarding hospital pharmacies that compound pharmaceutical preparations if a registered alternative is available on the market. This communication was reinforced in a letter dated November 18 to the Danish Ophthalmologica Society. [72] Consequently, as agreed with DMC, the comparative treatment in the initial dossier submitted to DMC, compounded unlicensed chlorhexidine (CHX) 0.02% +/- imported propamidine 0.1%, was no longer applicable and had to be replaced by 'no antiamoebic treatment' or 'placebo' (referenced as "EMA comparator – no AAT" arm in the current dossier).

Summary	
Prognosis with current treatment (comparator)	Acanthamoeba keratitis is a progressive parasitic eye infection. Historical control data on subjects who received no treatment, identified through a systematic literature review (n=56), show a clinical resolution rate with no surgery of 19.6% (95%CI: 10.2%, 32.4%). The remaining 80.4% of patients required surgery (keratoplasty [67.9%], enucleation [7.1%] or minor surgery [7.1%]). [1] [73] [75]
Type of evidence for the clinical evaluation	RCT: pivotal, double-masked, randomized, active-controlled phase III ODAK trial, assessing the efficacy and safety of Akantior [6] Historical control data on subjects who received no treatment. These subjects were identified through a systematic literature review (n=56). [1] [73] [75] DK experience: XXXX patients treated during pre-authorization under national license (Generel Udleveringstilladelse) from the Danish Medicines Agency (Lægemiddelstyrelsen 2023 [7], renewed in Feb 2024).
Most important efficacy endpoints (Difference/gain compared to comparator)	Crucial: rate of medical cure achieved within 12 months (MCR_12, primary endpoint in the phase III ODAK trial). Other: change in (vision-related) quality of life, the rate of therapeutic keratoplasties, reduction of eye pain, time to cure and no recurrences within 90 days after stop of anti-amoebic therapy. The absolute efficacy of AKANTIOR was determined by comparing results observed in the ODAK-trial with historical control data on subjects who received no anti-amoebic treatment, identified through a systematic literature review (n=56). [1] [73] [75] The clinical resolution rate with no surgery in this historical control was 19.6% (95%CI: 10.2%, 32.4%). The remaining 80.4% of patients required surgery (keratoplasty 38/56: 67.9% [48.0%, 83.0%]), enucleation 4/56: 7.1% [3.0%, 18.0%]) or minor surgery 4/56: 7.1% [1.0%, 29.0%])). The treatment effect (percentage of patients cured without surgery) of AKANTIOR versus absence of treatment (historical control) is shown in Table 2 of the SmPC [1]. A study effect of 30.7% (95%CI: 14.2%; 47.2%) was also estimated based on results observed for the chosen comparator in the ODAK-trial and the expanded retrospective study published by Papa et al. 2020. [3] By performing a crude adjustment method of adding this estimated value of 30.7%, the estimated placebo effect would reach a hypothetical clinical resolution of 50.3% (95%CI: 36.6%; 64.1%). The treatment effect-mean difference (binomial exact 95%CI) adjusting for the study effect was 34.5% (16.8%,49.8%). In the ODAK trial [6] 7.6% of Akantior-patients required therapeutic keratoplasty; eye pain showed a significant and clinically relevant reduction from baseline, while quality of

Summary	
	life improved. The median time to cure was 125 days in those patients who achieved cure within 12 months. There were no recurrences within 90 days. The high efficacy of Akantior in the ODAK trial is associated with: 1) the use of GMP-quality polihexanide in a high concentration of 0.8 mg/ml; 2) the use of a novel, patented, preservative-free, eye drop solution formulation supporting the performance of the polihexanide polymers; 3) a novel administration scheme with a lower dripping frequency, use as monotherapy and no night dosing; 4) the use as part of a validated protocol for the management of AK.
Most important serious adverse events for the intervention and comparator	Akantior was well tolerated, with most adverse events of mild or moderate severity. No serious drug-related adverse events occurred. [1] [6] A safety profile is not relevant for the comparator.
Impact on health-related quality of life	The Akantior-arm of the ODAK trial showed a significant and clinically relevant improvement in quality of life versus baseline (EQ–5D–5L VAS +14.5 points; VFQ–25 +22.1 points, p<0,001 for both). [6]
Type of economic analysis that is submitted	Type of analysis: cost-utility. Type of model: A de novo decision tree combined with a semi- Markov model.
Data sources used to model the clinical effects	Dart 2024 [6]; Papa 2025 [73];Veugen 2023 [8]; UK Delphi panel 2023 [9]; Papa 2020 [3]; De Francesco 2024 [5]; Robaei 2015 [10]; Clinical expert opinion.
Data sources used to model the health-related QoL	Dart 2024 [6]; Van Wilder 2019 [11]; Rentz 2014 [12]; Voretigene neparvovec NICE submission HST11 2019 [13].
Life years gained	Undiscounted XXXXX for both interventions.
QALYs gained	Undiscounted XXXXX QALY Akantior and XXXXX for the comparator. Differential: XXXX
Incremental costs	XXXXXXXX DKK (discounted) and XXXXXXXX DKK (undiscounted total cost)
ICER (DKK/QALY)	355,845 DKK/QALY (discounted)
Uncertainty associated with the ICER estimate	Absence of direct comparison RCT data vs. comparator
Number of eligible patients in Denmark	Annual incidence: XXX
Budget impact (in year 5)	XXXXXXXX DKK

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Acanthamoeba keratitis (AK) is a rare severe parasitic infection of the cornea, characterized by inflammation, intense pain, photophobia (sensitivity to light), and progressive vision loss [4], [14], [15], [16], [17], [18], [19], [20]. The parasite causing the infection belongs to the acanthamoeba species, a family of free-living, ubiquitous protozoa commonly found in water, dust, and soil. The parasite exists in two forms: an active form (trophozoite) and a dormant form (cyst). The trophozoite can reproduce by binary fission in optimal growth conditions and cause human infections. In unfavourable conditions, trophozoites can transform into cysts, which is the dormant and more resistant state of acanthamoeba. Under favourable conditions, cysts transform gradually into the trophozoite and the trophozoites emerge from cyst through channels called ostioles, leaving an empty double-wall shell. The cystic form is highly resistant to disinfectants and antimicrobial treatments [19], [20]. The cystic form of acanthamoeba is responsible for persistent disease over long periods of time. Effective therapy requires complete eradication of all trophozoites and cysts.

AK often arises without warning in otherwise healthy individuals, predominantly affecting young to middle-aged adults who wear contact lenses [17]. Infection occurs when the pathogen penetrates the corneal epithelium, often due to trauma or poor contact lens hygiene. Due to the complicated diagnostics, the challenging current treatment with unlicensed compounded biguanide eye drops and off-label used diamidine eye drops, and the usually bad compliance of the patients, acanthamoeba keratitis unfortunately very often takes a serious progression despite the current care, which may lead to, blindness, serious visual loss, pain and the need for perforating keratoplasty. With mentioned current treatment, 15–22% need therapeutic keratoplasty [3], [4]. If the infection spreads to the posterior segment of the eye, the prognosis becomes substantially worse, with pronounced vitritis and retinal necrosis often leading to enucleation (surgical removal of the eye). See Figure 1 for a depiction of the clinical evolution of AK.

Historical control data on subjects who received no current treatment as indicated above, identified through a systematic literature review (n=56), show a clinical resolution rate with no surgery of 19.6% (95%CI: 10.2%, 32.4%). [1] [73] [75] The remaining 80.4% of patients required surgery (keratoplasty [67.9%], enucleation [7.1%] or minor surgery [7.1%]).

The condition is severe and life changing, with excruciating pain and extreme light sensitivity commonly reported, such that patients can rarely work or lead a normal live

until the infection is resolved [21], [22]. As a result, AK impacts a patient's quality of life negatively. Lasting complications such as corneal scarring, visual impairment, blindness, and chronic pain can diminish daily functioning and well-being. Akantior was designated an 'orphan medicine' and the Committee for Orphan Medicinal Products (COMP) agreed that the condition is chronically debilitating due to the risk of loss of sight, resulting from the disease or from enucleation [23].

Diagnosing and treating AK is challenging, early detection and the prompt initiation of therapy is crucial for a favourable patient outcome. Prognosis significantly worsens if treatment is delayed by three weeks or more [24]. Late diagnosis often results in deeper corneal involvement and severe complications, necessitating more intensive treatments, including eye surgery. Diagnosis is confirmed through methods such as cytological staining of corneal scrapings, *in vivo* confocal microscopy (IVCM), culture, polymerase chain reaction (PCR), or histological examination of corneal biopsies, or combinations of these.

The primary objective of therapy is the eradication of all acanthamoeba cysts and trophozoites from corneal tissue and the resolution of inflammation [25]. Achieving these goals is typically a lengthy and complex process as the trophozoite form may respond to various therapies, but the cystic form is highly drug-resistant and can persist for months to years.

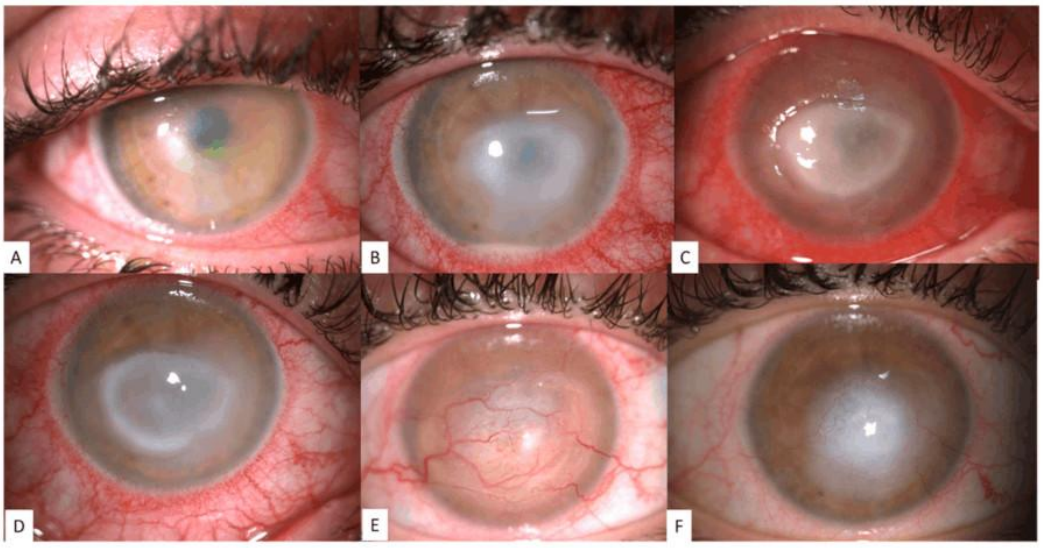


Figure 1 Representative images of the clinical evolution of Acanthamoeba keratitis (AK)

Explanation figure 1: early phase AK showing epithelial keratopathy (A, stage I), stromal involvement and sterile hypopyon (B, stage II), epithelial defect and ring stromal infiltrate (C,D, stage III), and corneal scarring with deep and superficial neovascularization (E,F) [24].

To further illustrate how patients are affected in their daily life with this sever condition, the patient initiative acanthamoeba Keratitis Eye Foundation web site provide resources and patient perspectives, www.akeyefoundation.com, and the video called "Life through our eyes" posted on their site documents the experience of living with acanthamoeba keratitis (https://youtu.be/VsyAGrQ6WzQ). Note that the treatment described in the video illustrates the current care before Akantior approval.

3.2 Patient population

AK can occur in all age groups, with real world data showing that the patient population that is diagnosed with and treated for AK are generally younger, lens wearing patients between ages 30 and 60 [4], [26], [27]. A Danish study analysed all cases of AK treated between 1994 and 2018 at Aarhus University Hospital's ophthalmology department, the only specialized corneal unit in western Denmark, serving a population of approximately 3 million [17]. The patients were relatively young, with a median age of 38 years (range: 15 to 70), 49% were female, and 89% were contact lens users.

A systematic review by Zhang *et al*. 2023 [28], including 36 studies and covering data from 20 countries, estimated the global annual incidence of AK to be 2.9 cases per 1,000,000 people. Epidemiological data from Denmark has shown a range of XXXX diagnosed cases of AK over the past decades, between 2014 and 2018 [17]. This observed increase in incidence was hypothesized to be partly attributable to increased awareness and improved diagnostic practices, as well as changes in contact lens hygiene habits and routines among users. According to Danish clinical practice , the incidence rate has remained around XXXX patient cases per year since 2018. Note, in this application for assessment we have chosen to use the higher patient number to reflect a reasonable view of potential product investment/cost.

Table 1 Incidence in Denmark 2014-2018

Year	2014	2015	2016	2017	2018
Incidence in Denmark	X	X	X	X	X

The patient population described above and that is expected to be treated with Akantior corresponds to the registered indication: *for the treatment of acanthamoeba keratitis in adults and children from 12 years of age*.

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	XX	XX	XX	XX	XX

3.3 Current treatment options

Early diagnosis and prompt medical intervention are critical to alleviating acute symptoms, eradicate the acanthamoeba in the cornea, and preventing severe damage leading to vision loss. Treatment aims to preserve vision and prevent vision loss.

Similar to most other European countries, no detailed national treatment guidelines exist for AK in Denmark. Current management in Europe, in case Akantior is not yet available,

typically consists of topical therapy with unauthorised and/or off-label anti-amoebic agents that must be compounded and/or imported. Such treatment regime is briefly outlined in the *lægehåndbogen* published by sundhed.dk where suggestions for medical treatment of AK include disinfecting agents *such as biguanides and diamidines* not approved for treatment of AK [29].

Compounding might not be carried out in compliance with Good Manufacturing Practice (GMP) and/or might not take place using GMP quality ingredients [47]; in rare cases leading to compounding error (see e.g. [30]).

The compounded topical treatments for AK in Europe ([31]) commonly include one of the following:

- Biguanides: polihexanide 0.02 mg/ml (PHMB, 0.2%) or chlorhexidine (CHX) 0.02%.
- Diamidines: propamidine 0.1% (e.g. Brolene 0.1%) or, less commonly, hexamidine.

These agents can be used in combination. Common combinations include:

- CHX 0.02% + propamidine 0.1% (e.g. Brolene 0.1%). This represented the most recent current care in Denmark.
- Polihexanide (0.2 mg/ml) + propamidine 0.1% (e.g. Brolene 0.1%).

Limited evidence for CHX 0.02% ± propamidine 0.1% shows a relatively low cure rate and high rate of therapeutic keratoplasties [3], [4], [5], [74]. A medical cure rate within 12 months for CHX 0.02% ± propamidine 0.1% of 46.4% (29.9, 63.0) was derived from individual patient data from a retrospective study [3] as part of an ITC with propensity score matching (PSM) [74] [76]. Randag 2019 [4] reports that 49 of 224 patients (22.4%) treated with CHX 0.02% ± propamidine 0.1% received therapeutic keratoplasty. One additional patient required enucleation.

The DMA informed recently the Danish holders of dispensing permits for Brolene (propamidine 0.1%) eye drops and their hospital pharmacies that the treatment of AK is no longer covered by the issued dispensing permits. Furthermore, the DMA also drew attention to the fact that the European Court of Justice applies strict legal practice regarding hospital pharmacies that compound pharmaceutical preparations if a registered alternative is available on the market. This communication was reinforced in a letter dated November 18 to the Danish Ophthalmology Society [72]. Consequently, as agreed with DMC, the comparative treatment in the initial dossier submitted to DMC, compounded unlicensed chlorhexidine (CHX) 0.02% +/- imported propamidine 0.1%, was no longer applicable and had to be replaced by 'no antiamoebic treatment' or 'placebo' (referenced as "EMA comparator – no AAT" in the current application).

3.4 The intervention

Pharmacotherapeutic category: Sensory organs, Ophthalmologicals, Other anti-infectives, ATC code: S01AX24.

Akantior (polihexanide, 0.8 mg/ml eye drops) is the first authorised medicinal product targeting AK. Akantior is used as monotherapy, which means that no other anti-amoebic agent is added to Akantior for the eradication of the acanthamoeba. The management of acanthamoeba keratitis may require the use of other medicines, e.g. cortico-steroids.

The active substance of Akantior is polihexanide, which is homopolymer of N-(3-aminopropyl)-imidodicarbonimidic diamide. The active substance is also known under the name polyhexamethylene biguanide hydrochloride (polihexanide). Polihexanide acts on both the active trophozoite and dormant cystal forms of acanthamoeba. Polihexanide has a mechanism of action that targets two processes essential for the acanthamoeba life cycle: (1) disruption of acanthamoeba cell membranes and (2) DNA binding, leading to blocking the DNA replication process of acanthamoeba.

The research & development (R&D) programme was initiated more than 17 years ago when polihexanide received orphan designation from the European Medicines Agency (EMA) in 2007 (COMP 2024 [23]). Polihexanide subsequently received orphan designation in 2017 from the FDA in the US (FDA 2017). The finished product Akantior contains polihexanide with consistent molecular weight at a concentration of 0.8 mg/ml (0.08%). Akantior is available in an eye drops solution, with a novel, patented, preservative-free eye drop formulation with specific osmolality and pH in single-use containers. The formulation supports the performance of the polihexanide polymers. The product is immediately available “off-the-shelf”, allowing treatment to commence rapidly. Each container is for single use only, and must be used immediately after opening, with the remainder then discarded (AKANTIOR Patent 2022 [32], SmPC 2024 [1]).

Overview of intervention	
Indication relevant for the assessment	Akantior is indicated for the treatment of acanthamoeba keratitis in adults and children from 12 years of age. [1]
ATMP	No
Method of administration [1]	For ocular use. For single use only. The contents of the single-dose container must be used immediately after opening. *Patients should be instructed:* • To avoid contact between the single-dose container tip and the eye or eyelids. • To use the solution immediately after opening the single-dose container and to discard it afterwards. • To instil Akantior at least 5 minutes after any other ophthalmic product.
Dosing [1]	The regimen consists of two parts: 1) the intensive treatment phase that lasts for the first 19 days; and 2) the continuation treatment phase from day 20.

Overview of intervention	
	The recommended dose is 1 drop of Akantior in the affected eye as follows (SmPC Akantior 2024 [1]): Intensive 19-day treatment phase: • 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 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.
Dosing in the health economic model (including relative dose intensity)	As above
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Treatment until cure (i.e. corneal healing, absence of corneal inflammation or no evidence of infection) and for no longer than 12 months [1]. The median duration of treatment of Akantior is 100 days, with a mean duration of treatment of 101 days [2] Criteria for end of treatment is cure.
Necessary monitoring, both during administration and during the treatment period	No additional monitoring other than current clinical practice
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	In the case of clinical signs of acanthamoeba keratitis, diagnostics must be performed by *in vivo* confocal microscopy and/ or polymerase-chain-reaction (PCR) and/ or histopathological examination and/ or microbiological culture.
Package [1]	Akantior is contained in single-dose containers filled with 0.3 ml solution. Each ml of solution contains 0.8 mg polihexanide (0.08% w/w). The single-dose containers are moulded in 5-unit sealed strips which in turn are wrapped in a sachet and packaged inside a carton box. Each carton box contains 6 sachets/30 single-dose containers.

3.4.1 Description of ATMP

NA

3.4.2 The intervention in relation to Danish clinical practice

Akantior is a European Commission-authorised orphan medicinal product with a well characterised efficacy and safety profile for AK patients.

3.5 Choice of comparator(s)

The Danish guidelines for assessing new pharmaceuticals state that the comparator should always be the pharmaceutical(s) or other treatment(s) (including preventive and palliative treatments) in Danish clinical practice that represent real alternatives and current standard treatment [33]. During a pre-meeting between representatives of Avanzanite Bioscience (legal representative of SIFI S.p.A) and DMC, CHX 0.02% ± propamidine 0.1% was identified as the appropriate comparator, subsequently, the comparator in the initial application was CHX 0.02% ± propamidine 0.1%. This treatment was acknowledged as the commonly used therapeutic option for patients with AK in Denmark. However, the DMA informed the holders of dispensing permits for Brolene (propamidine 0.1%) eye drops and their hospital pharmacies that the treatment of AK is no longer covered by the issued dispensing permits. Furthermore, the DMA also drew attention to the fact that the European Court of Justice applies strict legal practice regarding hospital pharmacies that compound pharmaceutical preparations if a registered alternative is available on the market. This communication was reinforced in a letter dated November 18 to the Danish Ophthalmology Society [72]. Consequently, as agreed with DMC, the comparative treatment in the initial dossier submitted to DMC was no longer applicable and had to be replaced by 'no antiamoebic treatment' or 'placebo' (named as "EMA comparator – no AAT" in the current application).

Overview of new comparator 'no treatment'	
Generic name	NA
ATC code	NA
Mechanism of action	NA
Method of administration	NA
Dosing	NA
Dosing in the health economic model (including relative dose intensity)	NA

Overview of new comparator 'no treatment'	
Should the medicine be administered with other medicines?	NA
Treatment duration/ criteria for end of treatment	According to the systematic literature review (SLR) conducted which included patients with AK treated without products having established anti-amoebic activity against both trophozoites and cysts (biguanides or diamidines), a median duration of treatment of 56.7 days until cure was calculated based on individual patient data (IPD) from the 11 cases classified as cured [73] [75].
Need for diagnostics or other tests (i.e. companion diagnostics)	NA
Package size(s)	NA

3.6 Cost-effectiveness of the comparator(s)

The comparative treatment in the initial dossier submitted to DMC (CHX 0.02% ± propamidine 0.1%) is no longer applicable. The new comparator is 'no antiamoebic treatment' or 'placebo' ("EMA comparator – no AAT").

Due to lack of a head-to-head efficacy data between the intervention and the new comparator, an indirect treatment comparison was conducted considering historical control data from patients who had not received anti-amoebic treatment (AAT), to determine relative efficacy estimates of Akantior versus "EMA comparator – no AAT" arm [1] [73] [75]. Individual patient data (IPD) were available from the pivotal phase 3 randomized controlled trial (RCT) of polihexanide 0.8 mg/ml versus conventional polihexanide 0.2 mg/ml plus 0.01 mg/ml propamidine by Dart et al 2024 [6] and from a systematic literature review (SLR) on people with diagnosed AK who were untreated (to inform efficacy obtained for the intervention and the comparator arm, respectively) [75], allowing the performance of ITC analyses using propensity scoring analysis (PSA) with overlap weighting (OW) [1] [73] [76]. This approach uses weighted regression methods with adjustment for key effect modifiers and prognostic factors of AK (identified as potential confounding variables) to attempt to balance study populations before estimation of the treatment effect. The results of the PSA with OW analyses showed that polihexanide 0.8 mg/ml had a statistically significant higher cure rate than "EMA comparator – no AAT" arm.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The following crucial and other relevant efficacy endpoints are proposed, based on the advice of the European Medicines Agency (EMA) and an analysis of the endpoints applied in clinical studies with AK patients.

Crucial efficacy endpoint: percentage of patients with recovery within 12 months after starting treatment. The phase 3 ODAK trial provides a robust definition for this endpoint ('Clinical Resolution Rate' at 12 months, also named 'Medical Cure Rate' at 12 months, MCR_12)

Other relevant efficacy endpoints:

- Improvement in (vision-related) quality of life, measured at end-of-study visit.
- Percentage of patients requiring therapeutic keratoplasty.
- Reduction of pain, measured at end-of-study visit.
- Time to cure
- Percentage of patients with recurrence within 90 days.

Crucial Efficacy Endpoint: medical cure rate within 12 months. The primary endpoint of the prospective phase 3 ODAK trial [6], established in consultation with the EMA, was medical cure rate within 12 months. In the ODAK trial this was defined as the proportion of patients cured under each treatment arm without the need for eye surgery or a change of anti-amoebic therapy, irrespective of visual acuity, within 12 months of randomization. This measure is used to evaluate the effect of Akantior and the comparator in this application. This outcome was chosen due to the poor prognosis often associated with AK, which is partly attributable to the severity of the condition itself and partly to the toxicity of the medications. While the average treatment duration is 4 to 6 months, a substantial number of patients require extended treatment [19], [34]. A follow-up period of 12 months provides information for patients requiring longer treatment durations.

The primary endpoint of the phase 3 ODAK trial [6] was robust and reflected the resolution of infection and inflammation (cure) within a follow-up period of 12 months. Cure in the ODAK trial had to the meet the following conditions:

- No reoccurrence within 30 days after discontinuing all AK medications (this 30-day period falls within the 12-month follow-up)
- No reoccurrence within the subsequent 60 days (a total of 90 days after discontinuation of all study medications)
- No need for surgical procedures
- No changes in AK treatment
- No initiation of oral immunosuppressive therapy
- No adverse events considered related to the drug

Failure to meet these criteria was considered treatment failure.

Based on the primary endpoint of the ODAK trial, the following crucial efficacy outcome is proposed for the evaluation of Akantior and the comparator: *medical cure rate within 12 months,* operationalized as the time to meet the above criteria for healing within the 12-month follow-up period.

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Medical cure rate within 12 months	2017-2021 (ODAK trial)	Medical cure rate within 12 months	The measure was the primary outcome in the pivotal phase III clinical trial (ODAK) for Akantior [6]. The absolute efficacy of AKANTIOR was determined by comparing the results observed in ODAK with historical control data on subjects who received no antiamoebic treatment. These subjects were identified through a systematic literature review (n=56) [1] [73] [75].

** Time point for data collection used in analysis (follow up time for time-to-event measures)*

Other endpoints:

Improvement in (vision-related) quality of life, measured at end-of-study visit. Active infection has a significant impact on the quality of life. Quality of life is impacted by the efficacy (cure rate, time to cure, avoiding need for therapeutic keratoplasty) or other aspects of a specific treatment (ease of use, applicability of treatment, complications/side effects).

Percentage of patients requiring therapeutic keratoplasty. The rate of therapeutic keratoplasty is a relatively objective endpoint. Keratoplasty in the treatment of AK is associated with poor graft survival [8]. If topical treatment works well, therapeutic keratoplasty is not necessary. Therapeutic keratoplasty is a proxy for failure of topical therapy with obvious consequences for the patient.

Reduction of pain, measured at end-of-study visit. Patients with acanthamoeba keratitis may experience very intense pain. The domain of pain also appears is an important factor in the reduction of (vision-related) quality of life.

Time to cure. The faster cure takes place, the smaller the risk of corneal damage, the shorter the patient's suffering, and the earlier the patient can be alleviated from intensive care.

Percentage of patients with recurrence within 90 days. Recurrence of the infection has significant consequences for the patient. The risk of recurrence is very small beyond 90 days following stop of anti-amoebic treatment.

Validity of outcomes
Medical cure rate was chosen since the outcome is considered clinically relevant [10] (see extended rational above) and was accepted as a valid primary outcome in the evaluation of Akantior by EMA. Other endpoints are regarded as secondary and dependent on whether medical cure has been achieved.

Best corrected visual acuity (BCVA) is not considered an appropriate standalone endpoint for comparing treatments in AK. In clinical management of AK, the primary goal is to achieve cure using topical therapy alone. When topical therapy is insufficient, therapeutic keratoplasty is often required. Upon achieving cure, optimal clinical outcomes are characterized by preserved vision (as indicated by BCVA) without the need for further surgical intervention, such as optical keratoplasty, aimed solely at improving vision.

A review of the literature identified limitations across published studies in the reporting of follow-up timelines relevant to BCVA assessment and surgical procedures. Many studies did not specify the timing of BCVA measurements or the indications and timing of optical keratoplasty, which complicates interpretation of outcomes. The value of BCVA and the need for keratoplasty as endpoints depends on the timing of assessment; whether immediately after achieving cure (linked to treatment duration) or at a longer-term follow-up (e.g., up to 12 months), which may include patients who did not achieve cure.

Final BCVA outcomes are influenced by whether and when surgical interventions, particularly optical keratoplasty, were performed. Moreover, the decision to proceed with surgery is often dependent on BCVA itself, creating a circular dependency between the variable and the intervention it is intended to assess.

In several studies, BCVA and surgical procedures have been incorporated into composite definitions of treatment failure or poor outcome. These definitions often vary and are based on heterogeneous criteria, as shown in the examples below:

- Robaei et al. 2014 [10]: “Suboptimal visual outcome” defined as visual acuity (VA) ≤ 20/80 and/or corneal perforation and/or need for keratoplasty.
- Carnt et al. 2018 [19]: “Bad outcome” defined as VA ≤ 20/80 (6/24) in patients with a history of normal vision and/or corneal perforation and/or need for eye surgery (excluding biopsy) and/or treatment duration ≥10.5 months.
- Papa et al. 2020 [3]: “Poor outcome” defined as VA ≤ 6/24 and/or need for eye surgery.
- Randag et al. 2019 [4]: “Treatment failure” defined as VA ≤ 20/40 and/or need for keratoplasty.
- Carnt et al. 2022 [34]: “Poor AK outcome” defined as corneal perforation and/or need for eye surgery (excluding biopsy), treatment duration ≥12.6 months, and last recorded VA ≤ 20/80.

These examples show variability in the handling of BCVA and the need for surgery as components of treatment failure or poor outcome endpoints. Given this heterogeneity and the lack of standardized assessment timing, BCVA cannot be reliably processed into a meaningful endpoint for comparative assessment of therapeutic efficacy.

By contrast, the definition of failure used in the phase 3 ODAK trial provides a more consistent and clinically relevant endpoint. This definition is independent of follow-up BCVA and incorporates all types of eye surgery, thereby representing a more objective measure of therapeutic failure.

Based on the considerations outlined above, medical cure is considered a more appropriate endpoint for evaluating the therapeutic benefit of Akantior. This is further supported by clinical expert opinion, which consistently indicates that the primary goal of treatment in AK is the eradication of the pathogen, thereby achieving medical cure.

4. Health economic analysis

4.1 Model structure

4.1.1 Type of economic evaluation

This pharmacoeconomic model uses a cost-effectiveness analysis approach to compare costs and benefits in patients with AK of Akantior versus "EMA comparator – no AAT" (which considers patients with AK treated without products having established anti-amoebic activity against both trophozoites and cysts [biguanides or diamidines]). The model assesses costs and clinical outcomes, such as life-years (LY) and quality-adjusted life-years (QALYs). To be aligned with DMC pharmacoeconomic guidelines, the effectiveness outcome of interest is QALYs (i.e., the cost-effectiveness analysis adopts a cost-utility analysis approach) [33]. The ultimate results of the model are therefore expressed in terms of incremental cost per QALY gained over the model's time horizon, i.e., the incremental cost-effectiveness ratio (ICER), as calculated in the following formula:

$$ICER = \frac{Cost\ Target\ Intervention - Cost\ Comparator}{QALYs\ Target\ Intervention - QALYs\ Comparator}$$

The ICER is compared to the willingness-to-pay threshold (WTP), which defines the maximum cost that the payer is willing to pay for each additional QALY obtained from adopting the intervention the current clinical practice.

Currently, Denmark does not have an explicit cost-effectiveness threshold. However, a 2023 study analysing 131 decisions from the Danish Medicines Council found the implicit threshold to be between 458,134 DKK/QALY and 969,518 DKK/QALY [35]. Subsequently, the mid-point of these 2 values was applied as threshold in the model (713,826 DKK/QALY).

4.1.2 Target population

The target population comprises patients diagnosed with AK, in accordance with the EMA label for Akantior and the pivotal trial population.

Baseline cohort characteristics included the model:

- Mean initial age (years): 36.7. Source: Dart *et al*, 2023 [6]
- Percentage of males: 51.0%. Source: Nielsen *et al*, 2020 [17]
- Mean body weight: 80 kg. Source Statistics Denmark [36], University of Southern Denmark [37]

4.1.3 Intervention

The intervention in the analysis is Akantior, indicated for the treatment of acanthamoeba keratitis in adults and children from 12 years of age. Akantior is intended for use as monotherapy, with a schedule covering a 19-day intensive treatment phase, with no night-time dosing, followed by a continuation phase (until cure) consisting of 4-times daily administration (SmPC. Akantior [1]).

4.1.4 Comparator

Besides Akantior, there are currently no other approved medicinal therapies for the treatment of AK. Further, there is a lack of high-quality clinical evidence and consensus treatment guidelines and management protocols for acanthamoeba keratitis across the EU. As a result, practices vary greatly among treating physicians [1].

The comparative treatment in the initial dossier submitted to DMC (CHX 0.02% ± propamidine 0.1%) is no longer applicable. The DMA informed the holders of dispensing permits for Brolene (propamidine 0.1%) eye drops and their hospital pharmacies that the treatment of AK is no longer covered by the issued dispensing permits. Furthermore, the DMA also drew attention to the fact that the European Court of Justice applies strict legal practice regarding hospital pharmacies that compound pharmaceutical preparations if a registered alternative is available on the market. This communication was reinforced in a letter dated November 18 to the Danish Ophthalmological Society [72]. Therefore, since medicinal products with proven antiamoebic effect are not available in Denmark, the comparator if interest in the current application is defined as “EMA comparator – no AAT”.

4.1.5 Perspective

The analysis adopts a limited societal perspective, in line with the DMC methodological requirements. Within this framework, both health effects and all relevant costs associated with the treatment pathway are considered.

The inclusion of patient time costs is methodologically appropriate, as patients with AK are generally otherwise healthy individuals who would normally be able to engage in productive or utility-generating activities. As such, time spent on treatment administration and healthcare visits represents a genuine opportunity cost. Furthermore, the health-related quality of life (HRQoL) measures used in the analysis do not capture the disutility associated with this time burden, reinforcing the need to include patient time costs explicitly.

In accordance with DMC guidelines, the analysis includes estimates of the health effects for patients using QALYs and all relevant treatment-related costs. This also applies to derived effects and costs resulting from adverse effects and administration of the pharmaceutical. All relevant hospital-related costs, costs covered by public health services, treatment-related costs incurred by the patient and municipal costs are included. Relevant transport costs and time spent in connection with treatment for both patients and caregivers are also included in the model.

Overall, this approach ensures that the economic evaluation captures the full societal impact of the treatment pathway, while remaining consistent with the DMC methodological framework.

4.1.6 Discount rate

Discounting future costs and outcomes to present value is necessary to account for the time value of money, which helps in making a fair comparison across different interventions. Thus, costs and outcomes are projected over the time horizon of the analysis and are discounted accordingly. The discount rate is given by $\frac{1}{(1+r)^t}$ where *r* is the discount rate, and *t* represents time (in years).

In line with DMC guidelines, in the base case, the discount rate for costs and outcomes was set to 3.5% [33], [38].

4.1.7 Time horizon and model cycle

DMC guidelines state the time horizon for the analyses should be long enough to include all significant differences in health benefits and costs between the alternatives throughout the course of the disease [33]. In AK, the benefits and costs may accrue over many years, such that a lifetime horizon is selected as time scale for the cost-effectiveness analysis, given that the vision impairment persists for the remainder of the patient's life and reoccurrence of AK infections may occur in the long-term. The model simulation was conducted in cycles of one year over a lifetime horizon, until the cohort reaches 100 years of age. The cycle length is 12 months, in accordance with the primary endpoint of the ODAK trial. In addition, the reason for including a combined decision tree & Markov model was to allow for granularity in time of AK while still modelling cycles of 1 year after AK is resolved.

Half-cycle correction was implemented to account for transitions which may occur at any point during the cycle, not necessarily at the start or end of each cycle.

4.1.8 Model health-states

Health states are designed to capture all the relevant costs and consequences of the disease and its treatment pathway. The relevance of defining different health states is determined by considering the difference in costs and consequences compared with the other health states [39].

Costs and quality-of-life in patients with AK are expected to vary depending on whether the AK infection is active and on the level of visual impairment following AK infection resolution.

In the model, visual impairment was defined based on the BCVA levels of patients after achievement of AK infection resolution (with or without therapeutic keratoplasty). 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 a driving license in European countries [40],

[41]. 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*. study [3] and the classification of severity of vision impairment defined by World Health Organization (WHO) [42].

Definitions of model health states

Health state	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 ≥20/40
Poor vision	Patients who achieved a resolution of the AK infection (with or without therapeutic surgery) with BCVA ≥20/200 and <20/40
Severe vision loss	Patients who achieved a resolution of the AK infection (with or without therapeutic surgery) with BCVA <20/200
Loss of eye functionality	Patients who lose the eye functionality due to the removal of the eye's content and/or entire globe, or other type of surgeries, or in case patients do not undergo further procedures after a graft failure

AK: Acanthamoeba keratitis; AAT: Anti-amoebic therapy; BCVA: Best-corrected vision acuity

LogMAR is the recognized standard for assessing visual acuity (VA) in clinical research and trials (Elliott et al., 2016). BCVA reported using the Snellen chart can be converted to logMAR values according to the Royal College of Ophthalmologists' conversion table. This conversion leads to the following thresholds:

a. Good vision (BCVA ≥20/40): logMAR ≤ 0.30
b. Poor vision (BCVA ≥20/200 and <20/40): logMAR > 0.30 and ≤ 1.00
c. Severe vision loss (BCVA <20/200): logMAR > 1.00
d. Loss of eye functionality: no changes

4.1.9 Model structure

The model structure was developed in line with NICE [43] and DMC guidelines for assessing new pharmaceutical products [33].

A *de novo* decision tree combined with a semi-Markov model with time-dependent transitions was developed to assess the cost-effectiveness of Akantior in the treatment of AK. The model measures the development of the cohort through the health states defined above and estimates costs and impact on health (measured in QALYs). To capture the effectiveness of the pharmacological treatments included in the analysis, the nature of the disease, current AK treatments options available, surgeries, rehabilitation, and other key factors, such as outcomes and aspects associated with the prognosis, were taken into consideration:

- The AK infection can be either resolved medically with or without surgery:
- Medical therapy in AK aims for the eradication of viable cysts and trophozoites and rapid resolution of the associated inflammatory response [18]. The primary outcome measure was the medical cure rate (i.e. MCR_12m), defined as the

proportion of patients cured[1] by each treatment without the need for surgery or a change of AAT, irrespective of visual acuity, within 12 months of randomization [6].

- From published literature, it is known that there are patients that may undergo eye surgery, because of acanthamoeba keratitis not responding to pharmacologic therapy, progression of acanthamoeba keratitis towards the limbus, or impeding perforation [4]. In current clinical practice, therapeutic keratoplasty is usually used as a last resort of treatment, after treatment with biguanides with or without diamidines fail, and the infection has progressed to an advanced stage [44].
- AK can lead to loss of visual acuity, and in severe cases it can lead to blindness and loss of eye functionality [45]. Some patients may receive optical surgeries for vision rehabilitation (e.g., optical keratoplasty) after the infection is resolved.

The decision tree is shown in Figure 2 and the semi-Markov model structure in shown in 3.

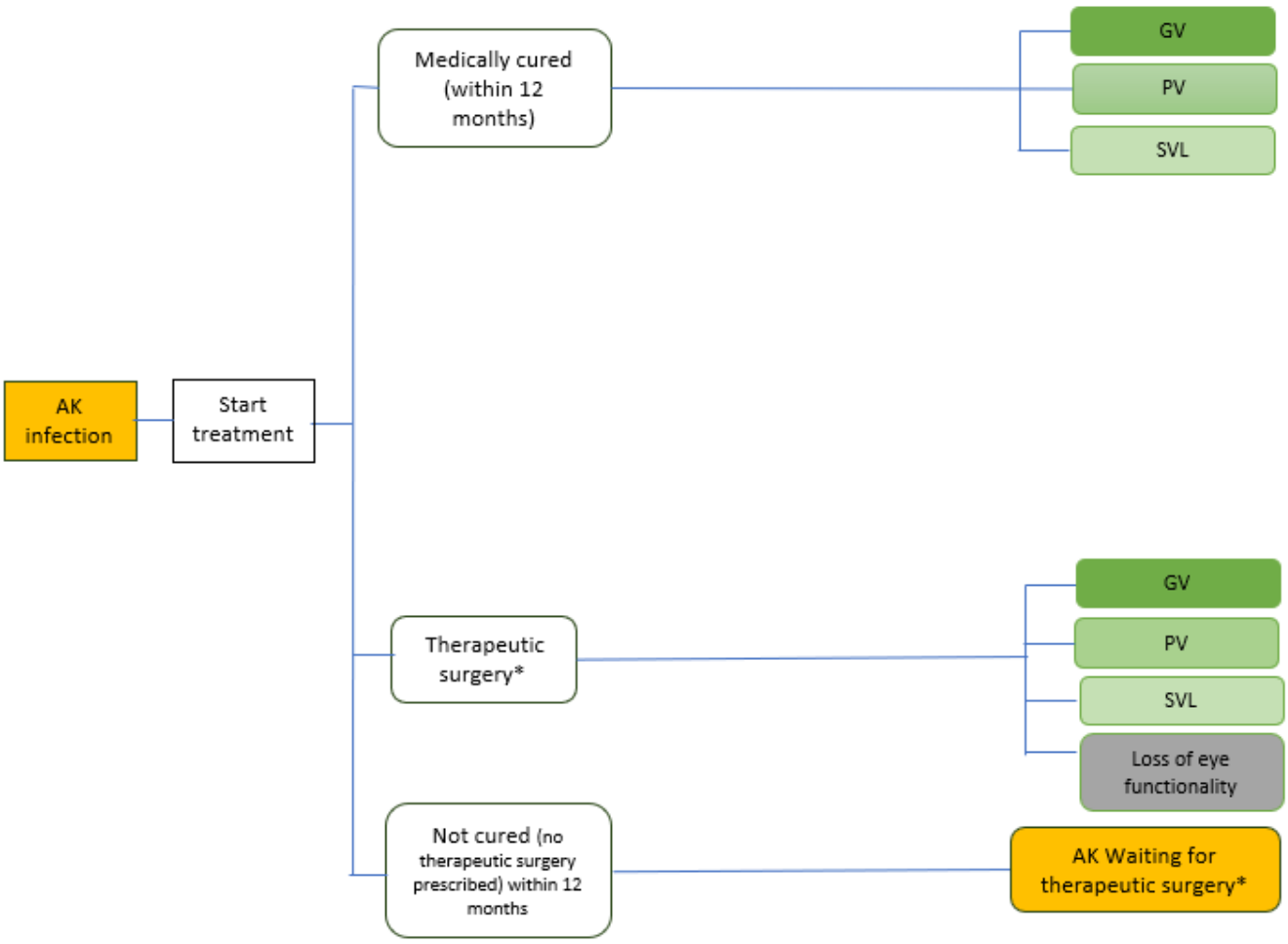


Figure 2 Decision tree structure (only for the first year)

* Depending on the waiting time and treatment duration of initial treatment, patients may undergo therapeutic surgery within first year

AK: Acanthamoeba keratitis; GV: Good vision; PV: Poor vision; SVL: Severe vision loss;
1 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 (confirmed at the end-of-study visit 90 days after treatment discontinuation) as determined by clinical examination.

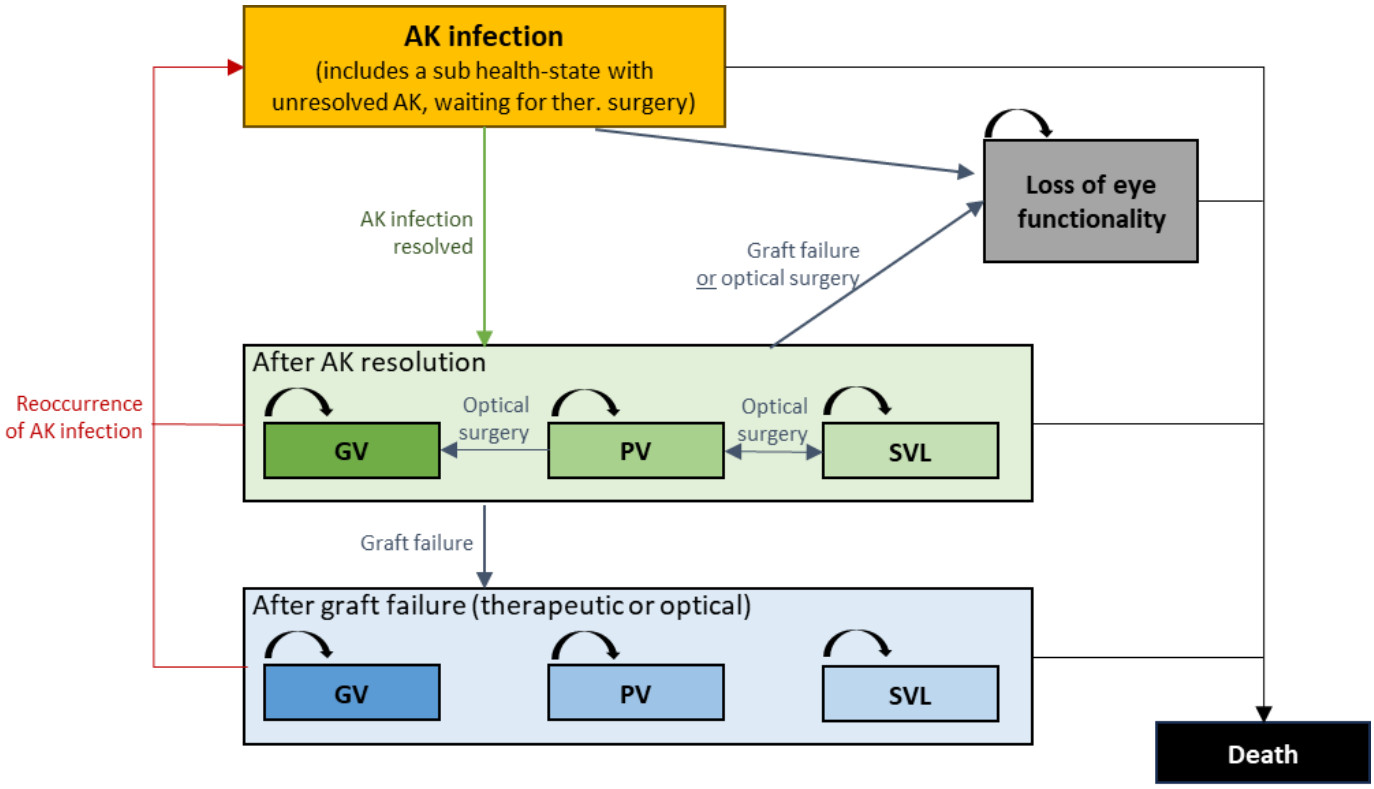


Figure 3 Semi-Markov model structure

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

The entire cohort enters the model in the AK infection node of the decision-tree, and they can follow any of the different pathways in the decision-tree:

1. Achieve a medical resolution of AK infection within 12 months (Section 8.1): the cohort can achieve a medical cure with the initial treatment with good vision, poor vision, or severe vision loss.
2. Therapeutic surgery (Section 8.3.1.1): a proportion of the cohort that were unresponsive to the initial treatment will undergo therapeutic surgery. Patients may be waiting for the therapeutic surgery for a certain time.
3. Not cured at end of year 1: a proportion of the cohort may not achieve a resolution of the AK infection during the first year. During the second year, it was assumed that all these patients undergo a therapeutic surgery and a similar pathway as explained above is followed. This assumption was validated with an AK leading clinician, who confirmed that a surgical intervention would remain the only option and that at such disease stage, with enucleation being the intervention mostly performed.

The decision tree allows estimation of the proportion of the cohort that remain on AK infection and in each of the BCVA levels or loss of eye functionality after AK infection resolution. It is important to note that:

i. If the duration of initial treatment plus the waiting time for the therapeutic surgery is less than one year, then the cohort still undergo therapeutic surgery within the first year and the proportion of the cohort in each of the BCVA levels and loss of eye functionality after surgery are estimated using the decision tree.
ii. 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, then the cohort still undergo therapeutic surgery within the first year (like the paragraph above).

After the cohort achieve a resolution of the infection (either medically or underwent a therapeutic surgery), they may remain on the same health state until one the following events occurs:

- **Optical surgery** (Section 8.3.1.2): A proportion of the cohort with poor vision or severe vision loss may undergo optical surgery. The cohort will be waiting for the optical surgery for a certain defined time (up to 3 years). Following the optical surgery the cohort may improve, worsen, remain on the same vision level, or even lose their eye functionality (Section 8.3.1.4).
- **Graft failure** (Section 8.3.1.3): The cohort may have graft failure up to three years after surgery (therapeutic or optical keratoplasties). Following the graft failure, patients will be distributed according to their BCVA level or loss of eye functionality (Section 8.3.1.4). Note that after a graft failure, patients either remain on the same health state, have a reoccurrence of AK infection, or die.
- **Recurrence of AK infection** (Section 8.3.1.5): 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) up to year 15 of the time horizon. The cohort that experiences a reoccurrence of AK infection will re-enter the AK infection node of the decision-tree.
- **Death** (Section 8.3.1.6): The cohort could transition to death from any other health state at any cycle, with probabilities based on national statistics for the age-specific mortality rate in the general population.

The model incorporated key clinical data from the ODAK phase 3 trial, insights from the results of a Delphi panel conducted in the United Kingdom (UK), and from published items in the scientific literature. An indirect treatment comparison (ITC) was conducted to obtain comparative efficacy estimates between Akantior and EMA comparator – no AAT arm, in terms of relative risk of achieving a medical cure within 12 months from start of the treatment [73] [76]. Due to lack of Danish local data to inform the economic analysis, information from the literature and from the UK Delphi panel/UK experts was used as representative for the Danish setting in the model.

The main objective of the conducted Delphi panel was the systematic collection and validation of relevant insights, such as available treatment patterns, pharmacological options, surgical options available to patients, visual outcomes after therapies, among others. Results from the expert panel with specialists from the UK having previous experience in the domain of the disease (which included 12 panellists on the first round and 10 panellists on the second round), have been implemented in the economic analysis

for Denmark and were considered representative of the Danish clinical practice. Apart from the evidence collected in the Delphi panel, Prof. Dart (Consultant Ophthalmologist in England who is a pioneer in AK clinical research over 30 years) and Dr. Sajjad Ahmad (Consultant Ophthalmic Surgeon in England) were consulted to validate the model structure, model health states definition, and key model assumptions.

Last, the model only considers unilateral AK infection in alignment with the ODAK trial design, where 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 (ODAK protocol and Dart et al. 2024).

4.2 Model features

Table 4 Features of the economic model

Model features	Description	Justification
Patient population	Patients diagnosed with AK, in accordance with the expected indication for Akantior and the pivotal trial population (>12 years old)	Indication
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime	To capture all health benefits and costs in line with DMC guidelines. Based on mean age at diagnosis in the phase 3 ODAK trial (36.7 years). Dart et al. 2024 [6] Validated, aligned with Danish clinical practice
Cycle length	12 months	Consistent with length of treatment cycle
Half-cycle correction	Yes	Implementation to account for transitions which may occur at any point during the cycle, not necessarily at the start or end of each cycle.
Discount rate	the discount rate for costs and outcomes was set to 3.5%	Consistent with the DMC requirements
Intervention	Akantior	
Comparator(s)	EMA comparator – no AAT arm	As agreed with DMC.
Outcomes	QALY	

5. Overview of literature

5.1 Literature used for the clinical assessment

The clinical assessment of Akantior and its comparator EMA comparator – no AAT arm is based on evidence from the pivotal phase III trial (ODAK) for Akantior and a systematic literature search which was conducted to identify published data about clinical outcomes in untreated cases of Acanthamoeba keratitis [1] [73] [75]. 'Untreated' was defined as not receiving a treatment with an established and clinically proven anti-amoebic activity as stated by the Centers for Disease Control and Prevention (CDC) (polihexanide, chlorhexidine, propamidine, hexamidine). The results of this systematic literature search were published by Papa et al. in 2025 [73] Also see table 5.

Table 5 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Dart, J. K., Papa, V., Rama, P., Knutsson, K. A., Ahmad, S., Hau, S., ... & Minassian, D. C. (2024). The orphan drug for acanthamoeba keratitis (ODAK) trial: PHMB 0.08% (polihexanide) and placebo versus PHMB 0.02% and propamidine 0.1%. *Ophthalmology*, *131*(3), 277-287. [6]	ODAK	NCT03274895	Start: 17/08/2017 Completion: 18/06/2021 Data cut-off 18/06/2021 Future data cut-offs N/A	Akantior (polihexanide 0.8 mg/ml) monotherapy (intervention)
Papa V, Bodicoat D, Duarte A, et al. The Natural History of Acanthamoeba Keratitis: A Systematic Literature Review. Ophthalmol Ther. 2025 Jul;14(7):1369-1383 [73]	n/a	n/a	Eligible studies were clinical studies, published between 1970-1995.	EMA comparator – no AAT

Sample text in table for full paper, data on file and conference abstract. *If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

A dedicated literature search was not conducted specifically for the Danish model included in this application. A global systematic literature review had already been performed and given the limited number of relevant publications related to AK, no additional literature searches were considered necessary for the Danish context. It is important to highlight that a de novo economic SLR and subsequent update (Appendix I) were conducted to identify cost-effectiveness, HSUVs and resource use data associated with the treatment options for patients with AK. No utility studies were identified that reported EQ-5D outcomes in patients with AK (Appendix B). There was captured only one relevant published study on AK patients in Denmark is Nielsen et al. [17], which was not utilized for HRQoL inputs. Instead, HRQoL data were sourced from the ODAK trial, which is regarded as the most representative study of AK patients in Europe. In its evaluation of Akantior, EMA noted that "*the patients involved in the clinical development of Akantior can most likely be considered representative of the European population. While the safety reports do not specify the ethnic origin of the patients, it is highly unlikely that the majority would be of non-European ancestry, and no further concerns were raised regarding this matter*" [47, p. 135]. Some additional sources were used for health states related to long-term conditions and loss of eye functionality that were not available in the ODAK trial.

The full report of the economic SLR that were conducted in 2022 and updated in May 2025 to ensure that any evidence identified is relevant to the current healthcare landscape, is included in Annex B.

Table 6 Relevant literature included for (documentation of) health-related quality of life

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Dart, J. K., Papa, V., Rama, P ... & Minassian, D. C. (2024). The orphan drug for acanthamoeba keratitis (ODAK) trial: PHMB 0.08% (polihexanide) and placebo versus PHMB 0.02% and propamidine 0.1%. Ophthalmology, 131(3), 277-287. [6]	AK infection Poor vision after AK resolution Severe vision loss after AK resolution	Section 10.3
Rentz, A. M., Kowalski, J. W., Walt, J. G., ... & Revicki, D. A. (2014). Development of a preference-based index from the national eye institute visual function questionnaire–25. JAMA ophthalmology, 132(3), 310-318.	Loss of eye functionality	Section 10.3
Data on file. Technical report: Results from two-round DELPHI panel on acanthamoeba keratitis in the United Kingdom [9]	Disutilities associated with long-term conditions	Section 10.2
Van Wilder, L., Rammant, E., Clays, E. … & De Smedt, D. (2019). A comprehensive catalogue of EQ-5D scores in chronic disease: results of a systematic review. Quality of Life Research, 28, 3153-3161. [11]	On-going disutilities associated with long-term conditions	Section 10.2.2
Ara, R., & Brazier, J. E. (2011). Using health state utility values from the general population to approximate baselines in decision analytic models when condition-specific data are not available. Value in Health, 14(4), 539-545. [48]	On-going disutilities associated with long-term conditions	Section 10.2.2

5.3 Literature used for inputs for the health economic model

Similar to the HRQoL no dedicated literature search was conducted specifically for the Danish model included in this application. A global systematic literature review had already been performed and given the limited number of relevant publications related to AK, no additional literature searches were considered necessary for the Danish context.

A systematic literature search was conducted to identify published data about clinical outcomes in untreated cases of Acanthamoeba keratitis [75]. 'Untreated' was defined as not receiving a treatment with an established and clinically proven anti-amoebic activity as stated by the CDC (polihexanide, chlorhexidine, propamidine, hexamidine). Eligible studies were clinical studies, published between 1970-1995 inclusive, with patients with a confirmed diagnosis of Acanthamoeba keratitis who were untreated for whom a clinical outcome (cure without surgery; keratoplasty; enucleation) was reported. Database searches conducted on 27th November and 2nd December 2023 (PubMed; Cochrane Database of Systematic Reviews; Prospero International Prospective Register of Systematic Reviews; Cochrane Central Register of Controlled Trials; ClinicalTrials.gov) were supplemented with references from a previous targeted literature review and citation chasing. Screening was conducted by two independent reviewers. One reviewer rated the certainty of the overall body of evidence using the GRADE framework. The proportion [95% confidence interval adjusted for study-level clustering] of patients experiencing each outcome is presented.

There were 37 eligible studies (56 patients in total), all of which were observational studies. The patients ranged between 13 and 71 years of age (mean = 34.9 years) and 50.0% were male. Most cases (n = 31; 55.4%) originated in the USA, with 10 (17.9%) from Europe. Most patients were administered corticosteroids (85.7%), antibiotics (82.1%), and/or antivirals (75.0%). The GRADE quality of evidence was low.

Overall, 11/56 medically untreated patients (0.20 [0.08, 0.40]) were cured without surgical intervention, 38/56 (0.68 [0.48, 0.83]) had a keratoplasty, 4/56 (0.07 [0.03, 0.18]) had an enucleation, and 4/56 (0.07 [0.01, 0.29]) had minor surgery that proceeded a cure. In Table 7, a summary of the key evidence used to inform the cost-effectiveness model is presented, including the results of the untreated cases of AK SLR. The full report of the clinical SLR of untreated cases of AK that were conducted in 2023 is included in Annex A. In addition, the results of this SLR were also published [73].

Table 7 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Dart, J. K., Papa, V., Rama, P... & Minassian, D. C. (2024). The orphan drug for acanthamoeba keratitis (ODAK) trial: PHMB 0.08% (polihexanide) and placebo versus PHMB 0.02% and propamidine 0.1%. *Ophthalmology*, *131*(3), 277-287. [6]	Medical cure rate - intervention AK infection Poor vision and severe vision loss health states Recurrence of AK infection	Pivotal phase 3 trial for AK	Section 3.7 Section 4.1.8 Section 6.1.4 Section 8.3.1 Section 8.3.1.5 Section 10.3
Papa V, Bodicoat DH, Duarte AA, Dart JKG, De Francesco M. The Natural History of Acanthamoeba Keratitis: A Systematic Literature Review. Ophthalmol Ther. 2025 Jul;14(7):1369-1383. Erratum in: Ophthalmol Ther. 2025 Oct;14(10):2617-2620. [73]	Medical cure rate – comparator	Systematic literature review	Section 5.3 Section 6.1.5
Papa, V., Rama, P., Radford, C … & Dart, J. K. (2020). Acanthamoeba keratitis therapy: time to cure and visual outcome analysis for different antiamoebic therapies in 227 cases. *British Journal of Ophthalmology*, *104*(4), 575-581.[3]	Therapeutic surgery	Part of clinical development program for Akantior	Section 8.3.1.1
Rentz, A. M., Kowalski, J. W., Walt, J. G... & Revicki, D. A. (2014). Development of a preference-based index from the national eye institute visual function questionnaire–25. *JAMA ophthalmology*, *132*(3), 310-318.	Loss of eye functionality	Literature search	Section 10.3

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Data on file. Technical report: Results from two-round DELPHI panel on acanthamoeba keratitis in the United Kingdom [9]	Optical surgery Graft failure BVCA after penetrating keratoplasty: Loss of eye functionality BVCA after undergoing an optical surgery BVCA after a graft failure Recurrence of AK infection	n/a	Section 8.3.1 Section 10.2

6. Efficacy

6.1 Efficacy of Akantior compared to 'EMA comparator – no AAT in patients with Acanthamoeba keratitis

6.1.1 Relevant studies

There is no clinical study assessing the efficacy of Akantior versus placebo.

In the ODAK trial [6] Akantior plus placebo is compared with polihexanide 0.2 mg/ml plus propamidine 0.1%. While the primary endpoint of the trial was met, EMA acknowledged the efficacy of Akantior could not be compared to an unlicensed active control arm with an unclear magnitude of efficacy in a noninferiority assessment due to study design limitations [47]. Additionally, the active control arm does not reflect any available (unauthorised) treatment or management regimen used in real-world practice, hence further limiting interpretation of the results. The control product in combination with propamidine 0.1% was used similar to Akantior with a novel administration scheme and as part of a new protocol for the management of acanthamoeba keratitis. The ODAK trial also implemented a strict clinical management protocol, in which the administration of the experimental study drugs was embedded (Suppl. Figure S1 Dart et al. 2024). Compared to the real-world practice the polihexanide 0.02% used in the control arm differed significantly from the compounded equivalent (formulation and GMP-quality similar to Akantior). The pivotal ODAK study was thus to be regarded as a single-arm trial in effect, and historical control data (see below) was used in an indirect comparison to establish the absolute benefit-risk [1] [47].
A systematic literature search which was conducted to identify published data about clinical outcomes in untreated cases of Acanthamoeba keratitis. 'Untreated' was defined as not receiving a treatment with an established and clinically proven anti-amoebic activity as stated by the CDC (polihexanide, chlorhexidine, propamidine, hexamidine). The results of this systematic literature search were published by Papa et al. in 2025 [73] [75]

Table 8 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
ODAK, NCT03274895 / Dart et al. 2024 [6]	Prospective, randomized, double-masked, active-controlled, multicentre, phase 3 study	17/08/2017-18/06/2021	12 years of age or older and in vivo confocal microscopy with clinical findings consistent with AK	Akantior (0.8 mg/ml) + placebo (eye drops)	Polihexanide 0.2 mg/ml (+ propamidine 0.1% (1 mg/ml) (eye drops)	Primary: medical cure rate within 12 months Secondary: best-corrected visual acuity and treatment failure rates
Papa et al. 2025 [73] [75]	Systematic literature search	n/a SLR covering period 1970–1995.	Patients diagnosed with AK	'No treatment'. Defined as not receiving a treatment with an established and clinically proven anti-amoebic activity as stated by the CDC (polihexanide, chlorhexidine, propamidine, hexamidine.	n/a	The outcomes of interest were medical cure, therapeutic keratoplasty and enucleation. Proportions and 95% confidence intervals were estimated.

6.1.2 Comparability of studies

Given the absence of a direct head-to-head comparison between Akantior and the no-treatment arm, indirect treatment comparison analyses were conducted to estimate the relative efficacy of polihexanide 0.8 mg/ml versus the EMA comparator (no AAT arm). To support these analyses, a historical case report dataset had to be constructed from published studies. As a result, a formal feasibility assessment was not undertaken.

A systematic literature review of historical data was performed to identify a cohort of "untreated" patients with AK, with eligibility restricted to papers published between 1970 and 1995 [73] [75]. From this review, 37 articles were selected, yielding 56 eligible case reports for inclusion. The primary outcome measure in the ODAK trial was considered for these analyses (i.e., absolute difference between the cure without surgery rates within 12 months, see section 3.7). However, in the untreated AK cases, it was not possible to define a timepoint from the start of treatment, so cure was not necessarily within 12 months.

Comparability of patients across studies

Table 9 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	ODAK [6]	SLR historical untreated AK cases [73] [75]
	Akantior (intervention)	EMA comparator – no AAT
Mean age, years	35.2	34.9
% Male	40.9 (27/66)	50.0 (28/56)
Median time to treatment delay, days	19.0 (1.0, 177.0)	Nor reported
% Stage 3	16.7 (11/66)	Nor reported
% with prior use of corticosteroids	47.0 (31/66)	Nor reported
% with prior use of antivirals	25.8 (17/66)	Nor reported

Baseline characteristics of patients in studies included for the comparative analysis reported in Table 9 were based on clinical feedback on which factors are potential prognostic factors and/or treatment effect modifiers. Weighted regression methods were used in the ITC to adjust for the six identified factors. The method used in the ITC was a propensity scoring matching (PSM) analysis with overlap weighting (OW) to balance study populations before estimation of the treatment effect. However, comparisons with the historical untreated AK cases data from the SLR were only adjusted for age and sex. Treatment delay and prior use of corticosteroids or antivirals before treatment could not be defined as the patients were untreated. Disease stage was not reported in any of the studies. See *section 7* for further information on the ITC.

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Table 10 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age, mean (range)	38 (15-70) [17]	36.7 [6]
Gender, % female	49% [17]	49% [17]
Patient weight, kg	~70 kg	80 [37], [49]

The population in the health economic model is similar to that of the Danish AK patient population as described by Nielsen *et al*. [17]. The sex distribution is derived from this study, while the mean age is based on data from the Phase 3 ODAK trial. Additionally, patient weight is sourced from official Danish statistics on average weight.

6.1.4 Efficacy – results per ODAK

The clinical efficacy of Akantior was assessed in a randomized, double-blind, active-controlled phase III clinical trial (ODAK) [6]. The pivotal ODAK trial was an assessor-masked, randomized, active-controlled phase III study that enrolled 135 patients with acanthamoeba keratitis in 6 European ophthalmology centres, including Moorfields Eye Hospital in London (site of Principal Investigator, Professor John Dart) and San Raffaele in Milan. Patients were randomised 1:1 to either Akantior plus placebo (n=69), or combination of polihexanide 0.2 mg/ml plus propamidine 0.1% (n=66). The primary endpoint was the rate of medical cure achieved within 12 months of initiation of therapy. Medical cure was defined as no corneal inflammation requiring treatment; no or mild conjunctival inflammation; no limbitis, scleritis or anterior chamber inflammation; and no relapse within 30 days of discontinuing all topical therapy. Patients who required keratoplasty or discontinued treatment prematurely were considered failures.

In the intention-to-treat population (n=127), Akantior demonstrated an 84.8% clinical resolution rate (95% CI: 73.9%, 92.5%), compared to 88.5% (95% CI: 77.8%, 95.3%) in the comparator group.

While the primary endpoint of the trial was met, EMA acknowledged the efficacy of Akantior could not be compared to an unlicensed active control arm (experimental formulation of polihexanide 0.2 mg/ml plus propamidine 0.1%) with an unclear magnitude of efficacy in a noninferiority assessment due to study design limitations. Additionally, the active control arm does not reflect any available (unauthorised) treatment or management regimen used in real-world practice setting, hence further limiting interpretation of the results. The pivotal ODAK study was thus to be regarded as a single-arm trial in effect, and historical control data was used in an indirect comparison to establish the absolute benefit-risk [1] [47]. Akantior demonstrated a medical cure rate of 84.8% (56/66) patients in the ODAK trial versus 19.6% in a historical cohort of 56 patients not previously treated with anti-amoebic agents. Based on this data EMA concluded in

their assessment report that the *Committee for Medicinal Products for Human Use* that there is a clear absolute benefit of treatment with Akantior compared to no treatment.

Other efficacy results Akantior from ODAK:

- Five out of 66 (7.6 %) patients who received Akantior and did not meet the primary endpoint, required therapeutic keratoplasty and none of the patients (0%) required optical keratoplasty.
- No patients receiving Akantior relapsed within 90 days after discontinuation of the study medication
- Akantior demonstrated a clinically relevant impact on patients' vision-related and health-related quality of life. The median change from baseline was 22.1 using VFQ-25 composite score, and 14.5 using the EQ-5D-5L VAS score (with both scales ranging from 1 to 100; $p<0.0001$).
- A significant improvement in best corrected visual acuity (BCVA) was observed at study end ($p<0.0001$) compared to baseline (Avanzanite 2024 [50]) with 44 of 66 (66.7%) of Akantior-treated patients achieving normal or near-normal vision (Snellen 20/25 or better). None of the patients required optical surgery to improve the vision.
- In addition, 31 of 66 (48.4%) of Akantior-treated patients had no cornea scarring at the end of treatment.
- The mean treatment duration with Akantior was 139 days (table 25 in EPAR [47]).

7. Comparative analyses of efficacy

The relevant comparator for the current reimbursement application in Denmark is "no antiamoebic treatment". No direct comparison evidence is available. As mentioned in section 6.1.2, the historical case report dataset (including all "historical" patients with AK not treated with a biguanide with or without a diamidine) was constructed from published papers for the purpose of conducting ITC analyses.

Considering that individual patient data (IPD) was available from the two key sources for informing efficacy of Akantior (intervention) and EMA comparator – no AAT arm in AK patients (i.e., pivotal phase 3 RCT of polihexanide 0.8 mg/ml [6] and historical case report dataset constructed after conducting the SLR on people with diagnosed AK who were untreated, respectively [75]), ITC analyses were conducted using propensity scoring analysis (PSA) with overlap weighting (OW), that uses weighted regression methods with adjustment for key effect modifiers and prognostic factors of AK (identified as potential confounding variables) to attempt to balance study populations before estimation of the treatment effect, ensuring a fair comparison between the populations in each arm [1] [73] [76].

Clinical feedback was sought to identify which factors are 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; the delay in starting treatment (time to treatment delay). Comparisons with the historical untreated AK cases data from the SLR were only

adjusted for age and sex. Treatment delay and prior use of corticosteroids or antivirals before treatment could not be defined as the patients were untreated. Disease stage was not reported in any of the studies.

For the outcome of interest (i.e., cure without surgery within 12 months of starting treatment), both the absolute difference and the relative risk (RR) of achieving cure without surgery were estimated, each accompanied by a 95% confidence interval (CI). The absolute difference was estimated using logistic regression methods. To estimate the RR of achieving cure without surgery, a generalized linear model (GLM) with a binary distribution and a log link function was used.

7.1.1 ITC methodology selection

The decision to pursue an unanchored ITC 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. While the comparator arm in the ODAK trial nominally includes the combination of polihexanide 0.02% and propamidine 0.1%, a head-to-head comparison between Akantior and no antiamoebic treatment or placebo has not been performed. In addition, given the availability of IPD, ITC analyses were conducted using propensity scoring analysis (PSA) with overlap weighting (OW), to attempt to balance study populations before estimation of the treatment effect as mentioned at the beginning of this section [73] [76].

7.1.2 Differences in definitions of outcomes between studies

As mentioned in section 6.1.2, the primary outcome measure in the ODAK trial of medical cure rate within 12 months, was considered for the ITC analyses (i.e., absolute difference between the cure without surgery rates within 12 months, see section 3.7). However, in the untreated AK cases, it was not possible to define a timepoint from the start of treatment, so cure was not necessarily within 12 months. Despite this limitation, the construction of a historical cohort including all patients with AK not treated with a biguanide with or without a diamidine, is the best estimation for assessing the efficacy of EMA comparator – no AAT, reflecting the progression of AK following the natural history of the disease in untreated patients (see the full SLR report in Appendix A).

7.1.3 Method of synthesis

An indirect treatment comparison (ITC) was conducted to obtain comparative efficacy estimates between Akantior and EMA comparator – no AAT, in terms of relative risk of achieving a *medical cure within 12 months* from start of the treatment [73] [76].

Since individual patient-level data (IPD) were available for both the ODAK trial and the historical cohort of untreated patients, the implementation of a population-adjusted comparison method, aligning populations by weighting patients in both studies based on the similarity of their covariates was possible. Specifically, an ITC with propensity score matching (PSM) method with overlap weighting (OW) was conducted to obtain

comparative efficacy estimates between Akantior from ODAK trial (n=66) and from the historical cohort of untreated patients identified from the papers captured in the SLR conducted (n=56 cases).

The ITC estimated the adjusted relative risk (RR) of achieving a medical cure within 12 months from start of the treatment, between Akantior and the comparator (EMA comparator – no AAT).

Clinical advice (see section 14) was asked to identify which factors are 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; the delay in starting treatment (time to treatment delay). However, these variables were not reported consistently by the studies captured in the SLR for the historical cohort of untreated AK patients (included in the ITC); therefore, was limited to those factors which were available in each comparator data source, specifically sex and age.

The PSM with OW used a weighted regression methods with adjustment for key effect modifiers and prognostic factors of AK (age, sex for the comparison versus EMA comparator – no AAT, given the available data from the cases identified from the SLR) 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 [69]. This approach is well-established in the scientific literature and increasingly accepted by health technology assessment (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) [70,71].

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 Akantior and EMA comparator – no AAT. This method tends to produce more stable estimates and better covariate balance compared with other propensity scores methodologies (i.e., inverse weighting average treatment effect (ATE) and-inverse weighting effect of treated (ATT)). In PSM with OW, the estimand is based on the average treatment effect which can be generalised to the wider population of patients with AK.

A detailed description of the methodology and the full report of the ITC is provided in Appendix C.

7.1.4 Results from the comparative analysis

Table 11 Results from the comparative analysis on medical cure rate of Akantior vs. EMA comparator – no AAT for AK patients

Outcome measure	Akantior n/N (%; 95% CI[b])	EMA comparator – no AAT n/N (%; 95% CI[b])	Absolute % difference in medical cure rate (95% CI) vs comparator	Relative Risk of medical cure (95% CI) vs comparator
Medical cure without surgery, within 12 months	*Unadjusted* 56/66 (84.8%; CI: 73.9%, 92.5%)	*Unadjusted* 11/56* (19.6%; CI: 10.2%, 32.4%)	*Unadjusted* **65.2% (CI: 49.3%, 77.5%)**	*Unadjusted* **4.32 (CI: 2.52, 7.41)**
	Adjusted 55.8/65.4 (84.5%; CI: 75.8%, 93.3%)	*Adjusted* 11.1/55.6 (19.8%; CI: 9.4%, 30.2%)	*Adjusted* **64.7% (CI: 51.0%, 78.5%)**	*Adjusted* **4.27 (CI: 2.49, 7.33)**

References: 1, 73. b, 95% CI is based on binomial proportion. Bold denotes statistical significance at 5% level

**Number of patients with medical cure obtained from individual patient level data from the historical cohort if untreated AK patients created from the 37 publications captured in the SLR.*

7.1.5 Efficacy – results per [outcome measure]

Akantior had a statistically significantly higher cure without surgery rate compared with no AAT before weighting (65.2% [49.3%, 77.5%]) and in PSA analyses after weighting (64.7% [51.0%, 78.5%]).

Given the importance of this comparison in understanding the efficacy of Akantior, a tipping point sensitivity analysis was performed to test the impact of potential bias selection in the untreated cases. These analyses estimated how many additional untreated cases would need to be cured without surgery before Akantior is equivalent to, or worse than, no AAT, and were conducted as follows. Additional hypothetical untreated cases were added to the set of observed historical cases in increments of 20 up to 700 additional cases. These hypothetical cases were added with 'cure' set as yes and effect modifiers randomly sampled from the same distributions as observed in the existing historical cases. The risk difference comparing Akantior with no AAT was estimated using the same PSA with OW approach as above. This was repeated for a total of 30 imputations, each time adding x random, hypothetical patients to the analysis dataset. The results of the 30 imputations were then pooled to get the overall result for x additional patients. The average proportion of CRR was calculated per arm and the risk difference between arms was then calculated. The results are summarised and presented in tabular format in Table 12.

The tipping point analyses show that approximately 240 more untreated patients who were cured without medical or surgical intervention, and no additional untreated patients who required keratoplasty or enucleation, would need to have existed and not been

identified in the SLR before Akantior has no effect compared with no AAT (i.e. a risk difference of 0.0).

Table 12. Tipping point analyses comparing polihexanide 0.8 mg/ml vs no AAT (based on historical data) with additional hypothetical patients randomly sampled in increments of 20

N sampled patients added	Mean % CRR Difference	Lower 95% CI	Upper 95% CI	P-value
0	64.7%	51.0%	78.5%	<0.0001
20	43.9%	29.7%	58.0%	<0.0001
40	31.7%	18.3%	45.1%	<0.0001
60	23.6%	11.1%	36.2%	0.0002
80	18.0%	6.1%	29.9%	0.0029
100	13.8%	2.5%	25.2%	0.0170
120	10.5%	-0.4%	21.4%	0.0594
140	7.9%	-2.7%	18.4%	0.1451
160	5.7%	-4.6%	16.0%	0.2763
180	3.9%	-6.2%	14.0%	0.4471
200	2.4%	-7.5%	12.3%	0.6299
220	1.1%	-8.6%	10.9%	0.8184
240	0.0%	-9.6%	9.7%	0.9955
260	3.2%	-5.6%	12.0%	0.4710
280	2.3%	-6.4%	11.1%	0.5974
300	1.6%	-7.0%	10.2%	0.7170
320	0.9%	-7.7%	9.4%	0.8399
340	0.3%	-8.2%	8.8%	0.9518

360	-0.3%	-8.8%	8.1%	0.9419
380	-0.8%	-9.3%	7.6%	0.8443
400	-1.3%	-9.7%	7.1%	0.7600
420	-1.7%	-10.1%	6.6%	0.6834
440	-2.1%	-10.4%	6.2%	0.6169
460	-2.5%	-10.8%	5.8%	0.5580
480	-2.8%	-11.1%	5.5%	0.5066
500	-3.1%	-11.4%	5.1%	0.4570
520	-3.4%	-11.6%	4.8%	0.4146
540	-3.7%	-11.9%	4.5%	0.3779
560	-3.9%	-12.1%	4.2%	0.3457
580	-4.2%	-12.3%	4.0%	0.3171
600	-4.4%	-12.6%	3.8%	0.2909
620	-4.6%	-12.8%	3.5%	0.2678
640	-4.8%	-12.9%	3.3%	0.2467
660	-5.0%	-13.1%	3.1%	0.2283
680	-5.2%	-13.3%	2.9%	0.2117
700	-5.3%	-13.4%	2.8%	0.1967

8. Modelling of efficacy in the health economic analysis

If a cost-minimization analysis is performed, there may be parts of this section that are not relevant to complete. Please write 'Not applicable' in this case.

Not applicable

8.1 Presentation of efficacy data from the clinical documentation used in the model

Medical cure rate

The medical cure rate within 12 months (MCR_12m) was the primary endpoint in the ODAK trial. MCR_12m 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 randomization.

Medical cure rate within 12 months for Akantior

Treatment	MCR_12m
Akantior	84.85%

MCR_12m: Medical cure rate within 12 months. Source: ODAK trial (Dart et al, 2024 [6])

An ITC via propensity score matching method (following NICE DSU guidance) was conducted to estimate the comparative efficacy in terms of MCR_12 of Akantior versus EMA comparator – no AAT [73] [76]. The ITC used individual patient data (IPD) from the following two sources:

- Pivotal ODAK trial of Akantior [6]
- Historical cohort of “untreated” AK patients identified via SLR [73] [75]

The outcome of interest was cure without surgery within 12 months of starting AAT. However, in the untreated AK cases, it was not possible to define a timepoint from the start of treatment, so cure was not necessarily within 12 months.

A feasibility assessment was not undertaken because the historical case report dataset was constructed from published papers for the purpose of conducting ITC analyses.

The covariates included for adjustments based on clinical feedback were age, gender, AK disease stage, prior use of corticosteroids, prior use of antivirals, the delay in starting AAT. Comparisons with the historical untreated AK cases data from the SLR were only adjusted for age and sex. Treatment delay and prior use of corticosteroids or antivirals before treatment could not be defined as the patients were untreated. Disease stage was not reported in any of the studies. For further details on the ITC methodology, please see the full ITC report provided in Appendix C.

The results of the ITC via propensity score matching showed that Akantior had a statistically significantly higher cure rate without surgery compared with EMA comparator – no AAT before weighting and in propensity score matching analysis after weighting, with a relative risk (RR) of achieving MCR_12 of 4.27 95%CI=[2.49 – 7.33].

The inverse of the RR between Akantior and EMA comparator – no AAT obtained from the ITC was then applied to the MCR_12 of Akantior (ODAK trial):

- $84.8\% * \frac{1}{RR}\ for\ polihexanide\ 0.08\%\ vs$ EMA comparator $-$ no AAT where 84.8% the MCR_12 in Akantior arm [6]

Relative risk for Akantior versus EMA comparator – no AAT, based on the ITC [73]

Comparator	Comparator study included in the ITC	MCR_12, RR of Akantior vs comparator [95%CI]	MCR_12 in comparator arm
EMA comparator – no AAT	Historical cases of "untreated" AK patients	4.27 95%CI=[2.49 – 7.33]	19.9 %

AK: Acanthamoeba keratitis; EMA: European Medicine Agency; CI: Confidence interval; ITC: indirect treatment comparison; RR: Relative risk

8.1.1 Extrapolation of efficacy data

Not applicable

8.1.1.1 Extrapolation of [effect measure 1]

Table 13 Summary of assumptions associated with extrapolation of [effect measure]

Method/approach	Description/assumption
Data input	Not applicable
Model	Not applicable
Assumption of proportional hazards between intervention and comparator	Not applicable
Function with best AIC fit	Not applicable
Function with best BIC fit	Not applicable
Function with best visual fit	Not applicable
Function with best fit according to evaluation of smoothed hazard assumptions	Not applicable

Method/approach	Description/assumption
Validation of selected extrapolated curves (external evidence)	Not applicable
Function with the best fit according to external evidence	Not applicable
Selected parametric function in base case analysis	Not applicable
Adjustment of background mortality with data from Statistics Denmark	Not applicable
Adjustment for treatment switching/cross-over	Not applicable
Assumptions of waning effect	Not applicable
Assumptions of cure point	Not applicable

8.1.1.2 Extrapolation of [effect measure 2]

Not applicable

8.1.2 Calculation of transition probabilities

Table 14 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
AK infection	Good vision	The proportion of patients cured based on the MCR _12 multiplied by proportion with good vision after medical cure. Then, follow proportion of patients undergoing therapeutic surgery multiplied by proportion of good vision after therapeutic surgery.	Dart *et al*, 2024 [6] ODAK study (2024, data on file) Papa *et al*, 2025 [73] Papa *et al*, 2020 [3] Robaei *et al*, 2015 [10]
	Poor vision	The proportion of patients cured based on the MCR _12 month multiplied by proportion with poor vision after medical cure. Then, follow proportion of patients undergoing therapeutic surgery multiplied by proportion of poor vision after therapeutic surgery.	Dart *et al*, 2024 [6] ODAK study (2024, data on file) Papa *et al*, 2025 [73] Papa *et al*, 2020 [3] Robaei *et al*, 2015 [10]

AK infection	Severe vision loss	The proportion of patients cured based on the MCR _12 month multiplied by proportion with severe vision loss after medical cure. Then, follow proportion of patients undergoing therapeutic surgery multiplied by proportion of severe vision loss after therapeutic surgery.	Dart *et al*, 2024 [6] ODAK study (2024, data on file) Papa *et al*, 2025 [73] Papa *et al*, 2020 [3] Robaei *et al*, 2015 [10]
Cured GV, Or Cured PV, Or Cured SVL	AK infection	Movement from each of the respective health states to AK infection based on the percentage of patients that have a relapse in both arms. Different probabilities are applied for the 1st year and 2nd year onwards.	Dart *et al*, 2024 [6] ODAK study (2024, data on file) UK Delphi panel, 2023 [9]
AK infection	Loss of eye functionality	Follow the proportion of patients undergoing therapeutic surgery multiplied by proportion with loss of eye functionality after therapeutic surgery.	Papa *et al*, 2020 [3] UK Delphi panel, 2023 [9]
Cured PV, Or Cured SVL	Loss of Eye functionality	The proportion of patients going through optical surgery multiplied by the proportion having a loss of eye functionality due to surgery	UK Delphi panel, 2023 [9]
Any Health state	Death	General Population life tables	Key Figures including general mortality within the Danish population (DMC 2024)

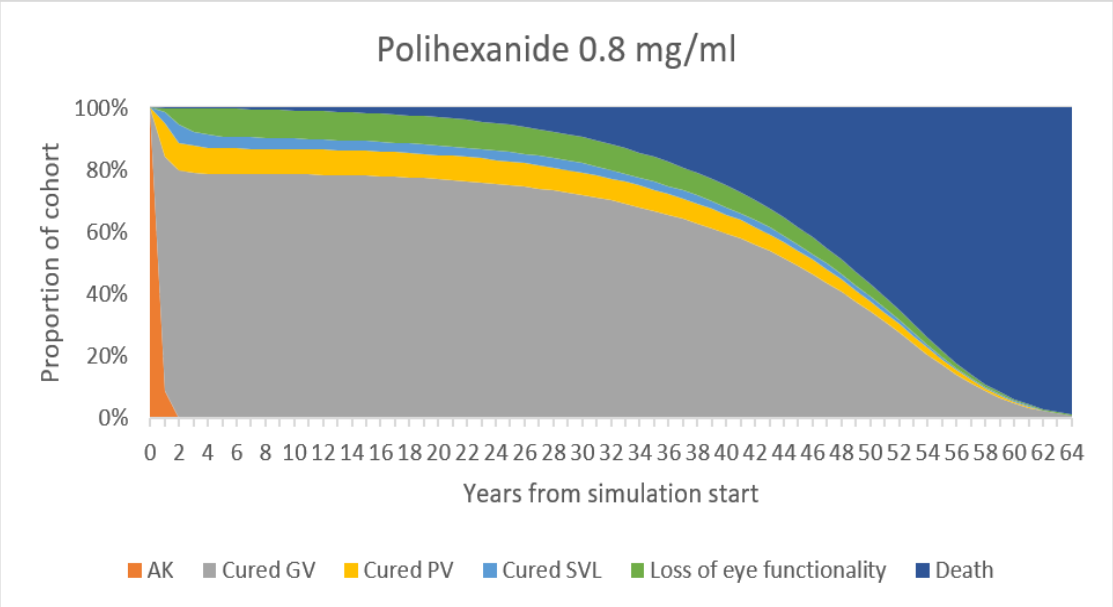


Figure 4 Proportion of patients in each health state in the Akantior arm

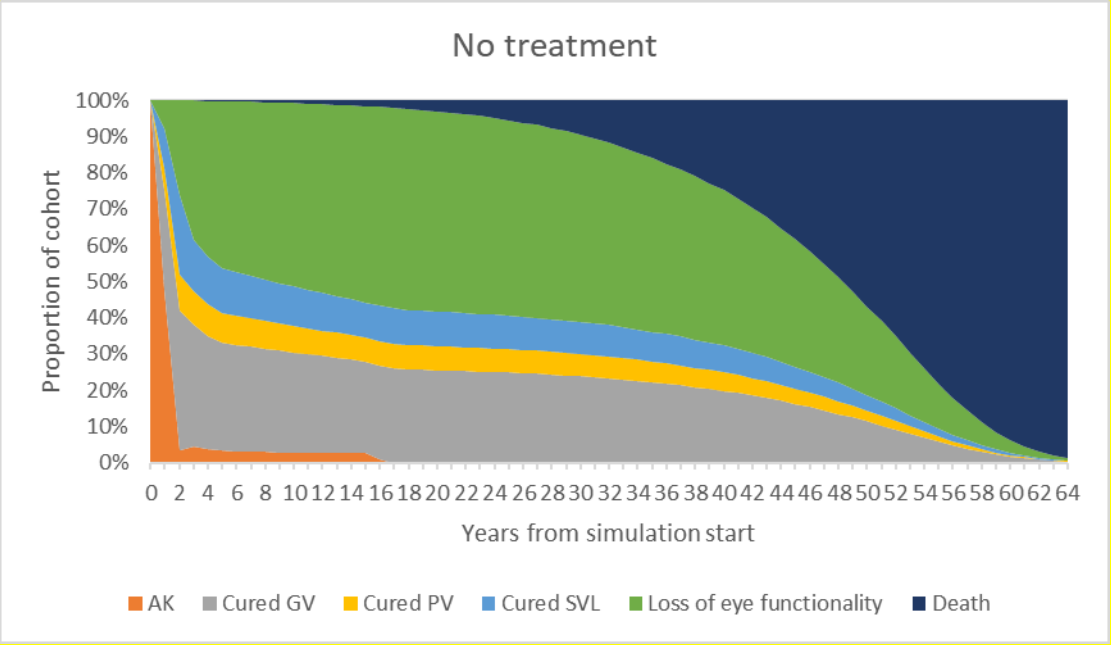


Figure 5 Proportion of patients in each health state in the EMA comparator – no AAT arm

8.2 Presentation of efficacy data from [additional documentation]

Not applicable

8.3 Modelling effects of subsequent treatments

Subsequent treatment lines do not differ between intervention and comparator. Subsequent treatment that is common for both intervention and comparator are presented under section *8.3.1 Clinical inputs*.

8.3.1 Clinical inputs

8.3.1.1 Therapeutic surgery

From published literature it is known that patients that may undergo a therapeutic keratoplasty, because of keratitis not responding to medical therapy, progression of keratitis towards the limbus, or impeding perforation [4], [51]. In the model, patients with AK unresponsive to medical 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 a study published by Papa et al [3] (see Table 15).

To estimate the proportion of patients that undergo therapeutic surgery in each treatment arm (Table 16), the proportion of patients undergoing surgery is applied to the proportion of patients that did not achieve a medical resolution with the initial treatment within 12 months.

Table 15 Proportion of patients undergoing therapeutic surgery

	Model input	Source/Notes
% patients not cured medically undergoing therapeutic surgery within 12 months	40.4% (=36/89)	Papa *et al* 2020 [3] Note: 89 is the number of patients who are not medically cured (either baseline AAT or after treatment switch) at 12 months: 227 (nr of patients in Blended AATs) 99 (nr of patients cured with baseline AAT) - 39 (nr of patients medically cured after treatment switch); 36 is the number of patients with surgery (Supplementary Appendix Table 1 in Papa et al [3]). The number of patients cured with baseline AAT (n=99) was provided by the authors, and it is not directly available in the publication.

Table 16 Proportion of patients estimated to undergo therapeutic surgery within 12 months per treatment arm:

	% patients undergoing therapeutic surgery within 12 months
Akantior	6.1%
EMA comparator – no AAT	32.4%

Source: Papa et al. 2020 [3], Dart et al. 2024 [6], RR for MCR_12m Akantior vs EMA comparator – no AAT from Papa et al. 2025 (historical cohort of « untreated » AK patients).

In current clinical practice, therapeutic surgeries are usually used as a last resort of treatment, after the recommended treatment of biguanides and diamidines fail, and the infection has progressed to an advanced stage [10], [44], [51]. Based on the UK Delphi panel, the mean typical time for a therapeutic surgery to take place is 141.7 days (approximately, 5 months) [9].

Note that all patients that do not achieve medical resolution within 2 years will be assumed to undergo therapeutic surgery. Often, following lack of response to available pharmacological treatment, cornea transplantation (which features, unfortunately, a high graft failure rate) may be attempted for some patients to prevent disease progression in emergency situations (therapeutic keratoplasty), or to restore vision (optical keratoplasty) [8], with some patients undergoing removal of the entire eye (enucleation/evisceration) as a rescue procedure.

Table 17 reports the type and distribution of therapeutic surgeries included in the analysis, which was based on a UK Delphi panel [9]. Table 18 reports the type and distribution of optical surgeries.

Table 17 Type and distribution of therapeutic surgeries included in the analysis

Therapeutic surgery	Distribution (%)
Penetrating keratoplasty	[redacted]
Deep anterior lamellar keratoplasty	[redacted]
Enucleation	[redacted]
Evisceration	[redacted]
Other	[redacted]

a Including amniotic membrane, combined amniotic membrane and penetrating keratoplasty, tarsorrhaphy, and conjunctival flap. The numbers were scaled to sum 100%.

8.3.1.2 Optical surgery

Optical surgeries are performed electively, for visual rehabilitation, on patients who had completed AAT, who were presumed to be cured of infection (resolved infection), and following resolution of ocular inflammation with significant corneal scarring and irregular astigmatism [10].

In the model, it was assumed that patients with PV or SVL who achieved resolution of infection with or without therapeutic surgery can undergo an optical surgery. Based on the UK Delphi panel, the percentage of patients undergoing optical surgery during their life is 41.9% and 46.0% for patients with PV and SVL, respectively [9]. The proportion of patients that are assumed to undergo optical surgery will first be on the waiting list for optical surgery and a mean waiting time for optical surgery is assumed to be 1 year; however, this has been validated by a UK clinician which mentioned that patients usually wait around 1 year (being the minimum 6 months).

It was assumed that patients who achieved a resolution of infection with good vision do not undergo an optical surgery. Based on feedback from UK clinicians, the decision to undergo an optical surgery is very patient specific, and a patient can undergo an optical surgery many years later. Nevertheless, there is a high burden on patients and their families and risk of transplant rejection and other complications.

The type and distribution of optical surgeries were derived from a Delphi panel held with clinical experts from the UK and are summarised in Table 18 [9].

Table 18 Type and distribution of optical surgeries included in the analysis

Therapeutic surgery	Distribution (%)
Optical keratoplasty	[redacted]
Evisceration	[redacted]
Cataract surgery	[redacted]
Deep anterior lamellar keratoplasty	[redacted]
Surgical correction for astigmatism	[redacted]

The numbers were scaled up to sum 100%.

8.3.1.3 Graft failure

Patients can experience a graft rejection after therapeutic or optical keratoplasty.

After a graft rejection, patients may or may not undergo further procedures (Table 19) as established based on the UK Delphi panel [9]. In the cases where patients will not undergo any further procedures, it was assumed that patients lose their eye functionality (see Section 8.3.1.4). For the patients that still undergo a graft failure, they will be distributed according to their BCVA (see Section 8.3.1.4).

Table 19 Procedures after a graft failure

Procedures after graft failure	Proportion (%)
Endothelial keratoplasty	[redacted]
Enucleation	[redacted]
Evisceration	[redacted]
No further procedures	[redacted]

Note that the numbers were scaled to sum 100%. Source: UK Delphi panel [9]

To estimate the probability of graft failure, data published by Veugen *et al* [8] was used. This study was a prospective Dutch registry study conducted to analyse graft survival after corneal transplantation for infectious keratitis (including AK) in the Netherlands. A total of 121 keratoplasties for AK were registered between 2007 and 2017.

Two Kaplan-Meier (KM) curves were available from Veugen *et al* [8]. The first KM curve, related to therapeutic keratoplasty, a second KM curve related to optical keratoplasty. Each of the Kaplan-Meier curves was digitized, and patient-level data were reconstructed relying on the Guyot method (based on the published numbers at risk). The number of patients at risk from year 3 onwards was rather small and for a model simplification, the probability of a graft failure was applied only up to 3 cycles (years) after surgery (Table 20

and Table 21). In the model, tunnel states were implemented to capture the moment in which patients underwent surgery.

In the model, it was assumed that the therapeutic surgeries for which graft failure could occur were penetrating keratoplasty, deep anterior lamellar keratoplasty, and other (amniotic membrane, amniotic membrane + penetrating keratoplasty, tarsorrhaphy, conjunctival flap). It was also assumed that the optical surgeries for which graft failure could occur were optical keratoplasty, deep anterior lamellar keratoplasty, and surgical correction.

Table 20 Yearly probability of graft failure - therapeutic keratoplasty

Year	S(t)*	1-year probability
0	100%	-
1	64%	0.36
2	52%	0.18
3	43%	0.17

* Reconstructed Kaplan-Meier data

Table 21 Yearly probability of graft failure - optical keratoplasty

Year	S(t)*	1-year probability
0	100%	-
1	92%	0.08
2	85%	0.08
3	78%	0.07

* Reconstructed Kaplan-Meier data

8.3.1.4 BCVA

After patients achieve a resolution of AK infection, they are distributed according to their vision outcomes, defined by the BCVA ranges: good vision, poor vision, severe vision loss, and loss of eye functionality. Note that the model allows for definition of a different distribution of the patients depending on whether patients were cured only medically or if a therapeutic surgery was required. Note that patients after a therapeutic surgery can lose the eye functionality and move to the health state “loss of eye functionality”.

Patients who achieved a clinical resolution of the infection can undergo an optical surgery for visual rehabilitation and are distributed according to the vision outcomes after the optical surgery. After a graft failure, patients are also distributed according to their vision outcomes.

8.3.1.4.1 After clinical resolution of the infection with medical treatment

Following cure, the cohort is distributed between vision acuity levels based on the observed distribution in patients achieving a medical cure in the Akantior arm of the ODAK trial. The same distribution is applied to both Akantior and EMA comparator – no AAT arms of the analyses (Table 22).

Table 22 BCVA after clinical resolution of the infection with medical treatment

BCVA	%	Notes/Source
Good vision	86.5%	Based on the end-of-study visit assessment available for 52 patients of Akantior arm from ODAK trial.
Poor vision	11.5%	
Severe vision loss	1.9%	

BCVA: Best-corrected vision acuity; IPD: Individual patient-level data [a] End-of-study visit

8.3.1.4.2 After clinical resolution of the infection with therapeutic surgery

The model allows setting different distributions of the patients for each type of surgery that they underwent (Table 23). Based on UK expert opinion, patients that undergo a therapeutic surgery tend to have a poorer outcome than patients achieving resolution of infection with medical treatment.

Table 23 BCVA after clinical resolution of the infection with therapeutic surgery

BCVA	%	Notes/Source
After penetrating keratoplasty		
Good vision	34.7%	Assumed to be the sum of the frequencies reported for "20/40", "20/30" and "20/20 or better" in Figure 1 from Robaei *et al* [10] Note that the plot was digitized with the software PlotDigitizer
Poor vision	11.6%	Assumed to be the sum of the frequencies reported for "20/200", "20/120", "20/80" and "20/60" in Figure 1 from Robaei *et al* [10] Note that the plot was digitized with the software PlotDigitizer
Severe vision loss	35.6%	Calculated as 1 minus the sum of the proportion with good vision, poor vision, and loss of eye functionality.
Loss of eye functionality	[redacted]	UK Delphi panel [9]
After deep lamellar keratoplasty		
Good vision	34.7%	Assumed the same as therapeutic keratoplasty
Poor vision	11.6%	
Severe vision loss	35.6%	
Loss of eye functionality	18.2%	
After enucleation		
Good vision	0.0%	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	0.0%	
Severe vision loss	0.0%	

BCVA	%	Notes/Source
Loss of eye functionality	100.0%	
After evisceration		
Good vision	0.0%	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	0.0%	
Severe vision loss	0.0%	
Loss of eye functionality	100.0%	
After others[a]		
Good vision	[redacted]	Assumed the same as therapeutic keratoplasty
Poor vision	[redacted]	
Severe vision loss	[redacted]	
Loss of eye functionality	[redacted]	

BCVA: Best-corrected vision acuity

8.3.1.4.3 After undergoing an optical surgery

Based on the literature, it is expected that the vision outcomes after an optical surgery are better than after a therapeutic surgery [10]. In the model, patients can either improve or worsen to the next BCVA range, remain on the same BCVA range, or lose the eye functionality. The distribution of the patients according to their BCVA after optical surgery is presented in Table 24 and was based on the findings of the UK Delphi panel [9].

Table 24 BCVA outcomes after an optical surgery

BCVA	%
Improved to the next BCVA range	[redacted]
Remain on the same BCVA range	[redacted]
Worsened to the next BCVA range	[redacted]
Loss of eye functionality	[redacted]

BCVA: Best-corrected vision acuity. Source: UK Delphi panel [9].

8.3.1.4.4 After a graft failure

The distribution of the patients according to their BCVA after a graft failure (either due to an optical or therapeutic surgery) is presented Table 25 and was based on the findings from the UK Delphi panel.

Table 25 BCVA outcomes after a graft failure

BCVA	%	Notes/Source
Good vision	[redacted]	[redacted] of the patients undergo an endothelial keratoplasty (Table 19) and of these [redacted] (Table 23) have good vision
Poor vision	[redacted]	[redacted] of the patients undergo an endothelial keratoplasty (Table 19) and of these [redacted] (Table 23) have poor vision
Severe vision loss	[redacted]	[redacted] of the patients undergo an endothelial keratoplasty (Table 19) and of these [redacted] (Table 23) have severe vision loss
Loss of eye functionality	[redacted]	[redacted] of the patients do not undergo further procedures after a graft failure. [redacted] of the patients undergo an enucleation (Table 19). [redacted] of the patients undergo an evisceration (Table 19) [redacted] of the patients undergo an endothelial keratoplasty (Table 19) and of these [redacted] (Table 23) lose their eye functionality

BCVA: Best-corrected vision acuity

8.3.1.5 Recurrence of the infection after clinical resolution of the infection

In the model, reoccurrence of AK infection is considered as an AK infection accruing after achieving a medical/surgical resolution of the infection and the patient is off treatment. 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). The cohort that experiences 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.

Note that in year 1, no reoccurrence of AK infection is applied for the Akantior arm as this reflects observations in the ODAK trial; this assumption is based on the fact that no recurrence of AK infection after achieving medical cure was observed during the ODAK trial or reported since the trial concluded. To date, no AK recurrence has been reported. Recurrence of infection is applied only in patients in the EMA comparator – no AAT arm that are in one of the good vision, poor vision, or severe vision loss health states, and it is derived from the feedback provided from the UK Delphi panel for the AK recurrence rate for current antimicrobial options to treat AK infections. As part of the scenario analyses presented in Section 12.2.3, a conservative assumption where recurrence rate for the comparator arm is set to 0% has been presented, given treatment specific data for this input is lacking for the no AAT arm.

The probability of reoccurrence of AK infection included in the model are presented on Table 26. Note that the probability of reoccurrence of AK infection is only applied up to 15 years of the time horizon. This assumption was validated by a UK clinician, who agreed 15

years appropriately represents the latest possible timepoint that AK may reoccur after an initial cure. In the base case for year 2+, no reoccurrence of AK infection is applied for the Akantior arm as this reflects data from the ODAK trial. Beyond Year 1, a lower probability of recurrence is applied in the model for the comparator arm to reflect that if recurrence does not occur within the first months after stopping treatment, then the likelihood of a recurrence thereafter is smaller.

Table 26 Per-cycle probability of recurrence of AK infection

Treatment	Model input	Source/Assumption
Patients with good vision, poor vision and severe vision loss who have a reoccurrence of AK infection during the year following resolution (Year 1)		
Akantior	0.0%	Assumption based that no reoccurrence of infection was observed during the ODAK trial
EMA comparator – no AAT	[redacted]	UK Delphi panel. 2023 [9]
After therapeutic surgery	4.55%	Bagga *et al*. Indian J Ophthalmol. 2020 PMID: 32056998 [52]. Considering both Advanced and mild keratitis. Adjusted for 3-year cycles.
Patients with good vision, poor vision, and severe vision loss who have a reoccurrence of AK infection two years following resolution and thereafter (Year 2+)*		
Akantior	0.0%	It is expected that higher concentration has a higher chance to kill the amoeba in cyst form, therefore preventing reoccurrences
EMA comparator – no AAT	[redacted]	UK Delphi panel. 2023 [9]
After therapeutic surgery	4.55%	Bagga *et al*. Indian J Ophthalmol. 2020 PMID: 32056998. Considering both Advanced and mild keratitis. Adjusted for 3 year cycles.

* These probabilities are only applied up to 15 years of the time horizon. This assumption was validated by a UK clinician.

AK: Acanthamoeba keratitis; AAT: Anti-amoebic therapies; EMA: European Medicine Agency

After a recurrence of AK infection in the EMA comparator – no AAT arm, patients move back to "AK infection" and initiate treatment with EMA comparator – no AAT. Based on UK clinician feedback, patients can be re-treated with initial treatment after reoccurrence of AK infection.

8.3.1.6 Mortality

AK is a potentially sight threatening disease and patients can have severe pain and inflammation. Even though the disease is not life threatening, there are patients that reach the point of wanting to commit suicide (based on testimonies reported in the AK patient journey https://www.youtube.com/watch?v=VsyAGrQ6WzQ&t=9s). However, given the lack of data to support any claim of higher mortality in any of the model health states, the analysis considers only the mortality associated with the general population. General population mortality is defined as age- and gender-specific all-cause mortality and has been included in the model based on country-specific mortality tables. In the base case, life tables were obtained from the checklist for formal requirements in applications to the Danish Medicines Council. The general mortality rate used in the model corresponds to the age of the cohort at each given cycle and has been adjusted based on the proportion of males in the analysis

8.3.1.7 Adverse events

Overall, Akantior was well tolerated, with most adverse events of mild or moderate severity. Only 1 Akantior patient discontinued treatment due to presumed toxicity. Ocular administration of polihexanide did not indicate any systemic safety events of concern. Adverse events were not included in the model.

8.3.1.8 Health-related quality of life (HRQoL)

A constraint was imposed in the model calculations engine, ensuring that utilities at any time do not exceed the utility associated with the general population per corresponding age [53].

8.3.1.9 General population utility values

The age-specific utility of the Danish general population was used to adjust the utility values for aging of the cohort over the time horizon of the analysis. The utility in the Danish general population by age was obtained from DMC website [54] following the Danish Medicines Council's standard sheet for age adjustment of utility values.

Coefficients of the linear and mixed models

Age range of the general population	Utility value
18–29	0.871
30–39	0.848
40–49	0.834
50-69	0.818
70-79	0.813
80+	0.721

Thus, in the first model cycle, the utility values are the following:

- Good vision: 0.8167
- Poor vision: 0.6918
- Very poor vision: 0.6213
- Loss of vision function: 0.4649

Then, from cycle 2 onwards, the utility value per health state is estimated considering the Danish population norms by age over time [54].

8.4 Other assumptions regarding efficacy in the model

8.4.1 Overview of modelled average treatment length and time in model health state

An overview of the duration of treatment reported for Akantior in ODAK trial and real-world sources is listed below:

- The overall median time to cure was 146 days across all 66 patients in the ODAK trial. However, it is important to consider that investigators also assessed infection resolution in patients who healed after 12 months, though these individuals were no longer receiving Akantior at that point (Dart et al., 2024 [6]).
- Among the 56 patients (84.8%) who achieved resolution within 12 months in the Akantior treatment arm, the median time to cure was 125 days (CSR ODAK [55]).
- Of greater practical relevance is the mean duration of treatment, as it better reflects real-world clinical practice. Mean treatment duration is also important for budget impact assessments. In the ODAK study, the mean exposure to Akantior (i.e., mean treatment duration) in the Safety Analysis Set (69 patients) was 138.3 days (EPAR, Table 25 [47]). All patients discontinued treatment upon resolution, and none experienced a recurrence within three months post-treatment (confirmed at the end-of-study visit 90 days after treatment discontinuation).
- It's also relevant to consider mean treatment duration with Akantior monotherapy in routine clinical settings (Franch *et al*. 2024 [2]). Using ODAK trial protocols—which mandated treatment cessation once cure was confirmed—11 patients (12 eyes; including one with bilateral disease) were treated for a median of 100 days, with a mean duration of 101 days. This shorter treatment period may be attributed to the absence of a placebo containing preservatives, which was used in the phase 3 ODAK trial.

Application of the comparator treatment EMA comparator – no AAT is associated with a median time to cure of 56.7 days. This figure is derived from individual patient level data

from the historical cohort of “untreated” AK patients identified from the SLR conducted. Considering only the cured patients from this cohort (n=11), and the correspondent time to cure, the median treatment duration was estimated (see Appendix 1 of the “Untreated cases of Acanthamoeba keratitis: Systematic literature review report” included as Data on file [75]).

In the current model, the mean duration of treatment values reported in Franch et al. 2024 and from data derived from the AK “untreated” historical cases, were used to inform Akantior and EMA comparator – no AAT, respectively (Table 27).

Table 27 Estimates in the model

	Modelled treatment length (reference in Excel)	Description
Akantior	101 days	Mean duration of treatment with polihexanide 0.8 mg/ml considering 11 patients included in the Franch *et al*. 2024 study [2].
EMA comparator – no AAT	56.7 days	Median time to cure derived from the historical “untreated” AK patients from the Papa et al. 2025 study [73] (estimated from individual patient data only from the 11 cured cases).

Table 28 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Health State	Akantior (time in health state -years)	EMA comparator – no AAT (time in health state- years)
AK infection	1.083	1.670
Cured - Good Vision	35.704	12.276
Cured - Poor Vision	3.658	3.204
Cured - Severe Vision Loss	1.518	4.767
Loss of Eye Functionality	4.075	24.120
Total	46.037	46.037
Note: Half cycle correction was included		

9. Safety

9.1 Safety data from the clinical documentation

The safety profile of Akantior is based primarily on the pivotal ODAK trial [6] and was assessed by EMA in their evaluation of Akantior [47]. No equivalent safety data exist for the comparator.

Table 29 Overview of safety events. State the time period the table covers.

	Intervention (N=69) ODAK trial [6] Table S14, S13, EPAR [47] Table 16, p. 65	Comparator (N=x) (source)	Difference, % (95 % CI)
Number of adverse events, n	83	n/a	n/a
Number and proportion of patients with ≥1 adverse events, n (%)	31 (44.9%)	n/a	n/a
Number of serious adverse events*, n	0	n/a	n/a
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	0 (0%)	n/a	n/a
Number of CTCAE grade ≥ 3 events, n	7	n/a	n/a
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	4 (5.8%)	n/a	n/a
Number of adverse reactions, n	n/a	n/a	n/a
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	n/a	n/a	n/a
Number and proportion of patients who had a dose reduction, n (%)	0	n/a	n/a
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	9 (13%)	n/a	n/a
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	7 (10%)	n/a	n/a

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition). § CTCAE v. 5.0 must be used if available.

No serious adverse events had a frequency over 5 percent.

Table 30 Serious adverse events (time point)

Adverse events	Intervention (N=x)		Comparator (N=x)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	n/a	n/a	n/a	n/a
…	n/a	n/a	n/a	n/a

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Adverse events were not considered in the health economic model.

Table 31 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)	n/a	n/a	n/a	n/a
[Add a new row for each adverse event included in the model]	n/a	n/a	n/a	n/a

9.2 Safety data from external literature applied in the health economic model

Safety data from external literature was not considered in the economic model.

Table 32 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n								

10. Documentation of health-related quality of life (HRQoL)

Table 33 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	ODAK trial [6]	Included (dis)utilities: Health states Health events Long-term conditions Caregivers (used for scenario analyses, not part of the base case analysis)

10.1 Presentation of the health-related quality of life: EQ-5D-5L

10.1.1 Study design and measuring instrument

EQ-5D-5L was collected from the ODAK trial [6], [55]. This is the same trial that informed the clinical effectiveness of Akantior. EQ-5D-5L was measured at baseline and at end-of-study.

10.1.2 Data collection

In the ODAK phase 3 trial EQ-5D-5L was measured at two points in time: baseline and end-of-study. The EQ-5D-5L instrument is a five-item questionnaire evaluating mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The EQ-5D-5L scores obtained in the ODAK trial were subsequently converted into utility values using the Danish value set published by Jensen et al. (2021).

Persons with missing data were not used in the estimation of HRQoL. In the ODAK trial the amount of missing data was considered negligible and too few to allow recognition of a missingness pattern. Information obtained from Dart et al. [6] Table S10.

Table 34 Pattern of missing data and completion including the ODAK intervention and comparator arms

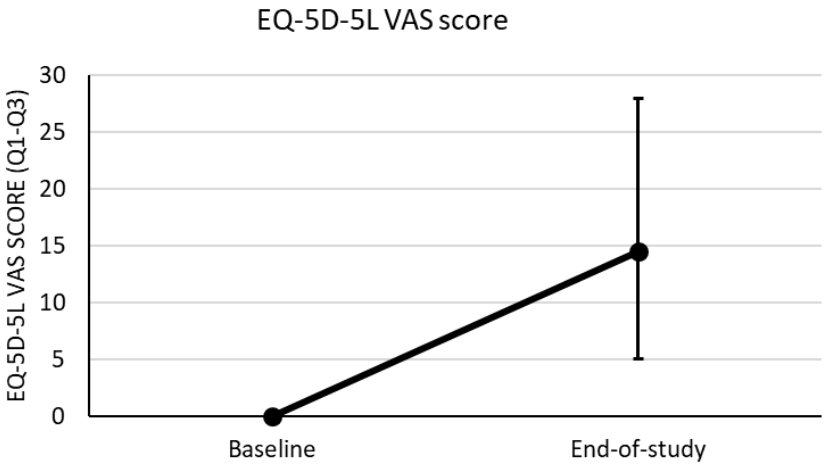
Intervention arm – ODAK study				
Time point	**HRQoL population N**	**Missing N (%)**	**Expected to complete N**	**Completion N (%)**
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	66	1 (1.5%)	65	65 (98.5%)
Time point 1 (end-of-study)	66	5 (8%)	61	61 (92%)
Baseline	61	3 (4.9%)	58	58 (95.0%)
Time point 1 (end-of-study)	61	6 (9.8%)	55	55 (90.2%)

Source: Dart et al. [6] Table S10

10.1.3 HRQoL results

The figure below illustrates the median change in EQ-5D-5L VAS scores from baseline to end-of-study for Akantior, as observed in the ODAK trial. The median change was 14.5 points on the EQ-5D-5L VAS scale. It should be noted that the ODAK trial did not include the comparator used in this application, and no equivalent data are available for the comparator. The error bars represent the first quartile (Q1) and third quartile (Q3) values for the change from baseline. 95% confidence intervals were not estimated.

Similarly, Table 35 presents the median EQ-5D-5L VAS scores at baseline and end-of-study, along with measures of statistical dispersion (Q1 and Q3). Standard errors or 95% confidence intervals were not computed.



No. of patients intervention	65	61

Median change in EQ-5D-5L VAS score from baseline, comparator (no data available on intervention) error bars represent Q1 and Q3.

Table 35 HRQoL EQ-5D-5L VAS score summary statistics

	Intervention		Comparator		Intervention vs. comparator
	N	Median (Q1, Q3)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	65	73.0 (57.5, 85.0)	n/a	n/a	n/a
End-of-study	61	95.0 80.0, 99.0)	n/a	n/a	n/a

Results of the EQ-5D-5L index score at baseline and end-of-study are described in Table 36.

Table 36. EQ-5D-5L index score - ODAK trial at baseline and at the end of study visit

	Intervention			Comparator		
	N	**Mean ± SE**	**Median (Min, Max)**	**N**	**Mean ± SE**	**Median (Min, Max)**
Baseline	64	0.74±0.03	0.84, (0.01 , 1.00)	59	0.69±0.04	0.80, (-0.004 , 1.00)

	Intervention			Comparator		
End-of-study	58	0.95±0.01	1.00, (0.47 , 1.00)	51	0.93±0.02	1.00, (0.21 , 1.00)

10.2 Health state utility values (HSUVs) used in the health economic model

Health states are designed to capture all the relevant costs and consequences of the disease and its treatment pathway. The relevance of defining different health states is determined by considering the difference in costs and consequences compared with the other health states [39].

Costs and quality-of-life in patients with AK are expected to vary depending on whether the AK infection is active and on the level of visual impairment achieved following AK infection resolution. In the model, visual impairment was defined based on the BCVA levels of patients after patients achieve AK infection resolution (with or without therapeutic surgery). 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 license in European countries [40], [41]. 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. study [3] and the classification of severity of vision impairment defined by World Health Organization (WHO) [42].

A constraint was imposed in the model calculations engine, ensuring that utilities at any time do not exceed the utility associated with the general population per corresponding age and gender [53].

Table 37 Definitions of model health states

Health state	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 ≥20/40
Poor vision	Patients who achieved a resolution of the AK infection (with or without therapeutic surgery) with BCVA ≥20/200 and <20/40
Severe vision loss	Patients who achieved a resolution of the AK infection (with or without therapeutic surgery) with BCVA <20/200
Loss of eye functionality	Patients who lose the eye functionality due to the removal of the eye's content and/or entire globe, or other type of

Health state	Definition
	surgeries, or in case patients do not undergo further procedures after a graft failure

AK: Acanthamoeba keratitis; AAT: Anti-amoebic therapy; BCVA: Best-corrected vision acuity

General population utility values

The gender- and age-specific utility of the Danish general population was used to adjust the utility values for aging of the cohort over the time horizon of the analysis. The utility in the Danish general population by age was obtained from DMC website [54].

Table 38 Coefficients of the linear and mixed models

Age range of the general population	Utility value
18–29	0.871
30–39	0.848
40–49	0.834
50–69	0.818
70–79	0.813
80+	0.721

10.2.1 HSUV calculation

Health related quality of life (HRQoL) estimates were collected during the ODAK trial (see Table 39). 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 scores obtained from the ODAK trial were mapped to Danish value set using Jensen et al. 2021 [57]. The utility values at baseline of the ODAK trial and stratified by visual acuity level are presented in Table 39 and Table 40, respectively.

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 Danish population. 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 41.

AK infection disutility

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 Danish value set published by Jensen et al. (2021). 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 0.7172, standard error [SE] = 0.023). Using a maximum utility of 1.0 as the anchor, the disutility of AK infection was calculated as:

Disutility = 0.7172– 1 = –0.2828 (value used in the submitted model)

An alternative scenario was also considered, in which the anchor was the average utility of patients in the ODAK trial who had good vision, estimated at 0.9553. Under this assumption, the disutility of AK infection was:

Disutility = 0.7172– 0.9553= –0.2381

Cured with good vision, cured with poor vision, cured with severe vision loss disutility

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-sates (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 utilized 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.

Loss of eye functionality disutility

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.) were used to derive utilities for this health state (see section 10.3).

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, with no disutility applied. A constraint

was imposed that utilities at any time cannot exceed the utility of the general population with corresponding age and sex.

Table 39. EQ5D utility values at baseline from ODAK trial (Denmark tariffs)

Parameter	**Mean** utility **± SE (N)**	**Source**
ODAK trial at baseline, Akantior arm	[redacted]	Post-hoc analysis of ODAK trial EQ-5D data, applying Danish tariffs (Jensen et al. 2021) – Descriptive analysis by arm, All subjects, baseline visit
ODAK trial at baseline – polihexanide 0.02% + propamidine 0.1% arm	[redacted]	
ODAK trial at baseline – all arms	[redacted]	

BCVA: Best-corrected vision acuity; MMRM: Mixed model repeated measure; QoL: quality of life

Table 40. Baseline utilities stratified visual acuity catergories - ODAK trial (Denmark tariffs)

Health state defined by BCVA	**Mean** utility **± SE (N)**	**Source**
Good vision	[redacted]	Post-hoc analysis of ODAK trial EQ-5D data, applying Danish tariffs (Jensen et al. 2021) – Descriptive analysis by BCVA status, All subjects
Poor vision	[redacted]	
Severe vision loss	[redacted]	

BCVA: Best-corrected vision acuity; MMRM: Mixed model repeated measure; QoL: quality of life

A mixed model for repeated measure (MMRM) was fitted to ODAK data to estimate health state utility values (Table 41). The analysis was conducted using SAS. The objective was to estimate EQ-5D-5L utility values associated with visual acuity category, defined based on BCVA, while appropriately accounting for repeated measurements within patients.

The mixed model is an extension of the linear model and is used to analyse longitudinal data from multiple patients. With longitudinal data, the EQ-5D observations belonging to the same patient have a higher correlation. Because of that, the results of a linear model could be misleading as they may reflect a pattern that is only observable in the aggregate data, but different from what would be observed if the data from a single patient were considered. The mixed model addresses this issue by acknowledging that the longitudinal EQ-5D observations from each patient may have a different pattern. Thus, the parameters of the model, which refer to the entire population and not to a specific patient, are subject to a certain degree of uncertainty and vary randomly within a certain range.

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-sates (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 utilized 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 MMRM was based on the following equation (repeated measures within patient were modeled using an unstructured covariance matrix for ε):

$$HRQoL=\beta 0+\beta PV(PoorVision)+\beta SVL(SevereVisionLoss)+\varepsilon$$

Where:

- β0 is the fixed term, which represents the HRQoL in the reference category (good vision).
- βPV: coeffient, mean difference (utility decrement) for poor vision vs good vision.
- βSVL: mean difference (utility decrement) for severe vision loss vs good vision.
- ε is the residual error term.

Table 41 Mixed model repeated measures (MMRM) using GV as intercept (pooled cured/not cured observations) based on ODAK study data

Disutility vs "Cured with good vision"	Estimate	Standard Error	95% Confidence intervals	
			Lower	Upper

AK infection[a]	-0.283	0.023	-0.328	-0.238
Good vision (Intercept) [a]	0.9553	0.0100	0.936	0.975
Poor vision after AK resolution[a]	-0.077	0.026	-0.128	-0.026
Severe vision loss after AK resolution[a]	-0.102	0.077	-0.254	0.049
Loss of eye functionality[b]	-0.248	0.025	-0.296	-0.199

AK: Acanthamoeba keratitis; BCVA: Best-corrected vision acuity; MMRM: Mixed model repeated measures; [a]Source: ODAK trial- Danish Tariffs; [b]Source: Rentz et al. 2014

10.2.1.1 Mapping

For the Danish EQ-5D-5L set, a nationally representative sample based on age (> 18 years), gender, education, and geographical region was recruited using data provided by Statistics Denmark. Computer-assisted personal interviews were carried out using the EQ-VT 2.1. Respondents each valued ten health states using composite time trade-off (cTTO) and seven health states using discrete-choice experiment (DCE). Different predictive models were explored using cTTO and DCE data alone or in combination as hybrid models [57].

10.2.2 Disutility calculation

Disutilities associated with events

In the base case, a disutility is applied for therapeutic and optical surgery (-0.14). This was previously used in the a NICE submission for cataract (HST11) and was considered acceptable.

In the base case, a graft failure disutility is also included, which is assumed to be the same as loss of eye functionality (Table 46). This is assumed to be 2/5 of the difference between 0.8835 (average between the utility scores estimated for “111111” and “211111” assumed to be good vision) and 0.264 (utility score for “555555” assumed to be loss of eye functionality) reported by Rentz et al [12]. The 2/5 estimation is to indicate relative QoL impact of unilateral vs bilateral blindness. This study looked at 607 participants from 4 countries to describe elicitation of preferences for health states generated from the Visual Function Questionnaire-Utility Index health state classification. Subsequently, it was deemed appropriate to use in the base case.

Table 42 Long-term conditions by health state

	Proportion of patients (%)	
	Intense and constant lacrimation / Photophobia / Pain	Depression / Anxiety
Good vision	[redacted]	[redacted]
Poor vision	[redacted]	[redacted]
Severe vision loss	[redacted]	[redacted]
Loss of eye functionality	[redacted]	[redacted]

Source: UK Delphi panel [9]

Table 43 Disutilities associated with long-term conditions by health state estimated using a multiplicative approach

	Model input
Good vision	[redacted]
Poor vision	[redacted]
Severe vision loss	[redacted]
Loss of eye functionality	[redacted]

Source: UK Delphi panel [9], Van Wilder [11] and Ara et Brazier [48]

On-going disutilities associated with long-term conditions

After achieving AK resolution, patients may still experience long-term pain, lacrimation, photophobia, anxiety, and depression which leads to poorer quality-of-life.

The disutilities by health state reported in Section 10.2 were estimated based on the data from the ODAK trial. Given that the trial had a 12-month duration, it is unlikely that the impact of long-term conditions, such as lacrimation/photophobia/pain and anxiety/depression, was captured. Therefore, disutilities associated with these long-term conditions were derived from and, combined using a multiplicative approach to calculate disutility for patients with multiple conditions based on the prevalence of each, and applied to each of the health states.

As previously discussed in this dossier, 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. Therefore, additional disutilities associated with these complications were derived from Van Wilder [11] (a comprehensive catalogue of EQ-5D utility decrements associated with chronic disorders)

and Ara et Brazier [48] (Table 44) and combined using a multiplicative approach to calculate disutilities for patients with multiple conditions based on the prevalence of each. The utility decrement was applied to each of the health states, based on the proportion of patients experiencing each complication, as reported in the Delphi panel. A summary of the disutilities associated with long-term complications following AK resolution is presented in Table 45. Disutilities were applied to both the Akantior and the comparator arm of the model.

Table 44: 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)
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; Ara and Brazier, 2011.

Table 45: Disutilities associated with long-term complications

Health state	Utility decrement
Cured with good vision	[redacted]
Cured with poor vision	[redacted]
Cured with severe vision loss	[redacted]
Loss of eye functionality	[redacted]

Sources: SIFI Delphi Panel 2023; Van Wilder 2019; Ara and Brazier 2011.

Caregivers

No studies were identified where caregivers' disutility in AK was reported.

In cases where the indication and its treatment impacts not only the quality of life (QoL) of patients, but also the QoL of their caregivers, it is appropriate to implement caregiver disutilities to complete a comprehensive cost-effectiveness assessment. Given the impairment of patients during the AK infection, the impairment associated with events such as surgeries and graft failure, and the likelihood of severe vision impairment thereafter, it was pertinent including the disutility associated with caregivers as part of the sensitivity analyses for the current model, considering DMC guidelines do not consider the inclusion of caregivers disutilities as part of the base case analysis.

A test was conducted where caregivers' disutilities and costs were considered. Given the nature of the illness, it was assumed the caregiver disutility is applicable to 100% of patients in this scenario. The approach for caregiver disutility implementation was nominal disutility applied over a timeframe. Under this approach, a utility decrement of -0.04, accounting for the disutility incurred by caregivers, is applied. The utility decrement

associated with the occurrence of each relevant clinical event is estimated by multiplying the utility decrement (-0.041) by the proportion of patients concerned for a certain duration (Table 46 *Caregivers' disutilities*). As this estimate is based on NICE HST11 [58], [59].

10.2.3 HSUV results

EQ-5D-5L is a generic instrument to capture patient-reported outcomes. For the Danish EQ-5D-5L set, a nationally representative sample based on age (> 18 years), gender, education, and geographical region was recruited using data provided by Statistics Denmark. Computer-assisted personal interviews were carried out using the EQ-VT 2.1. Respondents each valued ten health states using composite time trade-off (cTTO) and seven health states using discrete-choice experiment (DCE). Different predictive models were explored using cTTO and DCE data alone or in combination as hybrid models

In the base case analysis, the disutility values applied by health state are presented in Table 46. Note that for patients after AK infection resolution with good vision, it was assumed the same HRQoL as for the general population and no disutility is applied.

Table 46 Overview of health state utility values [and disutilities]				
	Results [95% CI]	**Instrument**	**Tariff (value set) used**	**Comments**
HSUVs				
AK infection	-0.283 (-0.328; -0.238)	EQ-5D-5L	DK	Assumption based on baseline utility value using data from the ODAK study (2024) [6]; Descriptive analysis of EQ5D utility values (Denmark tariffs, Jensen et al. 2021 [57]).
Cured with poor vision Cured with severe vision loss	-0.077 (-0.128;-0.026) -0.102 (-0.254;0.049)	EQ-5D-5L	DK	Based on Analyses from 03-12-2024 (data-on-file); MMRM using GV (pooled cured/not cured) as intercept- Danish Tariffs [56] See Table 41.
Loss of eye functionality	-0.248 (-0.296; -0.199)	EQ-5D-5L		Assumed 2/5 of the difference between 0.8835 (average between the utility scores estimated for "111111" and "211111" assumed to be good vision) and 0.264 (utility score for "555555" assumed to be loss of eye functionality) reported by Rentz et al [12]
Disutilities				
Therapeutic surgery	-0.140 (-0.167; -0.113)	EQ-5D-5L	UK	Duration:121.75 Assumed to be same as cataract reported on NICE HST11 [58] The duration is assumed to be the average 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. The maximum duration (4 months) was applied. (https://www.nhs.uk/conditions/cornea-transplant/recovery/)
Graft rejection	-0.248 (-0.296; -0.199)	EQ-5D-5L		Duration: 141.7 Assumed to be the same as loss of eye functionality The duration is assumed to be the same as waiting time to therapeutic surgery based on the UK Delphi panel [11].

Table 46 Overview of health state utility values [and disutilities]				
	Results [95% CI]	**Instrument**	**Tariff (value set) used**	**Comments**
Optical surgery	-0.140 (-0.167; -0.113)	EQ-5D-5L		Duration: 121.75 Assumed the same as therapeutic surgery.
On-going disutilities associated with long-term conditions				
Intense and constant lacrimation/ Photophobia/ Pain	-0.0647			Average between -0.03 (Lacrimal system disorder, GBR, Van Wilder 2019 [11]), -0.053 (Other eye complaints difference between 0.794 and 0.741, Ara & Brazier 2011 [48]), -0.111 (migraine/headaches; difference between 0.888 and 0.777; Ara & Brazier 2011 [48])
Depression/ Anxiety	-0.1910			Average between -0.1120 (depressive disorders, Van Wilder 2019) and -0.272 (mental illness/anxiety/depression; difference between 0.878 and 0.606; Ara et Brazier 2011) [11] [48]
Caregivers' disutilities (not included in the base case analysis)				
Therapeutic surgery Optical surgery	-0.040 (-0.48;-0.032) -0.040 (-0.48;-0.032)			Duration: 121.75 Proportion of patients to which caregivers' disutility is applied: 100% - assumption for application to any patient upon occurrence of event Duration: Patients can return to work between 2 weeks and 4 months. The maximum duration was applied. https://www.nhs.uk/conditions/cornea-transplant/recovery/
Graft failure	-0.040 (-0.48;-0.032)			Duration: 141.5 Proportion of patients to which caregivers' disutility is applied: 100% - assumption for application to any patient upon occurrence of event Proportion of patients to which graft failure is applied: 35% - % of patients with further procedures after a graft failure (UK Delphi panel) [9] Duration: Assumed the same as waiting time to therapeutic surgery (based on UK Delphi panel)
Severe vision loss or loss of eye functionality	-0.040 (-0.48;-0.032)			Duration: n/a

Table 46 Overview of health state utility values [and disutilities]			
Results [95% CI]	Instrument	Tariff (value set) used	Comments
			Proportion of patients concerned in base case: 100% - assumption for application to any patient upon occurrence of event

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Rentz *et al* [12] was used as the source for loss of eye functionality in the base case.

10.3.1 Study design

Rentz et al [12] 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). 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 Visual Function Questionnaire-25 (NEI VFQ-25) was selected as 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.

10.3.2 Data collection

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 characteristics of the sample were representative of adults in the selected countries rather than a clinical population with ocular conditions. This difference could affect the

generalisability of the utility values to patients with severe vision loss, as their experiences may give other valuations of health states. However, for the use case in this application and in the health economic model, the scale was considered the best available for inferring disutility related to loss of eye functionality (and other disutilities). Loss of eye functionality utility decrement is assumed to be 2/5 of the difference be-tween 0.8835 (average between the utility scores estimated for "111111" and "211111" assumed to be good vision) and 0.264 (utility score for "555555" assumed to be loss of eye functionality). The 2/5 estimation is to indicate relative QoL impact of unilateral vs bilateral blindness.

10.3.3 HRQoL Results

Not applicable.

10.3.4 HSUV and disutility results

Table 47 Overview of literature-based health state utility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Loss of eye functionality				
Rentz et al.	-0.248 (-0.296, -0.199)	EQ-5D-5L		Assumed 2/5 of the difference between 0.8835 (average between the utility scores estimated for "111111" and "211111" assumed to be good vision) and 0.264 (utility score for "555555" assumed to be loss of eye functionality) reported by Rentz et al [12]

As an alternative source for informing the utility decrement associated with Loss of eye functionality health state, the study by Brown et al. (2018) (Brown GC et al., Ophthalmology, 2018;125(7):965–971) was identified, which examined vision-related quality of life in patients with unilateral or bilateral ocular conditions. The study included a total of 586 patients with at least one ophthalmic disease (e.g., cataract, diabetic retinopathy, age-related macular degeneration). All participants had best-corrected visual acuity of 20/20 to 20/25 in at least one eye. This study has been selected as an alternative considering the lack of published literature on QoL impact in patients with unilateral AK; using this publication, unilateral visual impairment independently of the baseline disease can be considered as a proxy for the current application.

For the purposes of analysis, participants were categorized into six cohorts based on the best-corrected Snellen visual acuity in the poorer-seeing eye, while maintaining the requirement that the better-seeing eye had 20/20 to 20/25 vision:

- Cohort 1: No light perception
- Cohort 2: Counting fingers to light perception
- Cohort 3: 20/200 to 20/400
- Cohort 4: 20/60 to 20/100

- Cohort 5: 20/30 to 20/50
- Cohort 6: 20/20 to 20/25

This classification enabled the study to evaluate how decreasing vision in the poorer-seeing eye affects overall vision-related quality of life, even when the better-seeing eye retains normal or near-normal acuity.

Table 48. Brown et al. 2018 clarification

Visual Acuity in the Eye with Poorest Vision	Number of participants	Mean utility	Standard deviation	95% CI	Disutility (calculation vs Cohort 6)*
Cohort 1	21	0.79	0.19	0.73-0.89	-0.15
Cohort 2	67	0.87	0.17	0.83-0.91	-0.07
Cohort 3	43	0.88	0.16	0.84-0.90	-0.06
Cohort 4	70	0.88	0.16	0.84-0.91	-0.06
Cohort 5	106	0.87	0.14	0.84-0.90	-0.07
Cohort 6	279	0.94	0.12	0.93-0.95	Reference

*Calculation by the difference of the mean utility reported by cohort, using as reference cohort 6 (BCVA 20/20 to 20/25)

Given the existence of data from the primary clinical trial of Akantior to inform the utility decrement associated with AK infection, cured with poor vision, and cured with severe vision loss health states, these disutilities came from a reliable and robust source and are based on the best existing data specifically for AK patients. Given the lack of direct data from the ODAK trial to estimate utility decrement associated with loss of eye functionality health state, a scenario analysis using the disutility estimated from the publication by Brown et al 2018 has be tested.

11. Resource use and associated costs

The costs were presented in 2024 or 2025 DKK, based on the latest available data. The DMC guidelines for assessing new pharmaceuticals recommend “All costs that do not have a present value should be projected using the consumer price index without energy” using Table PRIS114 on the Statistics Denmark website [33]. Subsequently, where needed, costs were inflated to 2024 price levels using the Consumer Price Index from this source [60].

Furthermore, DMC guidelines state that “Exchange rates should be based on the annual average for the relevant year, as calculated by Denmark’s National bank (Central Bank of Denmark)” [61]. Subsequently, where required, costs were converted from EUR to DKK using the exchange rates provided by this source [62]. Other costs were taken directly from DRG Tariffs 2025, or medicinpriser.dk (2024 prices) [63].

Most of the prices included in the model were available and derived from medicinpriser.dk. When the price of a medication required in the model was not publicly available in Denmark, the cost was retrieved from other sources and converted to DKK as stated in the guidelines.

This price was retrieved from external sources:

- *Celluvisic (carmellose sodium 10 mg/ml) (S01XA20)*. No prices available at medicinpriser.dk. Retail price at Danish pharmacies for Celluvisc 30 pc. range between 54 to 63 DKK. Since no official AIP is available from Danish sources, the price from the Netherlands was used as a proxy for estimating a price relevant to the Danish context. The price used was 92.71 DKK (12.43 EUR) using the correspondent exchange factor reported in the Denmark’s National bank as per the local guidelines. This approach was decided given the lack of a publicly available localised AIP.

Overall, due to the absence of publicly available Danish prices and the exclusion of import costs, this approach should be considered a conservative estimate of the above drug cost.

The costs included in the analysis cover:

- Drug acquisition
- Concomitant medication
- Surgical procedures
    - Therapeutic surgeries: pre-surgery, surgery, complications, and systemic therapies
    - Optical surgeries: pre-surgery and surgery
    - Graft failure
- Health-care resource use
- Use of Time costs

11.1 Medicines - intervention and comparator

The comparator of interest for the current application does not consider treatments with antiamoebic properties. Thus, a description of the posology and frequency of administration of the intervention only, is presented in this section.

Table 49 Antiamoebic treatments in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing	Expiration (days) after opening
Akantior	0.3 ml	Not applicable	See Table 50	no	28

Table 50 Dose frequency and quantity per day for antiamoebic treatments

Treatment phase	Days	Dose frequency, hour interval (day-time only)	Nr. drops per day
Akantior			
Intensive	1–5	1	16
	6–12	2	8
	13–19	3	6
Maintenance	20+	4	4

AAT: Anti-amoebic therapy

Source: Clinical Study Report ODAK trial [55]; Source: UK clinical expert feedback

Akantior is the first licensed treatment for AK. It is administered in a day-time only regimen and overall less burdensome treatment protocol (

Table 50 for dosing).

In the base case, duration of treatment for Akantior is set to 101 days as reflected in real world evidence on AK according to the study by Franch *et al*. 2024 [2] that was conducted in 3 centres and included 11 patients with AK. These 3 centres were also part of the ODAK trial. Data reported by Franch *et al*. are expected to be the closest representation of the use of Akantior in the real clinical practice (outside the trial setting) and therefore were selected as source of treatment duration instead of data from the ODAK trial. The use of Franch *et al.* as source of Akantior monotherapy treatment duration in the model is also supported by a medical cure rate reported in the same patient group of 91.7%, thus aligned (if not better) with the efficacy of Akantior monotherapy observed in the ODAK trial. The mean duration of treatment for the comparator arm was derived from

calculations of the time to cure from the untreated AK historical cohort identified via SLR, and considering only data from cured patients (n=11) [73].

Table 51 Duration of treatment

Treatment phase	Duration of treatment (days)	Source
Akantior	101	Franch *et al.* 2024 [2]. RWE on AK. Mean duration of treatment of 11 patients included in the study was considered.
EMA comparator – no AAT	56.7	Historical ”untreated” AK patients cohort. Median duration of treatment derived from individual patient level data from cured patients only (time to cure) [73].

AAT: Anti-amoebic treatment

11.2 Medicines– co-administration

Not applicable

11.3 Administration costs

The initial management of AK is highly intensive, often involving multiple anti-amoebic therapies (AAT) administered hourly—including throughout the night—for the first two to three days. This is typically combined with additional topical medications such as analgesics and anti-inflammatory agents. As noted on the Moorfields Eye Hospital London website, multi-drug topical regimens require several minutes between the administration of different drops, further compounding the burden on patients (https://www.moorfields.nhs.uk/eye-conditions/acanthamoeba-keratitis/diagnosis-and-treatment#Treatment). As a result, patients receiving current AAT protocols are often unable to sleep during the initial 48 to 72 hours of treatment.

Hospitalization is especially considered for vulnerable groups, including children, elderly patients without caregivers, those with disabilities, or individuals affected in both eyes. To accurately reflect hospitalization needs in modelling treatment costs and logistics, data from published sources were incorporated to estimate hospitalization rates for patients with AK infection.

The proportion of patients used to inform the base case analysis for the EMA comparator - no AAT was derived from the SmPC of polihexanide 0.8 mg/ml [1]. The less burdensome tTreatment regimen with Akantior (daytime-only monotherapy) allows for patient self-administration at home. Administration costs are not applied for the intervention, neither the comparator.

11.4 Disease management costs

Table 52 Disease management costs used in the model.

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Fluoroquinolones	See Table 54-Table 56	27.72	n/a	Danish Medicines Agency MedicinPriser
Corticosteroids, plain	See Table 54-Table 56	67.73	n/a	Danish Medicines Agency MedicinPriser
Other ophthalmological	See Table 54-Table 56	973.50	n/a	Danish Medicines Agency MedicinPriser
Anticholinergics	See Table 54-Table 56	50.06	n/a	Danish Medicines Agency MedicinPriser
Antibiotics	See Table 54-Table 56	79.20	n/a	Danish Medicines Agency MedicinPriser
Acetic acid derivatives and related substances	See Table 54-Table 56	24.26	n/a	Danish Medicines Agency MedicinPriser
Anilides	See Table 54-Table 56	26.71	n/a	Danish Medicines Agency MedicinPriser
Propionic acid derivatives	See Table 54-Table 56	34.05	n/a	Danish Medicines Agency MedicinPriser
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	See Table 54-Table 56	19.90	n/a	Danish Medicines Agency MedicinPriser
Other ophthalmological - Carmellose sodium 10 mg/ml	See Table 54-Table 56	92.71	n/a	Retrived from: Medicijnkosten.nl. CELLUVISC UNIT DOSE EYE DROPS 10MG/ML TUBE 0.4ML. (https://www.medicijnkosten.nl/medicijn? artikel=CELLUVISC+UNIT+DOSE+OOGDRUPPELS+10MG%2FML+TUBE+0%2C4ML&id=9595f0051ac9d325d278b713df570d4e)

Pricing information was retrieved from Danish Medicines Agency MedicinPriser. Apotheek.nl, and the MIMS database when no local source was available. See Table 54-Table 56 for further details.

Patients with AK often require additional medication to manage the disease and complications. In the ODAK study, concomitant medication was defined as ongoing medication or medication stopped on or after baseline [55]. The use of additional medication during the study was equally distributed between the two treatment groups.

Concomitant medications were included to account for the additional costs incurred due to drug acquisition costs. Only concomitant medication with incidence of greater than 10% in the Akantior arm in the ODAK trial were considered (Table 53). Consider that, since the EMA comparator (no AAT arm) does not include any anti-amoebic medication, drug acquisition cost was assumed as 0 in the model. However, concomitant medication costs were applied for the comparator arm as for the intervention arm. Thus, the model considers the same costs across treatment arms.

Table 53 Concomitant medication in at least 10% of the patients in Akantior in ODAK study

Concomitant medication	Description	%
Ophthalmological		
Fluoroquinolones	Levofloxacina 5 mg/ml	51%
Corticosteroids, plain	Dexamethasone phos. 1mg/ml	36%
Other ophthalmological	Carmellose sodium 10 mg/ml	29%
Anticholinergics	Atropine sulf. 1%	14%
Antibiotics	Chloramphenicol 0.5%	16%
Anti-inflammatory and antirheumatic products		
Acetic acid derivatives and related substances	Aspirin tablet 500mg	32%
Propionic acid derivatives	Ibuprofen tab coated 600 mg	16%
Analgesics		
Anilids	Paracetamol tablets 500mg	16%
Antivirals for systemic use		
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	Aciylovir tablets 200mg	13%

Note: Antiseptics and disinfectants (such as biguanides and diamidines) were excluded considering the 'no AAT' approach. For concomitant treatments, the model considers the same costs across treatment arms.

Source: Table 14.1.4.2 in ODAK Clinical Study Report. Data on file. [55]

The information of the pack size, prices, and posology was taken from data services of the Danish Medicines Agency MedicinPriser (Table 54 and Table 55) and apotheek.nl when no local source was available (Table 56). The resulting cost associated with concomitant medication (DKK 362.19) was applied at once when patients started one of the initial therapies (Akantior or EMA comparator arm).

Table 54 Concomitant medication price - drops

Concomitant medication	Medication	Posology	ml per pack	Pack cost, DKK	Nr. drops per pack	Nr. Drops required	One-off cost, DKK
Ophthalmological							
Fluoroquinolones	Levofloxacina 5 mg/ml	1 or 2 drops into affected eye(s) every 2 hrs up to eight times daily while awake for first 2 days, then four times daily on days 3 to 5.	5	99.00	100	28[a]	27.72
Corticosteroids, plain	Dexamethasone phos. 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 hrs when inflammation subsides. Max duration 14 days.	40	129.00	160	84[b]	67.73
Other ophthalmological	Carmellose sodium 10 mg/ml	1 or 2 drops into affected eye(s) as required.	0.4	94.00	8	84[b]	973.50
Anticholinergics	Atropine sulf. 1%	1 drop as required.	5	59.60	100	84[c]	50.06
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 hrs after cure.	10	99.00	200	160[d]	79.20

a. considered 4 drops, once daily for 7 days; b. Assuming 1 drops, 6 times a day for 14 days; c. Assuming 2 drops, 3 times a day for 7 days; d. Assuming 2 drops, 10 times a day for 10 days.

Table 55 Concomitant medication price - tabs

Concomitant medication	Medication	Posology	mg per pack	Pack cost, DKK	Nr. tabs per pack	Nr. tabs required	One-off cost, DKK
Anti-inflammatory and antirheumatic products							
Acetic acid derivatives and related substances	Aspirin tablet 500mg	Adults 1-2 chewable tablets at a time, maximum 8 chewable tablets per 24 hours, divided into 4-6 doses. Max 5 days of treatment	75	60.66	100	40[a]	24.26
Propionic acid derivatives	Ibuprofen tab coated 600 mg	1.2—1.6g daily in divided doses (3-4doses) with food	600	81.07	100	42[b]	34.05
Analgesics							
Anilids	Paracetamol 325mg + tramadol 37.5mgAcetamol tablets 500mg	8 tablets (equivalent to 300 mg tramadol hydrochloride and 2600 mg paracetamol) per day.	500	9.54	20	56[c]	26.71
Antivirals for systemic use							

Concomitant medication	Medication	Posology	mg per pack	Pack cost, DKK	Nr. tabs per pack	Nr. tabs required	One-off cost, DKK
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	Acyclovir tablets 200mg	200 mg five times a day with a dosing interval of about 4 hours, with no dose taken at night. Usually for 5 days. In the case of a severe primary infection, the treatment period should be extended. In severely immunocompromised patients, the dose may be doubled to 400 mg acyclovir, or intravenous administration may be considered alternatively	200	79.60	100	25[d]	19.90

a. Assuming 2 tabs, 4 times a day for 5 days; b Assuming 1 tabs, 6 times a day for 7 days; c Assuming 2 tabs, 4 times a day for 7 days; d Assuming 5 tabs per day for 5 days
Sources: Danish Medicines Agency, MedicinPriser [63]

Table 56 Costs which were converted from EUR to DKK, and then inflated to 2024

Cost	Unit Cost, EUR	Source/Assumption	Unit cost, DKK 2023	Unit cost, DKK 2024
Other ophthalmological - Carmellose sodium 10 mg/ml	12.43	Medicijnkosten.nl. CELLUVISC UNIT DOSE EYE DROPS 10MG/ML TUBE 0.4ML (https://www.medicijnkosten.nl/medicijn?artikel= CELLUVISC+UNIT+DOSE+OOGDRUPPELS+10MG%2FML+TUBE+0%2C4ML&id=9595f0051ac9d325d278b713df570d4e)	92.62	92.71

11.5 Costs associated with management of adverse events

No adverse events were considered in the model.

Table 57 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff
N/A	N/A	N/A

11.6 Subsequent treatment costs

Some patients with AK require subsequent surgical treatment. Therapeutic and optical surgeries in patients with AK are performed in the setting of corneal perforation as a globe-saving measure, to eradicate the acanthamoeba organism when medical measures have failed, or electively for visual rehabilitation of the eye.

Table 58 Medicines of subsequent treatments.

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/A	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	N/A

This table was adapted into several tables below.

Therapeutic surgeries

The unit costs for the different types of therapeutic surgeries are presented in Table 62, for which the distributions are described in Section 8.3.1.4.3. A one-off cost of DKK [redacted] is applied in the model accounting for:

- Costs for different types of therapeutic surgery
- Pre-surgical cost
- Post-surgery cost associated with adjuvant systemic and systemic immunosuppressive therapies
- Cost to treat the surgical complications
- Distributions by type of therapeutic surgery

Complications associated with therapeutic surgeries

Patients can experience complications associated with therapeutic surgeries which may require further procedures. Table 59 shows the complications associated with therapeutic surgeries and the respective proportion of patients based on the UK Delphi panel [9].

Table 59 Complications associated with therapeutic surgeries

Complications	Proportion (%)
Glaucoma	[redacted]
Scleritis	[redacted]
Corneal melt	[redacted]
Neutrophic keratopathy	[redacted]
Perforation, wound leak	[redacted]
Re suturing	[redacted]
Corneal vascularization	[redacted]
Optic atrophy	[redacted]

Note: In the UK Delphi panel, the Key Opinion Leaders also included cataract, re-infection, and graft failure. However, these complications were not included to avoid double counting, given that the model already counts cataract as optical surgery, and graft failure and re-infection are modelled separately.

In addition to the complications listed in Table 59, a one-off cost of DKK [redacted] is included in the final value ([redacted]) applied for therapeutic surgery.

Systemic therapies

The use of systemic immunosuppressants and adjuvant systemic therapies after therapeutic surgery is important to reduce the risk of rejection and other complications. The percentage of patients requiring these therapies and mean time of treatment was obtained based on a Delphi panel with UK experts (Table 60) [9]. In Table 61 the number of units, packet size, costs and doses/administration are presented. The condensed pricing information is presented in Table 62. Two-unit costs were converted from EUR to DKK using the exchange rates provided in Denmark's National bank and later inflated to 2024 values using the CPI index [60], [62]. The others were taken from Danish Medicines Agency, MedicinPriser [63]. A one-off cost of [redacted] is included in the [redacted] value applied for therapeutic surgery.

Table 60 Systemic therapies

Systemic therapies	Proportion (%)	Mean time (in days)
Systemic immunosuppressive		
Cyclosporine	[redacted]	[redacted]
Azathioprine	[redacted]	[redacted]
Mycophenolate	[redacted]	[redacted]
Steroids	[redacted]	[redacted]
Tacrolimus	[redacted]	[redacted]
Adjuvant systemic therapies		
Miltefosine	[redacted]	[redacted]
Voriconazole	[redacted]	[redacted]
Prednisolone	[redacted]	[redacted]
Polihexanide 0.06%	[redacted]	[redacted]
Doxycycline	[redacted]	[redacted]

Source: UK Delphi panel [9].

Table 61 Systemic therapies - unit costs

Systemic therapies	Mg per unit	Units per pack	Pack cost, DKK	Cost per mg, DKK	Dose per administration	Nr of administration per day	Cost per treatment, DKK
Systemic immunosuppressive							

Systemic therapies	Mg per unit	Units per pack	Pack cost, DKK	Cost per mg, DKK	Dose per administration	Nr of administration per day	Cost per treatment, DKK
Cyclosporine	25	50	391.20	0.313	1200	1	81,682.56
Azathioprine	50	100	263.55	0.053	120	1	148.01
Mycophenolate	500	150	320.00	0.004	1000	2	2,640.21
Steroids	25	100	178.02	0.071	40	1	78.33
Tacrolimus	1	50	578.85	11.577	8	2	52,698.50
Adjuvant systemic therapies							
Miltefosine	Cost not available						
Voriconazole	50	30	3,430.00	2.29	200	2	34,117.07
Prednisolone	25	100	178.02	0.07	40	1	154.38
Doxycycline	100	10	145.51	0.15	200	1	2,226.30

The cost information is also reported in Table 62. Source: Danish Medicines Agency, MedicinPriser [63], MIMS database [67], medicijnkosten.nl [68]

Optical surgeries

The unit costs for the different types of optical surgeries are presented in Table 62, for which the distributions and rationale are described in section *8.3.1.2 Optical surgery.* A one-off cost of DKK XXXXXX is applied for optical surgery.

Graft failure

A graft failure cost of DKK 6,005.65 is applied as a one-off cost. This cost was estimated assuming the type of procedures after a graft failure reported in section *8.3.1.3 Graft failure* and the unit costs reported in Table 62.

Table 62 Cost associated with management of adverse events. Adapted to fit surgical treatments as well as drug treatments.

Adverse event	DRG code	Unit cost/DRG tariff
Therapeutic surgeries		
Pre-surgical costs	02SPO1	2,913.00
Keratoplasty	02MP01	25,349.00
Enucleation	02MP16	3,044.00
Deep lamellar keratoplasty	02MP05	22,280.00
Evisceration	02MP06	11,713.00
Other	Calculat	2,096.00
Amniotic membrane	02MP18	2,096.00

Adverse event	DRG code	Unit cost/DRG tariff
Amniotic membrane + penetrating keratoplasty	02MP18	2,096.00
Tarsorrhaphy	02MP18	2,096.00
Conjunctival flap	02MP18	2,096.00
Complications associated with therapeutic surgeries		
Glaucoma	02MP14	9,461.00
Scleritis	02SP01	25,349.00
Corneal melt	02SP01	25,349.00
Neutrophic keratopathy	02MP18	2,096.00
Perforation, wound leak	02MP18	2,096.00
Re suturing	02MP18	2,096.00
Corneal vascularization	02MP18	2,096.00
Optic atrophy	02MP18	2,096.00
Systemic therapies: Systemic immunosuppressive (see Table 60 ***for further information)***		
Cyclosporine	n/a	81,682.56
Azathioprine	n/a	148.01
Mycophenolate	n/a	2,640.21
Steroids	n/a	78.33
Tacrolimus	n/a	52,698.50
Systemic therapies: Adjuvant systemic therapies (see Table 60 ***for further information)***		
Miltefosine	n/a	0
Voriconazole	n/a	34,117.07
Prednisolone	n/a	154.38

Adverse event	DRG code	Unit cost/DRG tariff
Doxycycline	n/a	2,226.30
Optical surgery		
Pre-surgical costs	02SP01	2,913.00
Keratoplasty	02MP18	2,096.00
Evisceration	02MP18	2,096.00
Cataract	02MP18	2,096.00
Deep anterior lamellar keratoplasty	02MP18	2,096.00
Surgical correction for astigmatism	02MP18	2,096.00
Procedures after a graft failure		
Endothelial keratoplasty	02MP02	23,691.00
Enucleation	02MP18	2,096.00
Evisceration	02MP18	2,096.00
No further procedures		0

11.7 Health-care resource use

AK is associated with a high HCRU burden. Following treatment initiation, people with AK require frequent healthcare appointments, which only decrease based on the response to treatment. The Delphi panel estimated that XXXX of people with AK on current therapeutic approaches will require an average of XXXX ophthalmologist or optometrist visits per year. A combination of nurse (XXXX requiring XXXX visits per year) and psychiatric visits (XXXX requiring XXXX visits per year) may also be required. Disease monitoring appointments also cause burden for the healthcare system, with intraocular pressure check (XXXX times per year) and ophthalmoscopy (XXXX times per year) required most frequently. This cycle of frequent healthcare visits and failed treatments add significantly to the overall burden faced by both patients and healthcare systems, emphasising the need for effective treatment options.

In addition, as recognized by the Delphi panel, HCRU burden applies to patients with AK during the active infection phase, as well as after AK resolution of the infection, independently of the visual outcome obtain. However, the use of health care resources varies depending on the visual impairment of the patient as reported by the Delphi panel.

HCRU unit costs were based on the Danish Health Data Authority (2025 costs), as presented in Table 63 below . 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 64 and Table 65, respectively.

Table 63. HCRU unit costs

HCRU	Cost, DKK	Source
Ophthalmologist/Optometrist visit	3,201.00	02PR01 https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2025
Psychiatrist visits	2,168.00	https://sundhedsdatastyrelsen.dk/-/media/sds/filer/finansiering-og-afregning/takster/2025/psykiatritakster-2025.xlsx
Nurse visits	1,501.00	02PR02 https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2025
Intraocular pressure check	1,501.00	02PR02 https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2025
Scraping of the eye	3,201.00	02PR01 https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2025
Ophthalmoscopy	1,501.00	02PR02 https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2025
Low vision rehabilitation sessions	1,501.00	02PR02 https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2025
Visual aids – magnifiers	1,501.00	02PR02 https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2025
In vivo confocal microscopy	1,501.00	02PR02 https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2025
Visual aids – contact lens clinic (rigid gas permeable contact lens)	1,501.00	02PR02 https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2025

Abbreviations: HCRU: healthcare resource utilisation

Table 64. Frequency of HCRU

Resource	Frequency of the intervention (times/year)						
	AK infection	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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatrist visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nurse visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intraocular pressure check	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scraping of the eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ophthalmoscopy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low vision rehabilitation sessions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual aids – magnifiers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
In vivo confocal microscopy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual aids – contact lens clinic (rigid gas permeable contact lens)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Source: SIFI Delphi Panel 2023.

Table 65. Patient distribution by HCRU

Resource	Patients (%)

	AK infection	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	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Psychiatrist visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nurse visits	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intraocular pressure check	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scraping of the eye	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ophthalmoscopy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Low vision rehabilitation sessions	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual aids – magnifiers	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
In vivo confocal microscopy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Visual aids – contact lens clinic (rigid gas permeable contact lens)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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

Source: SIFI Delphi Panel 2023.

The HCRU costs by health state and per cycle applied in the model are presented in Table 66.

Table 66. Health care resource use per cycle

Health state	HCRU cost per cycle, DKK
AK infection	87,941.00
Good vision after medical resolution of AK infection	19,773.44
Poor vision after medical resolution of AK infection	41,690.72
Severe vision loss after medical resolution of AK infection	50,170.33

Good vision after surgical resolution of AK infection	43,351.21
Poor vision after surgical resolution of AK infection	56,449.54
Severe vision loss after surgical resolution of AK infection	57,518.23
Loss of eye functionality	27,968.97

11.8 Patient costs

Transportation cost

Transportation costs are included in the model assuming one return journey to the hospital/health-care setting for: (a) Therapeutic surgery (b) Optical surgery (c) Graft failure. The average km per visit considering a return journey, and the most updated cost (DKK) per km reported by the DMC were used for the estimation of transportation cost of 140.40 DKK

Table 67 Transportation unit cost

Health state	Mean	Source
Average km per visit (return journey)	44	https://medicinraadet.dk/media/aunbprvg/værdisætning-af-enhedsomkostninger-vers-1-6_adlegacy.pdf (20km per one-way journey and estimating 40km per return journey)
Cost per km (DKK)	3.51	https://medicinraadet.dk/media/aunbprvg/værdisætning-af-enhedsomkostninger-vers-1-6_adlegacy.pdf
Transportation cost (DKK)	140.40	Calculation based on the average km per visit and cost per km.

Use of time for patients and caregivers

In accordance with the DMC guidelines, the model considers costs associated with use of time for patients associated with treatment. These correspond to the use of time for administration during the AK intensive treatment phase, use of time for administration during AK infection after intensive treatment period, number of days for therapeutic surgery and number of days for optical surgery. The use of time for caregivers in connection with treatment is presented as part of the scenario analyses and has been excluded from the base case.

The inclusion of patient time costs in the current economic evaluation is methodologically appropriate because AK patients are generally otherwise healthy individuals capable of engaging in utility-generating activities; treatment time therefore represents a genuine opportunity cost. In addition, the HRQoL measures applied in the analysis do not capture the disutility associated with time spent on treatment administration and healthcare visits. Accordingly, inclusion of patient time costs ensures that the economic evaluation reflects the full societal impact of the treatment pathway and is consistent with the Danish Medicines Council's methodological framework.

Please find below the key considerations in accordance with the Danish Medicines Council's methodological guidance on the criteria to include patient time costs in the analyses:

1. Patients' general health status and opportunity cost of time: Acanthamoeba keratitis is a severe ocular infection that affects the cornea but does not generally impair patients' overall systemic health. The condition frequently affects otherwise healthy individuals, commonly contact lens users, who are often of working age. Despite the significant ocular symptoms (e.g., pain, photophobia, visual impairment), patients' general health status outside the affected eye remains sufficiently preserved. In the absence of treatment-related activities (e.g., frequent ophthalmology visits, medication administration, monitoring), patients would be able to engage in utility-generating activities (such as paid employment, education, household production, leisure activities, among others).

As mentioned in the current application, the treatment of AK is intensive and may involve very frequent eye drop administration, repeated outpatient visits and monitoring appointments over a prolonged period. Time spent on these activities represents a real opportunity cost, as it substitutes time that would otherwise have been available for work or leisure. Therefore, the first condition of the DMC methodological guidance is fulfilled: patients are in sufficiently good general health that treatment-related time displaces utility-generating activities.

2. The health-related quality of life measurement is not expected to capture the utility loss associated with patient time: The health-related quality of life (HRQoL) data applied in the model capture the impact of AK on health status. However, standard HRQoL instruments such as EQ-5D that measure health state related utility, do not explicitly account for time spent attending healthcare visits or capture time spent administering complex treatment regimens. In addition, these instruments do not measure productivity loss or leisure time foregone due to treatment logistics. Although AK symptoms may reduce "usual activities" scores, this reflects disease burden rather than the opportunity cost of time required for treatment administration and healthcare visits. Consequently, the utility decrement associated specifically with treatment-related time is not captured in the HRQoL inputs used in the model. Thus, the second condition of the DMC guidance is also fulfilled.

The value of time is calculated at a common rate for patients. As stated in the guidelines, time spent for patients and relatives should be valued using a rate equivalent to the average hourly rate of an employee in Denmark after tax.

For the patient, the number of hours per day for treatment administration during AK intensive period, and in AK infection after the intensive period, were estimated considering the treatment duration and treatment scheme of antiamoebic treatment (number of drops in the treatment phase divided by the duration of the treatment phase in days), applicable only to the intervention arm. Therefore, since EMA comparator – no treatment arm does not include any treatment with proven antiamoebic activity, the number of hours required per treatment administration per day was set to 0. Please refer to Table 51 for data on treatment duration and to

Table 50 for treatment scheme of polihexanide 0.08%.

Table 68 Use of time

Health state	Mean	Source
Value of 1 hour of time (DKK)	181.00	https://medicinraadet.dk/media/aunbprvq/værdisætning-af-enhedsomkostninger-vers-1-6_adlegacy.pdf
Hours per day to be valued	7.40	https://workplacedenmark.dk/working-conditions/pay-and-working-hours#:~:text=There%20must%20be%20no%20more,of%2048%20hours%2C%20including%20overtime

Table 69 Number of hours per day for treatment administration - during AK intensive period (intervention arm)

Treatment regimen	Mean
Akantior	9.37
Total drops per day – intensive period	178
Duration of treatment (days) – intensive period	19

Table 70 Number of hours per day for treatment administration - in AK infection after intensive period, by treatment arm

Treatment regimen	Mean
Akantior	4.00
Total drops per day – maintenance period	324
Duration of treatment (days) – maintenance period	81

Treatment regimen	Mean
EMA comparator – no AAT	0
Total drops per day – maintenance period	0
Duration of treatment (days) – maintenance period	0

In addition, the model assumes that patient time costs are incurred over a period of 121.75 days per surgery. This duration reflects the expected recovery time following corneal graft procedures and is based on published patient guidance. Specifically, the duration was derived as the average between a minimum recovery period of 2–3 weeks and a maximum of 3–4 months, depending on the nature of the patient's occupation. Patients engaged in non-physically demanding work may return to work after approximately 2–3 weeks, whereas those involved in manual labour or physically demanding activities may require up to 3–4 months before resuming work. In line with a conservative approach, the upper bound of 4 months was applied in the model. This assumption is supported by the Corneal Graft Post-Operative Advice document published by the NHS Leeds Teaching Hospitals Trust (available at: https://www.leedsth.nhs.uk/patients/resources/corneal-graft-post-operative-advice/). This patient guidance document provides recommendations for recovery following corneal graft procedures, including penetrating keratoplasty, DSEK, and DMEK.

Overall, this approach ensures that the model captures a realistic and conservative estimate of productivity loss associated with post-surgical recovery.

Table 71 Other parameters for patients use of time

Parameter	Mean
Number of days for therapeutic surgery (hospital inpatient time)	121.75
Number of days for optical surgery (hospital inpatient time)	121.75

Source: The Corneal Graft Post-Operative Advice document published by the NHS Leeds Teaching Hospitals Trust (available at: https://www.leedsth.nhs.uk/patients/resources/corneal-graft-post-operative-advice/).

As part of the scenarios presented in this dossier, caregivers use of time is considered. In this scenario, the hours per day in hospital was assumed to be 1. The use of time for caregivers was also calculated for the number of hours per day for treatment administration during AK intensive period, treatment administration in AK infection after the intensive period, therapeutic surgery and optical surgery. Note that caregivers costs are not included as part of the base case analysis.

Table 72 Hours in hospital

Parameter	Mean	Source
Hours per day in hospital	1	Considering 1 visit per day of hospitalization, minimum expected time of caregiver including transport time is likely to be 1 hour

Table 73 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
See tables above for full list.	

11.9 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Not included in the model.

12. Results

12.1 Base case overview

Table 74 Base case overview

Feature	Description
Comparator	EMA comparator – no AAT
Type of model	A *de novo* decision tree combined with a semi-Markov model with time-dependent transitions
Time horizon	Lifetime, until the cohort reaches 100 years of age
Treatment line	1st line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in Jensen et al. [57]. Danish population weights were used to estimate health-state utility values
Costs included	Drug acquisition Concomitant treatment Therapeutic surgeries Graft failure Optical surgeries Health care resource use Transportation Use of time for patients
Dosage of medicine	Dosage for anti-amoebic treatments: • Akantior- Protocol used on ODAK study, 2024 [6] • Not applicable for the comparator arm
Average time on treatment	Intervention: 101 days (Franch *et al.* 2024 [2]. RWE on AK. Mean duration of treatment with Akantior considering 11 patients included in the study) Comparator: 56.7 days (Papa *et al* 2025; Individual patient level data of the cured patients from the historical cohort of AK untreated patients. Median time to cure calculation [73].
Parametric function for PFS	Intervention: NA Comparator: NA
Parametric function for OS	Intervention: NA Comparator: NA

Feature	Description
Inclusion of waste	NA
Average time in model health state (Akantior) AK infection: 1.083 Cured- GV: 35.704 Cured- PV: 3.658 Cured- SVL: 1.518 Loss of eye functionality: 4.075 Average time in model health state (comparator) AK infection: 1.670 Cured- GV: 12.276 Cured- PV: 3.204 Cured- SVL: 4.767 Loss of eye functionality: 24.120	

12.1.1 Base case results

Table 75 Base case results, discounted estimates

	Akantior	EMA comparator – no AAT	Difference
Costs, DKK			
Medicine costs, DKK	[redacted]	[redacted]	[redacted]
Medicine costs – co-administration (concomitant treatment), DKK	400	646	-245
Disease management costs - Therapeutic surgeries, DKK	7,961	53,753	-45,792
Subsequent treatment costs Optical surgeries, DKK	324	610	-287
Subsequent treatment costs - Graft failures, DKK	349	2,045	-1,696

	Akantior	EMA comparator – no AAT	Difference
Disease management costs - HCRU, DKK	580,270	844,518	-264,248
Transportation costs, DKK	41	224	-183
Patient costs – Use of time, DKK	122,368	139,756	-17,388
Costs associated with management of adverse events, DKK	n/a	n/a	n/a
Total costs, DKK	[redacted]	[redacted]	[redacted]
Life Years (LYs)			
AK infection	1.073	1.567	-0.494
Good Vision	17.379	6.151	11.228
Poor Vision	1.800	1.610	0.190
Severe Vision Loss	0.773	2.452	-1.679
Loss of eye functionality	1.935	11.180	-9.246
Total LYs	**22.960**	**22.960**	**0.000**
Quality Adjusted Life Years (QALYs)			
AK infection	0.755	0.946	-0.191
Good Vision	13.743	4.872	8.871
Poor Vision	1.200	1.074	0.125
Severe Vision Loss	0.462	1.466	-1.004
Loss of eye functionality	0.847	4.882	-4.035
Therapeutic Surgery (Y2+)	-0.004	-0.026	0.022
Optical Surgery	-0.003	-0.006	0.003
Graft failures	-0.005	-0.032	0.027
Caregivers	0.000	0.000	0.000

	Akantior	EMA comparator – no AAT	Difference
Total QALYs	**16.994**	**13.176**	**3.818**

Incremental costs (DKK) per life year gained: NA

Incremental cost (DKK) per QALY gained (ICER): [redacted] DKK/QALY

12.2 Sensitivity analysis

12.2.1 Deterministic sensitivity analysis

The percentage change in base-case results following lower and upper variation in the 10 most influential model parameters is presented in the table and figure below. Overall, the ICER resulting from any of the univariate changes in parameters performed in the OWSA consistently remains below the willingness to pay threshold of 713,826 DKK/QALY (used in this model), indicating robust cost effectiveness model base case results.

Discount rate outcomes is the most influential parameter, as a significant proportion of the outcomes are from the 2nd year onwards, thus, lower discounting of health outcomes improves the results of the model in terms of ICER. MCR_12m for polihexanide 0.8 mg/ml is the second most influential parameter suggesting better cure rates reduce ICER substantially. In addition, the third parameter with more influence is RR for MCR_12m Akantior vs EMA comparator (no AAT); relative efficacy is a major driver, and stronger comparative cure rates lower ICER consequently.

Table 76 One-way sensitivity analyses results

Parameters	Lower value (%)	Upper value (%)
Discount rate outcomes	-51.8%	46.5%
MCR_12m - Polihexanide 0.8 mg/ml	31.1%	-19.2%
RR for MCR_12m Polihexanide 0.8 mg/ml vs EMA comparator (no AAT)	30.8%	-12.6%
Distribution of the patients by BCVA after medical cure (%) - Good vision	14.8%	-10.0%
Disutility vs "Cured with good vision"/General population - Loss of eye functionality	-10.6%	13.4%
Discount rate costs	-16.5%	5.1%

Disutility vs "Cured with good vision"/General population - Cured with severe vision loss	-6.4%	7.3%
On-going disutilities associated with long-term conditions* - Loss of eye functionality	-6.1%	6.9%
Distribution of the patients by BCVA after graft failure (%) - Loss of eye functionality	4.3%	-3.8%
Cost per cycle, DKK - Cured with good vision, after medical resolution	-4.0%	4.0%

BCVA: Best corrected vision acuity; EMA: European Medicines Agency; MCR_12m: Medical cure rate within 12 months; RR: Relative risk

Figure 6 Tornado diagram showing the impact of the most influential parameters on the ICER (DKK per QALY) from one-way sensitivity analysis.

12.2.2 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 assigned distributions. Population characteristics were not included in the PSA since they represent first order uncertainty.

Probability distributions were assigned to parameters, to characterise uncertainty associated with the precision of the mean values, based on the nature of each parameter.

Overall, the mean PSA results were similar to the base case results (Table 77). The cost-effectiveness plane, where each point represents the incremental cost and incremental QALYs from one iteration of the probabilistic sensitivity analysis, and acceptability curves are presented in Figure 6 and Figure 7, respectively.

Table 77 Summary base-case and PSA results in the comparison vs EMA comparator – no AAT arm

Category	Base Case	PSA Mean	PSA 95% CI Lower	PSA 95% CI Upper
Cost (DKK)				
Akantior	[redacted]	[redacted]	[redacted]	[redacted]
EMA comparator – no AAT	1,041,551	1,038,119	924,552	1,162,307
Incremental	[redacted]	[redacted]	[redacted]	[redacted]
QALYs				
Akantior	16.99	16.97	14.73	18.81
EMA comparator – no AAT	13.18	13.20	10.97	15.11
Incremental	3.82	3.77	3.75	3.70
ICER (DKK/QALY)	[redacted]	[redacted]	[redacted]	[redacted]

Figure 6 Cost-effectiveness cloud around the base case ICER for Akantior vs. EMA comparator – no AAT arm, based on 1,000 PSA simulations

Figure 7 Cost-effectiveness acceptability curve for Akantior vs EMA comparator – no AAT arm

12.2.3 Scenario analysis

A range of scenario analyses were conducted to test the robustness of the model results to alternative inputs/approaches. These results (Table 76) show the impact on the base-case ICER for each of the scenarios conducted.

The duration of Akantior treatment, based on the ODAK trial and adjusted to the definition of cure (126 days), was tested, resulting in a 32% increase in the ICER. In addition, as a conservative scenario (given the absence of data on recurrence among patients cured in the EMA comparator - no AAT arm) the recurrence rate was set to 0%, which led to an 11% increase in the ICER compared with the base case. Other scenarios included applying the average utility of patients in the ODAK trial who had good vision, estimated at 0.96 as anchor for the estimation of AK infection utility decrement (representing a 0.9% increase compared to the base-case ICER) and, given the lack of direct data from the ODAK trial to estimate utility decrement associated with loss of eye functionality health state, a scenario using the disutility estimated from the publication by Brown et al 2018 has be tested (representing a 31.7% increase compared to the base-case ICER). Finally, the inclusion of caregiver disutilities and costs contributed to an improvement in the ICER (percentual reduction of 16% versus base case ICER).

Table 78 Results of the scenario analyses

Scenario	Incremental costs, DKK	Incremental QALYs	ICER (DKK/QALY)	Absolute % Change in ICER
Base case	[redacted]	3.82	[redacted]	n/a
Akantior duration of treatment based on ODAK trial (adjusted by definition of cure used in the trial) of 126 days	[redacted]	3.80	[redacted]	32%
Recurrence in comparator arm = 0%	[redacted]	3.53	[redacted]	11%

Average utility of Good vision patients in the ODAK trial as anchor for the estimation of AK infection disutility	[redacted]	3.78	[redacted]	0.9%
Utility decrement for the loss of eye functionality health state from Brown et al. 2018 study	[redacted]	2.90	[redacted]	32%
Caregiver disutilities and costs included	[redacted]	4.50	[redacted]	-16%

ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life-years

13. Budget impact analysis

The budget impact analysis estimates the expected impact over a five-year period, comparing two scenarios: (1) the medicine is recommended as standard treatment, and (2) the medicine is not recommended. Patient numbers are based on the estimates provided in section 3.2. The analysis uses the per-patient, undiscounted cost estimates presented in section 11, in line with DMC requirements. The expected market share for each year is 100% in the recommended scenario and 0% in the not recommended scenario, as no uptake is assumed without recommendation.

Costs include pharmacy purchase price (AIP) for the medicine, as well as other treatment-related costs relevant to the regional hospital sector, such as surgeries, and health care resource use. Budget impact is presented annually and calculated as the difference in total costs between the two scenarios.

Number of patients (including assumptions of market share)

Table 79 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Akantior monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EMA comparator – no AAT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Akantior monotherapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EMA comparator – no AAT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget impact

Table 80 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
The medicine under consideration is NOT recommended (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation (DKK)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Total undiscounted medical related costs were considered for the analysis, including: medical treatment, concomitant treatment, therapeutic surgeries, optical surgeries, graft failures and healthcare resources costs. Transportation costs and use of time were not included for these estimates.

14. List of experts

Prof. Dart (Consultant Ophthalmologist who has researched AK disease for 30 years) and Dr. Sajjad Ahmad (Consultant Ophthalmic Surgeon).

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Appendix A. Main characteristics of studies included

Table 81 Main characteristic of studies included

Trial name: The Orphan Drug for Acanthamoeba Keratitis (ODAK) Trial [3]	NCT number: NCT03274895
Objective	To compare topical PHMB (polihexanide) 0.02% (0.2 mg/ml)+ propamidine 0.1% (1 mg/ml) with PHMB 0.08% (0.8 mg/ml)+ placebo (PHMB 0.08%) for Acanthamoeba keratitis (AK) treatment.
Publications – title, author, journal, year	The Orphan Drug for Acanthamoeba Keratitis (ODAK) Trial, Dart, John K.G. et al. Ophthalmology, Volume 131, Issue 3, 277 – 287, 2024
Study type and design	Prospective, randomized, double-masked, active-controlled, multicentre, phase 3 study. Patients were randomized 1:1 using a computer-generated block size of 4.
Sample size (n)	*135*
Main inclusion criteria	Principal inclusion criteria were as follows. (1) Participants were those of any race and sex who were 12 years of age or older and were enrolled by principal or coinvestigators. (2) Participants demonstrated clinical findings consistent with AK: principally corneal epithelial pathologic features (epithelial punctate keratopathy, epithelial infiltrates, epithelial defects, and dendritiform epithelial ulcers), corneal stromal pathologic features (perineural infiltrates, anterior stromal infiltrates, disciform corneal swelling, stromal ulceration, and ring abscess), and extracorneal pathologic features (limbitis and diffuse or nodular anterior scleral inflammation). (3) Participants demonstrated IVCM findings consistent with AK (polymerase chain reaction [PCR] and culture analysis also were carried out on all participants, but were not used for inclusion or exclusion). For participants with an IVCM diagnosis of AK and negative culture or PCR findings, or both, their IVCM files were reviewed by an expert coinvestigator (S.H.). Patients whose findings did not meet the IVCM criteria for an AK diagnosis were excluded from the full analysis set to minimize the inclusion of false-positive AK diagnoses. This expert review was not included in the protocol, but was instituted before the end of the trial.
Main exclusion criteria	Principal exclusion criteria included the following: (1) pregnancy or inability to use contraception (both men and women) from baseline and for specified periods after the last dose of study drugs; (2) a documented history or clinical signs of concomitant keratitis, or both, caused by herpes simplex virus or fungi; (3) treatment before baseline with antiamoebic agents (PHMB, CHX, propamidine, and hexamidine); (4) participants using systemic immunosuppressive therapy; and (5) participants requiring urgent surgical intervention for AK.
Intervention	Akantior (polihexanide 0.8 mg/ml) monotherapy with placebo

Trial name: The Orphan Drug for Acanthamoeba Keratitis (ODAK) Trial [3]	NCT number: NCT03274895
	Day 0 to 5* 1-hourly drops (16 drops in a day) for 5 days Day 6 to 12 2-hourly drops (8 drops in a day) for 7 days Day 13 to 19 3-hourly drops (6 drops in a day) for 7 days Day 20 Then 4x daily thereafter Patients: 66
Comparator(s)	PHMB 0.02% (polihexanide 0.2 mg/ml) with propamidine 0.1% (1 mg/ml) Day 0 to 5* 1-hourly drops (16 drops in a day) for 5 days Day 6 to 12 2-hourly drops (8 drops in a day) for 7 days Day 13 to 19 3-hourly drops (6 drops in a day) for 7 days Day 20 Then 4x daily thereafter Patients: 61
Follow-up time	Median number of days of treatment (exposure) 115.5 (min: 10, max: 387)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The prespecified primary outcome measure was the medical cure rate within 12 months from randomization. Prespecified secondary outcome measures were best-corrected visual acuity, corneal scarring rates, treatment failure rates, and patient-reported outcomes using the EuroQol 5 Dimension 5 Level health related quality of life questionnaire (EQ-5D-5L) and the 25 Item Visual Function Questionnaire (VFQ25) tools. **Other endpoints:** Prespecified safety outcome measures were adverse event reports and clinical laboratory assessments (hematology, biochemistry, and urinalysis) performed at baseline and at the end of the study visit (apart from urine pregnancy tests, which were carried out monthly in premenopausal women). Prespecified secondary safety outcome measures were repeat courses of intensive treatment for presumed relapses of infection, adjunctive topical steroid use, cataract, raised intraocular pressure, severe inflammatory disease onset after baseline (ring abscess, hypopyon, and scleritis), corneal vascularization, and chorioretinal disease. Safety outcomes were not implemented in the health economic model.
Method of analysis	Baseline differences in risk factors between the two treatment arms were not distributed evenly by the randomization because of

Trial name: The Orphan Drug for Acanthamoeba Keratitis (ODAK) Trial [3]	NCT number: NCT03274895
	recruitment numbers being relatively small; a multivariable analysis. As a result, multivariable analyses were applied to the primary outcome of the medical cure rate (MCR) within 12 months and, as a subgroup analysis, the MCR within 12 months outcomes for each AK disease stage at baseline. A Poisson model with robust variance was used to evaluate the unadjusted treatment effect and to estimate the difference in MCR within 12 months between the 2 treatments after adjustment for baseline covariates. Covariates selected as candidates for inclusion in the model-building process were those that were known prognostic factors affecting the outcome of AK (age, AK stage, delay in diagnosis, corticosteroid use before baseline, and antiviral use before baseline) or were suspected prognostic factors, including antibiotic use before baseline and study site (6 coded centers). The Kaplan-Meier curves were adjusted for covariates, as predicted by the Cox proportional hazards model, and were a time to- eventual-cure analysis that included all the trial failures at the point of a cure from Acanthamoeba infection as defined by having been discontinued from AAT. The amount of missing data was considered negligible and too few to allow recognition of a missingness pattern. The few missing days or months in the date fields were imputed to be first day or first month of the year data.
Subgroup analyses	Multivariable analyses were performed for each AK disease stage sub-group at baseline. No meaningful differences found in the proportions of participants with different AK disease stages at baseline. Not used in any stage of this application.
Other relevant information	

Trial name: Papa et al. 2025 [88]	NCT number: n/a
Objective	A systematic literature review (SLR) of historical data to identify a cohort of “untreated” patients with AK was carried out with several aims: (1) to provide an historical perspective, (2) to describe the natural history of AK in patients untreated with effective anti-cystic anti-amoebic drugs and (3) to provide a benchmark against which current treatments can be compared and the resulting changes in therapeutic outcomes compared to this “untreated” cohort.
Publications – title, author, journal, year	n/a (not a trial)
Study type and design	A systematic literature review for the period 1970–1995 using PRISMA guidelines [89]. The population of interest comprised patients with AK treated without products having established anti-amoebic activity against both trophozoites and cysts (biguanides or diamidines). The

Trial name: Papa et al. 2025 [88]	NCT number: n/a
	outcomes of interest were medical cure, TK and enucleation. Proportions and 95% confidence intervals were estimated.
Sample size (n)	*56 cases*
Main inclusion criteria	**Population of interest**: patients of any age with a confirmed diagnosis of AK not receiving treatment with products with an established anti-amoebic activity, i.e. PHMB, chlorhexidine, propamidine or hexamidine **AK diagnosis**: only cases with clinical findings, consistent with AK, associated with at least one of the following were evaluated: (1) positive culture from corneal tissues; (2) identification of Acanthamoeba in smears or histology; (3) perineural infiltrates or a positive culture from contact lens paraphernalia. **Outcome of interest**: medical cure, therapeutic keratoplasty, enucleation. **Data source:** Clinical trials, observational studies, case reports and case series were all eligible for inclusion. If a paper included a mixture of untreated and treated patients, it was considered eligible for inclusion only if data were reported separately for untreated patients. Originally, the inclusion dates were set as 1970 to 1990, as it was expected that there would be no untreated cases beyond 1985 when propamidine became available. However, during the screening, multiple papers published in 1990 were eligible. As a result, the search was extended to 1995. Only a single eligible paper was published in 1995; therefore, the search dates were not extended any further.
Main exclusion criteria	Not fulfilling the aspects included in the inclusion criteria
Intervention	Treatment in AK patients, except products with an established anti-amoebic activity, i.e. PHMB, chlorhexidine, propamidine or hexamidine
Comparator(s)	n/a
Follow-up time	Inclusion dates were set as 1970 to 1995
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** Endpoints evaluated were medical cure rate without any surgical intervention. **Other endpoints:** Therapeutic keratoplasty rates Enucleation rates

Trial name: Papa et al. 2025 [88]	NCT number: n/a
Method of analysis	The main effect measures were binary (yes/ no) for whether an outcome had occurred. For each outcome, proportion with 95% confidence interval (CI) was estimated with the CI based on binomial proportion. Analyses were conducted using Stata software v18.0. All eligible cases and studies were included in the analyses. There were no missing outcome data as an outcome of interest was required as part of the eligibility criteria.
Subgroup analyses	n/a
Other relevant information	Historical cohort of ”untreated” AK patients [89] was created for conducting an ITC to obtain relative efficacy estimated of Akantior vs EMA comparator – no AAT arm due to lack of direct head to head comparison [88, 90].

Appendix B. Efficacy results per study

Results per study

Table 82 Results per study

Results of ODAK (NCT03274895) [3]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Medical cure rate within 12 months	Polihexanide 0.8 mg/ml + placebo	66	84.85 % (73.90-92.49)	n/a	n/a	0.609	n/a	n/a	n/a	A Poisson model with robust variance was used to evaluate the unadjusted treatment effect	
	Polihexanide 0.2 mg/ml + propamidine 0.1%	61	88.52 % (77.78.3–24.3)								
Best-corrected visual acuity summary	Polihexanide 0.8 mg/ml + placebo	66	Mean (Snellen Feet) 20/40 Median (IQR) 20/20 (20/20-20/40)	n/a	n/a	n/a	n/a	n/a	n/a	Because no clinically or statistically significant differences were found between treatments, no P values or confidence intervals were added	
	Polihexanide 0.2 mg/ml + propamidine 0.1%	61	Mean (Snellen Feet) 20/40 +1 Median (IQR) 20/20 (20/25 +1 to 20/40)								
Corneal scarring, n (%)	Polihexanide 0.8 mg/ml + placebo	66	Baseline 0 (0%) End of Study 33 (51.6%)	n/a	n/a	n/a	n/a	n/a	n/a	Because no clinically or statistically significant differences were found between treatments, no P	

Results of ODAK (NCT03274895) [3]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	Polihexanide 0.2 mg/ml + propamidine 0.1%	61	Baseline 3 (4.9%) End of Study 30 (54.5%)							values or confidence intervals were added	
Trial failure, n (%)	Polihexanide 0.8 mg/ml + placebo	66	10 (15.2)	n/a	n/a	n/a	n/a	n/a	n/a	Because no clinically or statistically significant differences were found between treatments, no P values or confidence intervals were added	
	Polihexanide 0.2 mg/ml + propamidine 0.1%	61	7 (11.5)								
Quality-of-life score change from baseline to end of study, median (IQR)	Polihexanide 0.8 mg/ml + placebo	66	EQ-5D-5L VAS score 14.5 (5-28) VFQ-25 composite score 22.1 (7.9-37.3)	n/a	n/a	n/a	n/a	n/a	n/a	Because no clinically or statistically significant differences were found between treatments, no P values or confidence intervals were added	
	Polihexanide 0.2 mg/ml + propamidine 0.1%	61	EQ-5D-5L VAS score 15 (5-30) VFQ-25 composite score 21.4 (7.7-35.0)								

Results of Papa et al. 2025 [88] (table below adopted to fit results of this SLR conducted to identify a historical cohort of "untreated" AK patients. Primary outcome: Medical cure)

Outcomes of patients with AK not treated with anti-amoebic products

Outcome	N (%)	Proportion (95% CI)[c]
Cured without surgery	11/56 (19.6%)	0.20 (0.10, 0.32)
Cured with minor surgery [a]	4/56 (7.1%)	0.07 (0.02, 0.17)
T herapeutic keratoplasty	38/56 (67.9%)	0.68 (0.54, 0.80)
Enucleation [b]	3/56 (5.4%)	0.05 (0.02, 0.16)

AK Acanthamoeba keratitis, CI confidence intervals

[a] These patients did not have therapeutic keratoplasty and were cured after a subtotal epithelial debridement [b]One patient was enucleated after keratoplasty. In the present analysis, this patient was considered censored after the first event (keratoplasty) and is not included in the enucleation outcome category [c]CI interval based on binomial proportion

Appendix C. Comparative analysis of efficacy

C.1 Indirect Treatment Comparisons of Clinical Resolution Rates at 12 Months for Polihexanide 0.8 mg/ml vs Current Treatments in Acanthamoeba Keratitis

C.1.1 Overview

Acanthamoeba keratitis (AK) is an ultra-rare and highly debilitating corneal infection due to the protozoan *acanthamoeba*. The most common symptoms are ocular pain, redness, blurred vision, sensitivity to light, excessive tearing, and foreign body sensation. At early stages, it is often misdiagnosed, delaying treatment initiation, and making a cure more difficult. In fact, if not treated promptly, it can lead to visual impairment and even blindness. Until very recently, no drugs were indicated for treatment of AK and so current clinical practice is to use molecules off-label. This is an important issue as many treatments are not available from the pharmacy but need to be compounded in specific centres and then imported, leading to a delay in starting treatment, which in turn can impact outcomes (including treatment success rate).

The pivotal phase 3 randomised controlled trial (RCT; NCT03274895; Dart 2024[3]) evaluated polihexanide 0.8 mg/ml ophthalmic solution versus combination therapy with conventional compounded polihexanide 0.2 mg/ml plus 0.01 mg/ml propamidine. This RCT found that polihexanide 0.8 mg/ml was not statistically significantly superior to the active control arm for key outcome measures. Retrospective literature has shown that in the real-world the cure rate in AK patients with conventional compounded polihexanide 0.2 mg/ml plus 0.01 mg/ml propamidine and without surgery is much lower than the cure rate observed in the control arm of the ODAK trial. There are substantial differences between the treatment with the polihexanide 0.2 mg/ml plus 0.01 mg/ml used in the ODAK trial and the treatment with compounded polihexanide 0.2 mg/ml plus 0.01 mg/ml propamidine used in the real clinical practice, which disqualify the control arm of the ODAK trial as reflective of the standard of care. Such differences pertain to the availability, protocolized administration, the formulation and the quality of the products.

The Committee for Medicinal Products for Human Use (CHMP) explicitly stated in the European Public Assessment Report of Akantior (EPAR) that the ODAK control arm does not reflect current clinical practice and should not be considered a standard-of-care comparator: *'Considering that the active arm as applied in trial 043 contained a medicinal product manufactured to GMP quality, immediate availability and a standardized treatment protocol, it could not be considered a control representative of current practice'(EPAR, page 6).* This effectively classifies the ODAK trial as a two-arm experimental study.

C.1.2 Executive summary

Given the uncertainty of the representativeness of the comparative effect obtained from the pivotal trial of polihexanide 0.8 mg/ml versus polihexanide 0.2 mg/ml plus 0.01 mg/ml propamidine, the efficacy of polihexanide 0.8 mg/ml was indirectly compared (indirect treatment comparison [ITC]) with current treatments used in clinical practice for treating AK. Polihexanide 0.8 mg/ml was also indirectly compared with no AAT using historical case report data [89]. A feasibility assessment was not undertaken for these analyses because the historical case report dataset was constructed from published papers for the purpose of conducting ITC analyses.

Individual patient data (IPD) were available from these sources: 1) pivotal phase 3 randomized controlled trial (RCT) of polihexanide 0.8 mg/ml versus conventional polihexanide 0.2 mg/ml plus 0.01 mg/ml propamidine by Dart et al 2024[3] , 2) SLR of untreated cases of AK defined as confirmed cases of AK that did not receive treatment with a medication with anti-amoebic activity as defined by CDC (i.e. not treated with polihexanide, propamidine, chlorhexidine, or hexamidine) [89]

The outcome of interest was the absolute difference between the cure without surgery rates. Different ITC approaches were explored. As IPD were available for all data sources, analyses were conducted using propensity scoring analysis (PSA) with overlap weighting (OW). This approach uses weighted regression methods with adjustment for key effect modifiers and prognostic factors of AK (identified as potential confounding variables) to attempt to balance study populations before estimation of the treatment effect.

The results of the PSA with OW analyses showed that polihexanide 0.8 mg/ml (based on pivotal trial[3]) had a higher cure rate compared with no AAT (based on the historical cohort of AK "untreated" patients from the SLR conducted by Papa et al. 2025) [89, 90].

C.2 Identifying Appropriate ITC Methodology

ITC methods provide indirect comparative effect estimates for two or more treatments where direct head-to-head comparison data are not available from a RCT. Recommendations for ITC methodology have been published by the NICE Decision Support Unit[83]. Figure 15 outlines some of the commonly used ITC methods that are available.

Naïve comparisons are based on a comparison of interventions directly, without accounting for the comparator arm (which is either not present or is discarded). This approach is subject to bias and not recommended due to the comparison of absolute effects, instead of a comparison of relative treatment effects.

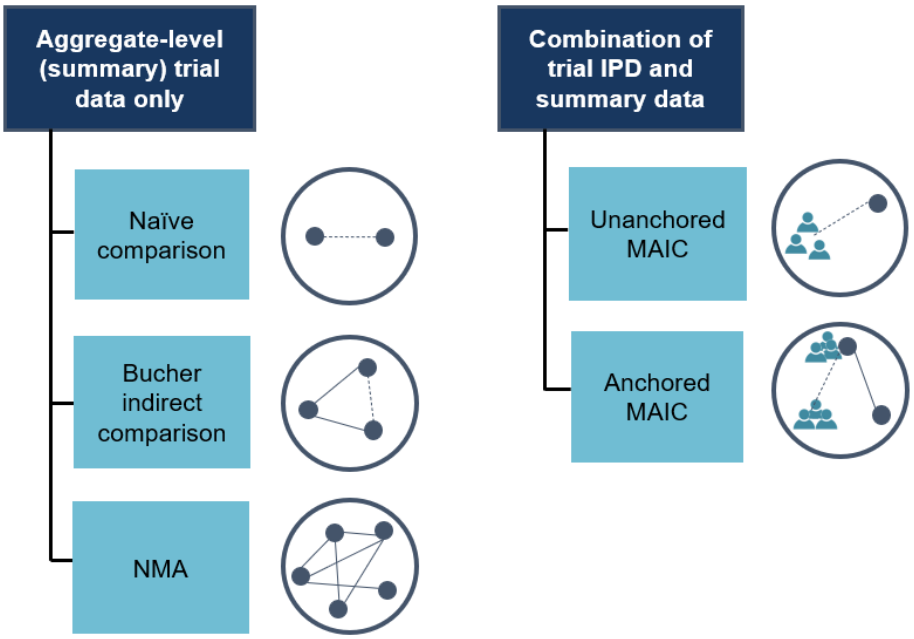
Bucher indirect comparisons improve on naïve comparisons, whereby the common comparator arm is accounted for (hence denoted an adjusted indirect comparison). This approach is simplistic by design and estimates comparative efficacy between two interventions. However, it does not account for any observed cross-trial differences, limiting the robustness of a comparison.

If additional comparators are present in the evidence base, network meta-analyses (NMA) may be considered as a robust approach to synthesis and an extension to a Bucher indirect comparison. NMA of aggregate-level data (i.e. summary clinical trial estimates) may be considered feasible where a connected network of evidence is available and it is considered that there is sufficient homogeneity across the studies under consideration for inclusion in an ITC analysis.

Targeted, population-adjusted ITC analyses may be explored if individual patient data (IPD) are available for at least one trial under assessment (denoted the index trial), including unanchored and anchored matching-adjusted indirect treatment comparisons (MAICs). Other methods, such as propensity scoring analyses (PSA) require IPD from both trials being analysed.

The following sections describe NMA, MAIC, and PSA in more detail.

Figure 15. Types of ITC methodologies that are available.



C.2.1 Network Meta-Analysis (NMA)

An NMA combines direct and indirect evidence to determine the relative effectiveness of a treatment compared with two or more other treatments. NMA methods therefore rely on a connected network of evidence of comparators under investigation. This approach uses trial-level aggregate data extracted from trial publications, which are synthesised in an NMA to estimate comparative efficacy. The Bayesian approach to synthesis uses Markov Chain Monte Carlo methods and combines prior distributions with the data to construct a posterior distribution as a basis for summary results. One advantage of NMA is its ability to estimate pairwise treatment effects between all interventions in the network. However, this approach can be limited in the presence of notable between-study heterogeneity. The NICE Decision Support Unit published TSDs to provide guidance and recommendations regarding best practice when conducting an NMA[85]. Additionally, guidance published by independent Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [IQWiG], Germany) also recommends the use of indirect comparisons and suggests the use of Bucher analysis or NMA may be appropriate forms of comparison (i.e. those which have a common comparator arm). However, this guidance does not recommend these methods in the presence of between-study heterogeneity[87].

C.2.2 Matching Adjusted Indirect Comparison (MAIC)

Cross-trial differences including the study design, inclusion/exclusion criteria, baseline characteristics, outcome definitions, and statistical methods can be sources of heterogeneity and can bias treatment effects obtained from an ITC analysis. However, a frequent scenario is for a manufacturer to have individual patient data available on its own trial but only published aggregate data for key comparator(s), typically consisting of average treatment effects and summary patient characteristics. Thus, it may be preferable to consider an alternative method of synthesis, based on population-adjustment. These methods include MAIC, which is based on re-weighting individual patient data from the index trial to try to overcome observed between-study differences. The MAIC approach was first published in 2010 by Signorovitch[84].

MAIC analyses use individual patient data from the index trial by weighting patients in an attempt to 'match' baseline summary characteristics reported from comparator trial(s) for which only aggregate data are available. Essentially, a MAIC approach estimates outcomes that could be expected if the index treatment were included as an additional arm in the comparator trial population (i.e. one-way matching).

A MAIC approach requires individual patient data to be available for the index trial and sufficient data on population characteristics to be available from the index and comparator studies. Additionally, this approach can only adjust for observed differences between studies; residual confounding may be present even after matching. This approach cannot overcome differences in outcome definitions or study design, and results based on matched populations may lack robustness where there is a lack of overlap of study populations.

In 2016, the NICE Decision Support Unit published guidance (TSD 18) about best practices for conducting population-adjusted ITC analyses where individual patient data are available only for the index trial[83]. The guidance states that anchored comparisons (i.e. through a common comparator arm) are preferred for indirect comparison, and that unanchored comparisons are likely to lack robustness and rely on strong assumptions that are infrequently met.

C.2.3 Propensity Scoring Analysis (PSA)

Where IPD are available from both the index and comparator study (i.e. all studies being evaluated in the ITC), PSA using OW can provide an estimation of the treatment effect. The theory is that having IPD for all studies enables a more robust comparison to be performed. However, it is rare that IPD are available for all studies of interest and so PSA methods are not often possible.

Unlike data from RCTs, observational data are generated in an uncontrolled environment. Non-random treatment assignment complicates the estimation of the treatment effect because it is possible that a patient may have received a particular treatment because of some (observable or unobservable) factors. This leads to potential selection bias when estimating the treatment effect. Selection bias arises from differences in the characteristics that have an independent influence on the outcome between the individuals in the treated and the control groups.

In 2015, the NICE DSU published guidance (TSD 17) for different statistical approaches for conducting an ITC where IPD are available for all trials in the comparison (which arise outside a head-to-head RCT) [86]. This guidance was restricted to methods that handle non-randomised comparative IPD, with a focus on the analytic methods available to estimate treatment effectiveness from two individual patient datasets. Differences in exposure to confounders can cause bias, which is inherent when comparing observational data. Each of the methods for estimating treatment effectiveness described in TSD 17 seek to overcome the problem of selection, which begins with the fact that the outcome is unknown for an individual both with the intervention and with the comparator. However, randomisation is not always possible, and statistical methods are required to try and achieve improved balance between intervention and comparator arms.

The guidance provides a review of various approaches for analysis of comparative IPD and makes recommendations for using comparative observational IPD to inform estimates of treatment effectiveness. The authors developed an algorithm for determining which methods may be appropriate in the case where comparative non-randomised data are available as IPD on both the treated and control individuals.

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 selection assignment differences between treatment and control groups. One of the biggest challenges with analysis of observational data is that the probability of treatment assignment is not random; 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.

It is important to identify a set of covariates to include in the PSA with OW model, i.e. those which are believed to be either prognostic of outcomes or potential treatment effect modifiers. These factors are then used to predict the probability of exposure and is considered a critical step of PSA.

Using comparative approaches where IPD are available for both studies included in the ITC can result in the calculation of different estimands (for example, the average treatment effect or the average treatment effect on the treated):

- Average treatment effect: the effect of treatment in the overall study population (treated and untreated). For purpose of health technology assessment submissions, typically the average treatment effect is the estimand of interest, since the average treatment effect can be generalised to the whole indicated population. The average treatment effect measures the expected gain of treatment, in the outcome of interest, for a randomly-selected individual from the indicated population
- Average treatment effect on the treated: utilises the treated cohort as the target population, meaning that the patients enrolled in the comparator study are re-weighted to match the index study population. The average treatment effect on the treated provides an estimate of how patients similar to those enrolled in index trial would have fared if they had been treated with the comparator arm instead.

For the analyses presented in this report, the estimand is based on the average treatment effect; an estimand which can be generalised to the wider population of patients with AK and is often preferred by NICE[84].

C.2.4 Statistical Methods

IPD were used from three sources for these ITC analyses:

- Pivotal RCT of polihexanide 0.8 mg/ml plus placebo vs polihexanide 0.2 mg/ml plus 0.01 mg/ml propamidine [3].
- SLR of untreated cases of AK defined as confirmed cases of AK that did not receive treatment with a medication with anti-amoebic activity as defined by CDC (i.e. not treated with polihexanide, propamidine, chlorhexidine, or hexamidine) [89].

ITC analyses using the MAIC and PSA with OW approaches were conducted to estimate the comparative efficacy in terms of cure without surgery.

Covariate adjustment

Clinical feedback was sought to identify which factors are 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; the delay in starting treatment (time to treatment delay). However, these variables were not reported; therefore, adjustment for cross-trial differences was limited to those factors which were available in each comparator data source.

Comparisons with the historical untreated AK cases data from the SLR were only adjusted for age and sex. Treatment delay and prior use of corticosteroids or antivirals before treatment could not be defined as the patients were untreated. Disease stage was not reported in any of the studies.

C.2.5 Outcome selection and definitions

The outcome of interest was cure without surgery within 12 months of starting treatment. In the untreated AK cases, it was not possible to define a timepoint from the start of treatment, so cure was not necessarily within 12 months. To measure the treatment effect, both the absolute difference and the relative risk (RR) of achieving cure without surgery were estimated, each accompanied by a 95% confidence interval (CI). The absolute difference was estimated using logistic regression methods. To estimate the RR of achieving cure without surgery, a generalized linear model (GLM) with a binary distribution and a log link function was used.

C.3 Results

Polihexanide 0.8 mg/ml had a statistically significantly higher cure without surgery rate compared with no AAT before weighting (65.2% [49.3%, 77.5%]) and in PSA analyses after weighting (64.7% [51.0%, 78.5%]).

Table 83: PSA with OW comparison of polihexanide 0.8 mg/ml (pivotal trial) vs no ATT

Study	Pivotal trial[3]		Untreated AK cases SLR	
Arm	Polihexanide 0.8 mg/ml		No AAT	
Weighting	Unadjusted	Adjusted	Unadjusted	Adjusted
N	**66**	**65.4[a]**	**56**	**55.6[a]**
Baseline Characteristics				
Mean age, years	35.2	35.0	34.9	35.0
% Male	40.9	45.8	50.0	45.8
Cure without surgery				
N (%; 95% CI[b]) responders	56 (84.8; 73.9, 92.5)	55.8 (84.5; 75.8; 93.3)	11 (19.6; 10.2, 32.4)	11.1 (19.8; 9.4; 30.2)
Absolute % difference (95% CI) vs comparator	Reference	Reference	**65.2%** **(49.3%, 77.5%)**	**64.7%** **(51.0%, 78.5%)**
RR (95% CI) vs comparator	Reference	Reference	**4.32** **(2.52, 7.41)** **p-value <0.0001**	**4.27** **(2.49, 7.33)** **p-value <0.0001**

References: 87, 90. Key: CI, confidence interval; ESS, effective sample size; N, number of patients; RR, relative risk.
Notes: a, ESS is estimated from weighted data; b, 95% CI is based on binomial proportion. Bold denotes statistical significance at 5% level.

Given the importance of this comparison in understanding the efficacy of polihexanide 0.8 mg/ml, a tipping point sensitivity analysis was performed to test the impact of potential bias selection in the untreated cases. These analyses estimated how many additional untreated cases would need to be cured without surgery before polihexanide 0.8 mg/ml is equivalent to, or worse than, no AAT, and were conducted as follows. Additional hypothetical untreated cases were added to the set of observed historical cases in increments of 20 up to 700 additional cases. These hypothetical cases were added with 'cure' set as yes and effect modifiers randomly sampled from the same distributions as observed in the existing historical cases. The risk difference comparing polihexanide 0.8 mg/ml with no AAT was estimated using the same PSA with OW approach as above. This was repeated for a total of 30 imputations, each time adding x random, hypothetical patients to the analysis dataset. The results of the 30 imputations were then pooled to get the overall result for x additional patients. The average proportion of CRR was calculated per arm and the risk difference between arms was then calculated. The results are summarised in Appendix 3 (Section 8) and presented in tabular format in Table 84.

The tipping point analyses show that approximately 240 more untreated patients who were cured without medical or surgical intervention, and no additional untreated patients who required keratoplasty or enucleation, would need to have existed and not been identified in the SLR before polihexanide 0.8 mg/ml has no effect compared with no AAT (i.e. a risk difference of 0.0).

Table 84. Tipping point analyses comparing polihexanide 0.8 mg/ml vs no AAT (based on historical data) with additional hypothetical patients randomly sampled in increments of 20.

N sampled patients added	Mean % CRR Difference	Lower 95% CI	Upper 95% CI	P-value
0	64.7%	51.0%	78.5%	<0.0001
20	43.9%	29.7%	58.0%	<0.0001
40	31.7%	18.3%	45.1%	<0.0001
60	23.6%	11.1%	36.2%	0.0002
80	18.0%	6.1%	29.9%	0.0029
100	13.8%	2.5%	25.2%	0.0170
120	10.5%	-0.4%	21.4%	0.0594
140	7.9%	-2.7%	18.4%	0.1451
160	5.7%	-4.6%	16.0%	0.2763
180	3.9%	-6.2%	14.0%	0.4471
200	2.4%	-7.5%	12.3%	0.6299
220	1.1%	-8.6%	10.9%	0.8184

240	0.0%	-9.6%	9.7%	0.9955
260	3.2%	-5.6%	12.0%	0.4710
280	2.3%	-6.4%	11.1%	0.5974
300	1.6%	-7.0%	10.2%	0.7170
320	0.9%	-7.7%	9.4%	0.8399
340	0.3%	-8.2%	8.8%	0.9518
360	-0.3%	-8.8%	8.1%	0.9419
380	-0.8%	-9.3%	7.6%	0.8443
400	-1.3%	-9.7%	7.1%	0.7600
420	-1.7%	-10.1%	6.6%	0.6834
440	-2.1%	-10.4%	6.2%	0.6169
460	-2.5%	-10.8%	5.8%	0.5580
480	-2.8%	-11.1%	5.5%	0.5066
500	-3.1%	-11.4%	5.1%	0.4570
520	-3.4%	-11.6%	4.8%	0.4146
540	-3.7%	-11.9%	4.5%	0.3779
560	-3.9%	-12.1%	4.2%	0.3457
580	-4.2%	-12.3%	4.0%	0.3171
600	-4.4%	-12.6%	3.8%	0.2909
620	-4.6%	-12.8%	3.5%	0.2678
640	-4.8%	-12.9%	3.3%	0.2467
660	-5.0%	-13.1%	3.1%	0.2283
680	-5.2%	-13.3%	2.9%	0.2117
700	-5.3%	-13.4%	2.8%	0.1967

C.4 Conclusions

The efficacy of polihexanide 0.8 mg/ml was indirectly compared with no AAT. For indirect comparisons, the PSA approach attempts to overcome imbalances in study populations and is an improvement to a naïve approach, which is considered to provide biased estimates of the treatment effect and is generally not recommended. However, population-adjustment methods can only go so far to account for observed cross-trial differences, meaning that there is the potential for residual confounding to be present because of cross-trial differences in patient characteristics that were not reported and/or adjusted for. To ensure appropriate factors were selected to estimate the weights, clinical feedback was used to identify covariates to include in the analysis for the matching.

Population-adjusted methods allow comparison between treatments which are disconnected in a network (e.g. no common comparator arm), meaning that conventional approaches to ITC (including NMA) are not possible. However, this form of ITC (i.e. an unanchored comparison) relies upon strong assumptions; primarily that matching was made on factors identified as prognostic of outcomes or influential on the treatment effect. Despite these limitations, previous submissions to NICE have been accepted for decision-making despite the reliance on unanchored comparisons.

In summary, IPD being available from all studies included in the ITC analysis, ITC via PSA is thought to be gold-standard and it is preferable, wherever possible, to conduct this type of comparison. This is because IPD allows for analyses which have greater statistical power and may require fewer assumptions and allows underlying assumptions to be tested. Therefore, PSA methodology using OW was performed.

The results of these analyses [90] showed that 1) polihexanide 0.8 mg/ml (based on pivotal trial3) had a higher cure rate compared with no AAT, based on data from the historical cohort of untreated AK patients identified via SLR. These finding has been officially published [87].

Appendix D. Extrapolation

Not applicable for the current submission

Appendix E. Serious adverse events

The safety and tolerability of polihexanide 0.8 mg/ml was investigated in the ODAK trial. Safety data are presented for all randomised patients i.e. the safety analysis set.
The ODAK trial is considered as a pseudo single-arm trial within this submission and therefore safety results were presented in the main submission for the study treatment arm only. Here, safety data for the polihexanide 0.8 mg/ml and 0.2 mg/ml polihexanide with propamidine 1 mg/ml treatment arms are presented for completeness.

E.1 Summary of adverse events

An overview of adverse events (AEs) in the ODAK trial for both treatment arms is presented in Table 85.

Table 85. Adverse events reported in the ODAK trial (safety analysis set)

Adverse event, n (%), #	0.8 mg/ml polihexanide + placebo (n=69)	0.2 mg/ml polihexanide + propamidine 1 mg/ml (n=65)
≥1 AE	31 (44.9), 83	29 (44.6), 69
≥1 SAE	0 (0.0), 0	0 (0.0), 0
Any AE leading to death	0 (0.0), 0	0 (0.0), 0
AEs 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
AEs 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
AEs 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

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.

Abbreviations: AE: adverse event; SAE: serious adverse event.

Sources: ODAK Phase 3 CSR: Table 12.2.[50]

Incidence of common AEs

A summary of AEs with an incidence >5% in either treatment arm by system organ class (SOC) and preferred term (PT) is presented in Table 86.

Table 86. Most commonly reported AEs (>5% of participants; safety analysis set)

Adverse event, n (%), #	0.8 mg/ml polihexanide + placebo (n=69)	0.2 mg/ml polihexanide + propamidine 1 mg/ml (n=65)
Any AE	31 (44.9), 83	29 (44.6), 69
Eye disorders	23 (33.3), 60	20 (30.8), 41

Eye pain	9 (13.0), 11	7 (10.8), 7
Ocular hyperaemia	8 (11.6), 9	7 (10.8), 9
Lacrimation increased	6 (8.7), 6	2 (3.1), 2
Eye irritation	1 (1.4), 1	4 (6.2), 4
Infections and infestations	9 (13.0), 9	8 (12.3), 8
General disorders and administration site conditions	4 (5.8), 5	5 (7.7), 6

Footnote: 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.[50]

Incidence of common AEs by severity

The most common AEs of any severity (reported in >5% of participants in either arm) are presented in Table 87.

Table 87. Most commonly reported AEs by severity (>5% of participants; safety analysis set)

Adverse event, n (%), #	0.8 mg/ml polihexanide + placebo (n=69)			0.2 mg/ml polihexanide + propamidine 1 mg/ml (n=65)		
	Mild	Moderate	Severe	Mild	Moderate	Severe
Any AE	24 (34.8), 46	12 (17.4), 30	4 (5.8), 7	24 (36.9), 50	11 (16.9), 13	5 (7.7), 6
Eye disorders	16 (23.2), 30	12 (17.4), 27	2 (2.9), 3	16 (24.6), 32	4 (6.2), 5	4 (6.2), 4
Eye pain	6 (8.7), 6	3 (4.3), 4	1 (1.4), 1	4 (6.2), 4	1 (1.5), 1	2 (3.1), 2
Ocular hyperaemia	4 (5.8), 4	5 (7.2), 5	0 (0.0), 0	6 (9.2), 8	1 (1.5), 1	0 (0.0), 0
Lacrimation increased	4 (5.8), 4	2 (2.9), 2	0 (0.0), 0	2 (3.1), 2	0 (0.0), 0	0 (0.0), 0
Infections and infestations	7 (10.1), 7	1 (1.4), 1	1 (1.4), 1	4 (6.2), 4	3 (4.6), 3	1 (1.5), 1
General disorders and administration site conditions	2 (2.9), 2	1 (1.4), 1	1 (1.4), 2	4 (6.2), 5	1 (1.5), 1	0 (0.0), 0

Footnote: 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.[50]

E.2 Study discontinuation

Reasons for study discontinuation of participants in either treatment arm are summarised in Table 88.

Table 88. Reasons for study discontinuations (safety analysis set)

Discontinuations, n (%)	0.8 mg/ml polihexanide + placebo (n=69)	0.2 mg/ml polihexanide + propamidine 1 mg/ml (n=65)
Prematurely discontinued study[a]	11 (15.9)	7 (10.8)
Primary reason for discontinuation[b]		
Adverse event	7 (63.6)	7 (100.0)

Lost to follow-up	1 (9.1)	0 (0.0)
Ocular intolerance	1 (9.1)	0 (0.0)
Other	2 (18.2)	0 (0.0)

Footnote: [a]Percentages are based on the number of patients within each treatment arm, n is the number of participants; [b]Percentages are based on the number of prematurely discontinued patients within each treatment arm.

Sources: ODAK Phase 3 CSR: Table 14.1.1.3.[50]

Appendix F. Health-related quality of life

Not applicable for the current submission

Appendix G. Probabilistic sensitivity analyses

Table 89. Overview of parameters in the PSA

Input parameter	Point estimate	OWSA		PSA
		Lower value	Upper value	Probability distribution
Efficacy outcome				
Medical cure rate within 12 months (MCR_12m)				
MCR_12m - Akantior	84.8%	68.2%	100.0%	Beta
RR for MCR_12m Akantior vs EMA comparator – no AAT	4.27	2.49	7.33	Log-normal
Therapeutic surgery				
Proportion of patients who underwent therapeutic surgery	40.4%	32.5%	48.4%	Beta
Mean waiting time for surgery (days)	141.70	108.32	175.08	Gamma
Average number of therapeutic surgeries	1.20	0.65	1.75	Gamma
Distribution of patients by type of therapeutic surgery (%)				
Ther. Keratoplasty	60.4%	48.6%	72.2%	Dirichlet
Enucleation	2.6%	2.1%	3.1%	Dirichlet
Deep lamellar keratoplasty	16.9%	13.6%	20.2%	Dirichlet
Evisceration	4.2%	3.4%	5.0%	Dirichlet
Others	15.9%	12.8%	19.0%	Dirichlet
Optical surgery				
Proportion of patients who achieve AK resolution with PV and undergoing optical surgery (lifetime)	41.9%	33.7%	50.1%	Beta
Proportion of patients who achieve AK resolution with SVL and undergoing optical surgery (lifetime)	46.0%	37.0%	55.0%	Beta
Waiting time for optical surgery	365.25	293.66	436.84	Beta
Distribution of patients by type of optical surgery (%)				
Optical keratoplasty	41.5%	33.4%	49.6%	Dirichlet
Evisceration	3.7%	3.0%	4.4%	Dirichlet
Cataract	43.7%	35.1%	52.3%	Dirichlet
DALK	5.8%	4.6%	6.9%	Dirichlet
Surgical correction for astigmatism	5.3%	4.3%	6.4%	Dirichlet
Distribution of the patients by BCVA after medical cure (%)				
Good vision	86.5%	69.6%	100.0%	Dirichlet
Poor vision	11.5%	9.3%	13.8%	Dirichlet

Input parameter	Point estimate	OWSA		PSA
		Lower value	Upper value	Probability distribution
Severe vision loss	1.9%	1.5%	2.3%	Dirichlet
Distribution of the patients by BCVA after therapeutic surgery - Ther. Keratoplasty (%)				
Good vision	34.7%	27.9%	41.5%	Dirichlet
Poor vision	11.6%	9.3%	13.8%	Dirichlet
Severe vision loss	35.6%	28.6%	42.5%	Dirichlet
Loss of eye functionality	18.2%	14.6%	21.8%	Dirichlet
Distribution of the patients by BCVA after therapeutic surgery - Enucleation (%)				
Good vision	0.0%	0.0%	0.0%	Dirichlet
Poor vision	0.0%	0.0%	0.0%	Dirichlet
Severe vision loss	0.0%	0.0%	0.0%	Dirichlet
Loss of eye functionality	100.0%	80.4%	100.0%	Dirichlet
Distribution of the patients by BCVA after therapeutic surgery - Deep lamellar keratoplasty (%)				
Good vision	34.7%	27.9%	41.5%	Dirichlet
Poor vision	11.6%	9.3%	13.8%	Dirichlet
Severe vision loss	35.6%	28.6%	42.5%	Dirichlet
Loss of eye functionality	18.2%	14.6%	21.8%	Dirichlet
Distribution of the patients by BCVA after therapeutic surgery - Evisceration (%)				
Good vision	0.0%	0.0%	0.0%	Dirichlet
Poor vision	0.0%	0.0%	0.0%	Dirichlet
Severe vision loss	0.0%	0.0%	0.0%	Dirichlet
Loss of eye functionality	100.0%	80.4%	100.0%	Dirichlet
Distribution of the patients by BCVA after therapeutic surgery - Others (%)				
Good vision	34.7%	27.9%	41.5%	Dirichlet
Poor vision	11.6%	9.3%	13.8%	Dirichlet
Severe vision loss	35.6%	28.6%	42.5%	Dirichlet
Loss of eye functionality	18.2%	14.6%	21.8%	Dirichlet
Distribution of the patients by BCVA after optical surgery (%)				
Improvement	49.7%	40.0%	59.4%	Dirichlet
No improvement	27.3%	21.9%	32.7%	Dirichlet
Worsening	16.3%	13.1%	19.5%	Dirichlet
Loss of eye functionality	6.7%	5.4%	8.0%	Dirichlet
Distribution of the patients by BCVA after graft failure (%)				
Good vision	8.5%	6.8%	10.1%	Dirichlet
Poor vision	2.8%	2.3%	3.4%	Dirichlet
Severe vision loss	8.7%	7.0%	10.4%	Dirichlet
Loss of eye functionality	80.0%	64.3%	95.7%	Dirichlet

Input parameter	Point estimate	OWSA		PSA
		Lower value	Upper value	Probability distribution
Recurrence - year 1				
Akantior	0.0%	0.0%	0.0%	Beta
EMA comparator – no AAT	11.5%	9.2%	13.8%	Beta
After therapeutic surgery	4.6%	3.7%	5.4%	Beta
Recurrence - year 2+				
Akantior	0.0%	0.0%	0.0%	Beta
EMA comparator – no AAT	0.0%	0.0%	0.0%	Beta
After therapeutic surgery	4.6%	3.7%	5.4%	Beta
Hazard ratio vs general population/good vision				
Cured with poor vision	1	1	1.20	Gamma
Cured with severe vision loss	1	1	1.20	Gamma
Concomitant therapy				
Cost of concomitant therapy (one-off)	366.13	294.37	437.89	Gamma
Cost for each type of therapeutic surgery, DKK				
Ther. Keratoplasty	25,349.00	20,380.60	30,317.40	Gamma
Enucleation	3,044.00	2,447.38	3,640.62	Gamma
Deep lamellar keratoplasty	22,280.00	17,913.12	26,646.88	Gamma
Evisceration	11,713.00	9,417.25	14,008.75	Gamma
Others	2,096.00	1,685.18	2,506.82	Gamma
Pre therapeutic surgery cost (one-off)	2,913.00	2,342.05	3,483.95	Gamma
Post-surgery cost associated with adjuvant systemic and systemic immunosuppressive therapies (one-off)	29,215.39	23,489.17	34,941.61	Gamma
Cost to treat the surgical complications (one-off)	8,821.99	7,092.88	10,551.10	Gamma
Graft failure				
One-off cost of graft failure, DKK	6,005.65	4,828.54	7,182.75	Gamma
Cost for each type of optical surgery, DKK				
Optical keratoplasty	2,096.00	1,685.18	2,506.82	Gamma
Evisceration	2,096.00	1,685.18	2,506.82	Gamma
Cataract	2,096.00	1,685.18	2,506.82	Gamma
DALK	2,096.00	1,685.18	2,506.82	Gamma
Surgical correction for astigmatism	2,096.00	1,685.18	2,506.82	Gamma
Pre optical surgery cost (one-off)	2,913.00	2,342.05	3,483.95	Gamma
Cost per cycle, DKK				
AK infection	87,941.00	70,704.57	105,177.44	Gamma

Input parameter	Point estimate	OWSA		PSA
		Lower value	Upper value	Probability distribution
Cured with good vision, after medical resolution	19,773.44	15,897.85	23,649.04	Gamma
Cured with poor vision, after medical resolution	41,690.72	33,519.34	49,862.10	Gamma
Cured with severe vision loss, after medical resolution	50,170.33	40,336.95	60,003.72	Gamma
Cured with good vision, after surgical resolution	43,351.21	34,854.37	51,848.05	Gamma
Cured with poor vision, after surgical resolution	56,449.54	45,385.43	67,513.65	Gamma
Cured with severe vision loss, after surgical resolution	57,518.23	46,244.66	68,791.81	Gamma
Loss of eye functionality	27,968.97	22,487.05	33,450.88	Gamma
HSUV				
Health related quality of life				
All, age 18–29	0.87	0.70	1.00	Beta
All, age 30–39	0.85	0.68	1.00	Beta
All, age 40–49	0.83	0.67	1.00	Beta
All, age 50–59	0.82	0.66	0.98	Beta
All, age 60–69	0.81	0.65	0.97	Beta
All, age 70+	0.72	0.58	0.86	Beta
Disutility vs "Cured with good vision"/General population				
AK infection	-0.28	-0.34	-0.23	Normal
Cured with poor vision	-0.08	-0.09	-0.06	Normal
Cured with severe vision loss	-0.10	-0.12	-0.08	Normal
Loss of eye functionality	-0.25	-0.30	-0.20	Normal
On-going disutilities associated with long-term conditions*				
Cured with good vision	-0.03	-0.04	-0.03	Normal
Cured with poor vision	-0.08	-0.09	-0.06	Normal
Cured with severe vision loss	-0.12	-0.15	-0.10	Normal
Loss of eye functionality	-0.14	-0.16	-0.11	Normal
Disutility per therapeutic surgery	-0.14	-0.17	-0.11	Normal
Duration (in days) of the disutility per therapeutic surgery	121.75	97.89	145.61	Gamma
Disutility per graft failure event	-0.25	-0.30	-0.20	Normal
Duration (in days) of the disutility per graft failure event	141.70	113.93	169.47	Gamma
Disutility per optical surgery	-0.14	-0.17	-0.11	Normal
Duration (in days) of the disutility per optical surgery	121.75	97.89	145.61	Gamma
Caregiver disutility associated with therapeutic surgery	-0.04	-0.05	-0.03	Normal
Caregiver disutility associated with graft failure	-0.04	-0.05	-0.03	Normal

Input parameter	Point estimate	OWSA		PSA
		Lower value	Upper value	Probability distribution
Caregiver disutility associated with loss of eye functionality and SVL	-0.04	-0.05	-0.03	Normal
Caregiver disutility associated with optical surgery	-0.04	-0.05	-0.03	Normal
% of patients to which the caregivers disutility is applied	100	80	100	Beta
% of patients to which the graft failure is applied	35	28	42	Beta
Transport costs				
Average km per visit (return journey)	35.00	28.14	41.86	Gamma
Cost per km (DKK)	3.79	3.05	4.53	Gamma
Economic value of use of time				
Value of 1 hour of time (DKK)	193.69	155.72	231.65	Gamma
Hours per day to be valued	7.40	5.95	8.85	Gamma
Number of hours per day for treatment administration - during AK intensive period, by treatment arm. Akantior	9.37	7.53	11.20	Gamma
Number of hours per day for treatment administration - during AK intensive period, by treatment arm. EMA comparator – no AAT	0.0	0.0	0.0	Gamma
Number of hours per day for treatment administration - in AK infection after intensive period, by treatment arm. Akantior	4.00	3.22	4.78	Gamma
Number of hours per day for treatment administration - in AK infection after intensive period, by treatment arm. EMA comparator – no AAT	0.0	0.0	0.0	Gamma
Patients use of time - number of days for therapeutic surgery (hospital inpatient time)	121.75	97.89	145.61	Gamma
number of days for optical surgery (hospital inpatient time)	121.75	97.89	145.61	Gamma
Caregivers use of time- Hours per day in hospital	1.00	0.80	1.20	Gamma

Appendix H. Literature searches for the clinical assessment

H.1 Identification and selection of relevant studies

A *de novo* systematic literature review (SLR) was conducted on 25th and 26th July 2022, and subsequently updated on 24th March 2025, for the initial dossier submission 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 (see the eligibility criteria of the SLR listed in Table 93). 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 performed in accordance with a pre-specified protocol. This involved searching electronic databases from 1995 to the date of the searches. Alongside these, hand searches were performed for key conference proceedings, clinical trial databases, and the bibliographies of any relevant articles and systematic reviews. Full details of the methodology for the SLR conducted for the initial dossier submission are maintained in this revised dossier in the sections below. However, for this revised dossier, with 'no treatment' as the new comparator, all publications related to any anti-amoebic treatment other than Akantior, can be excluded, resulting in only two publications, Dart et al. 2024 [3] (results ODAK trial) and Franch et al. 2024 [39] (real world efficacy data Akantior).

Furthermore, a systematic literature search was conducted to identify published data about clinical outcomes in untreated cases of Acanthamoeba keratitis [89]. 'Untreated' was defined as not receiving a treatment with an established and clinically proven anti-amoebic activity as stated by the CDC (polihexanide, chlorhexidine, propamidine, hexamidine). Eligible studies were clinical studies, published between 1970-1995 inclusive, with patients with a confirmed diagnosis of Acanthamoeba keratitis who were untreated for whom a clinical outcome (cure without surgery; keratoplasty; enucleation) was reported. Database searches conducted on 27th November and 2nd December 2023 (PubMed; Cochrane Database of Systematic Reviews; Prospero International Prospective Register of Systematic Reviews; Cochrane Central Register of Controlled Trials; ClinicalTrials.gov) were supplemented with references from a previous targeted literature review and citation chasing. Screening was conducted by two independent reviewers. One reviewer rated the certainty of the overall body of evidence using the GRADE framework. The proportion [95% confidence interval adjusted for study-level clustering] of patients experiencing each outcome is presented. There were 37 eligible studies (56 patients in total), all of which were observational studies. The patients ranged between 13 and 71 years of age (mean = 34.9 years) and 50.0% were male. Most cases (n = 31; 55.4%) originated in the USA, with 10 (17.9%) from Europe. Most patients were administered corticosteroids (85.7%), antibiotics (82.1%), and/or antivirals (75.0%). The GRADE quality of evidence was low.

Overall, 11/56 medically untreated patients (0.20 [0.08, 0.40]) were cured without surgical intervention, 38/56 (0.68 [0.48, 0.83]) had a keratoplasty, 4/56 (0.07 [0.03, 0.18]) had an enucleation, and 4/56 (0.07 [0.01, 0.29]) had minor surgery that proceeded a cure.

The main limitation of the review was that it relies heavily on case reports and case series, which are subject to inherent bias, and require caution when interpreting the findings. However, evidence suggests that up until 1985, all diagnosed cases of Acanthamoeba keratitis were published, regardless of outcome or severity. Therefore, the cases reports published up until 1985 are likely to be less prone to publication bias than those published after this date.

A full report of the SLR is provided as Data on file for the current submission, reference 89 (AKANTIOR Untreated AK SLR report v1.0") . In addition, this SLR has been officially published (Papa et al. 2025 [88]), and the pdf as well as the supplementary material are available as part of the reference pack for the current submission.

Below, only the specifications of the clinical SLR conducted for the initial dossier submission are included. As indicated above, with 'no treatment' as the new comparator, all publications related to any anti-amoebic treatment other than Akantior, can be excluded, resulting in only two publications, Dart et al. 2024 3 (results ODAK trial) and Franch et al. 2024 39 (real world efficacy data Akantior).

H.2 Search strategy

Electronic databases

Database searches were conducted on 26th July 2022 and 24th March 2025. The following electronic databases were searched using a pre-defined search strategy:

- PubMed
- The Cochrane Central Register of Controlled Trials
- The Cochrane Database of Systematic Reviews
- Prospero

The search strategy was based on terms to identify the population, intervention and outcomes of interest. For each term, at least one free text term was included, along with a Medical Subject Heading (MeSH) term if available. The search strategy and search terms for PubMed and the Cochrane Library are presented in Table 90 and Table 91, respectively. The search strategy for the Prospero database is presented in Table 92.

Congress proceedings

Websites of the following organisations, and their annual conferences listed below, were hand-searched by one reviewer on 25th July 2022 to identify conference abstracts that had not been indexed in a medical literature database:

- Conference proceedings from 2017–2022 were searched for the following conferences:
    - Association for Research in Vision and Ophthalmology via Investigative Ophthalmology and Visual Science
    - European Association for Vision and Eye Research
    - American Association of Ophthalmology
    - American Society of Corneal and refractive Surgery

- European Society of Corneal and Refractive Surgeons
- Cornea Society

It was also planned that the proceedings of the American Optometric Association would be searched; however, the conference proceedings could not be found online.

In the SLR update, the proceedings from 2022–2024 (2025 not yet available) of the conferences listed below were hand-searched by one reviewer on 24th March 2025 to identify potentially eligible abstracts since the last search. It was planned that the proceedings of the American Optometric Association, American Society of Corneal and Refractive Surgery, European Society of Corneal and Refractive Surgeons and Cornea Society would be searched; however, the conference proceedings could not be found online or a conference had not taken place since 2022.

- Conference proceedings from 2022–2024 were searched for the following conferences:
  - Association for Research in Vision and Ophthalmology via Investigative Ophthalmology and Visual Science
  - European Association for Vision and Eye Research
  - American Association of Ophthalmology

Websites

To identify any further relevant clinical evidence, the following websites and Summary of Product Characteristics (SmPCs) of the below medications were hand-searched by one reviewer on 25th July 2022 and 24th March 2025. In some instances, a manufacturer website could not be identified and so another reputable website with relevant product information was hand-searched instead.

- Brolene®: https://www.medicines.org.uk/emc/product/13181/smpc#gref
- Chlorhexidine: https://www.uspharmacist.com/article/chlorhexidine-004-ophthalmic-solution
- Desomedine™:https://www.bausch.com.sg/en/our-products/pharmaceuticals/allergy-and-inflammation/desomedine-eye-drops/
- Gramicidin®: https://www.medicines.org.uk/emc/product/2253/smpc#gref
- Maxitrol®: https://www.medicines.org.uk/emc/product/841/smpc#gref
- Neocin-PG®: https://labeling.pfizer.com/showlabeling.aspx?id=704
- Neosporin Ophthalmic Solution®: https://www.pfizermedicalinformation.com/en-us/neosporin-ophthalmic-solution-sterile
- On 26th October 2022, the website and SmPC for Impavido (US label for oral miltefosine) was also searched (https://www.impavido.com/). No studies for AK were identified.
- ClinicalTrials.gov (https://clinicaltrials.gov/) was also searched on 26th July 2022 and 24th March 2025.

Bibliography searches

Reference lists from any identified SLRs were searched for further studies of interest to supplement the articles retrieved from the standard medical databases.

Citation chasing was undertaken using two different approaches:

- Original 2022 SLR: Reference lists of eligible articles were hand-searched by a single reviewer to identify further potentially eligible articles. Forward citation searching of eligible articles was also conducted in Google Scholar by a single reviewer
- 2025 SLR update: Both backward and forward searching were conducted using the Citation Chaser Shiny app, with identified abstracts uploaded to Covidence and screened by two reviewers.

Search terms

Searches were conducted using a combination of free-text search terms and controlled vocabulary terms specific to each database as recommended by Cochrane. The searches were limited to publications from 1995 onwards to ensure that any evidence identified was relevant to the current healthcare landscape. Additionally, a clinical expert confirmed that the formulations of anti-amoebic therapies (AATs) have not changed since this date. Regarding conference proceedings, only studies from the last eight years were searched, based on the assumption that complete publication of conference articles occurs within this timeframe. No additional limits were applied to the searches. Regarding websites, ClinicalTrials.gov was searched using the free-text search term "Acanthamoeba Keratitis" and therefore individual hits/search items are not available. The search strategies for the electronic databases are presented in Table 90 (PubMed), Table 91 (Cochrane) and Table 92 (Prospero). It should be noted that the search term for the PubMed database was used as one continuous search item and therefore individual hits/search terms are not available.

Table 90: Search strategy for PubMed for the clinical SLR

Search terms

("Acanthamoeba Keratitis"[Title/Abstract] OR (Acanthamoeba Keratitis[MeSH Terms]))

AND

("eye drop*"[Title/Abstract] OR "Ophthalmic Solution*"[Title/Abstract] OR Biguanide[Title/Abstract] OR Polihexanide[Title/Abstract] OR polyhexanide[Title/Abstract] OR PHMB[Title/Abstract] OR miltefosine[Title/Abstract] OR Chlorhexidine[Title/Abstract] OR Diamidine[Title/Abstract] OR Propamidine[Title/Abstract] OR Brolene[Title/Abstract] OR Hexamidine[Title/Abstract] OR Desomedine[Title/Abstract] OR Neomycin[Title/Abstract] OR Maxitrol[Title/Abstract] OR "polymyxin B"[Title/Abstract] OR gramicidin[Title/Abstract] OR Neosporin[Title/Abstract] OR (Neocin-PG[Title/Abstract]) OR Imidazole[Title/Abstract] OR Voriconazole[Title/Abstract] OR "antiamoebic therap*"[Title/Abstract] OR pentamidine[Title/Abstract] OR lomidine[Title/Abstract] OR nebuPent[Title/Abstract] OR pentacarinat[Title/Abstract] OR pentam[Title/Abstract] OR entamidin[Title/Abstract] OR MK-412A[Title/Abstract] OR novalsan[Title/Abstract] OR sebidin[Title/Abstract] OR tubulicid[Title/Abstract] OR Povidone[Title/Abstract] OR Iodine[Title/Abstract] OR (Ophthalmic Solutions[MeSH Terms]) OR (Biguanides[MeSH Terms]) OR (Chlorhexidine[MeSH Terms]) OR (Pentamidine[MeSH Terms]) OR (Benzamidines[MeSH Terms]) OR (Neomycin[MeSH Terms]) OR (Polymyxin B[MeSH Terms]) OR (Gramicidin[MeSH Terms]) OR (Imidazoles[MeSH Terms]) OR (Voriconazole[MeSH Terms]) OR (Povidone[MeSH Terms]) OR (Iodine[MeSH Terms]))

AND

("clinical resolution"[Title/Abstract] OR cure*[Title/Abstract] OR "visual acuity"[Title/Abstract] OR (cornea* n2 scar*[Title/Abstract]) OR (cornea* n2 ulcer*[Title/Abstract]) OR Conjunctiva[Title/Abstract] OR Erythema[Title/Abstract] OR Edema[Title/Abstract] OR Discharge[Title/Abstract] OR Papillae[Title/Abstract] OR Follicles[Title/Abstract] OR (Lens near2 abnormal*[Title/Abstract]) OR (pupil near2 abnormal*[Title/Abstract]) OR ("Anterior chamber" near2 inflam*[Title/Abstract]) OR "Anterior uveitis"[Title/Abstract] OR EQ-5D*[Title/Abstract] OR "quality of life"[Title/Abstract] OR qol[Title/Abstract] OR "quality-of-life"[Title/Abstract] OR hrqol[Title/Abstract] OR VFQ-25[Title/Abstract] OR NEIVFQ-25[Title/Abstract] OR "visual function questionnaire"[Title/Abstract] OR "Corneal epithelial"[Title/Abstract] OR "Corneal stromal"[Title/Abstract] OR opacity[Title/Abstract] OR infiltrate[Title/Abstract] OR compliance[Title/Abstract] OR "adverse event*"[Title/Abstract] OR Ophthalmoscopy[Title/Abstract] OR "Intraocular pressure"[Title/Abstract] OR relapse[Title/Abstract] OR recurrence[Title/Abstract] OR “eye* n2 removal*”[Title/Abstract] OR (Visual Acuity[MeSH Terms]) OR (Corneal Injuries[MeSH Terms]) OR (Conjunctiva[MeSH Terms]) OR (Erythema[MeSH Terms]) OR (Edema[MeSH Terms]) OR (Uveitis, Anterior[MeSH Terms]) OR (Quality of Life[MeSH Terms]) OR (Corneal Ulcer[MeSH Terms]) OR (Patient Compliance[MeSH Terms]) OR (Drug-Related Side Effects and Adverse Reactions[MeSH Terms]) OR Ophthalmoscopy[MeSH Terms] OR (Intraocular Pressure[MeSH Terms]) OR Recurrence[MeSH Terms])

Abbreviations: SLR: systematic literature review.

Table 91: Search strategy for the Cochrane Library (Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews) for the clinical SLR

Search number	Search terms	Results (26th July 2022)	Results (24th March 2025)
1	"Acanthamoeba Keratitis"	30	36
2	MeSH descriptor: [Acanthamoeba Keratitis] explode all trees	11	16
3	#1 OR #2	30	36

4	"eye drop" OR “eye drops” OR "Ophthalmic Solution" OR Biguanide OR Polihexanide OR polyhexanide OR PHMB OR miltefosine OR Chlorhexidine OR Diamidine OR Propamidine OR Brolene OR Hexamidine OR Desomedine OR Neomycin OR Maxitrol OR "polymyxin B" OR gramicidin OR Neosporin OR (Neocin-PG) OR Imidazole OR Voriconazole OR "antiamoebic therapy" OR “"antiamoebic therapies” OR pentamidine OR lomidine OR nebuPent OR pentacarinat OR pentam OR entamidin OR MK-412A OR novalsan OR sebidin OR tubulicid OR Povidone OR Iodine	15636	17877
5	MeSH descriptor: [Ophthalmic Solutions] explode all trees	3720	4290
6	MeSH descriptor: [Biguanides] explode all trees	7277	8619
7	MeSH descriptor: [Chlorhexidine] explode all trees	2390	2821
8	MeSH descriptor: [Pentamidine] explode all trees	117	130
9	MeSH descriptor: [Benzamidines] explode all trees	167	193
10	MeSH descriptor: [Neomycin] explode all trees	400	433
11	MeSH descriptor: [Polymyxin B] explode all trees	185	206
12	MeSH descriptor: [Gramicidin] explode all trees	33	34
13	MeSH descriptor: [Imidazoles] explode all trees	22440	26968
14	MeSH descriptor: [Voriconazole] explode all trees	208	260
15	MeSH descriptor: [Povidone] explode all trees	802	998
16	MeSH descriptor: [Iodine] explode all trees	1417	1717
17	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16	22968	52870
18	"clinical resolution" OR cure OR "visual acuity" OR (cornea near2 scar) OR (corneal near2 scar) OR (cornea near2 ulcer) OR (corneal near2 ulcer) OR Conjunctiva OR Erythema OR Edema OR Discharge OR Papillae OR Follicles OR (Lens near2 abnormal) OR (pupil near2 abnormal) OR (pupil near2 abnormality) OR ("Anterior chamber" near2 inflammation) OR "Anterior uveitis" OR EQ-5D* OR "quality of life" OR qol OR "quality-of-life" OR hrqol OR VFQ-25 OR NEIVFQ-25 OR "visual function questionnaire" OR "Corneal epithelial" OR "Corneal stromal" OR opacity OR infiltrate OR compliance OR "adverse event" OR "adverse events" OR Ophthalmoscopy OR "Intraocular pressure" OR relapse OR recurrence OR “eye near2 removal*” OR enucleation	465352	543166
19	MeSH descriptor: [Visual Acuity] explode all trees	5710	7130
20	MeSH descriptor: [Corneal Injuries] explode all trees	87	103
21	MeSH descriptor: [Conjunctiva] explode all trees	727	865

22	MeSH descriptor: [Erythema] explode all trees	1071	1356
23	MeSH descriptor: [Edema] explode all trees	1955	2355
24	MeSH descriptor: [Uveitis, Anterior] explode all trees	335	383
25	MeSH descriptor: [Quality of Life] explode all trees	29130	44016
26	MeSH descriptor: [Corneal Ulcer] explode all trees	170	197
27	MeSH descriptor: [Patient Compliance] explode all trees	12696	20160
28	MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees	3877	5106
29	MeSH descriptor: [Ophthalmoscopy] explode all trees	215	262
30	MeSH descriptor: [Intraocular Pressure] explode all trees	3548	4183
31	MeSH descriptor: [Recurrence] explode all trees	12840	16357
32	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31	466965	552310
33	#3 AND #17 AND #32	13	3

Abbreviations: SLR: systematic literature review.

Table 92: Search strategy for Prospero for the clinical SLR

Search number	Search terms	Results (26th July 2022)	Results (24th March 2025)
1	"Acanthamoeba Keratitis"	5	15
2	MeSH descriptor: [Acanthamoeba Keratitis] explode all trees	2	8
3	#1 OR #2	5	10

Abbreviations: SLR: systematic literature review.

H.3 Study selection

Study selection process

Once all abstracts of potentially relevant published articles had been identified, the study selection process was performed to determine study eligibility based on eligibility criteria of the clinical SLR presented in Table 93 below. The eligibility criteria were developed in line with the Population, Intervention, Comparison, Outcomes and Study (PICOS) criteria and included considerations for the population and disease condition, interventions, comparators, outcomes and study types mentioned in each identified study.

Table 93. PICOS eligibility criteria for the clinical SLR

Criteria	Explanation

Population	Patients (of any age) with a confirmed diagnosis of AK. Mixed populations of patients with AK or other IK infections with results reported separately for the population of interest
Interventions	All or a subset of study participants used oral miltefosine or an ophthalmic eye drop medication as part of the study in any concentration or combination[a] including, but not limited to: • Polihexanide (polyhexamethylene biguanide) • Chlorhexidine • Propamidine (Brolene®) • Hexamidine (Desomedine™) • Neomycin (Maxitrol®) • Neomycin/polymyxin B/gramicidin (Gramicidin®, Neosporin Ophthalmic Solution®, Neocin-PG®) • Imidazole • Voriconazole • Pentamidine • Povidone • Iodine
Comparators	Any control (including other active eye drop medication or placebo) or no control (i.e. single arm study)
• Outcomes	• At least one relevant efficacy our safety outcome reported. • Efficacy: • Clinical resolution rate • Best-corrected visual acuity (BCVA) • Corneal scarring • Corneal ulceration severity (only AK-Related) • Conjunctiva (erythema grade; oedema grade; discharge; papillae; follicles) • Lens abnormalities • Pupil abnormalities • Anterior chamber inflammation • EQ-5D

- Visual Functioning Questionnaire-25 (VFQ-25)
- Time to cure
- Corneal epithelial defects
- Corneal epithelial opacity/infiltrate
- Cornel stromal opacity/infiltrate
- Treatment adherence/compliance

Safety:

- Total adverse events
- Serious adverse events
- Dose limiting adverse events
- Treatment related adverse events
- Ophthalmoscopy
- Worsening of disease condition
- Intraocular pressure
- Adjunctive therapy
- Any corneal surgery
- Secondary complications
- Relapse rate
- Discontinuation rate
- Eye removal

Study design	Any controlled trial design or observational study design (including cross-sectional, case-control, cohort, or retrospective cohort) with at least five participants
Setting	Primary, secondary or tertiary care
Geographic location	Any
Language of publication	English
Date of publication	Full-text publications: Article published in the last 30 years (i.e. from January 1995 inclusive)
	Conference abstract: 2017–2024

Footnotes: [a]Note that a treatment regimen can include a combination of treatments (e.g. polihexanide plus propamidine). 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.

Abbreviations: AK: *Acanthamoeba* keratitis; BCVA: best-corrected visual acuity; IK: infectious keratitis; VFQ-25: Visual Functioning Questionnaire-25.

Title/abstract review

Studies identified from the electronic databases and the internet searches were combined into a single list and de-duplicated. Titles and abstracts of the de-duplicated list of articles were double screened by two independent reviewers to determine eligibility according to the inclusion criteria described in Table 93. If there was disagreement about study relevance, a conservative approach was taken and the record proceeded to the next stage of screening.

Full text review

For the studies included from the title/abstract review, full-texts were obtained and double-screened by two independent researchers using the inclusion criteria described in Table 93 to determine eligibility for inclusion. If there was disagreement about study relevance, it was planned for consensus to be reached through a third researcher. However, an agreement was reached by the two reviewers in all cases of initial conflict.

Any potentially eligible articles found through citation chasing methods (see Appendix H.2) went through the same process of eligibility checking (title/abstract screening followed by full text screening by two independent reviewers), along with any potentially eligible articles identified from the reference lists of published SLRs in AK. Any of the articles that were found to be eligible underwent backward and forward citation chasing. This circular process was repeated until no new articles were identified.

Data extraction

Data from the included full-text articles were extracted by one researcher into predesigned data extraction tables. Data extraction was independently validated by a second researcher. For the original 2022 SLR, all extracted data underwent this quality control. For the 2025 SLR update, a randomised 50% of eligible papers were subject to validation. The researchers discussed any conflicts. If there was disagreement, it was planned for consensus to be reached through a third researcher. However, an agreement was reached by the two researchers in all cases of initial conflict.

Data extraction was based on the published information and only outcomes reported by treatment were extracted. Outcomes for all treatment groups were extracted, even if the treatment group included fewer than five patients. Where it was not stated whether data were reported at patient-level or eye-level, it was assumed that data were reported at eye-level, unless there was evidence to contradict this assumption in the report.

Where data were not available in the published report, they were marked as missing and no attempt was made to obtain these data. However, an exception was made for medical cure rate (MCR)/clinical resolution (primary endpoint in the ODAK pivotal trial). For all eligible studies, it was pre-planned that an email would be sent to the corresponding author asking for the following information:

- Where no clinical resolution data were available in the published article, the corresponding author was asked whether clinical resolution data were recorded in the study and, if so, whether they would be able to share a summary of these data
- Where clinical resolution data were available in the published article, the corresponding author was asked whether clinical resolution data were recorded at a timepoint closer to 12 months and whether

they would be able to share a summary of these data. One eligible study (Papa et al. 2020) reported clinical resolution data at the 12-month timepoint; however, a different definition of clinical resolution was used to the ODAK trial. Therefore, the corresponding author was emailed to determine whether data using the same definition as the clinical trial were available. These data allowed the definition of MCR in the study to be aligned with that in the ODAK trial by treating discontinuation of baseline AAT as a failure. In the original publication, discontinuations of baseline AAT were not treated as failures and so the MCR in this report, based on data from the corresponding author, is lower than that in the original publication.

The corresponding authors were emailed for 32 (66.7%) studies. Authors of the remaining studies were not contacted due to a lack of available contact details.

Quality assessment

Risk of bias (RoB) in individual studies was assessed at the study level. Risk of bias was not assessed at the outcome level given the large number of outcomes of interest. For each study, the risk of bias assessment was conducted using the appropriate tool from the National Heart, Lung and Blood Institute's Study Quality Assessment Tools:[2]

- **RCTs and other controlled trials:** Controlled intervention studies tool
- **Cross-sectional, prospective, and retrospective cohort studies:** Observational cohort and cross-sectional studies tool
- **Case-series/retrospective analyses of routine data:** Case series studies tool
- **Case-control studies:** Case-control studies tool

Two approaches were taken to the risk of bias assessment:

- Original 2022 SLR: Two reviewers independently undertook the RoB assessment using the published information available (i.e. no attempts were made to obtain information not available in the published report). The reviewers read the guidance for each tool before starting the assessment. The quality assessment was only applied to the extracted outcomes. After completing the assessment independently, the reviewers discussed any conflicts. The two reviewers reached an agreement in all cases of initial conflict
- 2025 SLR update: The same approach was taken, except that only one reviewer undertook the RoB assessment

The reviewers agreed an overall rating for RoB (good, fair, poor) for each study based on a subjective assessment of the RoB considering the study's individual scores, in line with the guidance for the Study Quality Assessment Tools.[2] It is now generally accepted that overall ratings for risk of bias have limited use, and it is more informative to understand the areas where bias may occur, particularly if patterns emerge across the studies. As a result, the individual scores are also reported.

H.4 Description of identified studies

The PRISMA flow diagram for the clinical SLR is presented in Figure 8.

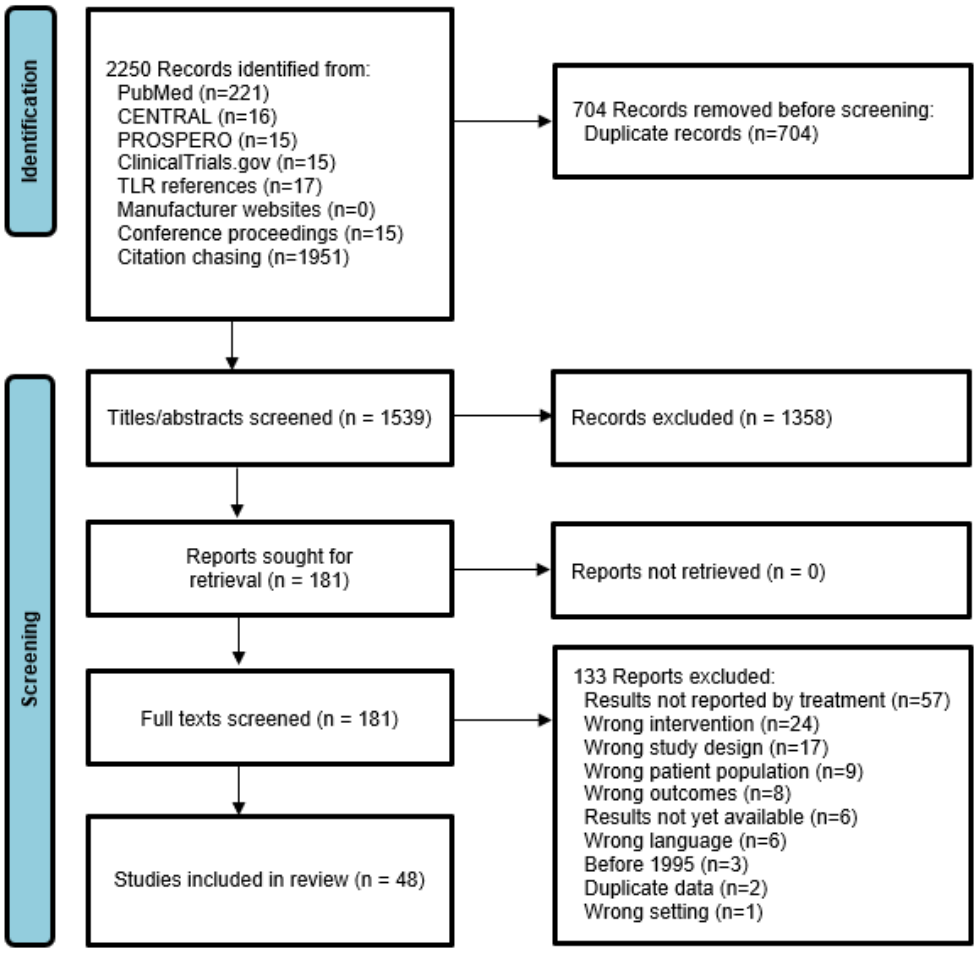
In total, 2250 records were identified for screening from all sources. The electronic database searches yielded 252 records alongside 15 records from the ClinicalTrials.gov website, 15 from conference proceedings and

1968 from bibliography searches (TLR references and citation chasing). After removal of duplicates (n=704), a total of 1,539 records (titles and abstracts) were selected for manual screening.

Titles and abstracts of the records identified from the searches were reviewed according to pre-defined eligibility criteria presented in Table 93, yielding 181 potentially relevant records (1,358 records excluded).

Following a detailed examination of the 181 full text records, 133 records were excluded, resulting in 48 records, meeting the pre-defined inclusion criteria of the clinical SLR. Among the 133 records included in the SLR, three were RCTs, 34 were retrospective analyses of routine data, eight were prospective single-arm interventional studies, two were case-control studies and one was a cohort study.

Figure 8. PRISMA flow diagram for the clinical SLR



Abbreviations: SLR: systematic literature review; TLR: targeted literature review.

H.5 Summary of published clinical studies identified in the review

All studies included following full text screening are presented in Table 94.

Table 94. Studies included in the clinical SLR

Study	Country	Study years	AK Population	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[3]	Italy, Poland, UK	2017–21	All	134	NR (NR-95)	36.5 (15-73)	NR	42	NR	0	21	I: 17 II: 69 III: 14
Bagga, 2021[4]	India	2016–18	All	23	*85* (14-NR)	39.8 (19-67)	NR	61.1	NR	NR	11.1	NR
Lim, 2008[5]	UK	1995–2001	All	50	NR	*31* *(NR)*	NR	46	98	2.00	NR	NR
Retrospective analyses of routine data												
Arnaiz-Camacho, 2025[6]	Spain	2014–24	Contact lens-associated AK	13	660 (90-NR)	30 (15-44)	5 (NR)	38.5	100	0	46.2	NR
Zhao, 2025[7]	China	2021–24	Overnight Orthokeratology -related AK	11	396 (234-888)	14.7 (11-22)	*5* (2-150)	27.3	100	27.3	NR	NR
Blaser,	Switzerland	2010–23	All	52	NR	*33*	18	40.4	92.3	7.7	NR	NR

2024[8]						*(13-90)*	(3-70)					
Messina, 2024[9]	Italy	2020–21	Contact lens-associated AK	8	NR (60-180)	27.8 (18-45)	NR	37.5	100	12.5	25	Severe: 12.5%
Agarwal, 2023[10]	India	2015–19	All	24	NR	NR	42 (NR)	NR	NR	NR	NR	NR
Roth, 2023[11]	Germany	1993–2021	All	75	NR	*37* *(15-73)*	47 (14-100)	30.3	84	1.3	NR	NR
Ahmed, 2022[12]	India	2016–20	All	7	NR	35 (20-55)	NR	100	NR	0	25	NR
Bonini, 2021[13]	Italy	1994–2012	All	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[14]	Singapore	2012–16	All	18	NR	24.4 (15-40)	NR	33.3	77.8	0	26.7	NR
Nasef, 2021[15]	Egypt	2016–20	All	42	NR	31.6 (18-65)	20.2 (1-40)	28.5	77	NR	25	NR
Jo, 2020[16]	Korea	2013–18	Contact lens-associated AK	16	NR	21.1 (13-42)	7.1 (1-21)	12.5	100	15.8	NR	I: 68.4% II: 31.6%
Megha,	India	2014–18	All	11	NR	*33*	22.2	72.73	27.3	9.09	NR	NR

2020[17]						*(21-73)*	(3-84)					
Musayeva, 2020[18]	Germany	2014–17	All	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%
Papa, 2020[1]	Italy UK	1991–2012	All	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[19]	UK	2017–18	All	9	NR	33.6 (22-61)	NR (NR-10)	11.11	100	0	NR	NR
Li, 2019[20]	China	2007–15	All	37	NR	48.8 (18-76)	NR	51.4	NR	0	NR	NR
Orosz, 2019[21]	Hungary	2015–18	Contact lens-associated AK	7	NR	30.7 (NR)	1.4 (NR)	43.0	100	NR	NR	NR
Randag, 2019[c,22]	Netherlands	2009–15	All	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[23]	UK	1991–2012	All	194	Bad outcomes: *896* (420-1624) Better outcomes:	*34* *(15-76)*	NR (8-65)	48	94	NR	47	I: 10% II: 56% III: 34%

					196 (112-308)							
Zhong, 2017[24]	China	2004–14	All	15	840 (168-1008)	42.3 (19-63)	52 (20-120)	66.67	6.67	0	NR	NR
Jiang, 2015[25]	China	1991–2013	Advanced stage	259	NR	NR (7-82)	NR	56.37	29.8	0.39	NR	Advanc-ed: 100%
Arnalich-Montiel, 2014[26]	Spain	2009–13	All	17	NR	38 (13-60)	NR	23.5	88.2	5.9	NR	NR
Erdem, 2014[27]	Turkey	2010–12	Non–contact lens–wearing	26	NR (NR-672)	49.3 (10-83)	24.8 (5-123)	61.54	0	0	0	NR
Cheng, 2009[28]	Hong Kong	2005–07	All	7	369 (NR)	23.1 (14-38)	7.6 (NR-28)	0	100	28.6	14.3	NR
Ku, 2009[29]	Australia	2003–07	All	13	386 (84-1484)	35 (23-56)	NR	62	92	0	69	NR
Lin, 2009[30]	Taiwan	2001–06	All	11	NR	23.7 (7-66)	26.1 (7-56)	82	NR	0	NR	NR
Mathers, 2006[31]	USA	NR	All	8	NR	NR	NR	NR	NR	NR	NR	Mild: 86.2% Severe:13.8%
Sun, 2006[32]	China	1997–2003	All	20	266 (77-770)	26 (12-50)	42 (7-182)	60	60	0	NR	NR

Perez-Santonja, 2003[33]	UK	1990–2000	Positive cultures after treatment[c]	8	375 (126-868)	36.4 (26-56)	9.75 (1-24)	50	75	NR	NR	NR
Donoso, 2002[34]	Chile	NR	All	27	NR	NR	NR (28-140)	NR	96	14.81	NR	NR
Parija, 2001[35]	India	1997–2000	All	11	NR	NR (15-57)	NR	73	0	NR	NR	NR
Azuara-Blanco, 1997[36]	UK	1994–97	All	10	NR	30 (19-40)	12.7 (2-26)	60	100	0	NR	NR
Duguid, 1997[37]	UK	1992–95	All	105	NR	32 (16-64)	NR	57.14	91.9	5.4	NR	NR
Skarin, 1996[38]	Sweden	1991–93	All	8	NR (NR-672)	37 (22-69)	81.2 (28-308)	62.5	62.5	0	25	NR
Prospective single-arm interventional study												
Franch, 2024[39]	Italy	2023	Contact lens-associated AK	11	NR	41.4 (17-67)	NR	36	100	9.1	91	I: 17% II: 33% III: 50%
Caruso, 2020[40]	Italy	2018–19	All	29	NR (NR-84)	27.0 (NR)	NR	31.04	55.17	NR	NR	III: 100%

Bagga, 2019[41]	India	2018–18	All	5	NR	41.5 (30-58)	33 (10-90)	0	NR	NR	NR	NR
Revathi, 2018[42]	NR	NR	All	25	NR	NR	23 (NR)	NR	NR	NR	NR	NR
Rahimi, 2014[43]	Iran	NR	All	25	NR	NR	NR	NR	NR	8	NR	NR
Hargrave, 1999[44]	USA	NR	All	83	NR	33 (18-72)	68 (NR)	NR	75	3	35	NR
Kosrirukvongs, 1999[45]	Thailand	1996–96	Not responded to neomycin	5	NR	53 (33-77)	NR	40	20	20	NR	NR
Seal, 1996[46]	UK	NR	All	12	NR (168-NR)	30.9 (14-50)	30.9 (7-98)	41.67	100	NR	25	NR
Case-control study												
Hsu, 2022[47]	Taiwan	2001–16	Contact lens-associated AK	35	NR	22.9 (11-55)	18.3 (7-56)	37.14	100	11.43	NR	NR
Wouters, 2022[d,48]	Netherlands	2003–17	All	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[49]	UK	1992–96	All	243	NR	31.5 (4-64)	NR	56	88	7	NR	NR

Note: [a]Values in italics are medians. [b]Time from symptom initiation to diagnosis. [c]Two 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.

H.6 Excluded studies

The primary reason for exclusion at full-text screening was that results were not reported by treatment group (57 records). Additional reasons for exclusion are presented in Figure 8. A full list of studies excluded at full-text screening with the rationale for exclusion is presented in Table 95 below.

Table 95. Studies excluded at full text screening

#	Citation	Reason for exclusion
1	Fuchsluger et al. Acanthamoeba keratitis - pKP versus conservative treatment in a 20-year follow-up study. 2017. Acta Ophthalmol; 95 (S259)	Results not reported by treatment
2	Guenena et al. Acanthamoeba Keratitis in Residents' Clinic Compared with a Faculty Private Practice. 2018. ASCRS 2018 Abstracts	Results not reported by treatment
3	Lozano et al. Systemic Miltefosine as an Adjunct Treatment of Progressive Acanthamoeba Keratitis. 2019. Conference abstract/reference unknown	Results not reported by treatment
4	Bacon et al. A review of 72 consecutive cases of Acanthamoeba keratitis, 1984-1992. 1993. Eye; 7 (6)	Results not reported by treatment
5	Thibodeau et al. Opioid Prescribing Patterns for Ulcerative Keratitis. 2021. Cornea; 41 (4)	Results not reported by treatment
6	Kent et al. Painless Acanthamoeba keratitis. 2012. Can J Ophthalmol; 47 (4)	Results not reported by treatment
7	Oldenburg et al. Microbiological cure times in acanthamoeba keratitis. 2011. Eye; 25 (9)	Results not reported by treatment
8	Przybek-Skrzypecka et al. Impact of First Healthcare Provider on Acanthamoeba Keratitis Course: How to Overcome Poor Prognosis in Acanthamoeba Keratitis Treatment? A Single Tertiary Centre, Observational Study. 2023. Clin Ophthalmol; 17	Results not reported by treatment
9	Wanachiwanawin et al. Clinical features of Acanthamoeba keratitis in contact lens wearers and non-wearers. 2012. Southeast Asian J Trop Med Public Health; 43 (3)	Results not reported by treatment
10	Lee et al. Risk factors, demographics and clinical profile of Acanthamoeba keratitis in Melbourne: an 18-year retrospective study. 2017. Br J Ophthalmol; 102 (5)	Results not reported by treatment

11	Pang et al. Acanthamoeba Keratitis in China: Genotypic and Clinical Correlations. 2024. Transl Vis Sci Technol; 13 (2)	Results not reported by treatment
12	AlOwaifeer et al. Incidence and Risk Factors of Ocular Hypertension and Glaucoma in Patients With Acanthamoeba Keratitis. 2021. Eye Contact Lens; 47 (11)	Results not reported by treatment
13	Lee et al. Utility of In Vivo Confocal Microscopy in Diagnosis of Acanthamoeba Keratitis: A Comparison of Patient Outcomes. 2022. Cornea; 42 (2)	Results not reported by treatment
14	Hwang et al. PCR-based diagnosis and clinical insights into parasitic keratitis. 2025. J Microbiol Immunol Infect; 58 (3)	Results not reported by treatment
15	DosSantos et al. Acanthamoeba keratitis in Porto Alegre (southern Brazil): 28 cases and risk factors. 2018. Parasitol Res; 117 (3)	Results not reported by treatment
16	Illingworth et al. Acanthamoeba keratitis: risk factors and outcome. 1995. Br J Ophthalmol; 79 (12)	Results not reported by treatment
17	Nadia et al. Acanthamoeba keratitis in contact lens wearers in a tertiary centre of Tunisia, North Africa. 2021. Ann Med Surg; 70	Results not reported by treatment
18	Yamazoe et al. Visual outcome in Japanese patients with Acanthamoeba keratitis. 2012. Eye; 26 (4)	Results not reported by treatment
19	Wilhelmus et al. Bilateral acanthamoeba keratitis. 2008. Am J Ophthalmol; 145 (2)	Results not reported by treatment
20	Radford et al. Acanthamoeba keratitis in England and Wales: incidence, outcome, and risk factors. 2002. Br J Ophthalmol; 86 (5)	Results not reported by treatment
21	Robaei et al. The impact of topical corticosteroid use before diagnosis on the outcome of Acanthamoeba keratitis. 2014. Ophthalmology; 121 (7)	Results not reported by treatment
22	Patel et al. Resurgence of Acanthamoeba keratitis in Auckland, New Zealand: a 7-year review of presentation and outcomes. 2010. Clin Exp Ophthalmol; 38 (1)	Results not reported by treatment
23	Qian et al. Clinical experience with Acanthamoeba keratitis at the cole eye institute, 1999-2008. 2010. Cornea; 29 (9)	Results not reported by treatment
24	Ross et al. Clinical characteristics of Acanthamoeba keratitis infections in 28 states, 2008 to 2011. 2014. Cornea; 33 (2)	Results not reported by treatment
25	Srinivasan et al. Non-contact lens related Acanthamoeba keratitis at a tertiary eye care centre in south India: Implications for eye care programs in the region. 2003. Med Sci Monit; 9 (4)	Results not reported by treatment

26	Thebpatiphat et al. Acanthamoeba keratitis: a parasite on the rise. 2007. Cornea; 26 (6)	Results not reported by treatment
27	Tu et al. Prognostic factors affecting visual outcome in Acanthamoeba keratitis. 2008. Ophthalmology; 115 (11)	Results not reported by treatment
28	Claerhout et al. Delay in diagnosis and outcome of Acanthamoeba keratitis. 2004. Graefes Arch Clin Exp Ophthalmol; 242 (8)	Results not reported by treatment
29	Lee et al. Risk factors, demographics and clinical profile of Acanthamoeba keratitis in Melbourne: an 18-year retrospective study. 2018. Br J Ophthalmol; 102 (5)	Results not reported by treatment
30	Chew et al. Clinical outcomes and prognostic factors associated with acanthamoeba keratitis. 2011. Cornea; 30 (4)	Results not reported by treatment
31	Park et al. The role of topical corticosteroids in the management of Acanthamoeba keratitis. 1997. Cornea; 16 (3)	Results not reported by treatment
32	Butler et al. Six-year review of Acanthamoeba keratitis in New South Wales, Australia: 1997-2002. 2005. Clin Exp Ophthalmol; 33 (1)	Results not reported by treatment
33	Nielsen et al. Increasing incidence of Acanthamoeba keratitis in a large tertiary ophthalmology department from year 1994 to 2018. 2019. Acta Ophthalmol; 98 (5)	Results not reported by treatment
34	Bharathi et al. A study of the spectrum of Acanthamoeba keratitis: a three-year study at a tertiary eye care referral center in South India. 2007. Indian J Ophthalmol; 55 (1)	Results not reported by treatment
35	Chin et al. Acanthamoeba keratitis: 10-year study at a tertiary eye care centre in Hong Kong. 2015. Cont Lens Anterior Eye; 38 (2)	Results not reported by treatment
36	Bouheraoua et al. Prognostic factors associated with the need for surgical treatments in acanthamoeba keratitis. 2013. Cornea; 32 (2)	Results not reported by treatment
37	Carnt et al. The Impact of Topical Corticosteroids Used in Conjunction with Antiamoebic Therapy on the Outcome of Acanthamoeba Keratitis. 2016. Ophthalmol; 123 (5)	Results not reported by treatment
38	Kasparova et al. Clinical features, diagnosis, the results of therapeutic and surgical treatment of acanthamoebic keratitis. 2017. Ophthalmology in Russia; 14 (4)	Results not reported by treatment
39	List et al. Evaluation of Acanthamoeba keratitis cases in a tertiary medical care centre over 21 years. 2021. Sci Rep; 11 (1)	Results not reported by treatment
40	Li et al. Acanthamoeba keratitis related to contact lens use in a tertiary hospital in China. 2019. BMC Ophthalmol; 19 (1)	Results not reported by treatment

41	Liu et al. Clinical features and outcomes of Acanthamoeba keratitis in a tertiary hospital over 20- year period. 2020. J Formos Med Assoc; 119 (1)	Results not reported by treatment
42	McKelvie et al. The rising tide of Acanthamoeba keratitis in Auckland, New Zealand: a 7-year review of presentation, diagnosis and outcomes (2009-2016). 2018. Clin Exp Ophthalmol; 46 (6)	Results not reported by treatment
43	D'Aversa et al. Diagnosis and successful medical treatment of Acanthamoeba keratitis. 1995. Arch Ophthalmol; 113 (9)	Results not reported by treatment
44	Toba et al. Use of in vivo confocal microscopy in suspected Acanthamoeba keratitis: a 12-year real-world data study at a Swedish regional referral center.. 2024. J Ophthalmic Inflam Infect; 14 (1)	Results not reported by treatment
45	Przybek-Skrzypecka et al. Impact of first health care provider on Acanthamoeba keratitis course. How to overcome poor prognosis in AK treatment? Single tertiary center, observational study. 2023. Clin Ophthalmol; 17	Results not reported by treatment
46	Roozbahani et al. Acanthamoeba Keratitis: Are Recent Cases More Severe? 2018. Cornea; 37 (11)	Results not reported by treatment
47	Scruggs et al. Risk factors, management, and outcomes of Acanthamoeba keratitis: A retrospective analysis of 110 cases. 2022. Am J Ophthalmol Case Rep; 25	Results not reported by treatment
48	Chynn et al. Acanthamoeba keratitis. Contact lens and noncontact lens characteristics. 1995. Ophthalmology; 102 (9)	Results not reported by treatment
49	Höllhumer et al. Acanthamoeba keratitis in Australia: demographics, associated factors, presentation and outcomes: a 15-year case review. 2020. Eye; 34 (4)	Results not reported by treatment
50	Sharma et al. Patient characteristics, diagnosis, and treatment of non-contact lens related Acanthamoeba keratitis. 2000. Br J Ophthalmol; 84 (10)	Results not reported by treatment
51	Rahimi et al. Chlorhexidine Monotherapy with Adjunctive Topical Corticosteroids for Acanthamoeba Keratitis. 2015. J Ophthalmic Vis Res; 10 (2)	Results not reported by treatment
52	Papa et al. Orphan Drug for Acanthamoeba Keratitis (ODAK) project: results of a 10-Year retrospective study in Italy and in the United Kingdom. 2014. IOVS; 55 (13)	Results not reported by treatment
53	Kaiserman et al. Prognostic factors in Acanthamoeba keratitis. 2012. Can J Ophthalmol; 47 (3)	Results not reported by treatment

54	Ikeda et al. Assessment of real-time polymerase chain reaction detection of Acanthamoeba and prognosis determinants of Acanthamoeba keratitis. 2012. Ophthalmology; 119 (6)	Results not reported by treatment
55	Lee et al. Acanthamoeba sclerokeratitis: treatment with systemic immunosuppression. 2002. Ophthalmology; 109 (6)	Results not reported by treatment
56	Por et al. Acanthamoeba keratitis associated with contact lens wear in Singapore. 2009. Am J Ophthalmol; 148 (1)	Results not reported by treatment
57	Fong et al. Clinical characteristics of microbial keratitis in a university hospital in Taiwan. 2004. Am J Ophthalmol; 137 (2)	Results not reported by treatment
58	Ardjomand et al. Excimer-Laser and mitomycin C 0.02% to treatment acanthamoeba keratitis. 2019. IOVS; 60 (9)	Wrong intervention
59	Jain et al. Clinico-microbiological review of non-contact-lens-associated acanthamoeba keratitis. 2013. Semin Ophthalmol; 30 (4)	Wrong intervention
60	Sepulveda-Beltran et al. Rose Bengal Photodynamic Antimicrobial Therapy: A Review of the Intermediate-Term Clinical and Surgical Outcomes. 2022. Am J Ophthalmol; 243	Wrong intervention
61	Lin et al. Effect of ethanol pretreatment in Acanthamoeba keratitis: a long-term follow-up study. 2018. Infect Drug Resist; 11	Wrong intervention
62	Cristian et al. Accelerated collagen cross-linking in the management of advanced Acanthamoeba keratitis. 2019. Arq Bras Oftalmol; 82 (2)	Wrong intervention
63	Nguyen et al. Penetrating keratoplasty in active Acanthamoeba keratitis. 2010. Cornea; 29 (9)	Wrong intervention
64	Sarnicola et al. Early Deep Anterior Lamellar Keratoplasty (DALK) for Acanthamoeba Keratitis Poorly Responsive to Medical Treatment. 2016. Cornea; 35 (1)	Wrong intervention
65	Shi et al. Perioperative treatment and prognostic factors for penetrating keratoplasty in Acanthamoeba keratitis unresponsive to medical treatment. 2009. Graefes Arch Clin Exp Ophthalmol; 247 (10)	Wrong intervention
66	Page et al. Acanthamoeba keratitis: a 12-year experience covering a wide spectrum of presentations, diagnoses, and outcomes. 2013. J Ophthalmol; 2013	Wrong intervention
67	Lin et al. Effect of ethanol pretreatment in Acanthamoeba keratitis: a long-term follow-up study. 2018. Infect Drug Resist; 11	Wrong intervention
68	Carnt et al. Impact of Acanthamoeba Keratitis on the Vision-Related Quality of Life of Contact Lens Wearers. 2022. Cornea; 41 (2)	Wrong intervention

69	Cardine et al. [Clinical management and prognosis in Acanthamoeba keratitis: a retrospective study of 25 cases]. 2002. J Fr Ophtalmol; 25 (10)	Wrong intervention
70	Mutoh et al. A retrospective study of nine cases of Acanthamoeba keratitis. 2010. Clin Ophthalmol; 4	Wrong intervention
71	Shah et al. Delayed diagnoses of Acanthamoeba keratitis at a tertiary care medical centre. 2021. Acta Ophthalmol; 99 (8)	Wrong intervention
72	Moe et al. Outcomes of amoebic, fungal, and bacterial keratitis: A retrospective cohort study. 2022. PLoS One; 17 (2)	Wrong intervention
73	Veugen et al. Corneal Transplantation for Infectious Keratitis: A Prospective Dutch Registry Study. 2023. Cornea; 42 (11)	Wrong intervention
74	Naranjo et al. Rose Bengal Photodynamic Antimicrobial Therapy for Patients With Progressive Infectious Keratitis: A Pilot Clinical Study. 2019. Am J Ophthalmol; 208	Wrong intervention
75	Naranjo et al. Systemic Miltefosine as an Adjunct Treatment of Progressive Acanthamoeba Keratitis. 2021. Ocul Immunol Inflamm; 29 (7-8)	Wrong intervention
76	Wang et al. Clinical features and outcome of Acanthamoeba keratitis. 1997. J Formos Med Assoc; 96 (11)	Wrong intervention
77	Posarelli et al. The incidence of severe complications in acanthamoeba keratitis: Qualitative and quantitative systematic assessment. 2024. Surv Ophthalmol; 69 (5)	Wrong intervention
78	Bagga et al. Outcome of photodynamic therapy with Rose Bengal in conjunction with topical PHMB and chlorhexidine combination in Acanthamoeba keratitis. 2025. J Ophthalmic Inflam Infect; 15 (1)	Wrong intervention
79	Laurik et al. Early Penetrating Keratoplasty Ã€ Chaud May Improve Outcome in Therapy-Resistant Acanthamoeba Keratitis. 2019. Adv Ther; 36 (9)	Wrong intervention
80	Posarelli et al. Efficacy of Topical 2% Cyclosporine in Controlling the Inflammation and Improving the Treatment Outcomes in Patients with Acanthamoeba Keratitis. 2023. IOVS; 64 (8)	Wrong intervention
81	Vilares-Morgado et al. Clinical outcomes and prognostic factors in Acanthamoeba keratitis. 2024. Cont Lens Anterior Eye; 47 (2)	Wrong intervention
82	Ho et al. Letter to the Editor. Acanthamoeba Keratitis. 2006. Ophthalmology; 113 (12)	Wrong study design

83	Carnt et al. Clinical Aspects and Immunobiology of Acanthamoeba Keratitis. 2024. In book: Reference Module in Neuroscience and Biobehavioural Psychology	Wrong study design
84	Mooney et al. Alkylphosphocholines and Quaternary Ammonium Compounds against Acanthamoeba Keratitis. 2020. J Mol Clin Ophthalmol; 2 (2)	Wrong study design
85	Kitagawa et al. A novel combination treatment of chlorhexidine gluconate, natamycin (pimaricin) and debridement for a Acanthamoeba keratitis. 2003. Jpn J Ophthalmol; 47 (6)	Wrong study design
86	Seal et al. Chlorhexidine or polyhexamethylene biguanide for acanthamoeba keratitis. 1995. Lancet; 345 (8942)	Wrong study design
87	Elder et al. Chemotherapy for acanthamoeba keratitis. 1995. Lancet; 345 (8952)	Wrong study design
88	Tay-Kearney et al. Acanthamoeba keratitis. A masquerade of presentation in six cases. 1993. Aust N Z J Ophthalmol; 21 (4)	Wrong study design
89	Thulasi et al. Oral Miltefosine as Salvage Therapy for Refractory Acanthamoeba Keratitis. 2021. Am J Ophthalmol; 223	Wrong study design
90	Tanhehco et al. The clinical experience of Acanthamoeba keratitis at a tertiary care eye hospital. 2010. Cornea; 29 (9)	Wrong study design
91	Walochnik et al. Twenty years of acanthamoeba diagnostics in Austria. 2014. J Eukaryot Microbiol; 62 (1)	Wrong study design
92	Mills et al. Polyhexamethylene biguanide in the treatment of Acanthamoeba keratitis. 1993. Aust N Z J Ophthalmol; 21 (4)	Wrong study design
93	Larkin et al. Treatment of Acanthamoeba keratitis with polyhexamethylene biguanide. 1992. Ophthalmology; 99 (2)	Wrong study design
94	Kinnear et al. Abuse of brolene eye drops with putative corneal infection. 1996. J Infect; 32 (2)	Wrong study design
95	Kelley et al. Secondary glaucoma associated with advanced acanthamoeba keratitis. 2006. Eye Contact Lens; 32 (4)	Wrong study design
96	Kumar et al. Should we be using polyhexamethylene biguanide to treat Acanthamoeba keratitis. 1997. Aus N Z J Ophthalmol; 25 (2)	Wrong study design
97	Matsumoto et al. The Relation of Ocular Surface Irregularity and Visual Disturbance in Early Stage Acanthamoeba Keratitis. 2017. Eye Contact Lens; 43 (1)	Wrong study design

98	Nagpal et al. Comment on: Rose Bengal Photodynamic Antimicrobial Therapy for Patients With Progressive Infectious Keratitis: A Pilot Clinical Study. 2020. Am J Ophthalmol; 214	Wrong study design
99	Papa et al. Safety and tolerability of topical polyhexamethylene biguanide: a randomised clinical trial in healthy adult volunteers. 2020. Br J Ophthalmol; 106 (2)	Wrong patient population
100	Iovieno et al. Acanthamoeba sclerokeratitis: epidemiology, clinical features, and treatment outcomes. 2014. Ophthalmology; 121 (12)	Wrong patient population
101	Harbiyeli et al. Clinical aspects and prognosis of polymicrobial keratitis caused by different microbial combinations: a retrospective comparative case study. 2021. Int Ophthalmol; 41 (11)	Wrong patient population
102	Lune et al. A Study of Clinico-Microbiological Profile and Treatment Outcomes of Infectious Keratitis. 2024. Cureus; 16 (10)	Wrong patient population
103	AbuDail et al. Rethinking Keratoplasty for Patients with Acanthamoeba Keratitis: Early "Low Load Keratoplasty" in Contrast to Late Optical and Therapeutic Keratoplasty. 2024. Microorganisms; 12 (9)	Wrong patient population
104	Pinna et al. Free-Living Amoebae Keratitis. 2017. Cornea; 36 (7)	Wrong patient population
105	Awwad et al. Severe reactive ischemic posterior segment inflammation in acanthamoeba keratitis: a new potentially blinding syndrome. 2006. Ophthalmology; 114 (2)	Wrong patient population
106	Vemuganti et al. Granulomatous inflammation in Acanthamoeba keratitis: an immunohistochemical study of five cases and review of literature. 2005. Indian J Med Microbiol; 23 (4)	Wrong patient population
107	Arnalich-Montiel et al. Co-isolation of Vahlkampfia and acanthamoeba in acanthamoeba-like keratitis in a Spanish population. 2013. Cornea; 32 (5)	Wrong patient population
108	Murdoch et al. Acanthamoeba keratitis in New Zealand, including two cases with in vivo resistance to polyhexamethylene biguanide. 1998. Aust N Z J Ophthalmol; 26 (3)	Wrong outcomes
109	Itahashi et al. Utility of real-time polymerase chain reaction in diagnosing and treating acanthamoeba keratitis. 2011. Cornea; 30 (11)	Wrong outcomes
110	Imam et al. Acanthamoeba keratitis in Sudan: outcome of ketoconazole treatment in six patients. 2006. Sudan J Med Sci; 1 (1)	Wrong outcomes
111	Lindsay et al. Acanthamoeba keratitis and contact lens wear. 2007. Clin Exp Optom; 90 (5)	Wrong outcomes

112	Rahimi et al. Acanthamoeba Keratitis and Its Associated Risk Factors in Farabi Eye Hospital of Tehran. 2013. Iranian J Ophthalmol; 25 (4)	Wrong outcomes
113	McAllum et al. Prescribing trends in infectious keratitis: a survey of New Zealand ophthalmologists. 2003. Clin Exp Ohthalmol; 31 (6)	Wrong outcomes
114	Chidambaram et al. Epidemiology, risk factors, and clinical outcomes in severe microbial keratitis in South India. 2018. Ophthalmic Epidemiol; 25 (4)	Wrong outcomes
115	Herz et al. Rapidly progressive cataract and iris atrophy during treatment of Acanthamoeba keratitis. 2008. Ophthalmology; 115 (5)	Wrong outcomes
116	JPRN-UMIN000017019. Topical application of polyhexamethylene biguanide on Acanthamoeba keratitis	Results not yet available
117	Prajna et al. A double-masked, sham-controlled trial of rose bengal photodynamic therapy for the treatment of fungal and acanthamoeba keratitis: Rose Bengal Electromagnetic Activation with Green Light for Infection Reduction (REAGIR) study. 2024	Results not yet available
118	NCT06641882. 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	Results not yet available
119	NCT06213649. Parasitic Ulcer Treatment Trial	Results not yet available
120	NCT03484507. Parasitic Ulcer Treatment Trial Pilot	Results not yet available
121	NCT05110001. Rose Bengal Electromagnetic Activation With Green Light for Infection Reduction	Results not yet available
122	Alfonso-Muñoz et al. A report of 10 patients with Acanthamoeba keratitis. 2018. Arch Soc Esp Oftalmol; 93 (10)	Wrong language
123	Landeo et al. Diagnóstico y tratamiento de queratitis por Acanthamoeba and treatment of Keratitis Acanthamoeba. 2012. Rev Horiz Med; 12 (4)	Wrong language
124	Daas et al. [The German Acanthamoeba keratitis register: Initial results of a multicenter study]. 2015. Ophthalmologe; 112 (9)	Wrong language
125	Böhm et al. [Microbiological analysis in contact lens-associated keratits]. 2011. Klin Monbl Augenheilkd; 228 (9)	Wrong language
126	Guisasola et al. Queratitis por Acanthamoeba. Análisis de casos en el Hospital Oftalmológico Santa Lucia (2009-2010). 2011. Unknown	Wrong language
127	Obrubov et al. Contact lens-related keratitis and purulent corneal ulcers. 2018. Vestnik oftalmologii; 134 (4)	Wrong language

128	Bacon et al. Acanthamoeba keratitis. The value of early diagnosis. 1993. Ophthalmology; 100 (8)	Published before 1995
129	Varga et al. Combined treatment of Acanthamoeba keratitis with propamidine, neomycin, and polyhexamethylene biguanide. 1993. Am J Ophthalmol; 115 (4)	Published before 1995
130	Elder et al. A clinicopathologic study of in vitro sensitivity testing and Acanthamoeba keratitis. 1994. Invest Ophthalmol Vis Sci; 35 (3)	Published before 1995
131	Dart et al. The Orphan Drug for Acanthamoeba Keratitis (ODAK) Trial: PHMB 0.08% (Polihexanide) and Placebo versus PHMB 0.02% and Propamidine 0.1. 2023. Ophthalmology; 131 (3)	Duplicate article
132	Ficker et al. Efficacy of chlorhexidine- versus phmb for acanthamoeba keratitis. 1999. IOVS; 40 (2894)	Duplicate article
133	Kobayashi et al. Efficacy of commercial soft contact lens disinfectant solutions against Acanthamoeba. 2011. Jpn J Ophthalmol; 55 (5)	Wrong setting

Appendix I. Literature searches for health-related quality of life

I.1 Identification and selection of relevant studies

A *de novo* economic SLR was conducted on 25th July 2022 and subsequently updated on 14th April 2025 to simultaneously identify published cost-effectiveness studies, health-related quality-of-life studies and healthcare resource use studies for therapeutic approaches in AK or MK. The SLR was designed to capture data in patients with a confirmed diagnosis of AK or MK, who were treated with an ophthalmic eye drop medication or oral miltefosine in any concentration or combination. Further information on the identification and selection of relevant studies can be found in Appendix J.

I.2 Search Strategy

Electronic databases
Electronic databases were searched on 25th July 2022 and 14th April 2025 in line with the strategy outlined in Appendix J.2.
Congress proceedings
Conference proceedings were searched on 25th July 2022 in line with the strategy outlined in Appendix J.2..
Websites
SmPCs of relevant medications were searched on 25th July 2022 and 24th March 2025 and ClinicalTrials.gov was searched in line with the strategy outlined in Appendix J.2..
Bibliography searches
Reference lists from any eligible articles were hand-searched using citation searching in line with the strategy outlined in Appendix J.2.
Search terms
The search strategy for PubMed, the Cochrane Library, the Prospero and International HTA databases, the Centre for Reviews and Dissemination Database and ScHARRUD are presented in Appendix J.2.

I.3 Study selection

The methods used for study selection, including study eligibility, title/abstract review, full text review, data extraction and quality assessment are detailed in Appendix J.3. The review of abstracts and full texts was performed using predefined eligibility criteria developed using the PICOS framework.

I.4 Description of identified studies

The PRISMA flow diagram is presented in Figure 9. In total, 2734 records were identified for screening from all sources, with 32 records included in the economic SLR; full details can be found in Appendix J.4. afull list of studies excluded at full-text screening with the rationale for exclusion is presented in that section. Of the 32 included studies, five unique studies reported on HRQoL.

I.5 Summary of HRQoL studies identified in the review

Five unique studies reported on HRQoL measures, however, only studies reporting VQ-25 (reported in the ODAK trial) and EQ-5D (used to generate utilities) are reported below. Three studies (two RCTs and one observational) reported data on VFQ-25 scores (211 patients; 215 eyes),[3, 13, 52] two of which were in patients with AK.[3, 13] EQ-5D was reported in one study.[3]

Table 96: VFQ-25 scores reported in eligible studies.

Study (Country)	Population	Treatments	N patients (eyes)	Time	Value type	Mean (SD) or Mean difference between groups [95% CI]		Median (IQR)
						VFQ-25 – Composite score	VFQ-25 - Near activities visual function	EQ-5D-5L VAS score
Randomised controlled trial								
Dart,[a] 2024[3] (Italy; Poland; UK)	AK	Polihexanide 0.8 mg/ml	60 (60)	End of study	Change from baseline	23.5 (19.4)	22.4 (23.5)	15 (5–30)
		Polihexanide 0.2 mg/ml; propamidine 1 mg/ml	55 (55)			23.7 (19.7)	18 (19.8)	14.5 (5–28)
Cursiefen, 2014[52] (France; Germany; Switzerland)	Bacterial, viral, or traumatic keratitis or keratouveitis	Aganirsen 0.86 mg/ml vs placebo	69 (69)	Day 90	Absolute	2.21 [-2.74, 7.16]	[9.96 (3.00, 16.91]	-
Retrospective analysis of routine data								
Bonini, 2021[13] (Italy)	AK	Propamidine 0.1%; Polihexanide 0.1%	27 (31)	Final follow-up	Absolute	80.6 (17)	-	-

Note: aAdditional VFQ-25 domains were reported in only one study (Dart 2024) and so are not included in this table.

Abbreviations: AK, Acanthamoeba Keratitis; CI, Confidence Interval, IQR: interquartile range; SD, Standard Deviation; VAS: visual analogue scale; VFQ: visual functioning questionnaire.

Appendix J. Literature searches for input to the health economic model

J.1 Identification and selection of relevant studies

A *de novo* economic SLR was conducted on 25th July 2022 and subsequently updated on 14th April 2025 to simultaneously identify published cost-effectiveness studies, health-related quality-of-life studies and healthcare resource use studies for therapeutic approaches in AK or microbial keratitis (MK).

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 (see the eligibility criteria of the SLR listed in Table 102. Given limited data was identified in scoping search in AK, the SLR was designed to capture data from patients with a confirmed diagnosis of AK or MK, who were treated with an ophthalmic eye drop medication or oral miltefosine in any concentration or combination.

The SLR was performed in accordance with a pre-specified protocol. This involved searching electronic databases from 1995 to the date of the searches. Alongside these, hand searches were performed for key conference proceedings, the International HTA database and clinical trial databases, manufacturer websites and SmPCs, and the bibliographies of any relevant articles and systematic reviews. Full details of the methodology for the SLR are presented in the sections below.

J.2 Search strategy

Electronic databases

Database searches were conducted on 25th July 2022 and 14th April 2025. The following electronic databases were searched using a pre-defined search strategy:

- PubMed
- Cochrane Central Register of Controlled Trials
- Cochrane Database of Systematic Reviews
- Prospero
- International HTA database
- University of York Centre for Reviews and Dissemination Database
- School of Health and Related Research Health Utility Database (ScHARRHUD)

The search strategy was based on terms to identify the population, intervention and outcomes of interest. For each term, at least one free text term was included, along with a Medical Subject Heading (MeSH) term if available. The search strategy for PubMed and the Cochrane Library are presented in Table 97 and **Table 98**, respectively. The search strategy for the Prospero and International HTA databases are presented in Table 99 and Table 100, respectively. The search terms for the Centre for Reviews and Dissemination Database and ScHARRUD are presented in Table 101. MeSH terms cannot be searched in the Centre for Reviews and Dissemination Database and ScHARRHUD so all records pertaining to AK or MK in these databases were

included in the title/abstract screening. ScHARRHUD was not searched in the SLR update (14th April 2025) as it had been discontinued.

Congress proceedings

Websites of the following organisations, and their annual conferences listed below, were hand-searched by one reviewer on 25th July 2022 to identify conference abstracts that had not been indexed in a medical literature database:

Conference proceedings from 2017–2022 were searched for the following conferences:

- Association for Research in Vision and Ophthalmology via Investigative Ophthalmology and Visual Science
- European Association for Vision and Eye Research
- American Association of Ophthalmology
- American Society of Corneal and refractive Surgery
- European Society of Corneal and Refractive Surgeons
- Cornea Society

It was also planned that the proceedings of the American Optometric Association would be searched; however, the conference proceedings could not be found online.

In the SLR update, the proceedings from 2022–2024 (2025 not yet available) of the conferences listed below were hand-searched by one reviewer on 24th March 2025 to identify potentially eligible abstracts since the last search. It was planned that the proceedings of the American Optometric Association, American Society of Corneal and Refractive Surgery, European Society of Corneal and Refractive Surgeons and Cornea Society would be searched; however, the conference proceedings could not be found online, or a conference had not taken place since 2022.

Conference proceedings from 2022–2024 were searched for the following conferences:

- Association for Research in Vision and Ophthalmology via Investigative Ophthalmology and Visual Science
- European Association for Vision and Eye Research
- American Association of Ophthalmology

Websites

To identify any further relevant economic evidence, the following websites and SmPCs of the below medications were hand-searched by one reviewer on 25th July 2022 and 24th March 2025. In some instances, a manufacturer website could not be identified and so another reputable website with relevant product information was hand-searched instead.

- Brolene®: https://www.medicines.org.uk/emc/product/13181/smpc#gref
- Chlorhexidine: https://www.uspharmacist.com/article/chlorhexidine-004-ophthalmic-solution

- Desomedine™:https://www.bausch.com.sg/en/our-products/pharmaceuticals/allergy-and-inflammation/desomedine-eye-drops/
- Gramicidin®: https://www.medicines.org.uk/emc/product/2253/smpc#gref
- Maxitrol®: https://www.medicines.org.uk/emc/product/841/smpc#gref
- Neocin-PG®: https://labeling.pfizer.com/showlabeling.aspx?id=704
- Neosporin Ophthalmic Solution®: https://www.pfizermedicalinformation.com/en-us/neosporin-ophthalmic-solution-sterile
- On 26th October 2022, the website and SmPC for Impavido (US label for oral miltefosine) was also searched (https://www.impavido.com/). No studies for AK or MK were identified.
- ClinicalTrials.gov (https://clinicaltrials.gov/) was also searched on 25th July 2022 and 14th April 2025. The search terms are presented in Table 101.

Bibliography searches

Reference lists from any eligible articles were searched for further studies of interest to supplement the articles retrieved from the standard medical databases.

Citation chasing was undertaken using two different approaches:

- Original 2022 SLR: Reference lists of eligible articles were hand-searched by a single reviewer to identify further potentially eligible articles. Forward citation searching of eligible articles was also conducted in Google Scholar by a single reviewer
- 2025 SLR update: Both backward and forward searching were conducted using the Citation Chaser Shiny app, with identified abstracts uploaded to Covidence and screened by two reviewers.

Search terms

Searches were conducted using a combination of free-text search terms and controlled vocabulary terms specific to each database as recommended by Cochrane. The searches were limited to publications from 1995 onwards. Additionally, a clinical expert confirmed that the formulations of AATs have not changed since this date. Regarding conference proceedings, only studies from the last eight years were searched, based on the assumption that complete publication of conference articles occurs within this timeframe. No additional limits were applied to the searches. The search strategies for the electronic databases are presented in Table 97 (PubMed), Table 98 (Cochrane), Table 99 (Prospero) and Table 100 (International HTA database). In the 2025 SLR update, wildcards were removed from the search terms with quotes for the Cochrane search as these were not allowed. The free-text search strategies for websites are presented in Table 101 (ClinicalTrials.gov, Centre for Reviews and Dissemination and ScHARRUD). It should be noted that for PubMed, the international HTA database and websites, search terms were used as one continuous search item and therefore individual hits/search terms are not available.

Table 97: Search strategy for PubMed for the economic SLR

Search terms

("Acanthamoeba Keratitis"[Title/Abstract] OR (Acanthamoeba Keratitis[MeSH Terms]) OR "Microbial Keratitis"[Title/Abstract] OR Keratitis[MeSH Terms])

AND

("eye drop*"[Title/Abstract] OR "Ophthalmic Solution*"[Title/Abstract] OR Biguanide[Title/Abstract] OR Polihexanide[Title/Abstract] OR polyhexanide[Title/Abstract] OR PHMB[Title/Abstract] OR miltefosine[Title/Abstract] OR Chlorhexidine[Title/Abstract] OR Diamidine[Title/Abstract] OR Propamidine[Title/Abstract] OR Brolene[Title/Abstract] OR Hexamidine[Title/Abstract] OR Desomedine[Title/Abstract] OR Neomycin[Title/Abstract] OR Maxitrol[Title/Abstract] OR "polymyxin B"[Title/Abstract] OR gramicidin[Title/Abstract] OR Neosporin[Title/Abstract] OR (Neocin-PG[Title/Abstract]) OR Imidazole[Title/Abstract] OR Voriconazole[Title/Abstract] OR "antiamoebic therap*"[Title/Abstract] OR pentamidine[Title/Abstract] OR Iomidine[Title/Abstract] OR nebuPent[Title/Abstract] OR pentacarinat[Title/Abstract] OR pentamidin[Title/Abstract] OR MK-412A[Title/Abstract] OR novalsan[Title/Abstract] OR sebidin[Title/Abstract] OR tubulicid[Title/Abstract] OR Povidone[Title/Abstract] OR Iodine[Title/Abstract] OR (Ophthalmic Solutions[MeSH Terms]) OR (Biguanides[MeSH Terms]) OR (Chlorhexidine[MeSH Terms]) OR (Pentamidine[MeSH Terms]) OR (Benzamidines[MeSH Terms]) OR (Neomycin[MeSH Terms]) OR (Polymyxin B[MeSH Terms]) OR (Gramicidin[MeSH Terms]) OR (Imidazoles[MeSH Terms]) OR (Voriconazole[MeSH Terms]) OR (Povidone[MeSH Terms]) OR (Iodine[MeSH Terms]))

AND

(cost*[Title/Abstract] OR expenditure*[Title/Abstract] OR economic*[Title/Abstract] OR pharmacoeconomic*[Title/Abstract] OR qaly*[Title/Abstract] OR "life-year*"[Title/Abstract] OR "life year*"[Title/Abstract] OR daly*[Title/Abstract] OR "budget n2 impact"[Title/Abstract] OR utilit*[Title/Abstract] OR disutilit*[Title/Abstract] OR resource*[Title/Abstract] OR qol[Title/Abstract] OR hrqol[Title/Abstract] OR "quality of life"[Title/Abstract] OR "quality-of-life"[Title/Abstract] OR productiv*[Title/Abstract] OR EQ5D*[Title/Abstract] OR EQ-5D*[Title/Abstract] OR SF12[Title/Abstract] OR SF36[Title/Abstract] OR VFQ-25[Title/Abstract] OR NEIVFQ-25[Title/Abstract] OR "visual function questionnaire"[Title/Abstract] OR (quality-adjusted life years[MeSH Terms]) OR (cost-benefit analysis[MeSH Terms]) OR (Costs and Cost Analysis[MeSH Terms]) OR (Cost of Illness[MeSH Terms]) OR (Cost Savings[MeSH Terms]) OR (Health Care Costs[MeSH Terms]) OR (Health Expenditures[MeSH Terms]) OR (Direct Service Costs[MeSH Terms]) OR (Hospital Costs[MeSH Terms]) OR (Employer Health Costs[MeSH Terms]) OR (Drug Costs[MeSH Terms]) OR (Models, Economic[MeSH Terms]) OR (Economics, Pharmaceutical[MeSH Terms]) OR (Disability-Adjusted Life Years[MeSH Terms]) OR (Health Resources[MeSH Terms]) OR (Quality of Life[MeSH Terms]))

Abbreviations: SLR: systematic literature review.

Table 98: Search strategy for the Cochrane Library (Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews) for the economic SLR

Search number	Search terms	Results (25th July 2022)	Results (14th April 2025)
1	"Acanthamoeba Keratitis" OR "Microbial Keratitis"	83	102
2	MeSH descriptor: [Acanthamoeba Keratitis] explode all trees	11	16
3	MeSH descriptor: [Keratitis] explode all trees	1083	1296

4	#1 OR #2 OR #3	1138	1361
5	"eye drop" OR “eye drops” OR "Ophthalmic Solution" OR Biguanide OR Polihexanide OR polyhexanide OR PHMB OR miltefosine OR Chlorhexidine OR Diamidine OR Propamidine OR Brolene OR Hexamidine OR Desomedine OR Neomycin OR Maxitrol OR "polymyxin B" OR gramicidin OR Neosporin OR (Neocin-PG) OR Imidazole OR Voriconazole OR "antiamoebic therapy" OR "antiamoebic therapies" OR pentamidine OR lomidine OR nebuPent OR pentacarinat OR pentam OR entamidin OR MK-412A OR novalsan OR sebidin OR tubulicid OR Povidone OR Iodine	15636	18167
6	MeSH descriptor: [Ophthalmic Solutions] explode all trees	3720	4339
7	MeSH descriptor: [Biguanides] explode all trees	7277	8716
8	MeSH descriptor: [Chlorhexidine] explode all trees	2390	2857
9	MeSH descriptor: [Pentamidine] explode all trees	117	130
10	MeSH descriptor: [Benzamidines] explode all trees	167	192
11	MeSH descriptor: [Neomycin] explode all trees	400	432
12	MeSH descriptor: [Polymyxin B] explode all trees	185	208
13	MeSH descriptor: [Gramicidin] explode all trees	33	36
14	MeSH descriptor: [Imidazoles] explode all trees	22440	27156
15	MeSH descriptor: [Voriconazole] explode all trees	208	260
16	MeSH descriptor: [Povidone] explode all trees	802	1011
17	MeSH descriptor: [Iodine] explode all trees	1417	1722
18	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	22968	53438
19	cost* OR expenditure* OR economic* OR pharmacoeconomic* OR qaly* OR "life-year*" OR "life year*" OR daly* OR “budget n2 impact” OR utilit* OR disutilit* OR resource* OR qol OR hrqol OR "quality of life" OR "quality-of-life" OR productiv* OR EQ5D* OR EQ-5D* OR SF12 OR SF36 OR VFQ-25 OR NEIVFQ-25 OR “visual function questionnaire”	255565	328572
20	MeSH descriptor: [quality-adjusted life years] explode all trees	1395	2473
21	MeSH descriptor: [cost-benefit analysis] explode all trees	7762	11527
22	MeSH descriptor: [Costs and Cost Analysis] explode all trees	11515	16567
23	MeSH descriptor: [Cost of Illness] explode all trees	864	1169
24	MeSH descriptor: [Cost Savings] explode all trees	452	602

25	MeSH descriptor: [Health Care Costs] explode all trees	3591	4732
26	MeSH descriptor: [Health Expenditures] explode all trees	263	383
27	MeSH descriptor: [Direct Service Costs] explode all trees	74	88
28	MeSH descriptor: [Hospital Costs] explode all trees	638	779
29	MeSH descriptor: [Employer Health Costs] explode all trees	8	10
30	MeSH descriptor: [Drug Costs] explode all trees	794	1148
31	MeSH descriptor: [Models, Economic] explode all trees	371	684
32	MeSH descriptor: [Economics, Pharmaceutical] explode all trees	65	141
33	MeSH descriptor: [Disability-Adjusted Life Years] explode all trees	2	4
34	MeSH descriptor: [Health Resources] explode all trees	455	584
35	MeSH descriptor: [Quality of Life] explode all trees	29130	44954
36	#19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35	255595	328642
37	#4 OR #18 OR #36	37	9

Abbreviations: SLR: systematic literature review.

Table 99: Search strategy for Prospero for the economic SLR

Search number	Search terms	Results (25th July 2022)	Results (14th April 2025)
1	"Acanthamoeba Keratitis"	5	15
2	MeSH descriptor: [Acanthamoeba Keratitis] explode all trees	2	8
3	“Microbial Keratitis”	7	18
4	MeSH descriptor: [Keratitis] explode all trees	8	53
5	#1 OR #2 OR #3 OR #4	12	48

Abbreviations: SLR: systematic literature review.

Table 100: Search strategy for the International HTA database for the economic SLR

Search number	Search terms
#1	"Acanthamoeba Keratitis"
#2	MeSH DESCRIPTOR Acanthamoeba Keratitis EXPLODE ALL TREES
#3	"Microbial Keratitis"

#4	MeSH DESCRIPTOR Keratitis EXPLODE ALL TREES
#5	#1 OR #2 OR #3 OR #4

Abbreviations: SLR: systematic literature review.

Table 101: Search strategy for ClinicalTrials.gov, Centre for Reviews and Dissemination and ScHARRHUD for the economic SLR

Search terms
"Acanthamoeba Keratitis" OR “Microbial Keratitis”

Abbreviations: SLR: systematic literature review.

J.3 Study selection

Study selection process

Once all abstracts of potentially relevant published articles had been identified, the study selection process was performed to determine study eligibility based on eligibility criteria of the economic SLR presented in Table 102 below. The eligibility criteria were developed in line with the PICOS criteria and included considerations for the population and disease condition, interventions, comparators, outcomes and study types mentioned in each identified study.

Table 102. PICOS eligibility criteria for the cost-effectivness SLR

Criteria	Explanation
Population	Human studies (adults or children) where all or a subset of participants have a confirmed diagnosis of AK or MK
Interventions	All or a subset of study participants used an ophthalmic eye drop medication or oral miltefosine as part of the study in any concentration or combination including, but not limited to: • Polihexanide (polyhexamethylene biguanide) • Chlorhexidine • Propamidine (Brolene®) • Hexamidine (Desomedine™) • Neomycin (Maxitrol®) • Neomycin/polymyxin B/gramicidin (Gramicidin®, Neosporin Ophthalmic Solution®, Neocin-PG®) • Imidazole • Voriconazole • Pentamidine • Povidone

	• Iodine
Comparators	Any control (including other active eye drop medication or placebo)
Outcomes	At least one of the following outcomes is reported. **Economic:** • Direct costs, including medical resource use • Indirect costs, including work loss • Economic model results (e.g., incremental cost-effectiveness ratio, life year gained, cost per QALY) • Resource use • Budget impact **Humanistic:** • Utility/disutility scores • HRQoL measures (disease-specific and generic) • Loss of productivity
Study design	Primary, secondary, or tertiary care
Language of publication	English
Date of publication	Full-text publications: Article published in the last 30 years (i.e. from January 1995 inclusive)
	Conference abstract: 2017–2024

Abbreviations: AK: *Acanthamoeba* keratitis; HRQoL: health-related quality of life; MK: microbial keratitis; QALY: quality-adjusted life-year; SLR: systematic literature review

Title/abstract review

Studies identified from the electronic databases and the internet searches were combined into a single list and de-duplicated. Titles and abstracts of the de-duplicated list of articles were double screened by two independent reviewers to determine eligibility according to the inclusion criteria described in Table 102. If there was disagreement about study relevance, a conservative approach was taken and the record proceeded to the next stage of screening.

Full text review

For the studies included from the title/abstract review, full-texts were obtained and double-screened by two independent researchers using the inclusion criteria described in Table 102 to determine eligibility for inclusion. If there was disagreement about study relevance, consensus was reached through a third researcher.

Any potentially eligible articles found through these citation chasing methods (see Appendix J.2) went through the same process of eligibility checking (title/abstract screening followed by full text screening by two

independent reviewers), along with any potentially eligible articles identified from the reference lists of relevant, published SLRs in AK or MK. Any of the articles that were found to be eligible underwent backward and forward citation chasing. This circular process was repeated until no new articles were identified.

Data extraction

Data from the included full-text articles were extracted by one researcher into predesigned data extraction tables. Data extraction was independently validated by a second researcher. Any conflicts were discussed between the reviewers. The researchers discussed any conflicts. If there was disagreement, it was planned for consensus to be reached through a third researcher. However, an agreement was reached by the two researchers in all cases of initial conflict.

Data extraction was based on the published information available. Where data were not available in the published report, no attempt was made to obtain these data and missing data were marked as 'not reported'.

Quality assessment

RoB in individual studies was assessed at study-level. RoB was not assessed at the outcome level given the large number of outcomes of interest. For each study, the RoB assessment was conducted using the appropriate tool from the National Heart, Lung and Blood Institute's Study Quality Assessment Tools:[2]

- **RCTs and other controlled trials:** Controlled intervention studies tool
- **Cross-sectional, prospective, and retrospective cohort studies/non-randomised experimental studies:** Observational cohort and cross-sectional studies tool
- **Case-series/retrospective analyses of routine data/case-control:** Case series studies tool

The RoB assessment was performed using the published information available (i.e. no attempts were made to obtain information not available in the published report). The reviewers read the guidance for each tool before starting the assessment. The quality assessment was only applied to the extracted outcomes.

In line with the guidance for the Study Quality Assessment Tools, the reviewers agreed an overall rating for risk of bias (good, fair, poor) for each study based on a subjective assessment of the RoB, rather than a numerical total score. It is now generally accepted that overall ratings for risk of bias have limited use, and it is more informative to understand the areas where bias may occur, particularly if patterns emerge across the studies. Therefore, the individual scores are also reported.

J.4 Description of identified studies

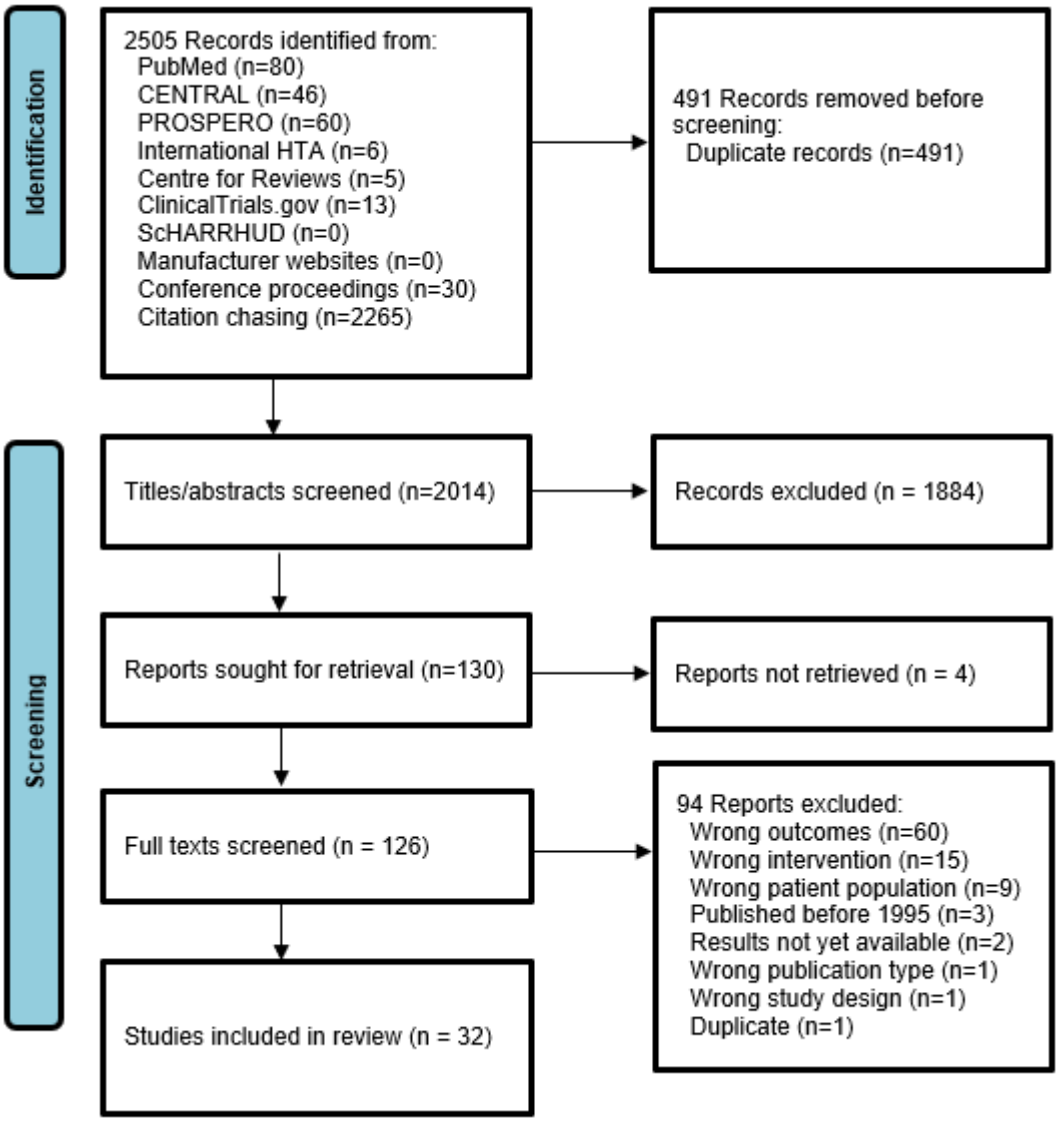
The PRISMA flow diagram for the economic SLR is presented in Figure 9.

In total, 2505 records were identified for screening from all sources. The electronic database searches yielded 197 records alongside 13 records from the ClinicalTrials.gov website, 30 from conference proceedings and 2265 from bibliography searches (TLR references and citation chasing). After removal of duplicates (n=568), a total of 2,014 records (titles and abstracts) were selected for manual screening.

Titles and abstracts of the records identified from the searches were reviewed according to pre-defined eligibility criteria presented in Table 102, yielding 130 potentially relevant records (1,884 records excluded). Four texts could not be retrieved, so 126 full text records were manually screened.

Following a detailed examination of the 126 full text records, 94 records were excluded, resulting in 32 records, meeting the pre-defined inclusion criteria of the economic SLR. Among the 32 records included in the SLR, three were RCTs, 25 were retrospective analyses of routine data and one each of a non-randomised experimental study, case-series study, cohort study and case-control study. None of those studies identified reported the development of economic models in AK.

Figure 9. PRISMA flow diagram for the economic SLR



J.5 Studies identified in the economic review

All studies included following full text screening are presented in Table 103.

Table 103. Studies included in the economic SLR

Study	Country (Study years)	Population	Mean (range) age, years	Percentage				Stages
				Male	Contact lens wearers	Bilateral keratitis	Corticosteroid before treatment	
Randomised controlled trial								
Dart, 2024[3]	Italy; Poland; UK (2017 – 21)	AK	36.5 (15 – 73)	41.8	NR	0	21	I: 17.3 II: 68.5 III: 14.2
Prajna,[c] 2023[51]	India (2016 – 18)	FK	Treatment 1: 45.9 (NR) Treatment 2: 54.4 (NR) Treatment 3: 48.2 (NR) Treatment 4: 54.0 (NR)	Treatment 1: 71.4 Treatment 2: 55.6 Treatment 3: 46.2 Treatment 4: 56.5	NR	NR	NR	NR
Cursiefen, 2014[52]	France; Germany; Switzerland (2009 – 13)	Bacterial, viral, or traumatic keratitis or keratouveitis	51.3 (18 – 81)	62.3	NR	NR	NR	NR

Retrospective analysis of routine data

Przybek-Skrzypecka, 2025[53]	Poland (2008 - 23)	MK	NR (43 - 74)	44.3	15	NR	NR	Severe: 100%
Daley, 2023[54]	Australia (2015 – 20)	MK	57.6 (5 - 101)	57.5	NR	NR	NR	NR
Harbiyeli, 2022[55]	Turkey (2014 – 20)	Contact lens-related MK	26.9 (1.5 - 76)	27.3	100	0	NR	NR
Radhakrishnan, 2022[56]	India (2017 – 18)	BK or FK	BK: 54.5 FK: 52.9	59.8	NR	NR	NR	NR
Tutaş Günaydin, 2022[57]	Turkey (2017 - 21)	IK	59.9 (16 - 93)	56.1	5.9	0	NR	Severe: 100%
Bonini, 2021[13]	Italy (1994 – 2012)	AK	30 (12 - 67)	56	NR	18	NR	I: 19% II: 35% III: 47%
Lim Wen Siang, 2021[58]	Malaysia (2018 – 20)	Admitted with MK	48.0 (15 - 85)	93.2	NR	1.4	NR	NR
List, 2021[59]	Austria (1997 – 2018)	AK	31 (16 – 65)	54.5	93.2	9.1	NR	NR
Ting, 2021[60]	UK (2011 - 20)	FK	59 (4 - 92)	48.7	23.9	0	NR	NR

Hollhumer, 2020[61]	Australia (2002 – 16)	AK	39 (14 – 89)	40.4	83	7.7	NR	I: 17% II: 69% III: 14%
Knyazer,[d] 2020[62]	Israel (2012 – 17)	Presumed BK	Treatment 1: 48.62 Treatment 2: 71.23	Treatment 1: 61.5 Treatment 2: 58.1	NR	0	NR	NR
Koh, 2020[63]	Taiwan (2000 – 13)	MK	42.7 (NR)	45.9	NR	NR	NR	NR
AlMahmoud, 2019[64]	United Arab Emirates (2011 – 16)	Admitted with MK	NR (1 – 91)	79.7	NR	4.1	NR	NR
Ballouz, 2019[65]	USA (2015 – 18)	MK	50.6 (19 - 88)	44	NR	NR	NR	NR
Obrubov, 2018[66]	Russia (2009 - 16)	Contact lens-related IK or corneal ulcers	NR	NR	100	6.2	NR	NR
Iselin, 2017[67]	Switzerland (2010 – 15)	FK	52 (19 – 86)	41	65	NR	29.4	NR
Marasini, 2018[68]	New Zealand (2006 - 14)	Admitted with BK	2006/07: 40 2013/14: 47	2006/07: 27 2013/14: 54	82	0	0	NR

Lin, 2015[69]	Taiwan (20023 – 12)	Admitted with MK	50.3 (2 - 100)	51.1	24.0	0	NR	NR
Robaei,[a] 2014[70]	UK (1991 – 2012)	AK	Treatment 1: 40.2 (NR) Treatment 2: 33.6 (NR)	47	93	2	50	I: 17% II: 57% III: 23%
Bouheraoua, 2013[71]	France (2004 – 08)	AK	43 (14 – 90)	28	80	4.65	NR	III: 23% IV: 66% V: 11%
Saeed, 2009[72]	Ireland (2001 – 03)	Admitted with presumed MK[b]	45 (5 – 63)	52	41	NR	NR	NR
Keay, 2006[73]	Australia (2001 – 03)	MK	NR (15 – 64)	63.6	33.68	NR	NR	NR
Keay, 2006[74]	Australia (NR)	Contact-lens related MK	35 (NR)	39	100	NR	0.7	NR
Wong, 2003[75]	New Zealand (1999 - 2001)	Presumed IK	45 (NR)	57	26	0	17.5	NR
Gangopadhyay, 2000[76]	Australia (1993 – 97)	BK	65.5 (NR)	59.3	14.4	NR	NR	NR
Non-randomised experimental								

Jimmy, 2009[77]	Singapore (2006 – 09)	Admitted with MK	NR	NR	NR	0	NR	NR
Cohort								
Prajna, 2007[78]	India (2004)	Corneal ulcers	42.8 (5 - 85)	56.2	NR	NR	NR	NR
Case series								
Keay, 2008[79]	Australia; New Zealand (2003 – 04)	Contact lens-related MK	35 (NR)	39	100	NR	NR	Mild: 33% Severe: 67%
Case-Control								
Arunga, 2019[80]	Uganda (2016 - 18)	MK	NR (35 - 60)	56	NR	NR	NR	NR

Footnotes: [a]Treatment 1: Biguanide, diamidine, and corticosteroid. Treatment 2: Biguanide and diamidine. bNo data on the confirmation of diagnosis were presented in the published paper. Presumed MK cases were identified from hospital records using ICD codes 3700–37009, 37050–37059, and 0068, which relate to corneal ulcers, corneal abscesses, and *acanthamoeba* keratitis, respectively. Within the treating hospital, the policy was that patients with presumed MK were admitted at initial presentation where the clinical findings were such that it was deemed that a fortified antimicrobial preparation would be required to eliminate the causative organism, if hypopyon was evident, if *acanthamoeba* or fungal infection was suspected, or if compliance with the prescribed antimicrobial monotherapy therapy was doubtful. [c]Treatment 1: Natamycin. Treatment 2: Natamycin plus CXL. Treatment 3: Amphotericin. Treatment 4: Amphotericin plus CXL. [d]Treatment 1: PACK-CXL. Treatment 2: Vancomycin / ceftazidime.

Abbreviations: AK: *Acanthamoeba* Keratitis; BK: Bacterial Keratitis; FK: Fungal Keratitis; IK: Infective Keratitis; MK: Microbial Keratitis; NR: Not Reported.

J.6 Excluded studies

The primary reason for exclusion at full-text screening was the absence of reported outcomes of interest (60 records). Additional reasons for exclusion are presented in Figure 9. A full list of studies excluded at full-text screening with the rationale for exclusion is presented in Table 104 below.

Table 104: Studies excluded at full text screening

#	Citation	Reason for exclusion
1	Lozano et al. Systemic Miltefosine as an Adjunct Treatment of Progressive Acanthamoeba Keratitis. 2019. Conference abstract/reference unknown	Wrong outcomes
2	Hoffman et al. Topical Chlorhexidine 0.2% versus Topical Natamycin 5% for the Treatment of Fungal Keratitis in Nepal: A Randomized Controlled Noninferiority Trial. 2022. Ophthalmology; 129 (5)	Wrong outcomes
3	Jain et al. Use of topical colistin in multiple drug-resistant Pseudomonas aeruginosa bacterial keratitis. 2014. Cornea; 33 (9)	Wrong outcomes
4	Khokhar et al. Comparison of topical 0.3% ofloxacin to fortified tobramycin-cefazolin in the therapy of bacterial keratitis. 2000. Infection; 28 (3)	Wrong outcomes
5	Panda et al. Comparison of topical 0.3% ofloxacin with fortified tobramycin plus cefazolin in the treatment of bacterial keratitis. 1999. Eye; 13 (6)	Wrong outcomes
6	Pickel et al. The Prognostic Value of Persistent Culture Positivity in Fungal Keratitis in the Mycotic Antimicrobial Localized Injection Trial. 2020. Am J Ophthalmol; 215	Wrong outcomes
7	Prajna et al. Predictors of Corneal Perforation or Need for Therapeutic Keratoplasty in Severe Fungal Keratitis: A Secondary Analysis of the Mycotic Ulcer Treatment Trial II. 2017. JAMA Ophthalmol; 135 (9)	Wrong outcomes
8	Rasool et al. Development and clinical evaluation of clotrimazole-Î²-cyclodextrin eyedrops for the treatment of fungal keratitis. 2012. AAPS PharmSciTech; 13 (3)	Wrong outcomes
9	Bagga 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 k. 2021. Eye; 35 (5)	Wrong outcomes

10	Bhadange et al. Comparison of culture-negative and culture-positive microbial keratitis: cause of culture negativity, clinical features and final outcome. 2015. Br J Ophthalmol; 99 (11)	Wrong outcomes
11	Butler et al. Six-year review of Acanthamoeba keratitis in New South Wales, Australia: 1997-2002. 2005. Clin Exp Ophthalmol; 33 (1)	Wrong outcomes
12	Claerhout et al. Delay in diagnosis and outcome of Acanthamoeba keratitis. 2004. Graefes Arch Clin Exp Ophthalmol; 242 (8)	Wrong outcomes
13	Cunha et al. A 10-Year Retrospective Clinical Analysis of Fungal Keratitis in a Portuguese Tertiary Centre. 2020. Clin Ophthalmol; 14	Wrong outcomes
14	Duguid et al. Outcome of acanthamoeba keratitis treated with polyhexamethyl biguanide and propamidine. 1997. Ophthalmology; 104 (10)	Wrong outcomes
15	Hafezi et al. PACK-CXL vs. antimicrobial therapy for bacterial, fungal, and mixed infectious keratitis: a prospective randomized phase 3 trial. 2022. Eye Vis; 9 (1)	Wrong outcomes
16	Kaiserman et al. Prognostic factors in Acanthamoeba keratitis. 2012. Can J Ophthalmol; 47 (3)	Wrong outcomes
17	Lim et al. Comparison of polyhexamethylene biguanide and chlorhexidine as monotherapy agents in the treatment of Acanthamoeba keratitis. 2008. Am J Ophthalmol; 145 (1)	Wrong outcomes
18	Mathers et al. Use of higher medication concentrations in the treatment of acanthamoeba keratitis. 2006. Arch Ophthalmol; 124 (6)	Wrong outcomes
19	Pérez-Santonja et al. Persistently culture positive acanthamoeba keratitis: in vivo resistance and in vitro sensitivity. 2003. Ophthalmology; 110 (8)	Wrong outcomes
20	Qian et al. Clinical experience with Acanthamoeba keratitis at the cole eye institute, 1999-2008. 2010. Cornea; 29 (9)	Wrong outcomes
21	Radford et al. Acanthamoeba keratitis: multicentre survey in England 1992-6. National Acanthamoeba Keratitis Study Group. 1998. Br J Ophthalmol; 82 (12)	Wrong outcomes

22	Radford et al. Acanthamoeba keratitis in England and Wales: incidence, outcome, and risk factors. 2002. Br J Ophthalmol; 86 (5)	Wrong outcomes
23	Ross et al. Clinical characteristics of Acanthamoeba keratitis infections in 28 states, 2008 to 2011. 2014. Cornea; 33 (2)	Wrong outcomes
24	Sharma et al. Patient characteristics, diagnosis, and treatment of non-contact lens related Acanthamoeba keratitis. 2000. Br J Ophthalmol; 84 (10)	Wrong outcomes
25	Sun et al. Acanthamoeba keratitis: clinical characteristics and management. 2006. Ophthalmology; 113 (3)	Wrong outcomes
26	Tu et al. Prognostic factors affecting visual outcome in Acanthamoeba keratitis. 2008. Ophthalmology; 115 (11)	Wrong outcomes
27	Song et al. A Multi-Center, Cross-Sectional Study on the Burden of Infectious Keratitis in China. 2014. PloS One; 9 (12)	Wrong outcomes
28	Arnaiz-Camacho et al. Acanthamoeba keratitis in the last decade. What have we learned? 2024. Archiv Soc Esp Oftalmol; 100 (1)	Wrong outcomes
29	Przybek-Skrzypecka et al. Impact of First Healthcare Provider on Acanthamoeba Keratitis Course: How to Overcome Poor Prognosis in Acanthamoeba Keratitis Treatment? A Single Tertiary Center, Observational Study. 2023. Clin Ophthalmol; 17	Wrong outcomes
30	Walkden et al. Impact of first health care provider on Acanthamoeba keratitis course. How to overcome poor prognosis in AK treatment? Single tertiary centre, observational study. 2023. ResearchSquare	Wrong outcomes
31	Ibrahim et al. Epidemiological characteristics, predisposing factors and microbiological profiles of infectious corneal ulcers: the Portsmouth corneal ulcer study. 2009. Br J Ophthalmol; 93 (10)	Wrong outcomes
32	Keay et al. Signs, symptoms, and comorbidities in contact lens-related microbial keratitis. 2009. Optom Vis Sci; 86 (7)	Wrong outcomes
33	Shah et al. Randomized clinical study for comparative evaluation of fourth-generation fluoroquinolones with the combination of fortified antibiotics in the treatment of bacterial corneal ulcers. 2010. Cornea; 29 (7)	Wrong outcomes

34	Srinivasan et al. The steroids for corneal ulcers trial (SCUT): secondary 12-month clinical outcomes of a randomized controlled trial. 2013. Am J Ophthalmol; 157 (2)	Wrong outcomes
35	Nayel et al. A comparison of antimicrobial regimen outcomes and antibiogram development in microbial keratitis: a prospective cohort study in Alexandria, Egypt. 2024. Graefes Arch Clin Exp Ophthalmol; 262 (6)	Wrong outcomes
36	Torres et al. CXL for Treating Infectious Keratitis: Final Results of the Prospective Randomized Controlled Multicenter Trial. 2020. American Academy of Ophthalmology 2020	Wrong outcomes
37	Ardjomand et al. Excimer-Laser and mitomycin C 0.02% to treatment acanthamoeba keratitis. 2019. IOVS; 60 (9)	Wrong outcomes
38	Bagga et al. Efficacy of voriconazole on Acanthamoeba Keratitis: Prospective Randomized Double masked trial. 2019. IOVS; 60 (9)	Wrong outcomes
39	Praestegaard et al. Clinical efficacy of MC2-03 (ciclosporin eye drop) in treatment of dry eye disease patients with severe keratitis randomized in the NORTHERN LIGHTS phase 2b trial. 2019. Acta Ophthalmologica; 97 (S263)	Wrong outcomes
40	Guenena et al. Acanthamoeba Keratitis in Residents' Clinic Compared with a Faculty Private Practice. 2018. ASCRS 2018	Wrong outcomes
41	Akova-Budak et al. Microbial Keratitis Following Penetrating Keratoplasty. 2019. ASCRS 2019	Wrong outcomes
42	Polania-Baron et al. Clinical-Microbiological profile and antibiotic sensitivity in microbial keratitis in elderly patients. 2019. IOVS; 60 (9)	Wrong outcomes
43	Revathi et al. Efficacy and Safety of Combination Therapy With Two Biguanides in Higher Concentration in Acanthamoeba Keratitis. 2018. Conference abstract / reference unknown	Wrong outcomes
44	Stanfield et al. Visual Outcome, Microbiological Profile and Antibiotic Sensitivity of Infectious Keratitis in a Tertiary Referral Center. 2020. IOVS; 61 (7)	Wrong outcomes

45	Fuchsluger et al. Acanthamoeba keratitis – pKP versus conservative treatment in a 20-year follow-up study. 2017. Acta Ophthalmol; 95 (S259)	Wrong outcomes
46	Mendoza et al. Microbial Profile of Bacterial and Fungal Keratitis at a Midwestern Tertiary Referral Centre. 2018. Conference abstract / reference unknown	Wrong outcomes
47	Potter et al. A Study of the Pathogens and Antibiotic Susceptibilities of Microbial Keratitis at an Ophthalmology Residency Program in Memphis Tennessee. 2019. ASCRS 2019	Wrong outcomes
48	Varma et al. Seasonal Variation in Microbial Keratitis at a Midwest Tertiary Referral Center: Five-Year Review. 2018. ASCRS 2018	Wrong outcomes
49	Loja et al. A 10-Year Clinical Analysis of Fungal Keratitis at CHUSJ. 2020. Unknown	Wrong outcomes
50	Akova et al. Microbial keratitis following penetrating keratoplasty. 1999. Ophthalmic Surg Lasers; 30 (6)	Wrong outcomes
51	Chitamparam et al. Mycotic Keratitis in a Tertiary Hospital in Northeastern Malaysia. 2020. Turk J Ophthalmol; 50 (6)	Wrong outcomes
52	Illingworth et al. Acanthamoeba keratitis: risk factors and outcome. 1995. Br J Ophthalmol; 79 (12)	Wrong outcomes
53	Park et al. The role of topical corticosteroids in the management of Acanthamoeba keratitis. 1997. Cornea; 16 (3)	Wrong outcomes
54	Patel et al. Resurgence of Acanthamoeba keratitis in Auckland, New Zealand: a 7-year review of presentation and outcomes. 2010. Clin Exp Ophthalmol; 38 (1)	Wrong outcomes
55	Scruggs et al. Risk factors, management, and outcomes of Acanthamoeba keratitis: A retrospective analysis of 110 cases. 2022. Am J Ophthalmol Case Rep; 25	Wrong outcomes
56	Tanhehco et al. The clinical experience of Acanthamoeba keratitis at a tertiary care eye hospital. 2010. Cornea; 29 (9)	Wrong outcomes

57	Cai et al. Retrospective analysis on the outcomes of contact lens-associated keratitis in a tertiary centre: an evidence-based management protocol to optimise resource allocation. 2024. Br J Ophthalmol; 109 (1)	Wrong outcomes
58	ISRCTN14332621. Chlorhexidine 0.2% vs Natamycin 5% for the treatment of fungal corneal infections	Wrong outcomes
59	Nowik et al. A single-centre retrospective observational study of fungal keratitis in Poland with a review of findings in Europe. 2020. Ann Agric Environ Med; 27 (3)	Wrong outcomes
60	Cheng et al. Incidence of contact-lens-associated microbial keratitis and its related morbidity. 1999. Lancet; 354 (9174)	Wrong outcomes
61	Collier et al. Estimated burden of keratitis--United States, 2010. 2014. MMWR; 63 (45)	Wrong intervention
62	Kampitak et al. Cost evaluation of corneal ulcer treatment. 2013. J Med Assoc Thailand; 96 (4)	Wrong intervention
63	Chantra et al. Assessment of Direct Costs of Admission Due to Presumed Microbial Keratitis in a Tertiary Referral Hospital in Thailand: A 7-Year Retrospective Study. 2023. Clin Ophthalmol; 17	Wrong intervention
64	Chantra et al. Estimated direct and indirect health care costs of severe infectious keratitis by cultured organisms in Thailand: An 8-year retrospective study. 2023. PloS one; 18 (7)	Wrong intervention
65	Akosman et al. Sociodemographic and Clinical Predictors of Prolonged Length of Corneal Ulcer Hospitalisations. 2024. JAMA Ophthalmol; 142 (3)	Wrong intervention
66	Moussa et al. Calculating the economic burden of presumed microbial keratitis admissions at a tertiary referral centre in the UK. 2020. Eye; 35 (8)	Wrong intervention
67	Shah et al. Demographic and socioeconomic barriers and treatment seeking behaviors of patients with infectious keratitis requiring therapeutic penetrating keratoplasty. 2019. Indian J Ophthalmol; 67 (10)	Wrong intervention
68	Shi et al. Direct Cost Analysis of Microbial Keratitis in North China: A Hospital-Based Retrospective Study. 2024. Pathogens; 13 (8)	Wrong intervention

69	Reynaud et al. Persistent Impairment of Quality of Life in Patients with Herpes Simplex Keratitis. 2016. Ophthalmology; 124 (2)	Wrong intervention
70	Lopez et al. Characterization of Infectious Keratitis in Opioid Users in a County Hospital Setting. 2023. Cornea Open; 2 (1)	Wrong intervention
71	Tuohy et al. Patient Reported Outcomes in Microbial Keratitis. 2021. Cornea; 40 (1)	Wrong intervention
72	Ashfaq et al. Procedures, Visits, and Procedure Costs in the Management of Microbial Keratitis. 2021. Cornea; 40 (4)	Wrong intervention
73	Carnt et al. Impact of Acanthamoeba Keratitis on the Vision-Related Quality of Life of Contact Lens Wearers. 2022. Cornea; 41 (2)	Wrong intervention
74	Keay et al. Grading contact lens-related microbial keratitis: relevance to disease burden. 2008. Optom Vis Sci; 85 (7)	Wrong intervention
75	Br et al. Epidemiological Characteristics of Corneal Ulcers in South Sharqiya Region. 2008. Oman Med J; 23 (1)	Wrong intervention
76	Frick et al. Economic Impact of Visual Impairment and Blindness in the United States. 2007. Arch Ophthalmol; 125 (4)	Wrong patient population
77	Le et al. The pattern of eye disease in a provincial ophthalmic hospital of Viet Nam. 2024. Indian J Clin Exp Ophthalmol; 10 (1)	Wrong patient population
78	McLeod et al. The Importance of Initial Management in the Treatment of Severe Infectious Corneal Ulcers. 1995. Ophthalmology; 102 (12)	Wrong patient population
79	Kovai et al. An Estimate of Patient Costs and Benefits of the New Primary Eye Care Model Utilization Through Vision Centers in Andhra Pradesh, India. 2010. Asia Pac J Public Health; 22 (4)	Wrong patient population
80	Hsu et al. Utilization of inpatient ophthalmology services in Taiwan-A nationwide population study. 2023. BMC Ophthalmol; 23 (1)	Wrong patient population

81	Li et al. Vision-Related Quality of Life in Patients with Infectious Keratitis. 2014. Optom Vis Sci; 91 (3)	Wrong patient population
82	Robert et al. Efficacy and safety of a cationic emulsion in the treatment of moderate to severe dry eye disease: a randomized controlled study. 2016. Eur J Ophthalmol; 26 (6)	Wrong patient population
83	Rose-Nussbaumer et al. Vision-Related Quality-of-Life Outcomes in the Mycotic Ulcer Treatment Trial I: A Randomized Clinical Trial. 2015. JAMA Ophthalmol; 133 (6)	Wrong patient population
84	Rose-Nussbaumer et al. Risk factors for low vision related functioning in the Mycotic Ulcer Treatment Trial: a randomised trial comparing natamycin with voriconazole. 2016. Br J Ophthalmol; 100 (7)	Wrong patient population
85	Park et al. Community care of corneal ulcers. 1992. Am J Ophthalmol; 114 (5)	Published before 1995
86	Bacon et al. A review of 72 consecutive cases of Acanthamoeba keratitis, 1984-1992. 1993. Eye; 7 (6)	Published before 1995
87	Bacon et al. Acanthamoeba keratitis. The value of early diagnosis. 1993. Ophthalmology; 100 (8)	Published before 1995
88	ISRCTN87195453. A comparison of two treatments for the treatment of fungal corneal infections in East Africa	Results not yet available
89	ISRCTN95560917. Comparing a comprehensive package of primary care to the standard of care to reduce blindness caused by severe corneal infections in Nepal	Results not yet available
90	Chandrappa et al. Cost variation analysis of various brands of topical eye preparations currently available in Indian pharmaceutical market. 2018. Int J Basic Clin Pharmacol; 7 (12)	Wrong indication
91	Agrawal et al. Cost analysis of various topical eye preparations currently available in Indian market. 2019. Int J Basic Clin Pharmacol; 8 (8)	Wrong indication

92	Carrijo-Carvalho et al. Therapeutic agents and biocides for ocular infections by free-living amoebae of Acanthamoeba genus. 2017. Surv Ophthalmol; 62 (2)	Wrong publication type
93	Ting et al. Effectiveness and safety of early adjuvant amniotic membrane transplant versus standard antimicrobial therapy in infectious keratitis. 2020. JBI Evid Synth; 18 (8)	Wrong study design
94	Woodward et al. Medication burden for patients with bacterial keratitis. 2019. IOVS; 60 (9)	Duplicate

J.7 Summary of cost effectiveness studies identified in the review

No studies reporting on the development of economic models were identified in the economic SLR.

Appendix K. Delphi panel report

To better understand AK treatment in the UK, the submitting Company implemented an online two-round Delphi panel which elicited expert opinion from UK specialists who have previous experience in treating patients with AK. The methodology and results of the Delphi panel are presented in this section.

K.1 Methodology

Panellists and Panel Implementation

The two-round Delphi panel was implemented using the Alchemer online survey platform, during the months of June and July 2023. A total of 13 ophthalmologists with experience treating AK patients in the UK, accepted to take part as the panel of experts. One HCP withdrew from the panel, 12 physicians took part in the first round (11 completed the questionnaire and one HCP submitted the survey partially completed), and 10 panellists fully completed the second round of the panel. These physicians had clinical experience treating AK and were affiliated with UK NHS institutions in different regions of the UK.

Panellists were initially presented with a first-round electronic questionnaire to be responded remotely. It was indicated to each panellist to provide their response relying on their own experience and taking the perspective of their own practice/hospital during the last year. The first round was applied during the second week of June 2023, and the second round was carried out during the second week of July 25th, 2023.

Following the descriptive statistical analysis of the data collected during the first round, where mean values and uncertainty measures (SD, 10th percentile; 90th percentile) were calculated for each question, a second-round questionnaire was developed. The second round aimed to foster convergence of the answers collected during the first round (reflecting the individual setting of the panellist [their practice/hospital]) towards results in the second round representing the wider UK clinical setting, collecting level of certainty that HCPs have on their final estimates as well.

In this second electronic questionnaire, the panellists were asked to revisit the questions formulated during round one and re-assess/confirm a final estimate to each question after reviewing the consolidated results produced by the panel in round one (for each of the questions). Further, during the second round, each panellist was asked to assume the perspective of what they would consider to best reflect clinical practice for the whole of the country (and score the level of certainty they feel about their final answers).

Uncertainty surrounding point estimates calculated in round two

Based on the answers collected in round two, a second descriptive statistical analysis was completed. Using the data analysis module included in MS-Excel, the following measures were calculated for each question:

- Mean
- Standard Error (SE)
- SD
- Minimum
- Maximum
- Confidence Level (90.0%)
- 90% Confidence interval (CI): Upper bound CI and lower bound CI

Lastly, after providing their final answer to each question, panellists were asked to select a category (associated with a score) reflecting their level of confidence in each of their final answers provided for round two. The ad-hoc validity scale presented in Table 105 was used. Additionally, in order to provide for uncertainty measures, point estimates obtained from round two are presented accompanied by the 90% CI, the average certainty score (ACS) and the range in ACS (minimum–maximum score), as per Table 105.

Table 105: Categories and score assignation according to certainty level of respondent in round two

Category	Interpretation	Score
Unreliable	Great risk of the figure being wrong, i.e., respondent assesses more than a 40% relative divergence possible	1
Risky	Substantial risk of being wrong, i.e., respondent assesses a up to 40% relative divergence possible	2
Reliable	Some risk of being wrong, i.e., respondent assesses a up to 20% relative divergence possible	3
Certain	Low risk of the figure being wrong, i.e., respondent assesses a up to 10% relative divergence possible	4

K.2 Results

In this section, results are presented based on the answers to the second and final round of the Delphi panel, where convergence was the objective (provided by 10 participants, representing 8 centres).

K.2.1 Epidemiology of AK in the UK

The epidemiology estimates from the panel are presented in Table 106.

Table 106: Overview of estimates for the epidemiology of AK in the UK

Parameter	Estimates R2 (considering uncertainty)	
	Mean (90% CI)	ACS (range)
Incidence of AK in the UK (cases per million people/year)	XXXX	XXXX
Prevalence of AK in the last 12 months in the UK (%)	XXXX	XXXX
Proportion of patients that get medical treatment after having been diagnosed with AK (%)	XXXX	XXXX
Typical time (in days) between AK initial diagnosis and medical treatment initiation	XXXX	XXXX

Abbreviations: ACS: Average certainty score; AK: *Acanthamoeba* keratitis; CI: confidence interval; R2: second round; UK: United Kindgom.

K.2.2 Current pharmacological treatment options

Distribution of available treatments

Considering the distribution of available treatment in the UK setting, the panel advanced the estimates in Table 107.

Table 107: Overview of estimates for current pharmacological options – UK setting

Parameter	Estimates R2 (considering uncertainty)	
	Mean distribution, % (90% CI)	ACS (range)
Polihexanide 0.2 mg/ml + diamidine	XXXX	XXXX
Polihexanide 0.2 mg/ml monotherapy	XXXX	XXXX
Diamidine monotherapy	XXXX	XXXX
Diamidine + chlorhexidine (0.2 mg/ml)	XXXX	XXXX
Chlorhexidine monotherapy (0.2 mg/ml)	XXXX	XXXX
Polihexanide 0.2 mg/ml + chlorhexidine	XXXX	XXXX
Polihexanide 0.2 mg/ml + chlorhexidine + diamidine	XXXX	XXXX
Polihexanide 0.6 mg/ml monotherapy	XXXX	XXXX

Polihexanide 0.6 mg/ml + diamidine	XXXX	XXXX

Abbreviations: ACS: Average certainty score; CI: confidence interval; R2: second round; UK: United Kingdom.

Local treatment patterns

The panel was asked to provide their best estimate when considering patients diagnosed with AK treated with combined topical anti-microbials for the proportion of patients requiring hospitalisation during the initial intensive therapeutic phase (Table 108). The panel advanced a mean proportion of XXXX of patients require hospitalisation during the initial intensive therapeutic phase, with a mean duration of XXX days (XXXXXX) in the UK.

Table 108: Overview of estimates for treatment patterns – UK setting

Parameter	Estimates R2 (considering uncertainty)	
	Mean (90% CI)	ACS (range)
Proportion of patients require hospitalisation during the intensive phase (%)	XXXXXX	XXXX
Duration of hospitalisation in days	XXXXXX	XXXX

Abbreviations: ACS: Average certainty score; CI: confidence interval; R2: second round; UK: United Kingdom.

K.2.3 Inadequate response to pharmacological therapy in the UK

In the Delphi Panel, cure was defined as clinical evidence of elimination of *acanthamoeba*, an intact corneal epithelium with no clinical signs of ocular inflammation after discontinuing topical anti-microbials for 30 days. Likewise, medical cure rate within 12 months was defined as cure without the need for surgery, independent of visual acuity (including blindness). The panel estimated the proportion of patients with inadequate response to pharmacological therapy in the UK (Table 109).

Table 109: Overview of estimates for inadequate response to pharmacological therapy – UK setting

Parameter	Estimates R2 (considering uncertainty)	
	Mean (90% CI)	ACS (range)
Proportion of patients who switch to an alternative pharmacological option after 12 months (%)	XXXXXX	XXXX
From patients that switched to an alternative pharmacological treatment, Proportion cured after 12 months (%)	XXXXXX	XXXX

Abbreviations: ACS: Average certainty score; CI: confidence interval; R2: second round; UK: United Kingdom.

K.2.4 Therapeutic surgeries for AK in the UK

Therapeutic surgeries were considered as surgical interventions performed to deal with an active AK infection. Likewise, assessment for cure was defined as clinical evidence of elimination of *Acanthamoeba*, an intact corneal epithelium with no clinical signs of ocular inflammation.

Therapeutic surgery after initial medical therapy

The panel estimated the distribution of therapeutic surgeries in people with AK (Table 110).

Table 110: Overview of estimates for therapeutic surgeries for AK after initial medical therapy – UK setting.

Parameter	Estimates R2 (considering uncertainty)	
	Mean (90% CI)	ACS (range)
AK patients not cured with medical treatment, underwent therapeutic surgery (%)	XXXXXX	XXXX
Distribution of surgeries (%): AK patients who will need to go through surgery		
Therapeutic keratoplasty	XXXXXX	XXXX
Deep anterior lamellar keratoplasty	XXXXXX	XXXX
Enucleation	XXXXXX	XXXX
Evisceration	XXXXXX	XXXX
Amniotic membrane	XXXXXX	XXXX
Amniotic membrane + penetrating keratoplasty	XXXXXX	XXXX
Tarsorrhaphy	XXXXXX	XXXX
Conjunctival flap	XXXXXX	XXXXX
Time from therapeutic surgery prescription to surgery to take place (days)	XXXXXXX	XXXX

Abbreviations: ACS: Average certainty score; AK: *Acanthamoeba* keratitis; CI: confidence interval; R2: second round; UK: United Kingdom.

Complications

The panel was asked to provide the distribution of complications (besides graft rejection) related to therapeutic surgical interventions in the UK and the percentage of patients that would have each complication after the intervention within the three years than follow (Table 111).

Table 111: Distribution of complications related to therapeutic surgeries for AK – UK setting

Parameter	Estimates R2 (considering uncertainty)	
	Mean (90% CI)	ACS (range)
Distribution of complications related to therapeutic surgical interventions: (% of patients that would have each complication after the intervention within the 3 years than follow)		
Glaucoma	XXXXXX	XXXX
Cataract	XXXXXX	XXXX
Scleritis	XXXXXX	XXXX
Corneal melt	XXXXXX	XXXX
Regraft	XXXXXX	XXXX
Neurotrophic keratopathy	XXXXXX	XXXX
Perforation, wound leak	XXXXXX	XXXX
Reinfection	XXXXXX	XXXX
Re suturing	XXXXXX	XXXX
Corneal vascularisation	XXXXXX	XXXX
Optic atrophy	XXXXXX	XXXX

Abbreviations: ACS: Average certainty score; AK: *Acanthamoeba* keratitis; CI: confidence interval; R2: second round; UK: United Kingdom.

Systemic immunosuppressive therapies after therapeutic surgery

Considering the use of systemic immunosuppressive therapies after therapeutic surgery to reduce the risk of rejection, or after the occurrence of rejection, the panel advanced the distribution for the UK setting as shown in Table 112 (proportion of patients that would require each medication and length of treatment duration).

Table 112: Distribution of systemic immunosuppressive therapies after therapeutic surgeries for AK – UK setting

Parameter	Estimates R2 (considering uncertainty)	
	Mean (90% CI)	ACS (range)

Distribution of systemic immunosuppressive therapies after therapeutic surgery: % of patients that would require each medication and for how long		
Cyclosporine	XXXXXX	XXXX
Time (days) of use	XXXXXX	XXXX
Azathioprine	XXXXXX	XXXX
Time (days) of use	XXXXXX	XXXX
Mycophenolate	XXXXXX	XXXX
Time (days) of use	XXXXXX	XXXX
Steroids	XXXXXX	XXXX
Time (days) of use	XXXXXX	XXXX
Tacrolimus	XXXXXX	XXXX
Time (days) of use	XXXXXX	XXXX

Abbreviations: ACS: Average certainty score; AK: *Acanthamoeba* keratitis; CI: confidence interval; R2: second round; UK: United Kingdom.

Adjuvant medication after therapeutic surgery

For the proportion of patients using adjuvant medications after therapeutic surgery, the panel estimated the distribution for the UK setting (proportion of patients that would require each medication and length of treatment duration; Table 113).

Table 113: Distribution of adjuvant medication after therapeutic surgeries for AK – UK setting

Parameter	Estimates R2 (considering uncertainty)	
	Mean (90% CI)	ACS (range)
Distribution of adjuvant medication after therapeutic surgery: % of patients that would require each medication and for how long		
Miltefosine	XXXXXX	XXXX
Time (days) of use	XXXXXX	XXXX
Voriconazole	XXXXXX	XXXX
Time (days) of use	XXXXXX	XXXX
Prednisolone	XXXXXX	XXXX
Time (days) of use	XXXXXX	XXXX

Polihexanide 0.6 mg/ml	XXXXXX	XXXX
Time (days) of use	XXXXXX	XXXX
Doxycycline	XXXXXX	XXXX
Time (days) of use	XXXXXX	XXXX

Abbreviations: ACS: Average certainty score; AK: *Acanthamoeba* keratitis; CI: confidence interval; R2: second round; UK: United Kingdom.

Graft rejection

Specifically, for AK patients after graft rejection, the panel estimated the distribution for the available procedures considered for this group of patients in the UK (Table 114). The option of 'no further procedures was also included in the selection of alternatives.

Table 114: Distribution of available procedures after graft rejection – UK setting

Parameter	Estimates R2 (considering uncertainty)	
	Mean (90% CI)	ACS (range)
% of patients after graft rejection requiring the following procedures:		
Endothelial keratoplasty	XXXXXX	XXXX
Enucleation	XXXXXX	XXXX
Evisceration	XXXXXX	XXXX
No further procedures	XXXXXX	XXXX

Abbreviations: ACS: Average certainty score; AK: *Acanthamoeba* keratitis; CI: confidence interval; R2: second round; UK: United Kingdom.

Follow-up therapeutic surgeries

The panel estimated the mean number of follow-up therapeutic surgeries and the proportion of patients with eye loss functionality/no light perception following keratoplasty or graft failure (Table 115).

Table 115: Overview of estimates for therapeutic surgeries for AK – UK setting

Parameter	Estimates R2 (considering uncertainty)	
	Mean (90% CI)	ACS (range)
Number of follow up therapeutic surgeries (after an initial corneal transplantation) before AK infection resolution	XXXXXX	XXXX
% of patients with eye loss functionality/no light perception		

After keratoplasty	XXXXXX	XXXX
After graft failure	XXXXXX	XXXX

Abbreviations: ACS: Average certainty score; AK: *Acanthamoeba* keratitis; CI: confidence interval; R2: second round; UK: United Kingdom.

K.2.5 Optical surgeries for AK in the UK

Optical surgeries were considered as interventions that can be performed electively, for visual rehabilitation, on patients who had completed a course of pharmacological therapy and who had medical/surgical resolution of infection. Panellists were also asked to consider what would be typical for the lifetime of the patient for their estimations.

BCVA outcomes in cured AK patients

Regarding the characterisation of available optical surgeries for AK in the UK and considering all externalities and waiting times associated with the health system, the panel estimated the mean percentage of cured AK patients featuring poor vision or severe vision loss, undergoing optical surgery (Table 116).

Table 116: Distribution BCVA outcomes considering cures AK patients that undergo optical surgery – UK setting

Parameter	Estimates R2 (considering uncertainty)	
	Mean (90% CI)	ACS (range)
% cured AK patients that undergo optical surgery		
Featuring poor vision	XXXXXX	XXXX
Featuring severe vision loss	XXXXXX	XXXX

Abbreviations: ACS: Average certainty score; AK: *Acanthamoeba* keratitis; CI: confidence interval; R2: second round; UK: United Kingdom.

Distribution optical surgeries

The available optical surgeries performed on patients that achieve medical/surgical infection resolution were provided by the panel (Table 117), considering what would be typical for the lifetime of the patient.

Table 117: Distribution of available optical surgeries on patients that achieve infection resolution – UK setting

Parameter	Estimates R2 (considering uncertainty)	
	Mean (90% CI)	ACS (range)

Distribution of available optical surgeries on patients that achieve medical/surgical infection resolution (%)		
Cataract	XXXXXX	XXXX
DALK	XXXXXX	XXXX
Keratoplasty	XXXXXX	XXXXX
Surgical correction astigmatism	XXXXXX	XXXX
% of patients that achieve medical/surgical infection resolution that undergo to an evisceration on their lifetime	XXXXXX	XXXX

Abbreviations: ACS: Average certainty score; AK: *Acanthamoeba* keratitis; CI: confidence interval; R2: second round; UK: United Kingdom.

K.2.6 Recurrence after AK cure in the UK

For this section, the panellists were asked to consider clinical resolution of an AK infection defined as follows:

- Cure has been established 30 days and up to 3 months following the suspension of anti-microbial treatment.
- Steroids have been suspended one-month prior to anti-microbial treatment suspension.
- Recurrence should be considered as infection after the statement of cure.

The panellists estimated the proportion of AK reoccurrence following initial Ak infection following various types of AK treatment (Table 118).

Table 118: Overview of estimates for reoccurrence after AK cure – UK setting

Parameter	Estimates R2 (considering uncertainty)	
	Mean (90% CI)	ACS (range)
% AK patients featuring a reoccurrence of the infection following initial AK infection resolution		
After medical pharmacological treatment: % of reoccurrence within the year	XXXXXX	XXXX
Medical pharmacological treatment: % of reoccurrence from the second year	XXXXXX	XXXX

After therapeutic surgery: % of reoccurrence within 3 years.	XXXXXX	XXXX

Abbreviations: ACS: Average certainty score; AK: *Acanthamoeba* keratitis; CI: confidence interval; R2: second round; UK: United Kingdom.

K.2.7 Visual outcomes according to BCVA after surgery in the UK

The panel advanced the distribution of visual outcomes (improvement to a better BCVA category, remains within the same BCVA category, worsening or eye functionality loss) according to BCVA after optical surgery (Table 119).

Table 119: Overview of estimates for visual outcomes after optical surgery – UK setting

Parameter	Estimates R2 (considering uncertainty)	
	Mean (90% CI)	ACS (range)
Improvement to a better BCVA category (%) after optical surgery	XXXXXX	XXXX
Remains within the same BCVA category (%) after optical surgery	XXXXXX	XXXX
Worsening in BCVA category (%) after optical surgery	XXXXXX	XXXX
Eye functionality loss (%) after optical surgery	XXXXXX	XXXX

Abbreviations: ACS: Average certainty score; AK: *Acanthamoeba* keratitis; CI: confidence interval; R2: second round; UK: United Kingdom.

K.2.8 HRQoL after achieving AK resolution in the UK

The panel estimated the proportion of patients that feature any of the following conditions (intense and constant lacrimation, photophobia, pain, depression, anxiety) after achieving clinical resolution of the infection conditioned by BCVA categories (Table 120).

Table 120: Overview of estimates of health-related quality of life after achieving *acanthamoeba* keratitis resolution – UK setting

Parameter	Estimates R2 (considering uncertainty)	
	Mean (90% CI)	ACS (range)
Proportion of cured patients that feature intense and constant lacrimation/photophobia/pain, by BCVA category (%):		
Good vision	XXXXXX	XXX

Poor vision	XXXXXX	XXX
Severe vision loss	XXXXXX	XXX
Eye functionality loss	XXXXXX	XXX
Proportion of cured patients that feature depression/anxiety, by BCVA category (%):		
Good vision	XXXXXX	XXX
Poor vision	XXXXXX	XXX
Severe vision loss	XXXXXX	XXX
Eye functionality loss	XXXXXX	XXX

Note: BCVA categories: good vision: BCVA ≥20/40, poor vision: BCVA ≥20/200 and <20/40; severe vision loss: <20/200. **Abbreviations:** ACS: Average certainty score; BCVA: best corrected visual acuity; CI: confidence interval; R2: second round; UK: United Kingdom.

K.2.9 Health care resource needs associated with AK in the UK

The following estimates were provided from the panel regarding the health care resource needs associated with AK during the relevant states of the disease, including:

- AK active infection while on pharmacological treatment (Table 121)
- Following infection resolution (cure) after pharmacological treatment (patient achieving good vision, poor vision, severe vision loss outcome) (Table 122, Table 123)
- Following infection resolution (cure) after surgery (patient achieving good vision, poor vision, severe vision loss outcome) (Table 125, Table 126, Table 127)
- In case of eye functionality loss (Table 128)

On pharmacological treatment

Table 121: Overview of estimates of health care resource needs during the period of AK active infection while on pharmacological treatment – UK setting

Parameter		Estimates R2 (considering uncertainty)	
		Mean (90% CI)	ACS (range)
Ophthalmologist / Optometrist visits (with or without slit lamp	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX

examination, pupil test, etc.)			
Psychiatrist visits	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Nurse visits	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Intraocular pressure check	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Scraping of the eye	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Ophthalmoscopy	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Low vision rehabilitation sessions	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Visual aids - magnifiers	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
IVCM	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX

Note: BCVA categories: good vision: BCVA ≥20/40, poor vision: BCVA ≥20/200 and <20/40; severe vision loss: <20/200. **Abbreviations:** ACS: Average certainty score; BCVA: best corrected visual acuity; CI: confidence interval; IVCM: in vivo confocal microscopy; R2: second round; UK: United Kingdom.

Following infection resolution (cure) after pharmacological treatment, patient achieving good vision outcome

Table 122: Overview of estimates of health care resource needs following infection resolution (cure) after pharmacological treatment, patient achieving good vision outcome – UK setting

Parameter		Estimates R2 (considering uncertainty)	
		Mean (90% CI)	ACS (range)
Ophthalmologist / Optometrist visits (with or without slit lamp examination, pupil test, etc.)	Frequency of the intervention (times/year)	[redacted]	[redacted]
	% of total patients	[redacted]	[redacted]
Psychiatrist visits	Frequency of the intervention (times/year)	[redacted]	[redacted]
	% of total patients	[redacted]	[redacted]
Nurse visits	Frequency of the intervention (times/year)	[redacted]	[redacted]
	% of total patients	[redacted]	[redacted]
Intraocular pressure check	Frequency of the intervention (times/year)	[redacted]	[redacted]
	% of total patients	[redacted]	[redacted]
Scraping of the eye	Frequency of the intervention (times/year)	[redacted]	[redacted]
	% of total patients	[redacted]	[redacted]
Ophthalmoscopy	Frequency of the intervention (times/year)	[redacted]	[redacted]
	% of total patients	[redacted]	[redacted]
Low vision rehabilitation sessions	Frequency of the intervention (times/year)	[redacted]	[redacted]
	% of total patients	[redacted]	[redacted]
IVCM	Frequency of the intervention (times/year)	[redacted]	[redacted]
	% of total patients	[redacted]	[redacted]

Note: BCVA categories: good vision: BCVA ≥20/40, poor vision: BCVA ≥20/200 and <20/40; severe vision loss: <20/200. **Abbreviations:** ACS: Average certainty score; BCVA: best corrected visual acuity; CI: confidence interval; IVCM: in vivo confocal microscopy; R2: second round; UK: United Kingdom.

Following infection resolution (cure) after pharmacological treatment, patient achieving poor vision outcome

Table 123: Overview of estimates of health care resource needs Following infection resolution (cure) after pharmacological treatment, patient achieving poor vision outcome – UK setting

Parameter		Estimates R2 (considering uncertainty)	
		Mean (90% CI)	ACS (range)
Ophthalmologist / Optometrist visits (with or without slit lamp examination, pupil test, etc.)	Frequency of the intervention (times/year)	[redacted]	[redacted]
	% of total patients	[redacted]	[redacted]
Psychiatrist visits	Frequency of the intervention (times/year)	[redacted]	[redacted]
	% of total patients	[redacted]	[redacted]
Nurse visits	Frequency of the intervention (times/year)	[redacted]	[redacted]
	% of total patients	[redacted]	[redacted]
Intraocular pressure check	Frequency of the intervention (times/year)	[redacted]	[redacted]
	% of total patients	[redacted]	[redacted]
Scraping of the eye	Frequency of the intervention (times/year)	[redacted]	[redacted]
	% of total patients	[redacted]	[redacted]
Ophthalmoscopy	Frequency of the intervention (times/year)	[redacted]	[redacted]
	% of total patients	[redacted]	[redacted]
Low vision rehabilitation sessions	Frequency of the intervention (times/year)	[redacted]	[redacted]
	% of total patients	[redacted]	[redacted]
Visual aids - magnifiers	Frequency of the intervention (times/year)	[redacted]	[redacted]

	% of total patients	XXXXXX	XXX

Note: BCVA categories: good vision: BCVA ≥20/40, poor vision: BCVA ≥20/200 and <20/40; severe vision loss: <20/200. **Abbreviations:** ACS: Average certainty score; BCVA: best corrected visual acuity; CI: confidence interval; R2: second round; UK: United Kingdom.

Following infection resolution (cure) after pharmacological treatment, patient achieving severe vision loss outcome

Table 124: Overview of estimates of health care resource needs Following infection resolution (cure) after pharmacological treatment, patient achieving severe vision loss outcome – UK setting

Parameter		Estimates R2 (considering uncertainty)	
		Mean (90% CI)	ACS (range)
Ophthalmologist / Optometrist visits (with or without slit lamp examination, pupil test, etc.)	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Psychiatrist visits	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Nurse visits	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Intraocular pressure check	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Scraping of the eye	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Ophthalmoscopy	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
	Frequency of the intervention (times/year)	XXXXXX	XXX

Low vision rehabilitation sessions	% of total patients	XXXXXX	XXX
Visual aids - magnifiers	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX

Note: BCVA categories: good vision: BCVA ≥20/40, poor vision: BCVA ≥20/200 and <20/40; severe vision loss: <20/200.**Abbreviations:** ACS: Average certainty score; BCVA: best corrected visual acuity; CI: confidence interval; R2: second round; UK: United Kingdom.

Following infection resolution (cure) after surgery, patient achieving good vision outcome

Table 125: Overview of estimates of health care resource needs Following infection resolution (cure) after surgery, patient achieving good vision outcome – UK setting

Parameter		Estimates R2 (considering uncertainty)	
		Mean (90% CI)	ACS (range)
Ophthalmologist / Optometrist visits (with or without slit lamp examination, pupil test, etc.)	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Psychiatrist visits	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Nurse visits	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Intraocular pressure check	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Scraping of the eye	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX

Ophthalmoscopy	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Low vision rehabilitation sessions	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX

Note: BCVA categories: good vision: BCVA ≥20/40, poor vision: BCVA ≥20/200 and <20/40; severe vision loss: <20/200.**Abbreviations:** ACS: Average certainty score; BCVA: best corrected visual acuity; CI: confidence interval; R2: second round; UK: United Kingdom.

Following infection resolution (cure) after surgery, patient achieving poor vision outcome

Table 126: Overview of estimates of health care resource needs Following infection resolution (cure) after surgery, patient achieving poor vision outcome – parameters UK setting

Parameter		Estimates R2 (considering uncertainty)	
		Mean (90% CI)	ACS (range)
Ophthalmologist / Optometrist visits (with or without slit lamp examination, pupil test, etc.)	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Psychiatrist visits	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Nurse visits	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Intraocular pressure check	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Scraping of the eye	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX

Ophthalmoscopy	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Low vision rehabilitation sessions	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Visual aids - contact lens clinic (Rigid gas permeable contact lens)	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Visual aids - magnifiers	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX

Note: BCVA categories: good vision: BCVA ≥20/40, poor vision: BCVA ≥20/200 and <20/40; severe vision loss: <20/200. **Abbreviations:** ACS: Average certainty score; BCVA: best corrected visual acuity; CI: confidence interval; R2: second round; UK: United Kingdom.

Following infection resolution (cure) after surgery, patient achieving severe vision loss outcome

Table 127: Overview of estimates of health care resource needs Following infection resolution (cure) after surgery, patient achieving severe vision loss outcome – parameters UK setting

Parameter		Estimates R2 (considering uncertainty)	
		Mean (90% CI)	ACS (range)
Ophthalmologist / Optometrist visits (with or without slit lamp examination, pupil test, etc.)	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Psychiatrist visits	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Nurse visits	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX

Intraocular pressure check	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Scraping of the eye	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Ophthalmoscopy	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Low vision rehabilitation sessions	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Visual aids - contact lens clinic (Rigid gas permeable contact lens)	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Visual aids - magnifiers	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX

Note: BCVA categories: good vision: BCVA ≥20/40, poor vision: BCVA ≥20/200 and <20/40; severe vision loss: <20/200. **Abbreviations:** ACS: Average certainty score; BCVA: best corrected visual acuity; CI: confidence interval; R2: second round; UK: United Kingdom.

In case of eye functionality loss

Table 128: Overview of estimates of health care resource in case of eye functionality loss – UK setting

Parameter		Estimates R2 (considering uncertainty)	
		Mean (90% CI)	ACS (range)
Ophthalmologist / Optometrist visits (with or without slit lamp examination, pupil test, etc.)	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX

Psychiatrist visits	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Nurse visits	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Intraocular pressure check	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Scraping of the eye	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Ophthalmoscopy	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX
Low vision rehabilitation sessions	Frequency of the intervention (times/year)	XXXXXX	XXX
	% of total patients	XXXXXX	XXX

Note: BCVA categories: good vision: BCVA ≥20/40, poor vision: BCVA ≥20/200 and <20/40; severe vision loss: <20/200.**Abbreviations:** ACS: Average certainty score; BCVA: best corrected visual acuity; CI: confidence interval; R2: second round; UK: United Kingdom.

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