National Institute for Health and Care Excellence

Health Technology Evaluation

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

Response to stakeholder organisation comments on the draft remit and draft scope

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Company, SIFI S.p.A	**SIFI considers it highly appropriate for polihexanide 0.8 mg/ml to be referred to the National Institute for Health and Care Excellence (NICE) for appraisal in Acanthamoeba keratitis (AK) at this time. However, SIFI proposes that a highly specialised technology (HST) evaluation is the most appropriate route.** Polihexanide 0.8 mg/ml fits the vision and remit for the HST programme and is an ideal candidate for the HST evaluation route. Polihexanide 0.8 mg/ml is for a very severe and ultra-rare condition with which only a very small number of people are diagnosed in England and Wales. This population's medical need is unmet, with no treatments currently approved. Polihexanide 0.8 mg/ml clearly meets each of the four routing criteria for the HST programme. SIFI has submitted a justification against each of the four HST routing criteria in the accompanying HST checklist, as summarised below: • **HST Routing Criterion 1:** AK is clinically distinct from the other diseases included in the infectious keratitis (IK) umbrella term and was	Comment noted. Following consultation and presentation to the NICE prioritisation board it was decided that this topic will proceed as a Single Technology Appraisal. In accordance with the highly specialised technologies routing criteria, this decision was informed by information such as the disease prevalence, availability of existing

		noted to be “a distinct medical entity and thus a valid condition” by the European Medicines Agency (EMA) Committee for Orphan Medicinal Products (COMP).[1] Unlike other microorganisms that can cause keratitis, A*canthamoeba* can exist in two life-cycle stages, an active motile trophozoite and a resilient dormant cyst.[2] The interchanging between these stages prevents many therapies from working, making AK more challenging to treat compared with other microbial corneal infections.[2, 3] This necessitates a distinct treatment approach, highlighting the need to treat and consider AK separately to the wider IK patient population. Surgical outcomes for AK tend to be worse than for other keratitis forms,[4, 5] whilst initial misdiagnosis of AK for other forms of keratitis leads to delays in treatment and can lead to patients receiving inappropriate therapy options, both leading to poorer overall outcomes.[6, 7] Despite accounting for 5% of corneal infections worldwide, AK is disproportionately responsible for over 50% of corneal infections resulting in vision loss.[6, 8] It is subsequently clear that AK requires a distinct management approach from IK, and therefore AK is the relevant condition for this evaluation. As acknowledged by NICE, AK has an estimated incidence of 0.1175 cases per 50,000 people per year in the UK.[9] This is aligned with a two-round Delphi panel conducted by SIFI in 2023 in which a mean incidence of AK in the UK was estimated at [redacted] cases per 50,000 people per year by the experts.[10] • **HST Routing Criterion 2:** Fewer than 300 people with AK would be eligible for treatment with polihexanide 0.8 mg/ml per year in England, based on the results from the study conducted by Jasim et al., 2024.[9] As noted by NICE, polihexanide 0.8 mg/ml does not have any licensed indications in the UK. • **HST Routing Criterion 3:** AK causes severely painful and disabling symptoms, including redness, swelling, blurred vision, constant lacrimation and acute photophobia (light sensitivity), with many cases resulting in vision loss.[2, 11] These symptoms result in a significant	treatments, and impact on length and quality of life.

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		quality of life (QoL) burden, as evidenced by direct patient testimonies and poor QoL scores reported in clinical trials.[2, 12] In addition, patients with untreated or inadequately treated AK infections face a high risk of permanent vision loss, causing concerns about potential blindness and its effects on their work, family, and daily life.[2, 7] Many patients must undergo surgical interventions, which are associated with potential complications and long wait times.[10] This can cause anxiety and psychological stress in patients, further adding to the devastating QoL burden experienced by individuals with AK.[2] • **HST Routing Criterion 4:** There are currently no licensed therapeutic approaches available in England and Wales for patients with AK, with no standard treatment pathway and no standard of care.[13] Therefore, patients with AK receive a heterogenous combination of off-label and unlicensed anti-amoebic agents including biguanides and diamidines as initial therapies within clinical practice.[10, 11] The current reliance of ophthalmologists on off-label and unlicensed therapeutic approaches puts healthcare practitioners in the untenable position of having no option but to prescribe therapeutic approaches that are not supported by regulatory approval.[14-16] These consist of eye drops which are not always readily available for use, with biguanides often needing to be compounded at request, with good manufacturing practice (GMP) not always satisfied.[14-16] This leads to treatment delays and poorer quality products which are associated with poorer prognosis for patients.[17, 18] Failure of topical approaches often results in the use of surgical interventions, such as keratoplasty. Patients who choose not to undergo surgery typically experience a decline in visual acuity.[17] Furthermore, current therapeutic approaches are associated with a considerable burden of administration: patients need to apply eye drops at regular intervals both day and night in the initial phases of	

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		treatment, meaning that they are unable to sleep in this initial phase of treatment.[12] • Based on the results from the Orphan Drug for *Acanthamoeba* Keratitis (ODAK) trial and subsequent indirect treatment comparisons (ITCs), it is clear that polihexanide 0.8 mg/ml is likely to offer significant additional benefit over current therapeutic approaches in people with AK. The high medical cure rate seen in ODAK (84.85%) is confirmed by initial reports from an ongoing compassionate use programme in Italy, in which patients with AK received polihexanide 0.8 mg/ml.[19] As well as offering improved cure rates, polihexanide 0.8 mg/ml will provide a less burdensome dosing regimen (avoiding the need to regularly administer eye drops overnight which disrupts sleep), compared with currently available therapeutic approaches. Polihexanide 0.8 mg/ml will also provide a rapid treatment option for people with AK at diagnosis without delays associated with compounding.[16, 20] • In summary, polihexanide 0.8 mg/ml clearly meets the criteria for HST evaluation routing. Full details of the relevant supporting evidence have been provided in the accompanying HST checklist.	
	Royal College of Ophthalmologists	Single technology appraisal route is appropriate.	Comment noted.
Wording	Company, SIFI S.p.A	SIFI agrees with the wording of the remit in the draft scope and that it accurately reflects any considerations around clinical and cost-effectiveness regarding the intended licensing and marketing authorisation for polihexanide 0.8 mg/ml.	Comment noted.

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Timing issues	Company, SIFI S.p.A	There is a high degree of urgency for NICE to undertake a technology appraisal in people with AK. The medical need of people with AK is unmet in UK clinical practice, with therapeutic approaches limited to a small number of off-label and unlicensed anti-amoebic agents including biguanides and diamidines, with no established standard of care.[13] Healthcare professionals often face delays accessing biguanide therapies because they require compounding for individuals due to the short shelf life, which significantly impacts the prognosis for patients.[18, 21] Whilst diamidines are not compounded, the UK Royal College of Optometrists does not recommend their use as a monotherapy, and they are typically only used to temporarily manage patients when biguanides are unavailable.[22, 23] Individuals with AK, caregivers, patient organisation representatives and clinicians have expressed a need for newer and better treatment options as soon as possible, highlighting the urgent remaining unmet need for an effective therapy.[2] Currently, there is no licensed therapeutic approach for people with AK in England and Wales, with no standard treatment pathway available for AK.[13] As a result, patients receive a range of unlicensed therapeutic approaches and experience heterogenous care across the UK. This is supported by both a SIFI-conducted Delphi panel in 2023, which elicited expert advice from [redacted] ophthalmologists with experience treating patients with AK, and SIFI-conducted patient research. Both reported heterogenous use of a combination of off-label and unlicensed anti-amoebic agents including biguanides and diamidines.[10, 11] Rapid treatment of AK is crucial at diagnosis, as delayed treatment is associated with a poorer prognosis;[22] research by Bonini et al. shows significantly worse outcomes for patients receiving treatment >30 days post-diagnosis versus <30 days post-diagnosis.[17] Despite this, specialist centres such as Moorfields Eye Hospital, London, have been reported not to have	Comment noted. NICE aims to publish final guidance for all new technologies within 90 days of receiving marketing authorisation.

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		treatments required in stock at the time of diagnosis, and the SIFI-conducted Delphi Panel reported a typical time of [redacted] days between AK initial diagnosis and medical treatment initiation in the UK.[10, 23] Combined with high levels of initial misdiagnosis, such treatment delays can seriously worsen treatment outcomes for patients. Access to a licensed therapeutic approach, which does not require compounding and therefore would be available at the point of diagnosis, would allow these centres to treat patients more rapidly and improve treatment outcomes. The lack of standard of care in AK often results in unsatisfactory outcomes for patients with AK, with [redacted] (90% confidence interval [CI]: [redacted]) switching to an alternative therapeutic approach after 12 months.[10] When pharmacological approaches fail to clear the *Acanthamoeba* infection, patients may have to resort to surgical interventions, with [redacted]% (90% CI: [redacted];[redacted]) of patients who fail to achieve resolution of their infection with prior medical therapy undergoing therapeutic surgery, as reported in a SIFI-conducted Delphi panel.[10] As well as therapeutic surgeries, such as keratoplasty (corneal transplant), people with AK may also undergo optical surgeries in an attempt to improve their vision. However, improvement of visual outcomes is not guaranteed, with [redacted]% of people with AK experiencing worsening in best corrected visual acuity (BCVA) category or eye functionality loss and [redacted]% remaining in the same BCVA category after optical surgery.[10] Fast access to an effective therapeutic approach is crucial to reduce the number of patients needing to undergo surgery, which is associated with considerable burden for patients, as described in the Background information of Comment 2. Therefore, there is an urgent and significant unmet need for fast access to a licensed therapeutic approach that can reduce the need for surgeries and effectively improve QoL in people with AK.	

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Company, SIFI S.p.A	Consider the accuracy and completeness of this information. SIFI considers the information presented in the background section of the draft scope to be generally accurate for AK; however, SIFI would request further detail and clarification to be included with regards to the points outlined below. **SIFI would request that it is made clear that many patients need to receive surgery following failure of initial current medical treatment approaches and therefore experience significant burden associated with surgical interventions**. Therapeutic keratoplasties are conducted in the event of corneal perforation, or as a measure of last resort for either non-healing epithelial defects or eradicating the *Acanthamoeba* organism.[24] Once the infection is presumed to have been eradicated and inflammation is no longer present, an optical keratoplasty may be conducted to treat residual corneal scarring and irregular astigmatism.[24] In a SIFI-conducted UK Delphi Panel in 2023, clinical experts estimated that out of the [redacted]% of patients in the UK who underwent therapeutic surgery, following failed medical therapy, [redacted]% underwent therapeutic keratoplasty.[10] These surgical interventions are associated with a range of related complications, predominantly glaucoma and cataracts, which affect [redacted]% and [redacted]% of patients receiving therapeutic surgery, respectively.[10] Additionally, patients may experience graft rejection following therapeutic keratoplasty, often necessitating follow-up surgeries such as re-grafts. A study by Robaei et al. reported that 26.9% of patients who underwent therapeutic keratoplasty required a re-graft.[24] Patients can experience a significant psychological burden such as heightened anxiety and stress due to the uncertainty of surgical outcomes as well as resulting post-traumatic stress disorder (PTSD) from undergoing	Comment noted. The scope already notes that 'If there is much scarring of the cornea following the eventual elimination of the infection, and vision is badly affected, a corneal transplant (penetrating keratoplasty) may be recommended**'.** We typically, would not include any further detail on the technology at this stage. The additional benefits noted can be included in the company submission. Comment noted. Following consultation, clarification on treatment licencing has been added and we have reflected off label dosing in scope.

Section	Consultee/ Commentator	Comments [sic]	Action
		these procedures, exacerbating the associated treatment burden of AK for patients.[2] *"Through all the traumatic surgeries at a relatively young age, PTSD came fairly soon. It grew from fears of never leaving the cycle of surgery and doctor appointments and manifested in nightmares." – Person with AK.*[2] **SIFI would also request that it is clarified that propamidine eye drops are not licensed for AK infections specifically.**[25] Propamidine has been studied and tested for other diseases, but crucially not AK, with safety and efficacy proven in different conditions, using different treatment regimens. The Summary of Product Characteristics (SmPC) of Brolene® (whose active ingredient is propamidine isethionate), states that eye drops should be administered once or twice up to four times daily for the treatment of minor eye infections such as conjunctivitis and blepharitis.[26] This treatment regimen is much less aggressive than typical regimens for AK (see Criterion 4 of the HST criteria checklist), and the efficacy and safety of using Brolene® as part of more aggressive treatment regimens has not been sufficiently studied to be licensed for AK. Furthermore, Brolene® contains benzalkonium chloride which is associated with corneal neurotoxicity, therefore use of this treatment as part of a more frequent dosing regimen may cause further corneal damage.[26]	
	Royal College of Ophthalmologists	Background section: Diagnosis is made by testing samples of fluid or tissue from the eye, or by seeing signs of the infection clinically using slit-lamp microscopy or using a confocal microscope. If AK is suspected, urgent referral to a specialist is advised. Could also include a more recent publication - doi: 10.3390/diagnostics13162655 Technology section, could also reference doi: 10.1016/j.ophtha.2023.09.031	Comment noted. These suggestions have been added to scope.

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Population	Company, SIFI S.p.A	**Is the population defined appropriately?** The population is defined appropriately and is in line with the anticipated marketing authorisation (MA) for polihexanide 0.8 mg/ml.	No action required.
	Royal College of Ophthalmologists	**Yes**	No action required.
Subgroups	Company, SIFI S.p.A	**Are there groups within the population that should be considered separately? For example, are there subgroups in which the technology is expected to be more clinically or cost effective? If subgroups have been suggested in the scope, are these appropriate?** It is SIFI's position that polihexanide 0.8 mg/ml would be appropriate for all patients with AK over the age of 12 years, in line with the anticipated MA. There are no subgroups that are clinically relevant and for which polihexanide 0.8 mg/ml is expected to be more clinically or cost-effective. Furthermore, the population of patients with AK is very small, and it is therefore not appropriate to further reduce the population size by considering subgroups in terms of clinical outcomes or cost effectiveness**.**	Comment noted. No action required.
	Royal College of Ophthalmologists	**No**	No action required.
Comparators	Company, SIFI S.p.A	**Are the comparators listed considered to be the standard treatments currently used in the NHS with which the technology should be compared? Have all relevant comparators been included?** While there is no current standard of care in the UK, SIFI is in agreement with the comparators listed by NICE, although it would highlight that not all listed treatments are used to the same degree. Given that there is no clear	Comments noted. Following consultation specification that treatment can be delivered as dual, or

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		treatment pathway, the use of these therapeutic approaches is heterogenous from the aspect of chosen agents and dosing regimens across the UK and likely to differ between patients.[10, 11] With respect to inclusion of the diamidines (propamidine and hexamidine), SIFI suggests that these comparators should only be considered in combination with biguanides as diamidine monotherapy is not recommended and is only used in cases where people with AK are unable to receive biguanides at diagnosis due to stock issues.[22, 23] SIFI would also suggest that in the list of comparators, **propamidine and hexamidine should be grouped into one 'diamidines' comparator**. Key data sources for the submission provide evidence that is not differentiated by the type of diamidine used, as propamidine and hexamidine are considered to have similar levels of efficacy. SIFI has conducted an analysis investigating the characteristics and outcomes of patients treated with polihexanide 0.2 mg/ml plus a diamidine (n=111) included in the updated retrospective study (Papa et al. 2020) separately for hexamidine and propamidine.[23] 66 patients were treated with hexamidine and 45 with propamidine; the baseline characteristics were largely comparable in key demographics between the two treatment groups. The proportion of cure was 53.0% (35/66) for patients treated with polihexanide + hexamidine and 57.8% (26/45) for patients treated with polihexanide + propamidine. This resulted in a cure ratio of 1.09 (95% CI = 0.78, 1.53; p = 0.620) confirming that there is not a significantly different effect between diamidines and that they are chosen only according to local availability.[23]	monotherapy has been added to scope. Further details are not required within the scope and can be included in company submission.
	Royal College of Ophthalmologists	**Yes**	No action required.

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Outcomes	Company, SIFI S.p.A	**Are the outcomes listed appropriate? Will these outcome measures capture the most important health related benefits (and harms) of the technology?** SIFI considers the outcome measures listed in the draft scope to be appropriate and relevant to people with AK. SIFI would like to note that “reduction of symptoms” has not been explicitly captured in the ODAK trial but may be implicitly captured in the EQ-5D and Visual Function (VFQ-25) questionnaires that were used. For example, general pain is a dimension of health in the EQ-5D questionnaire, whilst the VFQ-25 questionnaire includes domains such as general vision and ocular pain. Another symptom not explicitly mentioned in the NICE draft scope is corneal scarring which was measured from baseline in the ODAK trial.	Comment noted. No action required.
	Royal College of Ophthalmologists	**Yes**	No action required.
Equality	Company, SIFI S.p.A	SIFI supports access to treatment for all people with AK regardless of their age, gender and socioeconomic background. We are aware that care of people with AK in the UK is currently mainly provided by specialist centres, such as the Moorfields Eye Hospital, London.[23] SIFI are aware of patients who are required to travel long distances at considerable cost, in order to access specialist care. Variable access to treatment centres is therefore a potential driver of health inequalities in AK, particularly given that rapid treatment is crucial to improve eventual prognosis.[18] Equality of access is a key consideration for SIFI, given the need to treat as quickly as possible from diagnosis and we are committed to supporting the	Comments noted.

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		availability of polihexanide 0.8 mg/ml to all eligible patients in England and Wales. Furthermore, the stated intent for NICE to route this evaluation through the single technology appraisal (STA) programme, rather than the more appropriate HST programme, could have implications for equity and equality for individuals with AK. If routed via an STA, polihexanide 0.8 mg/ml would be subject to a lower willingness-to-pay threshold compared with the HST programme. As with many rare diseases, not least AK, it is widely acknowledged that the small number of patients with the condition in question necessitates a relatively high cost per patient. It would therefore be less likely that a product such as this would be found to be cost-effective against the lower STA willingness-to-pay threshold. Routing via the STA programme does not fully consider the urgent, unmet need that can be addressed by polihexanide 0.8 mg/ml in the AK patient population and does not fully account for the ultra-rare nature of AK as recognised by the EMA's orphan designation confirmation.[27] An STA routing for polihexanide 0.8 mg/ml could therefore result in unjustifiable delays in access for this patient population.	
	Royal College of Ophthalmologists	No change is required.	No action required.
Other considerations	Company, SIFI S.p.A	Not applicable	No action required.
	Royal College of Ophthalmologists	None	No action required.

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Questions for consultation	Company, SIFI S.p.A	Please describe the current treatment pathway in the NHS for acanthamoeba keratitis? Following diagnosis, people with AK typically receive an intensive treatment regimen of anti-amoebic eye drops, depending on availability. These are taken at least hourly both day and night initially, then less frequently as the treatment progresses.[3, 12] The initial, intensive treatment phase may require hospitalisation; clinicians consulted as part of a Delphi panel estimated [redacted]% of patients require hospitalisation, for an average duration of [redacted]days in the UK. Continuous treatment may be necessary for weeks or months, tapered slowly in the long-term.[22] As discussed in response to Comment 1, there is no licensed medicinal product for AK in England and Wales, with healthcare professionals left with no option but to prescribe off-label and unlicensed/compounded therapeutic approaches, resulting in heterogenous care.[13] This is supported by both a SIFI-conducted Delphi panel in 2023 which elicited expert advice from [redacted] ophthalmologists with experience treating patients with AK, and SIFI-conducted patient research. Both reported heterogenous use of a combination of off-label and unlicensed anti-amoebic agents such as biguanides and diamidines applied in dosing regimens that are different from centre to centre.[10, 11] Furthermore, in the absence of a standard of care, clinicians must individually tailor treatments for each patient without relevant SmPCs to guide their use, such as determining when to discontinue, repeat, or intensify treatment. In addition to anti-amoebic therapies, medications for pain relief may be given, due to the intense pain associated with AK.[6] Topical corticosteroids and antibiotics may also be given, to limit severe inflammation, and to treat secondary bacterial infection, respectively.[22] However, the initiation of corticosteroids prior to anti-amoebic therapy is associated with a four-fold increase in suboptimal outcomes for patients with AK	Comment noted. No action required.

		(including visual acuity worse than or equal to 20/80, perforation and the need for keratoplasty).[6] As discussed previously, therapeutic keratoplasties are conducted in the event of corneal perforation, or as a measure of last resort for eradicating the *Acanthamoeba* organism.[24] Once the infection has been presumed to have been eradicated and inflammation is no longer present, an optical keratoplasty may be conducted to treat residual corneal scarring and irregular astigmatism.[24] Where do you consider polihexanide 0.8mg/ml will fit into the existing care pathway for acanthamoeba keratitis? As described above, currently there are no licensed therapeutic approaches available in England and Wales for patients with AK, with no standard treatment pathway.[13] It would therefore be anticipated for polihexanide 0.8 mg/ml to displace the off-label and unlicensed therapeutic approaches currently used in England and Wales and be used as first-line therapy for treatment of AK. An approval of polihexanide 0.8 mg/ml by NICE would represent an important step in formalising treatment for AK, providing patients with faster access to a long-overdue effective treatment and giving people an equal chance for cure across England and Wales. Are there areas of unmet need with current treatment options? In AK, current clinical practice in England and Wales is limited to the use of off-label and unlicensed therapeutic approaches.[15] Treatment delays are common with respect to provision of biguanides as it is often necessary for these treatments to be compounded specifically for individual patients.[20] Rapid treatment of AK is crucial at diagnosis, as delayed treatment is associated with a poorer prognosis;[22] research by Bonini et al. shows significantly worse outcomes for patients receiving treatment >30 days post-diagnosis versus <30 days post-diagnosis.[17] Despite this, specialist centres such as the Moorfields Eye Hospital, London, have been reported not to have treatments required in stock at the time of diagnosis, and the Delphi Panel reported a typical time of [redacted] days between AK initial diagnosis and medical	

		treatment initiation.[10, 23] Availability of a licensed treatment which could be kept in stock without the need for compounding, such as polihexanide 0.8 mg/ml, would therefore allow these centres to treat patients more rapidly. Furthermore, the lack of standard of care in clinical practice in England and Wales often results in a failure to resolve the infection, with expert consensus from the Delphi panel estimating that an average of [redacted]% (90% CI: [redacted];[redacted]) of patients will switch to an alternative pharmacological option after 12 months.[10] Of these patients, [redacted]% will not be cured after 12 months.[10] Failure of these topical treatments often results in the use of surgical interventions, with [redacted]% (90% CI: [redacted];[redacted]) of patients who fail to achieve resolution of their infection with prior medical therapy undergoing therapeutic surgery.[10] As discussed in response to Comments 1 and 2, these surgical interventions are associated with a large psychological burden on patients, with no guarantee of improvement in visual outcomes.[10] Additionally, with current therapeutic approaches, people with AK face a demanding treatment regimen, requiring the administration of eye drops at least every hour during both day and night.[12] The high frequency of treatment administration throughout the day and night can require hospitalisation, with [redacted]% of patients treated with topical anti-microbials requiring hospitalisation during the initial intensive therapeutic phase.[12] Polihexanide 0.8 mg/ml monotherapy offers a less burdensome dosing schedule, requiring the administration of eyedrops in the daytime only in the initial treatment stage, thus minimising sleep disruption compared with current therapeutic approaches.[10, 12] A recommendation by NICE of polihexanide 0.8 mg/ml in England and Wales would therefore relieve the burdensome regimens associated with current treatments, and reduce the need for hospitalisation. Are current treatment options widely accessible within the NHS? Expert ophthalmologists within a SIFI-conducted Delphi panel estimated that [redacted]% of patients would receive medical treatment in the UK following	

		diagnosis of AK.[10] However, as previously discussed, current therapeutic approaches for AK in England and Wales consist of off-label and unlicensed therapies, with biguanides requiring compounding for individual cases, resulting in a **significant delay** in treatment initiation for patients; [redacted]days between diagnosis and treatment initiation.[1, 10] This treatment delay is not captured within the treatment accessibility estimate, with delays in treatment initiation associated with poorer prognosis and worse visual outcomes.[18] Are there delays in accessing the current treatment options following diagnosis? As discussed above, off-label and unlicensed therapeutic approaches are used in clinical practice in England and Wales, involving the need for compounding of biguanide products by individual case, resulting in delayed treatment initiation for patients with AK.[15] During a SIFI-conducted Delphi panel, the time to treatment for patients was estimated at an average of [redacted] days between initial AK diagnosis and medical treatment initiation.[10] This is a considerable delay in the context of an AK infection, in which every day of delay in treatment initiation increases the likelihood of a poor outcome for patients; a retrospective study by Bonini et al. demonstrated that patients treated with current therapeutic approaches who did not undergo surgery experienced a decline in visual acuity.[1, 17, 18] Licensing of polihexanide 0.8 mg/ml in England and Wales would displace the current reliance on therapeutic approaches which require compounding, allowing faster access and thereby has the potential to improve prognosis for patients by reducing waiting times. What are the key outcomes for recovery or improvement when treating acanthamoeba keratitis? Clinical resolution or cure is considered the principal objective of the treatment of AK. It can be defined as: clinical evidence of elimination of *Acanthamoeba;* intact epithelium and no clinical signs of ocular inflammation after discontinuing anti-amoebic and anti-inflammatory treatments for one month.[16]	

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		Please select from the following, will polihexanide be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. C. Prescribed in secondary care with routine follow-up in secondary care. For comparators, the setting for prescribing and routine follow-up is not expected to differ. Would polihexanide be a candidate for managed access? At this current time, polihexanide is not anticipated to be a candidate for managed access; however, SIFI would be happy to discuss as an option, if deemed necessary for access. Do you consider that the use of polihexanide can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? Failure to cure AK due to the lack of current standard of care is not uncommon and often results in the use of surgical interventions, with [redacted]% (90% CI: [redacted]) of patients who fail to achieve resolution of their infection with prior medical therapy undergoing therapeutic surgery.[10] These surgical interventions include keratoplasty, amniotic membrane transplantation, conjunctival flap, glaucoma, cataract surgeries or enucleation.[2] The prospect of surgery brings heightened anxiety and stress due to the uncertainty of the outcomes and the fear of potential vision loss, which can dramatically affect a patient's QoL. Additionally, undergoing these procedures can result in a significant psychological burden such as PTSD.[2] Patients may experience distress while waiting for surgery, with extended wait times	

		exacerbating feelings of helplessness and uncertainty about their future vision health.[28] Ophthalmologists consulted as part of a Delphi panel estimated an average wait time of [redacted] days prior to receiving surgical treatment, the psychological impact of which may be difficult to quantify and capture in the quality-adjusted life years (QALYs).[10] Furthermore, given that an intensive treatment regimen is required when using current therapeutic approaches, use of polihexanide 0.8 mg/ml is expected to reduce the frequency of eye drop administration and remove the need to administer eye drops overnight, avoiding further sleep disruption.[28] Additionally, many therapeutic approaches currently use a combination of eye drops, which require patients to wait between administration of different eye drops; the use of a single eye drop would remove the need for this 'washout period', eliminating this additional treatment burden. Given that patients typically have reduced visual acuity due to AK, this may also reduce the need for caregiver support or hospitalisation when administering treatment. Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. Surveys and direct quotes from patients and caregivers can be used to provide context on the impact of the disease and the treatment benefit of polihexanide 0.8 mg/ml across clinical, humanistic and economic outcomes. Please indicate if any of the treatments in the scope are used in NHS practice differently than advised in their Summary of Product Characteristics. For example, if the dose or dosing schedule for a treatment is different in clinical practice. If so, please indicate the reasons for different usage of the treatment(s) in NHS practice. If stakeholders consider this a relevant issue, please provide references for data on the efficacy of any treatments in the pathway used differently than advised in the Summary of Product Characteristics. Dosing of topical eyedrops for AK in clinical practice is not specified in UK guidelines and may therefore vary by prescribing ophthalmologist.[22] As shown by responses to a Delphi panel of UK ophthalmologists, different	

		combinations of eye drops are used, at times at different concentrations, reflecting the lack of standardised treatment guidelines or protocols.[10] As discussed in Comment 2, current off-label therapeutic approaches such as propamidine have been studied and tested for other diseases, but crucially not AK, with safety and efficacy proven in different conditions, using different treatment regimens. The SmPC of Brolene® (whose active ingredient is propamidine isethionate), states that eye drops should be administered once or twice up to four times daily for the treatment of minor eye infections such as conjunctivitis and blepharitis.[26] This treatment regimen is much less aggressive than typical regimens for AK (see Criterion 4 of the HST criteria checklist), and the efficacy and safety of using Brolene® as part of more aggressive treatment regimens has not been sufficiently studied to be licensed for AK. Furthermore, Brolene® contains benzalkonium chloride which is associated with corneal neurotoxicity, therefore use of this treatment as part of a more frequent dosing regimen may cause further corneal damage.[26] NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope: • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which polihexanide will be licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** • **could have any adverse impact on people with a particular disability or disabilities.**	

Section	Consultee/ Commentator	Comments [sic]	Action
		Please refer to the "Equality" section of Comment 2 above.	
	Royal College of Ophthalmologists	Please describe the current treatment pathway in the NHS for acanthamoeba keratitis? Currently, patients present with AK in the NHS are usually treated with intensive topical anti-amoebic treatment (AAT), starting with hourly day and night for 2-3 days, then followed by hourly for 5-7 days, 2 hourly for another week, and slowly taper over a course of several months, depending on the treatment response. AAT may be administered as monotherapy or dual therapy, including PHMB 0.02%, chlorhexidine, and brolene/propamidine. Where do you consider polihexanide 0.8mg/ml will fit into the existing care pathway for acanthamoeba keratitis? The treatment may be used as the first-line treatment for AK, or as a second-line treatment if the current AAT fails. Are there areas of unmet need with current treatment options? Currently, there is no licenced AAT in the UK and most patients affected by AK require at least a few months of treatment. Are current treatment options widely accessible within the NHS? The current treatment is accessible within the NHS, though there is occasionally a shortage of AAT. Are there delays in accessing the current treatment options following diagnosis?	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Sometimes, the current AAT (e.g. PHMB 0.02%) may only be available in tertiary hospitals, which may result in delay in initiating the appropriate treatment for AK in non-tertiary hospitals. What are the key outcomes for recovery or improvement when treating acanthamoeba keratitis? 1. Time to complete resolution of clinical signs of infection and inflammation associated with AK 2. Improvement in pain 3. Improvement in vision Please select from the following, will polihexanide be: A. Prescribed in primary care with routine follow-up in primary care B. Prescribed in secondary care with routine follow-up in primary care C. Prescribed in secondary care with routine follow-up in secondary care D. Other (please give details): For comparators and subsequent treatments, please detail if the setting for prescribing and routine follow-up differs from the intervention. Same as above Would polihexanide be a candidate for managed access? Yes Do you consider that the use of polihexanide can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?	

Section	Consultee/ Commentator	Comments [sic]	Action
		No Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits. The data is primarily related to a recent phase 3 RCT comparing the efficacy and safety of polihexanide 0.08% versus polyhexanide 0.02% + propamidine.(Ref) doi: 10.1016/j.ophtha.2023.09.031	

Comment 3 provisional stakeholders list

Section	Consultee/ Commentator	Comments [sic]	Action
	Company, SIFI S.p.A	SIFI would recommend the inclusion of Beacon for Rare Diseases but otherwise agree with those suggested.	Comment noted. Stakeholder will be added to list.
	Royal College of Ophthalmologists	Comments on the provisional stakeholder list Could also include Acanthamoeba Keratitis Eye Foundation.	Comment noted. Stakeholder will be added to list.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

N/A