ERG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Cenegermin for treating neurotrophic keratitis [ID946]

Confidential until published

This report was commissioned by the NIHR HTA Programme as project number 16/54/06

Completed 24 January 2018

CONTAINS ACADEMIC IN CONFIDENCE AND COMMERCIAL IN CONFIDENCE DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Cenegermin for treating neurotrophic keratitis [ID946]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

Authors: Nigel Fleeman, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

James Mahon, Director, Coldingham Analytical Services, Berwickshire

Sarah Nevitt, Research Associate (Medical Statistician), LR*i*G, University of Liverpool

Rui Duarte, Health Technology Assessment Lead, LR*i*G, University of Liverpool

Angela Boland, Associate Director, LR*i*G, University of Liverpool

Eleanor Kotas, Information Specialist, LR*i*G, University of Liverpool

Yenal Dundar, Research Fellow (Clinical Effectiveness), LR*i*G, University of Liverpool

Joanne McEntee, Senior Medicines Information Pharmacist, North West Medicines Information Centre, Liverpool

Sajjad Ahmad, Consultant Ophthalmologist, Moorfields Eye Hospital, London

Correspondence to: Nigel Fleeman, Research Fellow, Liverpool Reviews and Implementation Group, University of Liverpool, Whelan Building, The Quadrangle, Brownlow Hill, Liverpool L69 3GB

Date completed: 24 January 2018

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 16/54/06.

Declared competing interests of the authors: Within the last 3 years**,** Sajjad Ahmad has been in receipt of reimbursement and hospitality for attending an educational symposium organised by Dompé.

Acknowledgements: The authors would like to thank Professor Stephen Kaye, who provided feedback on a final draft version of the report.

Rider on responsibility for report: The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Fleeman N, Mahon J, Nevitt S, Duarte R, Boland A, Kotas E, Dundar Y, McEntee J, Ahmad S. Cenegermin for treating neurotrophic keratitis [ID946]: A Single Technology Appraisal. LRiG, University of Liverpool, 2018.

Contributions of authors:

Fleeman N	Project lead and supervised the final report
James Mahon	Critical appraisal of the economic evidence
Sarah Nevitt	Critical appraisal of the statistical evidence
Rui Duarte	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence
Eleanor Kotas	Critical appraisal of the company's search strategies
Yenal Dundar	Critical appraisal of the adverse event data
Joanne McEntee	Critical appraisal of the company submission
Sajjad Ahmad	Clinical advice and critical appraisal of the clinical sections of the company submission

All authors read and commented on draft versions of this report.

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LIST OF ABBREVIATIONS

AE	adverse event
CHMP	Committee for Medicinal Products for Human Use
CS	company submission
CSR	clinical study report
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EQ-5D-5L	European Quality of Life - 5 Dimensions Questionnaire
ERG	Evidence Review Group
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost effectiveness ratio
ITT	intention-to-treat
LOCF	last observation carried forward
MTC	mixed treatment comparison
NEI-VFQ-25	national eye institute visual functioning questionnaire 25
NICE	National institute for Health and Care Excellence
NGF	nerve growth factor
NK	neurotrophic keratitis
OR	odds ratio
PED	persistent epithelial defects
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	quality adjusted life year
RCT	randomised controlled trial
rhNGF	recombinant human nerve growth factor
SAE	serious adverse event
SmPC	summary of product characteristics
SoC	standard of care
STA	single technology appraisal
TEAE	treatment emergent adverse event
TRAE	treatment-related adverse event
TSAP	trial statistical analysis plan
VAS	visual analogue scale

1 SUMMARY

1.1 Scope of the submission

The remit of the Evidence Review Group (ERG) is to comment on the clinical and cost effectiveness evidence submitted to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Clinical and economic evidence has been submitted to NICE by Dompé in support of the use of cenegermin for treating neurotrophic keratitis (NK).

1.2 Critique of the decision problem in the company submission

Cenegermin is indicated for adults with moderate (persistent epithelial defect) or severe (corneal ulcer) NK, i.e. stage 2 or stage 3 NK. The population addressed by the company's decision problem is identical to that specified in the NICE scope. This population is identical to the population for which cenegermin is licensed. The intervention specified in the NICE scope is cenegermin or recombinant human nerve growth factor (rhNGF). The company has presented evidence for rhNGF as cenegermin, a type of eye drop, at the licensed dose of 20 µg/ml. The comparator in the NICE scope was established clinical management without cenegermin (which may include treatment of any underlying causes, preservative free artificial tears, collagenase inhibitors, medical or surgical eyelid closure, serum eye drops, therapeutic contact lenses and surgery). The ERG considers that the company has made every effort to explore the evidence base for cenegermin versus established clinical management. All outcomes specified in the NICE scope were explored in the company submission (CS), namely: corneal healing, visual acuity (affected eye and both eyes), corneal sensitivity, need for further treatment or hospitalisation for NK, adverse effects (AEs) of treatment, health-related quality of life (HRQoL). As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a lifetime horizon (age of cohort reaching 100 years) and costs were considered from an NHS perspective. In the final scope issued by NICE, it is stated that if evidence allows, separate consideration will be given to people with NK associated with progressive or non-progressive underlying causes and subgroups based on the stage or severity of the disease. Subgroup data based on progressive disease are not available. Subgroup data based on underlying aetiology have been presented in the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) European Public Assessment Report (EPAR) and subgroup data by disease severity were provided by the company for corneal healing during the clarification process.

1.3 Summary of the clinical evidence submitted by the company

In July 2015, a systematic review was conducted by the company to identify published clinical trials considering management of patients with NK. In August 2017, the company updated their search to identify evidence published since the original review was conducted and also undertook a separate 'clinical extension review' to identify studies to inform a mixed treatment comparison (MTC) in order to compare cenegermin with all relevant comparators.

The searches conducted by the company identified two phase 2 randomised controlled trials (RCTs) of cenegermin (versus vehicle) directly relevant to the decision problem, the REPARO trial and Study 0214. Studies considered for inclusion in the MTC were the two cenegermin trials plus 23 studies of comparator treatments that were eligible for inclusion into the 'clinical extension review.' The company was only able to conduct an MTC based on very limited data and it considered the results were associated with such uncertainty that no conclusions could be drawn.

Two doses of cenegermin were investigated in the REPARO trial. The CS and this ERG report focus on data for the 20 µg/ml arm since this is the licensed dose (which was also the dose used in Study 0214). Excluding 52 patients treated at the unlicensed dose (10 µg/ml), the REPARO trial included approximately twice as many patients relevant to the decision problem (n=104) as Study 0214 (n=48). The licensed formulation of cenegermin contains an excipient, methionine. Methionine was added as an anti-oxidant in Study 0214 due to concerns that oxidation could affect stability of cenegermin. Both cenegermin and vehicle formulations contained methionine in Study 0214, but not in the REPARO trial. Although the REPARO trial was conducted in Europe and Study 0214 was conducted in the US, in most other respects, the study characteristics of the two cenegermin trials were very similar. Both trials permitted the use of some preservative-free topical antibiotics and preservative-free artificial tears.

In addition to a controlled treatment period of 8 weeks, both trials included an uncontrolled 8 week cenegermin treatment period and an extended follow-up period. Patients healed or not healed with cenegermin, and patients healed with vehicle, entered the extended follow-up period (48 weeks in the REPARO trial, 24 weeks in Study 0214) immediately after the controlled treatment period. Patients in the vehicle arm whose NK deteriorated or who were not healed within the controlled treatment period entered the uncontrolled treatment period (8 weeks of cenegermin) and then entered the extended follow-up period. Treatment with cenegermin was available for patients who deteriorated during the extended follow-up, but only if they had been completely healed previously. In total, for those initially randomised to cenegermin, and those randomised to vehicle and who achieved corneal healing at 8 weeks, the maximum follow-up was 56 weeks in the REPARO trial and 32 weeks in Study 0214. For

patients initially randomised to vehicle and who had not achieved corneal healing at Week 8, the maximum follow-up was 64 weeks in the REPARO trial and 40 weeks in Study 0214.

Corneal healing was the primary outcome in both trials. Although for the primary outcome, corneal healing was measured at 4 weeks in the REPARO trial and at 8 weeks in Study 0214, it was measured at 8 weeks in both trials. Corneal healing at 8 weeks is considered to be the most relevant outcome for the controlled treatment period of both trials. Corneal healing was predefined as the greatest diameter of the corneal fluorescein staining in the area of the persistent epithelial defects (PED) or corneal ulcer being <0.5 mm. At the request of the US Food and Drug Administration (FDA), corneal healing was also defined post-hoc as "no residual fluorescein staining in the area of the corneal lesion (0 mm) and no persistent staining elsewhere in the cornea," where persistent staining was defined as "staining not changing in shape and/or location of different time points." Within both studies, assessments of corneal healing were performed by assessors at a central reading centre who evaluated the clinical pictures of corneal fluorescein staining. These assessors were masked to the treatment arm from which the pictures of corneal fluorescein staining were derived. Secondary outcomes in the trials included complete corneal clearing, visual acuity, corneal sensitivity, deterioration in NK, recurrence of NK, AEs of treatment and HRQoL.

In the REPARO trial, 74% and 72% of patients treated with cenegermin achieved complete healing (<0.5 mm and 0 mm respectively) and in Study 0214, 69.6% and 65.2% achieved complete healing (<0.5 mm and 0 mm respectively). The difference in the percentage of patients achieving complete healing (<0.5 mm) between the cenegermin and vehicle arms at 8 weeks was 30.9% (97.06% confidence interval [CI] 10.60% to 51.13%; p=0.002) in the REPARO trial and 40.4% (95% CI 14.2% to 66.6%; p=0.006) in Study 0214. The difference in the percentage of patients achieving complete healing (0 mm) between the cenegermin and vehicle arms at 8 weeks was 38.7% (97.06% CI 18.72% to 58.62%; p<0.001) in the REPARO trial and 48.6% (95% CI 24.0% to 73.1%; p<0.001) in Study 0214.

Given the small number of patients in each subgroup, in response to an ERG request for corneal healing results by NK stage, the company provided pooled subgroup data of the REPARO trial and Study 0214. When data from all patients who initially received cenegermin in the two studies were pooled, 25 out of 40 (63%) patients with stage 2 NK and 28 out of 33 (85%) patients with stage 3 NK achieved corneal healing (<0.5 mm) at the end of the 8 week controlled treatment period. When data from all patients who initially received vehicle in the two studies were pooled, 15 out of 46 (33%) patients with stage 2 NK and 14 out of 29 (48%) patients with stage 3 NK achieved corneal healing (<0.5 mm) at the end of the 8 week controlled treatment period. The improvement in corneal healing for cenegermin compared

with vehicle was statistically significant for patients with stage 2 NK (p=0.006) and for patients with stage 3 NK (p=0.002).

The company also pooled outcome data for corneal healing at Week 8 in a meta-analysis for all patients in the two trials, i.e. regardless of stage of NK. This was conducted using both definitions of corneal healing. Both of the pooled odds ratios (ORs) were in favour of cenegermin versus vehicle. The meta-analysis of corneal healing to <0.5 mm at Week 8 provided a pooled OR of 4.24 (95% CI 2.11 to 8.50; p<0.001) and the meta-analysis of corneal healing to 0 mm in the lesion area, no persistent staining elsewhere at Week 8 provided a pooled OR of 6.09 (95% CI 2.97 to 12.50; p<0.001).

In both trials, the proportions of patients who achieved corneal healing at Week 8 and who remained healed at the end of the extended follow-up period (i.e. did not experience recurrence of NK) after completing treatment were reported in the CS. Recurrence rates were found to vary from 0% to 30% depending on the trial arm that patients were initially randomised to and whether complete healing was achieved during the controlled or uncontrolled treatment period. In the CS, the company noted these findings are “indicative only and do not permit firm conclusions to be drawn.”

There were no significant differences between trial arms for any of the secondary efficacy outcomes reported: complete corneal clearing, visual acuity, corneal sensitivity, or deterioration in NK.

Patients often reported multiple AEs in the trials. Hence, in the REPARO trial, 27/52 (51.9%) and 20/52 (38.5%) patients in the cenegermin and vehicle arms respectively reported a total of 51 and 50 AEs. In Study 0214, 21/23 (91.3%) and 18/23 (75.0%) patients in the cenegermin and vehicle arms respectively reported a total of 82 and 54 AEs. Eye disorders (such as eye pain) were the most common class of AEs experienced by patients in both arms of the REPARO trial (cenegermin: 13/52 [25.0%], vehicle: 16/52 [30.8%]) and Study 0214 (cenegermin: 18/23 [78.3%], vehicle: 14/24 [58.3%]). While AE frequencies differed quite markedly between trials, the company states that the safety evidence presented suggest that cenegermin was well tolerated since the majority of the serious AEs and treatment-related AEs were mild or moderate in severity and did not require treatment discontinuation or any corrective treatment. In total, 9/52 (17.3%) and 5/23 (21.7%) of patients treated with cenegermin in the REPARO trial and Study 0214 respectively discontinued treatment due to an AE. In the vehicle arms, 4/52 (7.7%) of patients in the REPARO trial and 7/24 (29.2%) of patients in Study 0214 discontinued treatment due to an AE.

HRQoL was measured in both trials using the European Quality of Life - 5 Dimensions Questionnaire (EQ-5D-5L), EQ-5D visual analytic scale (VAS) and national eye institute visual functioning questionnaire 25 (NEI-VFQ-25). The results from the EQ-5D-5L analyses are highly variable, with no consistent pattern in terms of change from baseline to Week 8 in either arm, for either trial or when using the pooled data, for any health state. In terms of EQ-5D VAS and NEI-VFQ-25, from baseline to Week 8, there were slight increases in scores for cenegermin and a slight decrease in scores for vehicle in both trials. The company notes that the baseline EQ-5D VAS and NEI-VFQ-25 scores in both arms of Study 0214 study were higher than the same scores in the REPARO trial. Regarding the least squares mean change for EQ-5D VAS and NEI-VFQ-25, no statistically significant differences between arms from baseline to Week 8 were found.

1.4 Summary of the ERG's critique of clinical effectiveness evidence submitted

Overall, the ERG considers that the methods used to conduct the clinical effectiveness systematic review and the 'clinical extension review', as described in the CS, are satisfactory.

The ERG considers that the methodological approaches carried out by the company to conduct its MTC are appropriate. However, the ERG also agrees with the company that the data were limited, and that the uncertainty associated with the results is so large that the results are difficult to interpret, and no firm conclusions can be drawn.

While the ERG noted some differences in baseline characteristics within and across the two cenegermin trials, the baseline characteristics of the patient populations in these trials appear to be similar to those who would be treated with cenegermin in NHS clinical practice.

The ERG concurs with the company that the vehicle used in the two cenegermin trials is similar in its composition to artificial tears as it contains ingredients widely used in commercially available preservative-free artificial tears.

Corneal healing is considered by the ERG to be the most appropriate outcome for measuring the efficacy of cenegermin and notes that it is a common outcome in trials of eye diseases. The ERG notes that outcomes relevant to the decision problem at 8 weeks (controlled treatment period) were reported for both trials, using the same outcome definitions across trials.

The ERG agrees with the company that generally the two trials were at low risk of bias. However, the ERG notes that withdrawal rates were quite high (up to 37.5% of patients withdrawn) and unbalanced across the treatment arms in both studies. The ERG notes that

several analysis approaches have been considered to take account of these missing data and considers some of these analyses, particularly the multiple imputation approach, to be appropriate.

The ERG is concerned about the use of the last observation carried forward (LOCF) method in the primary and secondary efficacy analyses as this method ignores the uncertainty introduced by missing response data. There is a large amount of missing data in the two trials. The ERG considers the multiple imputation approach used in the sensitivity analysis described by the company, which is more statistically powerful and captures the uncertainty introduced by the missing outcome data, to be the most appropriate method of handling missing data in these trials. The results of sensitivity analyses, including the multiple imputation approach, are however similar to the results using the LOCF approach although the LOCF approach appears to [redacted] difference between arms in the REPARO trial.

While the rates of corneal healing are reported to be broadly similar for patients treated with cenegermin in both the REPARO trial and Study 0214, the EMA notes that there are differences in the response rates for patients in the vehicle arms with and without methionine. At Week 8, 43.1% of patients in the vehicle arm (without methionine) of the REPARO trial had achieved corneal healing compared to 29.2% of the patients receiving vehicle (with methionine) in Study 0214. However, the EMA considered that the response rates in both trials were, nonetheless, in line with the estimated rates for vehicle used for study size and power calculations for both trials (approximately 30%).

The ERG considers that it was appropriate to pool data for the subgroup analysis of corneal healing by NK stage. The ERG considers the methodological approach employed by the company for pooling the subgroup data and for its meta-analysis to be appropriate.

The ERG considers that the evidence from the extended follow-up periods of both cenegermin trials suggests that a high proportion of patients who are healed after 8 weeks of treatment with cenegermin remain healed after a further 24 weeks and 48 weeks. However, the ERG agrees with the company that it is difficult to draw firm conclusions from these exploratory analyses.

The reasons for the differences in some AE frequencies across trials are unknown. In Study 0214, eye drops issued in both arms of the trial included methionine. The EMA highlights that while methionine has scarcely been used in ophthalmological preparations to date, it is a very common food ingredient with no reported toxicity issues. The EMA also highlights that the company has argued that US patients and physicians tend to report AEs more frequently than

Europeans, which could be a factor (as Study 0214 was conducted in the US and the REPARO trial was conducted in Europe). Given the uncertainty regarding the possible effects of methionine on tolerability, the EMA has recommended that the company generates further long-term data with the methionine-containing formulation of cenegermin (since the formulation of cenegermin which is licensed for use in clinical practice also contain methionine).

The company argues that transient reductions in visual acuity and transient ocular pain are not necessarily a sign of an AE and can both be related to the healing process in patients with NK, reflecting improved corneal sensitivity. The ERG concurs with the company.

The company also states that the variability of the EQ-5D-5L results may be a consequence of small patient numbers, particularly for patients in the 'not healed and deteriorating' health state. Therefore, it is argued that no robust interpretations or conclusions can be drawn from the results. The ERG concurs with the company. The ERG further notes that there appear to be only minimal changes in HRQoL in either arm of either trial as measured by the EQ-5D VAS and NEI-VFQ-25 scores and patient numbers are small. The ERG concurs with the company that the apparent lack of change in HRQoL is unsurprising given NK is, by definition, a largely asymptomatic disease.

1.5 Summary of cost effectiveness evidence submitted by the company

The company developed a de novo model structure in Microsoft Excel to compare the cost effectiveness of treatment with cenegermin with preservative-free artificial tears. The cost effectiveness model presented by the company comprises two-stages: a decision tree followed by a Markov model. The company states that the use of this model structure allows separation of the initial treatment period and healing outcome (decision tree) from maintenance treatment, recurrences and administration of further treatment options (Markov model). After the initial treatment period which determines the outcome associated with initial treatment, patients enter a Markov process with three NK states: sustained healing, non-healing or deteriorating, with death as an absorbing state. The company uses a cycle length set to 4 weeks. The company states that the economic evaluation is undertaken from the perspective of the NHS and the model time horizon in the base case is the lifetime of patients, set at 100 years of age for the cohort, with 5-, 10- and 20-year time horizons included as scenario analyses. Outcomes were measured in QALYs, and both costs and QALYs are discounted at a rate of 3.5% per annum as recommended by NICE. Resource use and costs for the different health states were estimated based on information from a telephone survey of 12 clinical experts conducted by the company.

In the company base case, cenegermin is dominant when compared to artificial tears, generating more benefits (+0.08 QALYs) at a decreased cost of £21,549. The company carried out a range of deterministic sensitivity analyses. Varying the utility of the non-healing health states in the follow-up model has the biggest effect on the company's cost effectiveness results, followed by the starting age, the discount rate and the probability of healing with cenegermin versus artificial tears, although cenegermin remained cost effective in all scenarios.

The company's probabilistic sensitivity analysis (PSA) involved varying only a limited number of parameters. The results of the company's PSA suggest that there is a 97.6% probability of treatment with cenegermin being cost effective at a willingness to pay threshold of £20,000 per QALY gained and a 97.7% probability of cenegermin being cost effective at a willingness to pay threshold of £30,000 per QALY gained.

The company carried out seven scenario analyses. The only scenario in which cenegermin was not dominant versus artificial tears was when considering a time horizon of 5 years. In this scenario, cenegermin generates more benefits than artificial tears (+0.02 QALYs) at an increased cost of £3,139. The ICER for this scenario for the comparison of cenegermin versus artificial tears is £127,390 per QALY gained.

1.6 Summary of the ERG's critique of cost effectiveness evidence submitted

The company has produced a model that the ERG does not consider fit for purpose. In the company model, it is assumed that patients who do not achieve sustained healing with initial treatment with cenegermin or artificial tears never achieve sustained healing and only have palliative treatments with frequent (up to 10 times per month) visits to specialists for the rest of their lives. The ERG considers this high number of visits to be implausible. The ERG also considers that the implicit assumed zero efficacy associated with treatments in the standard of care (SoC) "basket" at achieving sustained healing contrasts with the results of the company's own clinician survey.

Without restructuring and reconstructing the model, the ERG cannot present a plausible or preferred ICER per QALY gained. However, the company suggested that lower estimates for the number of specialist visits for patients without sustained healing would be appropriate. This change moves cenegermin from being dominant to having an ICER of £22,737 per QALY gained compared to artificial tears.

Even if the ERG was satisfied with the model structure, there were errors in the way utility values and the costs of one-off treatments were applied in the model. Making these

adjustments, together with the reduced number of specialist visits, would result in an ICER of £125,764 per QALY gained. Due to the model's structural flaw, the ERG does not present this figure as a preferred ICER but as a more accurate estimate of the company base case ICER within the confines of the flawed model structure. However, this value is still likely to be an underestimate of the base case ICER per QALY gained as:

- the average number of specialist visits for people initially treated with artificial tears seems implausibly high at approximately 450 over a patient's lifetime. If the value is lower than 450, the ICER for cenegermin would increase
- the utility decrements for tarsorrhaphy are uncertain but the values used would lead to an overestimate as all patients with tarsorrhaphy are assumed to suffer unilateral blindness from the procedure when this is not the case. If the utility decrement for tarsorrhaphy is lower than assumed in the model then the ICER per QALY gain for cenegermin would increase
- mortality in the model has likely been underestimated resulting in an overestimate of the QALY gain with cenegermin and an overestimate of the costs of treatment for patients initially treated with artificial tears.

1.7 ERG commentary on the robustness of evidence submitted by the company

1.7.1 Strengths

Clinical effectiveness evidence

- The company attempted to compare cenegermin with a range of relevant comparators by conducting a MTC.
- The company has presented evidence from two RCTs for treating NK. To date, there have been very few RCTs of interventions for treating NK.
- RCT evidence demonstrates the superiority of cenegermin versus vehicle, a proxy for artificial tears, at 8 Weeks, in relation to the important outcome of corneal healing.

Cost effectiveness evidence

- The company has produced an economic model that is algorithmically well constructed and easy to follow.
- The company attempted to identify all relevant evidence for the cost effectiveness analysis and addressed evidence gaps using a clinician survey.

1.7.2 Weaknesses and areas of uncertainty

Clinical effectiveness evidence

- To date, only 24 patients included in the trials were randomised to receive the formulation of cenegermin that is exactly the same as the intervention that is licensed (i.e. including methionine). These patients were all in Study 0214 where a further 10 patients who were initially randomised to vehicle also received this formulation in the uncontrolled treatment period.
- While vehicle may be a proxy for artificial tears, artificial tears alone are very rarely used to treat patients with stage 2 or stage 3 NK. Artificial tears are more commonly used alongside another treatment. The ERG considers the most appropriate comparators would have been amniotic membrane transplantation or serum eye drops (autologous or allogenic). Unfortunately, despite best efforts, the MTC conducted by the company was based on very limited data and the results were associated with such uncertainty that no firm conclusions could be drawn regarding the efficacy of cenegermin versus other comparators.
- As stated by the company, data for the effectiveness of cenegermin beyond 8 weeks can only be considered exploratory.
- The reasons for the differences in some AE frequencies across trials are unknown.
- No robust interpretations or conclusions can be drawn from the HRQoL results.
- It has been argued that while currently available treatments aim to promote corneal healing, they do not address the pathophysiology/cause of the disease (corneal nerve impairment). It is argued that cenegermin, on the other hand, does address the underlying cause of the disease. The ERG does not consider that there is evidence to demonstrate this. While the evidence shows that treatment with cenegermin results in corneal healing, this outcome does not measure whether a treatment addresses the pathophysiology of the disease. Rather, corneal healing is a measure of the size of PED and/or corneal ulcer by corneal fluorescein staining. The ERG does however note that it is reported in the EPAR that NGF has been shown to play a crucial role in the pathophysiology of NK and cenegermin is a recombinant form of NGF.
- Compared to vehicle, it appears from the results of a pooled subgroup analysis that cenegermin may be more effective for treating stage 3 NK than stage 2 NK, however, the numbers of patients in each subgroup are small.
- It is unclear where cenegermin would be best placed in the treatment pathway for NK. However, given previous tarsorrhaphy was an exclusion criterion for trial entry into both cenegermin trials, it is anticipated that cenegermin would precede tarsorrhaphy.

Cost effectiveness evidence

- The structure of the economic model does not allow patients to appropriately transition between states. As a result of this structural flaw, it is impossible for the model to generate robust ICERs per QALY gained for the comparison of cenegermin versus artificial tears.
- There were errors in the way utility values and the costs of one-off treatments were applied in the model
- The assumption of no efficacy gain from treatments in the SoC “basket” contrasts with the results of the company’s own clinician survey.

1.8 Summary of exploratory and sensitivity analyses undertaken by the ERG

Without restructuring and reconstructing the model, the ERG cannot present a plausible or preferred ICER per QALY gained. Due to the model's structural flaw, the ERG considers a more accurate estimate of the company base case ICER within the confines of the flawed model structure to be £125,764 per QALY gained. However, the ERG considers that this value is still likely to be an underestimate of the base case ICER per QALY gained.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company's description of the underlying health problem is presented in Section B1.3 of the company submission (CS). The Evidence Review Group (ERG) considers that the company's description presents an accurate summary of the underlying health problem. Key points made by the company and considered by the ERG to be of particular relevance for the current appraisal are presented in Box 1.

Box 1 Key points from the company's description of underlying health problem

Description of disease

- Neurotrophic keratitis (NK) is a rare disease of the cornea (the transparent part of the eye that is exposed to the external environment) which has been classified by the European Medicines Agency (EMA) as an orphan disease.[1]
- NK is caused by impairment of the trigeminal nerve, which innervates the cornea via branches of the ophthalmic nerve and regulates its normal functioning and homeostasis.[2,3] Trigeminal impairment can arise from a variety of causes, including ocular herpes infection, chemical burns, long-term use of contact lenses, chronic use of topical eye medications, ablative treatment of trigeminal neuralgia, and systemic conditions including diabetes and multiple sclerosis.[2,3]
- NK is characterised by reduced corneal sensitivity (the hallmark of the disease), spontaneous breakdown of the corneal epithelium, and impairment of corneal healing.[2,3] NK is usually unilateral (i.e. affecting one eye only).[2]
- Owing to the loss of corneal sensitivity, patients with NK do not usually report ocular surface discomfort.[3] Visual acuity is affected in some but not all cases.[4] While patients with NK rarely report symptoms of ocular surface discomfort, they may complain of blurred vision due to persistent epithelial defects (PED), corneal stroma scarring, and/or swelling.[3]
- NK has been described as 'one of the most difficult and challenging ocular diseases'.[3]

Stages of disease

- Stage 1 (mild NK): small areas of superficial damage to the cornea, known as punctate keratopathy. Patients do not usually notice symptoms.
- Stage 2 (moderate NK): PED of the cornea, defined as defects that do not heal within 2 weeks.
- Stage 3 (severe NK): ulceration of the cornea, which may then progress to corneal melting and finally perforation of the cornea.
- Once NK progresses to corneal ulceration, melting or perforation, the patient is at high risk of permanent loss of vision, either through permanent loss of corneal transparency (due to fibrotic scars), through anatomical loss of the eye, or through the need for surgical treatment designed to prevent anatomical loss of the eye, which does not offer the possibility of preserving vision.

Epidemiology

- Epidemiological data on NK are sparse. The prevalence of NK has been estimated as 1.6/10,000, based on the prevalence of conditions associated with NK: keratitis after herpes infection (simplex or zoster) and after surgery for trigeminal neuralgia.[3]
- It is estimated that approximately half of patients diagnosed with NK have stage 2 (moderate) or stage 3 (severe) disease.[5]

Humanistic and economic burden

- NK is associated with a substantial humanistic burden to patients, caregivers and family. This takes the form of fear of visual impairment or eye loss, including fear of recurrence after healing; the physical impact of complications such as serious eye infections; and the inconvenience and expense of recurrent medical examinations, often at specialist centres far from home.
- Patients who become partially sighted or blind may lose their job and/or their independence, leading to high costs to both the individual and to society.

Source: adapted from CS, Section B1.3

2.2 Critique of company's overview of current service provision

The company's overview of current service provision is presented in Section B1.3 of the CS. The ERG considers that the company's overview presents an accurate summary of current service provision and highlights the key points made by the company of particular relevance to the current appraisal in Box 2.

Box 2 Key points from the company's overview of current service provision

Treatment aims

- The goal of currently available treatments is to promote corneal healing in an attempt to prevent the progression of corneal damage.
- Neurotrophic keratitis (NK) requires prompt treatment to prevent progression of corneal damage.
- Stage 2 NK can progress rapidly to stage 3 NK if treatment does not result in corneal healing.

Treatment options

- NK is diagnosed and managed by eye specialists in tertiary care.
- Currently available treatments aim to promote corneal healing but do not address the pathophysiology/cause of the disease (corneal nerve impairment). Thus, they can be regarded as palliative in nature.
- There is a scarcity of data on the efficacy of currently available treatments.
- Neither NICE nor the Royal College of Ophthalmologists have published guidelines on the treatment of NK.
- There is no recognised 'standard of care' treatment; patients typically cycle through a variety of treatments in no set order, which do not address the pathophysiology of the disease.
- Preservative-free artificial tears (or other preservative-free ocular lubricants in the form of gels and ointments) are an important aspect of the treatment of all stages of NK, and often form a base therapy to which other treatments are added.[2]
- The non-surgical treatment options currently used in the UK in addition to preservative-free artificial tears and similar ointments and lubricants, are autologous or allogeneic serum (not available to all physicians), punctal plugs and therapeutic contact lenses.
- Surgical treatments are avoided where possible due to their potentially disfiguring effect. However, they are often required in both moderate and severe NK: sometimes early in the treatment approach due to unavailability of alternative therapies at some centres; or after other treatments have failed.
- The most frequently used surgical options are tarsorrhaphy (sewing or gluing the eyelid shut), conjunctival flap (in which a flap of conjunctiva is brought up and sutured to the cornea), and amniotic membrane transplant. Both tarsorrhaphy and conjunctival flap treatments have a poor cosmetic outcome and visual function is sacrificed.[3]
- There is a clear unmet need for a non-surgical treatment that is effective in achieving sustained corneal healing.

Source: adapted from CS, Section B1.3

Of note, while no UK guidelines for the treatment of NK exist, a review has been published (in 2014) describing the diagnosis and management of NK, by authors based in Italy.[3] Figure 2 of this review illustrates the stepwise approach to the diagnosis and treatment of NK. Artificial tears are shown to be a base therapy for stage 1 NK (as also stated in Box 1 of this ERG report), tarsorrhaphy and conjunctival flap are recommended for stage 2 NK and therapeutic contact lens and amniotic membrane transplantation are recommended for stage 3 NK. However, market research conducted by the company with 12 corneal specialists in the UK,[6] and reported in the CS (p85), indicates that clinical practice varies widely in the UK. The choice of treatment is heavily driven by severity of disease and patient need (what is convenient and

preferred by them, which is usually less invasive options such as preservative-free artificial tears).[7]

2.3 Technology being appraised

Cenegermin is a non-surgical treatment, administered as eye drops six times daily over a course of 8 weeks, proposed as a treatment option for moderate (stage 2) and severe (stage 3) NK.[8] Marketing authorisation was granted by the European Medicines Agency (EMA) on 6 July 2017. Further information is summarised in Table 1. The company considers treatment with cenegermin to be an innovative 'step-change' in the management of NK (CS, Section B2.12). Some of the reasons cited by the company to support this view are summarised in Box 3.

Box 3 Innovative characteristics of cenegermin highlighted by the company

- Unlike other treatments, which are purely symptomatic, cenegermin is thought to be disease-modifying, targeting the underlying cause of neurotrophic keratitis (NK) by addressing the pathophysiology of the disease and promoting restoration of corneal integrity (corneal healing).
- It is a simple, standardised, ready-prepared eye drop (in contrast to autologous serum, which has to be prepared individually for each patient from the patient's own blood) and requires no surgical procedures.
- Cenegermin was reviewed under the European Medicines Agency's accelerated assessment programme, in view of the lack of valid treatment options for patients and the innovative nature of the product.
- It is the only treatment specifically licensed for the treatment of NK.

Source: adapted from CS, Table 2 and Section B2.12

In addition to the reasons cited by the company, comments from the Royal College of Ophthalmologists also indicate that cenegermin represents a 'step-change' in the management of NK because "all current options are generic to ocular surface disease."[9] It is noted that autologous and allogeneic serum eyes drops may provide some overlap but there is no treatment that specifically targets the complications that occur due to loss of corneal innervation.[9] The ERG also notes the comments from a clinical expert that cenegermin is a 'step-change' in the management of the condition because it targets the underlying cause of NK by addressing the pathophysiology of the disease and promoting restoration of corneal integrity.[7] The clinical expert highlights that cenegermin is a readily-available eye drop which can be delivered as an out-patient procedure (in contrast to more complex therapy such as serum eye drops, which have to be prepared individually for each patient from the patient's own blood) and requires no surgical procedures.[7] The clinical expert also highlights that in his view, the key unmet need is that many of the currently available treatments only offer eye protection and lubrication without targeting the cause of the disease, resulting in many current treatments to be unreliable.[7]

Table 1 Technology being appraised

Feature	Description
Brand name	Brand name: OXERVATE 20 µg/ml, eye drops, solution
Manufacturer	Dompé farmaceutici
Mechanism of action	Cenegermin is a recombinant form of human nerve growth factor (NGF), an endogenous protein involved in the differentiation and maintenance of neurons. NGF acts through specific NGF receptors, which are present in the anterior segment of the eye (cornea, conjunctiva, iris, ciliary body, lens), in the lacrimal gland, and in the posterior segment of the eye. Treatment with cenegermin, administered as eye drops, is intended to allow restoration of corneal integrity (corneal healing).[8]
European Union marketing indication	Cenegermin is indicated for the treatment of moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratitis (NK) in adults.[8]
Method of administration, dosage, storage and shelf-life	Cenegermin is available in sterile, preservative-free multi-dose Type I glass vials, closed with a rubber stopper and an aluminium overseal with a polypropylene flip-off cap, presented in cardboard cartons. 7 multi-dose vials are included per carton. At the pharmacy, the weekly carton containing the vials must be stored in a freezer at a temperature of -20°C ± 5°C. Cenegermin is issued to patients on a weekly basis as a carton containing seven vials of cenegermin in an insulated pack. As soon as the patient is at home (and no later than 5 hours from when the patient receives the product at the pharmacy), the weekly carton should be placed into the refrigerator, at a temperature of 2°C to 8 °C. Opened vials can be stored at room temperature and must be used within 12 hours after which the vial contents should be discarded, regardless of whether some residual product remains in the vial. Cenegermin is self-administered by the patient as an eye drop in the affected eye(s), six times a day at 2-hourly intervals, starting from the morning and within 12 hours. Treatment should be continued for 8 weeks. The product is to be used with a delivery system consisting of vial-adapters, disposable pipettes (used to withdraw product from the vial in order to administer one ocular drop) and disinfectant wipes, which is not part of the finished product and is supplied separately to the patient.
Safety concerns	The EMA stated: • Important identified risks: none • Important potential risks: serious corneal disorders The EMA highlighted the following missing information as safety concerns: • Use in patients with active ocular cancer • Use in patients with active eye infections • Use in patients with corneal melting or impending perforation requiring immediate surgery • Concomitant use with topical ophthalmic products that impair the healing process including corticosteroids and eye drops containing preservatives such as benzalkonium chloride polyquaternium-1, benzododecinium bromide, cetrimide and other quaternary ammonium derivatives • Off label use • Use with contact lenses • Long-term safety data.
Average cost	£14,500 for an 8 week course of treatment (based on list price).

CS=company submission; EMA=European Medicines Agency
Source: CS, adapted from Table 2 and EMA,[10] adapted from Sections 2.2.2, 2.2.3 and 2.7 (Tables 25 and 26)

2.4 Number of people with NK eligible for treatment with cenegermin

The company has not estimated the number of patients who would potentially be eligible for treatment with cenegermin each year. Incidence data for NK are not reported in the CS. Using prevalence data reported by the company (see Box 2 of this ERG report) and population data published by the Office for National Statistics,[11] as a crude estimate, the ERG calculates there are approximately 500 patients with stage 2 or stage 3 NK in England and Wales (Table 2). As noted in Box 2, the prevalence is estimated from some conditions associated with NK, namely keratitis after herpes infection (simplex or zoster) and after surgery for trigeminal neuralgia.[3] However, it should be noted that the percentage of NK cases caused by other conditions cannot be estimated because no data are available in the literature. The ERG further notes that the incidence of NK increases with age,[12] but the estimates of prevalence are not age-adjusted. Therefore, it is not possible to reliably estimate the number of patients with NK in England and Wales nor is it possible to reliably estimate the incidence and therefore the number of patients who may be eligible for treatment with cenegermin each year.

Table 2 Crude estimate of the number of patients with neurotrophic keratitis (NK)

Parameter	England	Wales	Source
Population (2016 mid-year estimate)	55,268,100	3,113,200	ONS 2017[11]
Prevalence of NK (1.6 per 100,000)*	884	50	Sachetti & Lambiase 2014[3]
Patients with stage 2 and stage 3 NK (50%)	442	25	Dompé 2017[5]

*Crude prevalence rate, not age-adjusted

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

A summary of the ERG's comparison of the decision problem outlined in the final scope issued by NICE and that addressed within the CS is presented in Table 3. Each parameter is discussed in more detail in the text following the table (Section 3.1 to Section 3.7).

Table 3 Comparison between NICE scope and company's decision problem

Parameter	Specification in the final scope issued by NICE	Summary of a comparison between the decision problem stated in the NICE scope and addressed in the company submission
Population	Adults with moderate (persistent epithelial defect) or severe (corneal ulcer) neurotrophic keratitis (NK).	As per the scope, reflecting the licensed indication for cenegermin.
Intervention	Cenegermin or recombinant human nerve growth factor (rhNGF).	rhNGF as cenegermin, at the licensed dose of 20 µg/ml one drop six times daily for 8 weeks.
Comparator (s)	Established clinical management without cenegermin (which may include treatment of any underlying causes, preservative free artificial tears, collagenase inhibitors, medical or surgical eyelid closure, serum eye drops, therapeutic contact lenses and surgery).	Evidence in the CS is presented versus vehicle (a proxy for artificial tears). The feasibility of comparisons with other interventions which may constitute established clinical management without cenegermin was explored by the company. Collagenase inhibitors were, however, considered inappropriate since they should only be considered when stromal melting is present.
Outcomes	Corneal healing, visual acuity (affected eye and both eyes), corneal sensitivity, need for further treatment or hospitalisation for NK, adverse effects of treatment, health-related quality of life.	As per the scope, all outcomes specified in the scope were explored in the CS.
Economic analysis	Cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. Time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. Cost effectiveness analysis should include consideration of the benefit in the best and worst seeing eye.	As per the scope. It is however noted by the company that it was not possible to conduct a cost effectiveness evaluation of cenegermin compared to treatments other than preservative-free artificial tears due to insufficient evidence. The company also notes that the cost effectiveness model does not differentiate between the best- and worst-seeing eye because NK is primarily a unilateral disease and the clinical evidence base for cenegermin largely excludes bilateral cases.
Subgroups	If evidence allows, separate consideration will be given to people with NK associated with progressive or non-progressive underlying causes. If evidence allows, consideration will be given to subgroups based on the stage or severity of the NK.	Subgroups based on people with progressive or non-progressive underlying causes were not explored by the company. It is stated in the CS that subgroups based on the stage or severity of NK have been explored. These findings were not reported in the CS but were requested by the ERG as part of the clarification process.

CS=company submission; ERG=Evidence Review Group; NICE=National Institute for Health and Care Excellence
Source: CS, adapted from Table 1 and Appendix D4

3.1 Population

Cenegermin is indicated for adults with moderate (persistent epithelial defect [PED]) or severe (corneal ulcer) NK, i.e. stage 2 or stage 3 NK. The population addressed by the company in the CS is identical to that specified in the final scope issued by NICE and for which cenegermin is licensed.

Cenegermin was licensed largely as a result of the findings from two randomised controlled trials (RCTs): the REPARO trial and Study 0214. While the ERG noted some differences in baseline characteristics within and across the cenegermin trials (see Section 4.4.2), the baseline characteristics of the patient populations of these trials appear to be similar to those who would be treated with cenegermin in NHS clinical practice.

3.2 Intervention

The intervention specified in the NICE scope is cenegermin or recombinant human nerve growth factor (rhNGF). The company has presented evidence for rhNGF as cenegermin, a type of eye drop, at the licensed dose of 20 µg/ml.[13,14] Cenegermin is intended to be administered six times daily for 8 weeks, as described in the Summary of Product Characteristics (SmPC).[8] Cenegermin has also been investigated at a dose of 10 µg/ml; these data are not considered relevant to the decision problem by the company or the ERG.

3.3 Comparators

Primary evidence in support of cenegermin in the CS is presented versus vehicle (which is considered to be a proxy for artificial tears). The feasibility of comparisons with other interventions which may constitute established clinical management without cenegermin was explored by the company. The interventions explored as possible comparators included surgical eyelid closure (tarsorrhaphy), conjunctival flap, keratoplasty, amniotic membrane transplant, serum eye drops and therapeutic contact lenses. A critique of the company's attempt to compare cenegermin with these other treatment options is provided in Section 4.8.

Although specified as a comparator in the final scope issued by NICE, the company states that collagenase inhibitors should only be considered when stromal melting is present. Since cenegermin is not indicated for use in patients who have stromal melting, collagenase inhibitors were not, therefore, included as a comparator in the CS. The ERG concurs with the company.

The ERG considers that the company has made every effort to explore the evidence base for cenegermin versus established clinical management. The ERG agrees with the company that the vehicle used in the trials of cenegermin is similar in its composition to artificial tears as it

contains ingredients widely used in commercially available preservative-free artificial tears. However, the ERG highlights that for patients with stage 2 or stage 3 NK, artificial tears would rarely be used alone but, rather, alongside another treatment. Clinical advice given to the ERG suggests that perhaps the most appropriate comparators to cenegermin for patients with stage 2 or stage 3 NK would be amniotic membrane transplantation or serum eye drops (autologous or allogenic).

3.4 Outcomes

All outcomes specified in the final scope issued by NICE were explored in the CS. Corneal healing is considered by the company to be the most clinically relevant outcome measure for assessment of clinical effectiveness. As described by the company (CS, p15; see also Box 1 of this ERG report) and in the National Institute for Health Research (NIHR) Horizon Scanning Research & Intelligence Centre briefing document,[15] the aim of treatment for NK is to prevent progression of corneal damage and to promote epithelial healing.[16] Therefore, the ERG considers that corneal healing is the most appropriate outcome for measuring the efficacy of cenegermin. The ERG further notes that corneal healing is a common outcome in trials of eye diseases although notes the comment from a clinical expert that it is not consistently defined in all trials.[7]

Visual acuity (affected eye and both eyes) is specified as a secondary outcome for clinical efficacy. The company highlights that visual acuity is often unaffected in NK[4] and therefore, in contrast to many other ocular diseases, visual acuity is not the primary concern (CS, Table 1 and p89). The exception, as highlighted by the company, is where NK progresses to a large area of corneal ulceration or to stromal melting. Thus, the risk to vision in NK is not from progressive incremental loss of visual acuity but from progression of staging of NK disease. Progression of NK may result in corneal scarring and/or the need for surgical procedures which in turn may result in a loss of vision and potentially anatomical loss of the eye. The company highlights (CS, p15) that these consequences can be averted by prompt healing of the corneal lesion(s). Thus, provided that permanent corneal damage can be prevented, acuity should return to a normal or correctable state after healing.

Another secondary outcome specified in the NICE scope is corneal sensitivity. As highlighted by the company (CS, p15; see also Box 1 of this ERG report), the hallmark of NK is a decrease or absence of corneal sensation.[3] Clinical advice given to the ERG indicates that regaining corneal sensitivity is an important part of the healing process when treating NK.

Regarding other secondary outcomes, the ERG notes that while the need for further treatment or hospitalisation for NK was not an explicitly defined outcome measure by the company,

outcomes explored in the CS include deterioration and recurrence of NK, both of which would result in further treatment. Adverse effects (AEs) and health-related quality of life (HRQoL) associated with treatment were also explored by the company.

3.5 Economic analysis

As specified in the final scope issued by NICE, the cost effectiveness of treatments was expressed in terms of the incremental cost per quality adjusted life year (QALY) gained. Outcomes were assessed over a lifetime horizon (age of cohort reaching 100 years) and costs were considered from an NHS perspective.

It is noted by the company that it was not possible to conduct a cost effectiveness evaluation of cenegermin compared to treatments other than preservative-free artificial tears. It was further noted that the cost effectiveness model does not differentiate between the best- and worst-seeing eye. This is because NK is primarily a unilateral disease[2] and the clinical evidence base for cenegermin largely excludes bilateral cases.

3.6 Subgroups

In the final scope issued by NICE, it is stated that if evidence allows, separate consideration will be given to people with NK associated with progressive or non-progressive underlying causes. Subgroups based on people with progressive or non-progressive underlying causes were not explored by the company who stated (CS, Table 1) that they were advised by clinical experts that they never classify NK as progressive or non-progressive. Clinical advice to the ERG is that results from such a subgroup analysis could be useful and inform clinical decision making as patients with progressive disease may respond less favourably. The company acknowledges, however, that understanding the underlying causes of NK is important in management. Indeed, subgroup analyses were explored in the EMA Committee for Medicinal Products for Human Use (CHMP) European Public Assessment Report (EPAR)[10] based on underlying aetiology. The company considers there are however no data to support progressive or non-progressive subgroups in terms of differential approach to sequencing off label, unlicensed or surgical treatment options.

It is also stated in the final scope issued by NICE that if evidence allows, consideration will be given to subgroups based on the stage or severity of the disease. It is stated in the CS that subgroups based on the stage or severity of NK were explored. These findings were not reported in the CS but were provided by the company for the outcome measure of corneal healing during the clarification process.

3.7 Other considerations

The company does not anticipate that the use of cenegermin for the treatment of NK will give rise to any equality issues. On the other hand, the company notes that, currently, while surgical treatments for NK tend to be avoided where possible due to their potentially disfiguring effect, these are often required due to the unavailability of alternative therapies (in particular, autologous serum eye drops) at some centres (CS, pp20-21; see also Box 2 of this ERG report). The use of a licensed treatment such as cenegermin, if it is accessible to all patients with stage 2 or stage 3 NK, may therefore reduce inequalities across England and Wales.

The company also report that, based on telephone interviews with 12 UK clinical experts,[5] patients are typically seen once a week for moderate NK and more frequently for severe NK. Given that many specialist centres are likely to have wide catchment areas, there may currently be issues in terms of access to treatment (e.g. feasibility of being able to travel to attend specialist centres) for patients living at the outer reaches of these catchment areas. Given that cenegermin would be issued to patients weekly (via an outpatient appointment) and/or patients typically see a corneal specialist once a week until corneal healing (CS, p19) then the ERG notes that these issues may remain for some patients even if treatment with cenegermin was available.

4 CLINICAL EFFECTIVENESS

The company carried out a systematic review in July 2015 to identify published clinical trials investigating the efficacy and safety of cenegermin for the treatment of people with NK. The company updated the searches in August 2017 to identify evidence published since the original review was conducted.

The company also conducted a 'clinical extension review' in August 2017. The company states the aim of this review was to identify published clinical trials considering patients with NK as a subgroup of the overall population (CS, p22). This search was used to inform a mixed treatment comparison (MTC).

4.1 Review methods

4.1.1 Literature search methods

The electronic databases searched included Embase, MEDLINE and the Cochrane Library. Electronic searches were supplemented by hand searching the reference lists of included publications, relevant conference proceedings, and additional websites recommended by NICE, including clinicaltrials.gov for ongoing studies. Full details of the sources and search strategies used for the systematic review are reported in the CS, Section B.2.1 and Appendix D2. Full details of the sources and search strategies used for the 'clinical extension review' are reported in the CS, Appendix D3.

While the company appears to have searched relevant conference proceedings and clinical trial websites, it is stated that all of the databases were searched via the Ovid interface. However, it is not possible to search the Cochrane Library via the Ovid interface. It is therefore unclear if the company conducted its searches using the Cochrane Library interface or not at all. There are also some syntax errors with regard to the translation of the search strategies between databases, for example, the Cochrane Library interface does not use '.mp', 'adj' or 'exp' for the MeSH terms, therefore any search lines using these commands do not execute correctly in the Cochrane Library interface.

The ERG notes that fewer search terms were used in the 'clinical extension review' than employed in the systematic review. The ERG considers this simplified strategy to be no less effective in the identification of relevant studies. One syntax error was however found by the ERG, the term 'allogeneic' was spelt 'allogenic' which may have resulted in relevant studies being missed.

Overall, the ERG considers that the company's searches were carried out to an adequate standard, however they could have been executed more consistently with the relevant terms

included in all of the search strategies and using the correct database interface. The searches were relevant to the disease (NK) and treatments for the disease described in the final scope issued by NICE.

4.1.2 Eligibility criteria

The pre-defined eligibility criteria for the clinical systematic review is outlined in the CS, Table 2 of Appendix D2. The defined population was broader than that defined in the decision problem in that it included patients with stage 1 NK as well as patients with stage 2 and stage 3 NK. Studies that included other diseases were also eligible for inclusion in the review but only if at least five patients with NK were enrolled in the study. The types of studies to be included were RCTs, observational studies and case series. The ERG considers that the eligibility criteria were appropriate to the decision problem set out in the final scope issued by NICE.

The eligibility criteria for the 'clinical extension review' are presented in the CS, Table 4 of Appendix D3. The main difference between the eligibility criteria employed for the 'clinical extension review' and the systematic review is that the population for the 'clinical extension review' was specified as follows: "Patients with persistent epithelial defects, corneal ulcers, corneal melting, or corneal perforation (not restricted by age) – patients with NK should be considered as a sub-group". It is apparent from the CS (p22) that what the company means is that for a study to be eligible for inclusion in the 'clinical extension review', relevant outcome data were required for at least one NK patient.

Identified studies were independently assessed by two reviewers and any discrepancies were resolved by a third party. The ERG considers that the process for identifying studies to be included in the systematic review and 'clinical extension review' was appropriate.

4.1.3 Data extraction

After applying the eligibility criteria to the full-text papers, all of the papers meeting the inclusion criteria were retained for data extraction. Data were extracted by two reviewers independently. In cases of disagreement, the full-text paper was examined and reviewed by both reviewers until they reached an agreement. The ERG considers that the data extraction strategy was appropriate.

4.1.4 Quality assessment methods

The company carried out a risk of bias assessment for all of the studies included in their systematic review and 'clinical extension review' using approaches recommended by NICE.[17,18] Quality assessment was only completed for studies presented as full-text

publications since it was considered that the studies reported only as abstracts lacked sufficient detail to be appropriately assessed for quality. Results from the company's quality assessment exercise are reported in the CS, Appendix D2 and Appendix D3.

4.1.5 Data synthesis

Most of evidence presented in the CS is from studies which examined cenegermin in patients with NK. In addition to presenting data for each of the cenegermin RCTs separately, the company also pooled the data describing corneal healing from the two trials (see Sections 4.4.5 of this ERG report).

Data from studies which investigated other interventions for NK were reported in the appendices of the CS: Appendix D2 reports on the conduct and findings from the systematic review and Appendix D3 reports on the conduct and findings from the 'clinical extension review', including findings from the MTC (see also Section 4.8 of this ERG report for more information).

4.1.6 Critique of the review methods

Overall, the ERG considers the methods used to conduct the clinical effectiveness systematic review and 'clinical extension review' to be satisfactory.

4.2 Identified studies

The company's searches identified studies of cenegermin and studies of comparator treatments. Because of problems with conducting a MTC (as described in Section 4.8 of this ERG report), only the studies of cenegermin were considered to provide reliable evidence of clinical effectiveness for the current appraisal.

4.2.1 Studies of cenegermin

The searches conducted by the company identified two phase 2 RCTs of cenegermin, the REPARO trial and Study 0214. The results of these studies have not been published in full in a peer-reviewed journal. Limited data for the REPARO trial have been recently presented as a conference abstract,[19] and data from this trial were also reported in 2014 as conference abstracts,[20,21] prior to the trial being completed. Alongside the CS, the company made available the clinical study report (CSR)[13] and CSR final addendum for the REPARO trial.[22] For Study 0214, the company also made available the final CSR[23] and an addendum.[24] Both the RCTs of cenegermin compared cenegermin with vehicle, the latter is considered by the company to be a proxy for artificial tears.

4.2.2 Studies of comparator treatments

Brief details of the studies of the comparator treatments included in the company's systematic review, 'clinical extension review' and for consideration in the MTC are given in the appendices to this ERG report, Sections 9.1 to 9.3.

4.3 Key characteristics of the included trials of cenegermin

4.3.1 Trial characteristics

Two doses of cenegermin were investigated in the REPARO trial. Data from patients receiving a cenegermin dose other than the licensed dose of 20 µg/ml have not been considered in the CS or in this ERG report. Excluding 52 patients treated at the unlicensed dose (10 µg/ml), the REPARO trial included approximately twice as many patients relevant to the decision problem as Study 0214. Unlike in the REPARO trial, the cenegermin and vehicle formulations in Study 0214 included methionine. Methionine was added as an anti-oxidant due to concerns that oxidation could have affected the stability of cenegermin. It is the formulation of cenegermin including methionine, as used in Study 0214, which has been approved for use in clinical practice. As noted by the company (CS, p20), regardless of whether methionine was included as an excipient in the vehicle arm, vehicle in both trials was nonetheless similar in composition to preservative-free artificial tears. Thus, effectively, in both trials, the treatment arm was cenegermin *in addition to* preservative-free artificial tears, and the comparator arm represents preservative-free artificial tears only. Although the REPARO trial was conducted in 32 centres in six European countries, and Study 0214 was conducted in the US, in most other respects, the characteristics of the trials were very similar (Table 4). In particular, the ERG notes that outcomes relevant to the decision problem were reported in both trials, using the same outcome definitions across trials.

Table 4 Summary of study characteristics of the REPARO trial and Study 0214

Parameter	REPARO (N=156)[a]	Study 0214 (N=48)
Intervention	Cenegermin (n=52)[a]	Cenegermin (n=24)
Comparator	Vehicle (n=52)	Vehicle (n=24)
Concomitant medications	Some preservative-free topical antibiotics and preservative-free artificial tears were permitted by the trial protocols. Other topical ophthalmic medications were not permitted.	
Settings	Specialist treatment centres (University hospital eye centres, or similar).	
Study type and location	Phase 1/2 double-masked RCT conducted across 32 sites across Europe (Italy, Germany, UK, France, Spain, Poland).	Phase 2 double-masked RCT conducted across 11 sites in the US.
Eligibility criteria	Adults with unilateral stage 2 or stage 3 NK with corneal ulcer and refractory to one or more previous conventional non-surgical treatments were included. Patients with prior surgical procedures for NK and patients with corneal melting or perforation were excluded.	Adults with bilateral stage 2 or stage 3 NK with corneal ulcer and refractory to one or more previous conventional non-surgical treatments were included.[b] Patients with prior surgical procedures for NK and patients with corneal melting or perforation were excluded.
Outcomes relevant to the decision problem	Corneal healing, visual acuity, corneal sensitivity, deterioration NK, recurrence of NK, adverse effects of treatment and health-related quality of life.	

a Two doses of cenegermin were investigated in the REPARO trial. The CS and this ERG report data only for the 20 µg/ml dose since this is the licensed dose (which was also the dose used in Study 0214). An additional 52 patients did however receive cenegermin at a dose of 10 µg/ml in the REPARO trial, hence N=156 for this trial
b Although Study 0214 permitted the enrolment of patients with bilateral NK, only one of the eyes was included in the study (the worst-seeing eye)
Source: CS, adapted from Table 6

In addition to the controlled treatment period, for some patients, both trials also included an uncontrolled 8 week treatment period and an extended follow-up period (48 weeks in the REPARO trial, 24 weeks in Study 0214). For more information about the trial design (including the controlled, uncontrolled and extended follow-up periods, outcome definitions and time points the outcomes were collected), see Section 4.3.2 of this ERG report.

4.3.2 Statistical approach adopted

In this section, the ERG provides a description and critique of the statistical approaches used to analyse data collected during the REPARO trial and Study 0214 that relate to the outcomes stipulated in the final scope issued by NICE. Information relevant to the statistical approach taken by the company has been extracted the CSRs and CSR addendums, the trial protocols, [25,26] the trial statistical analysis plans (TSAPs)[27,28]and the CS.

The REPARO trial design

The REPARO trial was a three-arm, double-masked, randomised, multicentre, parallel group study with a phase 1 and phase 2 segment. The phase 1 segment of the trial was not randomised and not relevant to the submission so is not discussed further within this ERG report; a summary of phase 1 results can be found in the CS, Appendix L. The phase 2 segment of the REPARO trial was made up of three distinct periods (as displayed in Figure 2 of the CS). In summary:

1. *Controlled treatment period.* Patients were randomised 1:1:1 to cenegermin 10 µg/ml, 20 µg/ml or vehicle, one drop, six times per day for 8 weeks. Except for patients who deteriorated on treatment with cenegermin during the 8 weeks, who discontinued the study, patients could then either enter an uncontrolled treatment period and/or an extended follow-up period, as described below.

2. *Uncontrolled treatment period.* Only patients randomised to vehicle and who either deteriorated within 8 weeks of starting the controlled treatment period or who did not achieve corneal healing at the end of 8 weeks could enter the uncontrolled treatment period. All patients were reassigned to treatment with cenegermin 10 µg/ml or 20 µg/ml for 8 weeks (dose predefined according to the baseline randomisation scheme) during this period.

3. *Extended follow-up.* Following the 8 week controlled period, patients in the cenegermin arm who were completely healed and patients who were not completely healed (but who had not deteriorated either) entered the 48 week extended follow-up period. Patients in the vehicle arm who had deteriorated during the 8 week controlled period

and those who were not completely healed at the end of the 8 week treatment period entered the 8 week uncontrolled treatment period before entering the 48 week extended follow-up period following. The only patients randomised to vehicle who entered the extended follow-up period without the need for an uncontrolled treatment period were patients who achieved corneal healing during the controlled treatment period.

During this period, additional treatment with cenegermin was available for patients who had previously achieved complete healing with cenegermin or vehicle but who had a recurrence during the extended follow-up period. In total, therefore, the maximum follow-up time for those initially randomised to cenegermin was 56 weeks and for those initially randomised to vehicle was 64 weeks (including the second 8 week uncontrolled treatment period with cenegermin).

Study 0214 trial design

The design of Study 0214 was the same as the phase 2 segment of the REPARO trial, with the exception that:

1. Only treatment with cenegermin 20 µg/ml and vehicle were evaluated (and hence patients were initially randomised 1:1 to cenegermin or vehicle).

2. All patients who entered the uncontrolled treatment period received the licensed dose of cenegermin, i.e. 20 µg/ml (since the 10 µg/ml was not evaluated in this trial).

3. The extended follow-up period was 24 weeks rather than 48 weeks.

Therefore, the maximum follow-up for those initially randomised to cenegermin was 32 weeks and for those initially randomised to vehicle was 40 weeks (including the second 8 week uncontrolled treatment period with cenegermin). The study design and treatment periods are displayed in Figure 4 of the CS.

Outcomes and analysis approach in the included trials

The primary (null) hypothesis of the REPARO trial and Study 0214 was that there was no association between treatment with cenegermin or vehicle and response (corneal healing at 4 weeks or at 8 weeks respectively).

Definitions and methods of statistical analysis for the primary efficacy outcomes of the REPARO trial and Study 0214 are outlined in Table 5.

Table 5 Definition and analysis method for primary efficacy outcomes of the REPARO trial and Study 0214

Study	Outcome definition	Statistical analysis
REPARO	Percentage of patients experiencing corneal healing (defined as greatest diameter of the corneal fluorescein staining in the area of the PED or corneal ulcer being <0.5 mm) at Week 4, as determined by the central reading centre	Each comparison was conducted using a 2x2 Chi-squared test based on the null hypothesis of no association between treatment (with cenegermin 20 µg/ml, cenegermin 10 µg/ml or vehicle) and response (corneal healing at Week 4). As REPARO was a three-arm trial, the significance level of the Chi-squared test was corrected for multiplicity using the Pocock method,[29] and the two-sided significance level α for statistical tests was 0.0294.
Study 0214	[redacted] • Percentage of patients experiencing corneal healing (lesion size <0.5 mm, see definition above) at Week 8 by central reading centre • [redacted]	Corneal healing was analysed with a 2x2 Chi-squared test with a two-sided significance level of 0.10 to compare patients receiving 20 µg/ml cenegermin formulation to patients receiving vehicle.

µg=micrograms; ml=millilitres; mm=millimetres; PED=persistent epithelial defect
Source: CS adapted from Table 5, Table 6 and Table 8

Within the final TSAPs of both studies, the primary efficacy outcome (corneal healing) was predefined as being the greatest diameter of the corneal fluorescein staining in the area of the persistent epithelial defects (PED) or corneal ulcer that is <0.5 mm (Table 6). The company states that the definition had been agreed with the EMA to reflect the small areas of superficial corneal staining that would commonly be observed in healthy individuals.[30-32] Within an amendment to the protocol of Study 0214 (amendment date 19th April 2016), at the request of the US Food and Drug Administration (FDA), an additional [redacted] endpoint of corneal healing (also referred to as 'Completely Staining Free') was defined post-hoc as "no residual fluorescein staining in the area of the corneal lesion (0 mm) and no persistent staining elsewhere in the cornea", where persistent staining was defined as "staining not changing in shape and/or location of different time points." This additional [redacted] endpoint required an additional TSAP and results for this endpoint were reported in an addendum to the final CSR

of Study 0214. This additional endpoint was also included in a post-hoc analysis of data from the REPARO trial that was presented in the CS; the details are reproduced in Table 6 of the ERG report.

Within both studies, assessments of corneal healing were performed by assessors at a central reading centre who evaluated the clinical pictures of corneal fluorescein staining. These assessors were masked to the treatment arm from which the pictures of corneal fluorescein staining were derived.

Investigators also made assessments of corneal healing. The corneal healing findings assessed by investigators were included as a sensitivity analysis of both trials.

Definitions and methods of statistical analysis for important secondary efficacy outcomes of the REPARO trial and Study 0214 used within the economic model or relevant to the final scope issued by NICE are outlined in Table 6. Further details of other outcomes and time points measured within the studies during the controlled treatment periods and uncontrolled treatment periods are available in Table 3 and Table 5 of the CS.

The ERG is satisfied that the outcome definition and the analysis method for each of the pre-planned secondary efficacy outcomes were pre-specified in the final TSAP of each trial, and that all results are reported fully in the final CSRs of each trial.

Patient reported endpoints (i.e. HRQoL) and safety endpoints (i.e. AEs) were also measured in the REPARO trial and Study 0214. Further details of these outcomes are described in Section 4.6 and Section 4.7 of this ERG report respectively.

Table 6 Definition and analysis method for secondary efficacy outcomes of the REPARO trial and Study 0214

Outcome	Definition	Statistical analysis
Corneal healing [a]	• Percentage of patients experiencing corneal healing (defined as greatest diameter of the corneal fluorescein staining in the area of the PED or corneal ulcer being <0.5 mm) at Week 8, as determined by the central reading centre (REPARO only) and by the investigator (both studies) • Post-hoc analysis (REPARO trial only): In patients with lesion size 0 mm in the main analyses, the percentage of patients experiencing corneal healing was reanalysed under the FDA defined end point of 'no residual fluorescein staining in the area of the corneal lesion (0 mm) and no persistent staining elsewhere in the cornea' • Percentage of patients achieving corneal healing by Week 8/16 that remain healed (i.e. no recurrence of the PED and/or corneal ulcer) at Weeks 32/40 and 56/64	Corneal healing at Week 8 was analysed by 2x2 Chi-squared tests with adjustment for multiplicity in the REPARO trial as described in Table 5 and also at a two-sided significance level of 0.05 for both the REPARO trial and Study 0214 No formal statistical testing of data collected during the extended follow-up period was planned or conducted
Complete corneal clearing [a]	Percentage of patients experiencing complete corneal clearing (Grade 0 on the modified Oxford scale, i.e. no residual corneal staining) at 8 weeks	Analysed as described above for corneal healing at Week 8
Visual acuity[a]	• Mean change in BCDVA from Baseline to Week 8 • Percentage of patients achieving a ≥15 letter gain in BCDVA at 8 weeks	• Mean change in BCDVA from baseline to Week 8 was analysed using an ANCOVA model with treatment and baseline BCDVA score as fixed effects. Only ITT patients with baseline and Week 8 BCDVA scores were included in the model. • Percentage of patients achieving a ≥15 letter gain in BCDVA at 8 weeks was analysed as described above for corneal healing at Week 8
Corneal sensitivity [a]	Percentage of patients achieving an improvement in corneal sensitivity as measured by the Cochet-Bonnet aesthesiometer at 8 weeks	Analysed as described above for corneal healing at Week 8
Deterioration in NK [a]	Increase in lesion size ≥1mm, decrease in BCDVA by >5 ETDRS letters, progression in lesion depth to corneal melting or perforation, onset of infection, or 'other' (as reported on the electronic case report form) from Baseline or from a prior visit to Week 8.	Analysed as described above for corneal healing at Week 8

[a] The secondary outcomes considered within REPARO and Study 0214 were the same, with the exception that corneal healing at 8 weeks was one of the [redacted] endpoints of Study 0214 rather than a secondary outcome and that endpoints were not measured to 56/64 weeks in Study 0214

ANCOVA=analysis of covariance; BCDVA=best corrected distance visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; FDA=Food and Drug Administration; ITT=intention-to-treat; mm=millimetres; PED=persistent epithelial defect

Source: CS, Table 5, Table 6 and Table 8; REPARO TSAP; Study 0214 TSAP

ERG critique of statistical approach

A summary of the additional checks made by the ERG in relation to the pre-planned statistical approach used by the company to analyse data from the included trials is provided in Table 7. Having carried out these checks, the ERG considers that the pre-planned statistical approach employed by the company is mostly adequate, however, the ERG is concerned about the use of the Last Observation Carried Forward (LOCF) method in the primary and secondary efficacy analyses due to the biases associated with this method which ignores uncertainty introduced by missing response data[33] and the relatively large amount of missing data in these trials. The ERG considers the multiple imputation approach used in sensitivity analysis described by the company, which is more statistically powerful and captures the uncertainty introduced by the missing outcome data to be the most appropriate method of handling missing data in these trials.

The ERG acknowledges that the results of the sensitivity analyses of the primary efficacy endpoints do not lead to different conclusions regarding the comparative clinical effectiveness of cenegermin and vehicle and provide numerically similar estimates of treatment effect (see Table 12 of this ERG report and Section 4.5.1 for further discussion).

Table 7 ERG assessment of statistical approach used to analyse data from the REPARO trial and Study 0214

Component	Statistical approach with ERG comments
Analysis populations	The analysis populations of the REPARO trial and Study 0214 are reported in Table 8 of the CS. These populations were predefined on p34 of REPARO TSAP and on p18 of Study 0214 TSAP. Efficacy outcomes were analysed within the ITT population, defined as all randomised patients regardless of when they withdrew from the study and summarised according to the treatment to which they were randomised. In Study 0214, one patient withdrew at the time of randomisation and was not included in the analysis. Due to missing data, the denominators of patients used within analyses were the number of patients with an observation available (including LOCF, see 'Treatment of missing data' for further details). Safety outcomes were analysed within the safety population defined as all randomised patients who received at least one dose of study medication and summarised by actual treatment received.
Treatment of missing data	For the primary efficacy analysis of the primary endpoint(s) in both studies, missing data were imputed using LOCF methodology (i.e. the last post-baseline observation was carried forward in analysis up to and including the Week 8 visit). If no post-baseline observation was available, the patient was not included in the denominator for the analysis. LOCF methodology was also used for the secondary efficacy endpoints. Observed cases analyses as well as two sensitivity analyses were also planned for the primary endpoints. Firstly, all missing data at any visit (regardless of reason for missing data) were imputed as a treatment failure (i.e. not experiencing corneal healing). Secondly, a multiple imputation method[34] was used to replace missing values, taking account of any preceding measurement values as well as gender and age. The ERG is satisfied that the methodology for handling missing data was pre-specified (REPARO TSAP p54, 61-62 and Study 0124 TSAP p36) and that results for all analyses relating to missing data are reported in the final CSRs (REPARO CSR p130-132,135-139 and Study 0214 p93 and company response to ERG clarification letter). The ERG is concerned about the use of LOCF method in the primary and secondary efficacy analyses due to the biases associated with this method.[33] The ERG considers the multiple imputation approach used in sensitivity analysis described by the company to be the most appropriate method of handling missing data in these trials. The ERG acknowledges that results of sensitivity analyses of the primary efficacy endpoints do not lead to different conclusions regarding the comparative clinical effectiveness of cenegermin and vehicle and provide numerically similar estimates of treatment effect (see Table 12 of this ERG report), it is unlikely that the approach to handling missing data has introduced bias into the results of the primary efficacy outcomes of the REPARO trial and Study 0214.
Protocol amendments	All protocol amendments were provided by the company, in addition to the original protocol and the final protocol with all amendments incorporated for each study. The rationale for amendments and details of changes made to the protocol and TSAPs for both studies are clearly outlined. The ERG notes that for both studies, particularly Study 0214, amendments have been made to the primary efficacy outcome based on scientific advice provided by the EMA and the FDA. The largest amendment to Study 0214 (Amendment 3, 19th April 2016) required additional analyses in a separate TSAP (not provided to the ERG) to introduce an additional [redacted] endpoint "Completely Staining Free." Results of this endpoint were reported in an addendum to the final CSR of Study 0214. This endpoint was also presented for the REPARO trial as a post-hoc analysis in the CS. The ERG is satisfied with the rationale for the amendments and that all amendments were made before the study completion dates (date of last subject last visit for the REPARO trial was [redacted], CSR, p1 and date of last subject last visit for Study 0214 was [redacted], CSR, p1). Therefore amendments were unlikely to have been driven by the results of the trial.

Component	Statistical approach with ERG comments
Sample size calculation	The sample size calculations of the REPARO trial and Study 0214 are reported in Table 8 of the CS. These sample size calculations were pre-specified on p56 of REPARO TSAP and p64 of Study 0214 protocol. The sample size for the REPARO trial was conservatively based on the corneal healing rates of cenegermin and vehicle in [redacted] and the sample size for Study 0214 was based on the [redacted]. The ERG is satisfied that the sample size calculations were appropriate and pre-specified. The ERG notes that the sample size calculation of Study 0214 specified that the study was powered to a one-sided significance level of 5%, which was amended to a two-sided significance level of 10% in the final TSAP.
Pre-planned subgroup analyses	A pre-planned subgroup analysis was specified on p62 of the REPARO TSAP for primary and secondary analyses relating to corneal healing in patients with and without punctual occlusion. Results of this subgroup analysis are presented on p132 and p140 of the CSR. Post-hoc subgroups by specific aetiologies of NK were also specified in an addendum to the REPARO TSAP (p6) and results of these subgroup analysis are presented on p151-152 of the CSR. No subgroups were defined in the TSAP of Study 0214 (p18).
Pre-planned sensitivity analyses	Sensitivity analyses were pre-planned for handling of missing data for both studies (see 'Treatment of missing data' above for further details). No further sensitivity analyses were planned or presented for the REPARO trial. For Study 0214, an additional post-hoc sensitivity analysis excluding a site with suspected non-compliance and enrolment problems was conducted. Results of this sensitivity analysis are presented on p93-94 of the CSR.
Analysis of PROs	Both studies measured the change in NEI-VFQ-25 25 and EQ-5D (quality of life and health state questionnaires) scores from Baseline to Week 8. These analyses were pre-defined on p51-52 of REPARO TSAP and on p28 of Study 0214 TSAP. Summary results (mean, median, SD, SE, minimum and maximum scores at baseline and change from baseline at 8 weeks) are reported in Table 11 and Table 12 of the CS and discussed in Section 4.8 of this ERG report.
Analysis of AEs	Many different summaries of AEs are provided in the CSRs of both studies. All AEs, TEAEs, SAEs, deaths and AEs leading to treatment discontinuation are summarised by treatment arm, by study time period (controlled treatment period or extended follow-up period), by severity and by system organ class. Pre-specified TEAEs are presented separately. Number of events and number of patients experiencing an event are presented. The ERG is satisfied that the methodology used to analyse the AEs is appropriate and was pre-specified in the TSAPs (p52 of the REPARO TSAP and p37 of the Study 0214 TSAP) and that all summary tables of AEs are presented within the CSRs (p162-185 of the REPARO CSR and p112-125 of Study 0214 CSR).

AE=adverse event; CS=company submission; CSR=clinical study report; EMA=European Medicines Agency; EQ-5D=EuroQoL group 5 dimension; ERG=Evidence Review Group; FDA=Food and Drug Administration; ITT=intention-to-treat; LOCF=last observation carried forward; NEI-VFQ-25= National Eye Institute Visual Functioning Questionnaire; PRO=patient-reported outcome; SAE=serious adverse events SD=standard deviation; SE=standard error; SF-36=36 item short form; TEAE=treatment emergent adverse event; TSAP=trial statistical analysis plan
Source: adapted from the CS, REPARO CSR, REPARO protocol, REPARO TSAP, Study 0124 CSR and addendum, Study 0124 protocol, Study 0214 TSAP, the company's response to the ERG clarification letter, and ERG comment.

4.4 Characteristics of patients enrolled in the included trials

4.4.1 Patient disposition

Table 8 summarises the participant disposition and reasons for withdrawal at Week 8 in the REPARO trial and Study 0214 according to baseline randomised treatment. The most common reason given for study withdrawal for patients treated with cenegermin in both trials was experiencing an AE. For patients in the vehicle arms, the most common reason was given as "other".

Table 8 Participant disposition and reasons for withdrawal at Week 8 in the REPARO trial and Study 0214 according to baseline randomised treatment

	REPARO		Study 0214	
	Cenegermin	**Vehicle**	**Cenegermin**	**Vehicle**
Randomised at baseline	52	52	24	24
Completed 8 week controlled treatment period: n (%)[a]	39 (75%)	48 (92.3%)	18 (75%)	15 (62.5%)
Withdrawn from the study before or at Week 8: n (%)[a]	13 (25%)	4 (7.7%)	6 (25%)	9 (37.5%)
Primary reason for withdrawal				
Adverse event: n (%)[b]	9 (69.2%)	1 (25%)	4 (66.7%)	3 (33.3%)
Lack of efficacy / inadequate control of NK: n (%)[b]	1 (7.7%)	0 (0%)	0 (0%)	0 (0%)
Terminated and entered uncontrolled period (vehicle arm only): n (%)[b]	NA	0 (0%)	NA	6 (66.7%)
Other: n (%)[b,c]	3 (23.1%)	3 (75%)	2 (33.3%)	0 (0%)

a Denominator of the percentages is the number randomised at baseline
b Denominator of the percentages is the number of participants withdrawn from the study before or at Week 8
c Other reasons for withdrawal are listed in the final CSRs of REPARO (Listing 16.2.1b) and Study 0214 (Text Figure 2) and included: decision unrelated to an adverse event, [redacted]
NA=not applicable; NK=neurotropic keratitis
Source: CS, adapted from Appendix D1: Table 1, Table 2 and Figure 1. REPARO CSR Listing 16.2.1b

The REPARO trial

A total of 156 participants were randomised at baseline in phase 2 of the REPARO trial; 52 to cenegermin 20 µg/ml, 52 to cenegermin 10 µg/ml and 52 to vehicle. As the licensed dose of cenegermin is 20 µg/ml, no further information is presented regarding the disposition of the cenegermin 10 µg/ml arm in this ERG report. Henceforth cenegermin 20 µg/ml is referred to as cenegermin for brevity.

As shown in the CS, Appendix D1 (Table 1), out of the 104 participants randomised to cenegermin or vehicle, a total of 17 participants (16.3%) withdrew before or at Week 8 (the end of the controlled treatment period); 13 (25%) from the cenegermin arm and 4 (7.7%) from the vehicle arm. In the company response to the ERG clarification letter, the company stated that in the cenegermin arm, [redacted] withdrawals occurred at Week 8 and [redacted]

withdrawals occurred before week 8. [redacted].

In the company response to the ERG clarification letter, the company states that including both the healed and non-healed patients at Week 8, 39 (75%) patients entered the 48 week follow-up in the cenegermin arm and 33 (84.6%) of these patients completed the 48 week follow-up; 22 (39.3%) patients entered the 56 week follow-up in the vehicle arm and 16 (72.7%) of these patients completed the 56 week follow-up. The ERG interprets the 48 week follow-up referred to by the company to be the extended follow-up without the uncontrolled treatment period (i.e. total of 56 weeks follow-up) and the 56 week follow up period to be the extended follow-up with the uncontrolled treatment period (i.e. total of 64 weeks follow-up). However, from the CS, Appendix D1 (Table 1), the ERG observes that 25 (48.1%) patients in the vehicle arm entered the 48 week follow-up and 22 (57.9%) completed the 48 week follow-up. The ERG notes that if the 48 week follow-up referred to is the same as the extended follow-up without the uncontrolled treatment period, then the number of patients entering this period should be equivalent to the number of patients who achieved corneal healing in this arm, as only these patients from the vehicle arm were eligible for this period. However, the number of patients entering this period actually exceeds the number who achieved corneal healing after 8 weeks (see Section 4.5.2, Table 12 of this ERG report).

Study 0214

A total of 48 participants were randomised in Study 0214; 24 to cenegermin and 24 to vehicle. As shown in the CS, Appendix D1 (Figure 1), out of the 48 participants randomised to vehicle or cenegermin, a total of 15 participants (31.3%) withdrew before or at Week 8 (the end of the controlled treatment period); 6 (25%) from the cenegermin arm, including one patient that withdrew at the time of randomisation and was not included in the analysis and 9 (37.5%) from the vehicle arm. [redacted] (company response to the ERG clarification letter, Table 14.1-1.4).

In the company response to the ERG clarification letter, the company confirms that, as partially shown in the CS, Appendix D1 (Figure 1), 18 (75%) patients treated with cenegermin entered the extended follow-up period and [redacted] of these patients completed it (i.e. total of 32 weeks follow-up). In the vehicle arm, 8 (33.3%) patients entered the extended follow-up period without first entering the uncontrolled treatment period and all [redacted] completed it (i.e. total of 32 weeks follow-up). A further 13 (54.2%) patients initially randomised to vehicle entered the uncontrolled treatment period and extended follow-up period and [redacted] of these patients completed both periods (i.e. total of 40 weeks follow-up).

4.4.2 Baseline characteristics

Baseline characteristics of the patients in the two trials, for the licensed dose of cenegermin and the vehicle arms only, are summarised in Table 9. While the proportions of males in each trial were similar (REPARO trial: 39.1%; Study 0214: 39.6%) the mean age of patients in the REPARO trial was lower (60.6 years, range: 18 to 95 years) than in Study 0214 (65.2 years, range: 33 to 94 years). The EMA noted the higher proportion of patients from the REPARO trial with stage 3 NK meaning patients in this trial were more severely affected with NK than in Study 0214. The EMA also noted the time since diagnosis of stage 2 or stage 3 NK in the REPARO trial was double that in Study 0214 and this "…would be in line with the more advanced disease" of patients in this trial. The ERG also notes the statement from the Royal College of Ophthalmologists that, in clinical practice, stage 2 NK is rare if tarsorrhaphy is implemented early, as is common in the UK. The Royal College of Ophthalmologists and ERG note that previous tarsorrhaphy was an exclusion criterion for trial entry into both trials (See Table 4, Section 4.3.1 of this ERG report).

As noted in Section 4.3.1 of this ERG report, two of the main differences between the trials were that the REPARO trial was conducted in Europe whereas Study 0214 was conducted in the US and the REPARO trial only permitted trial entry to patients with unilateral NK whereas Study 0214 permitted patients with bilateral NK to be enrolled. Of note, 11 of the patients in the REPARO trial were further reported to be from the UK (from four centres) in the CS (p32) although it is unclear to which arms they were randomised. As the REPARO trial was a three-arm trial, this may have included patients who received the unlicensed dose of cenegermin (10 µg/ml). Only three patients were reported to have bilateral NK in Study 0214. It should further be noted that only the worst-seeing eye of these patients was included in the analysis of outcomes.

Baseline information is not provided on the initial size or location of the epithelial defect. Clinical advice to the ERG is that the rate of healing may differ depending on the size and location of the defect.

The ERG also observes that there were some differences between trial arms within the trials. In both trials, there were proportionately more males in the cenegermin arm than in the vehicle arm, this being most notable in the REPARO trial. Perhaps of more clinical significance, in the REPARO trial, [redacted] the median time since diagnosis of stage 2 or stage 3 NK in the cenegermin arm was double that of the vehicle arm. In Study 0214, [redacted]. While the median time since diagnosis of NK stage 2

or 3 was similar between arms, there were proportionately more patients with stage 3 NK in the cenegermin arm of Study 0214.

Table 9 Baseline characteristics of patients in the REPARO trial and Study 0214

Baseline characteristic	REPARO		Study 0214	
	Cenegermin (n=52)	Vehicle (n=52)	Cenegermin (n=24)	Vehicle (n=24)
Male, n (%)	22 (42.3)	17 (32.7)	10 (41.7)	9 (37.5)
Age				
Mean (SD)	62.5 (14.01)	60.4 (16.78)	65.9 (13.85)	64.5 (14.15)
Min, max	18, 95	23, 91	33, 94	35, 92
Race, n (%)				
White	51 (98.1)	45 (86.5)	20 (83.3)	20 (83.3)
Black / African American	0	1 (1.9)	3 (12.5)	2 (8.3)
Asian	0	1 (1.9)	1 (4.2)	0
Other	0	0	0	2 (8.3)
Not collected	1 (1.9)	5 (9.6)	0	0
Time since initial diagnosis of NK, months				
Median	[redacted]	[redacted]	[redacted]	[redacted]
Min, max	[redacted]	[redacted]	[redacted]	[redacted]
Time since diagnosis of NK stage 2 or 3, months				
Median	6.6	3.4	3.0	3.5
Min, max	0.4, 192.5	0.8, 271.6	0, 71	0, 28
NK stage, n (%)				
Stage 2	27 (51.9)	28 (53.8)	15 (62.5)	18 (75.0)
Stage 3	25 (48.1)	24 (46.2)	9 (37.5)	6 (25.0)

Source: CS, adapted from Table 7 and CSRs for REPARO (Table 29) and Study 0214 (Table 13)

In addition to the baseline characteristics summarised in Table 9, data are also reported in the CSRs, and in the EPAR, regarding the underlying cause of NK. In the REPARO trial, in most instances, the underlying cause of NK (in the cenegermin 20 µg/ml and vehicle arms only) was identified primarily as 'others' (21.2% in the cenegermin arm and 17.3% in the vehicle arm), herpes simplex (13.5%, 26.9%), ocular surgery procedure (9.6%, 11.5%) and dry eye disease (11.5%, 9.6%). In Study 0214, the most common underlying cause of NK in the study eye was identified as 'other' (58.3% in the cenegermin arm and 41.7% in the vehicle arm), dry eye disease (12.5% each), herpes zoster (8.3%; 12.5%) and ocular surgery procedure (8.3% each).

An important caveat should however be raised when comparing the data between arms within trials. In both trials (but in particular, in Study 0214), the number of patients in each arm was relatively small. Only a small difference in the number of patients with any given characteristic

can appear to be markedly greater when considering percentages (in a trial arm of 24, for example, 1 patient = 4%). The same caveat applies to comparing data between trials.

4.4.3 Exposure to treatment

This section reports data for the licensed dose of cenegermin (in the controlled and uncontrolled treatment periods) and the vehicle arms (in the controlled treatment period) only.

It is reported in the CS, Appendix F, that overall, in the REPARO trial, the mean number of days on study medication was 49.6 days (range: 1 to 112 days) in the cenegermin arm. In the CSR final addendum (Table 14.1.3c) it is reported that the mean number of days on study medication was [redacted] in the vehicle arm. During the controlled treatment period, the mean exposure was [redacted] in the cenegermin arm, and [redacted] in the vehicle arm. During the uncontrolled treatment period, the mean exposure to cenegermin, as experienced by [redacted] patients, was [redacted].

In Study 0214, it is reported in the CS, Appendix F, that the mean (median) treatment duration for all patients randomised to cenegermin for the controlled treatment period was 44.3 (54.0) days (range 0 to 57 days) and for all patients randomised to vehicle was 42.8 (55.0) days (range 5 to 59). In addition, it is noted, 13 patients initially randomised to vehicle were exposed to cenegermin in the uncontrolled treatment period. The extent of their exposure to cenegermin in days is not reported.

4.4.4 Concomitant medications

This section reports data for the licensed dose of cenegermin and the vehicle arms only. The ERG again highlights that the small number of patients in each trial arm means that interpretations of comparisons between arms and across trials should be made with caution.

It is noted in the EPAR that during the controlled treatment period, comparatively more patients in Study 0214 than in the REPARO trial took concomitant ocular preparations. In the REPARO trial, 26 (50.0%) of patients in the cenegermin arm and 21 (40.4%) of patients in the vehicle arm took concomitant ocular preparations during the controlled treatment period. It is reported in the CS, Appendix D1 (p26) that during the follow-up period, [redacted] of patients in the cenegermin arm and [redacted] of patients in the vehicle arm took concomitant ocular preparations. The ERG is unclear if data for the follow-up period include data for the uncontrolled treatment period (but assumes this to be the case). In Study 0214, [redacted] of patients in the cenegermin arm and [redacted] of patients in the vehicle arm took concomitant ocular preparations during the controlled treatment period. It is reported in the EPAR and CS,

Appendix D1 (p27) that the use of concomitant medications were “similar” in the uncontrolled treatment period as the controlled treatment period. The ERG is again unclear if data for the uncontrolled treatment period include data for the extended follow-up period (but assumes this to be the case).

4.4.5 Risk of bias assessment for the included trials of cenegermin

The company assessed the risk of bias in the REPARO trial and Study 0214 using the minimum criteria recommended by NICE.[18] The company’s risk of bias assessment for each study, and ERG comments, are presented in Table 10.

The ERG agrees with the company that methods of randomisation, allocation concealment and masking of care providers, participants and outcome assessors in both of the studies was adequate and the risk of bias relating to these criteria was low. The ERG also agrees that results for all outcomes and endpoints measured are presented within the CSRs for each study, therefore minimising the risk of selective outcome reporting bias. It is noted that the outcomes reported in the CS are those that were pre-specified in the final scope issued by NICE.

The ERG notes differences in the proportions of patients with some of the baseline characteristics between arms in both trials (see Section 4.4.2, cenegermin arm of Study 0214. of this ERG report). The ERG also considers that the withdrawal rates were quite high in in the cenegermin arms of both studies (25.0%) and the vehicle arm of Study 0214 (37.5%), see Section 4.4.1, Table 8 of this ERG report). The ERG notes that several analysis approaches have been employed to account for missing data and considers some of these analyses to be appropriate (see Section 4.3.2, Table 7 of this ERG report for further discussion).

Table 10 Risk of bias assessment of the REPARO trial and Study 0214

Study question	Company assessment		ERG comment
	REPARO	Study 0214	
Was randomisation carried out appropriately?	Yes	Yes	Agree
Was the concealment of treatment allocation adequate?	Yes	Yes	Agree
Were the arms similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes	Yes	The ERG notes differences in the proportions of patients with some of the baseline characteristics between arms in both trials.
Were the care providers, participants and outcome assessors masked to treatment allocation? If any of these people were not masked, what might be the likely impact on the risk of bias (for each outcome)?	Yes	Yes	Agree
Were there any unexpected imbalances in drop-outs between arms? If so, were they explained or adjusted for?	Not clear	Not clear	The ERG considers that the withdrawal rates were quite high and unbalanced across the arms in both studies (see Section 4.4.1, Table 8 of this ERG report). The ERG notes that analyses have been conducted to account for this missing data and considers some of these analyses to be appropriate (see Section 4.3.2, Table 7 of this ERG report for further discussion).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	CSR is available containing all outcomes	CSR is available containing all outcomes	Agree
Did the analysis include an intent-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes. No inappropriate methods were used. The extent of missing data and the valid denominators were made clear.	Yes. No inappropriate methods were used. The extent of missing data and the valid denominators were made clear.	The ERG considers some of the analyses conducted to account for missing data to be appropriate (see Section 4.3.2, Table 7 of this ERG report for further discussion).

CSR=Clinical Study Report; ERG=Evidence Review Group; NK=neurotrophic keratitis
Source: CS, Appendix D1.3, Table 3 and ERG comment

4.5 Efficacy results from the included trials

This section summarises the results of the primary efficacy outcomes and important secondary efficacy outcomes of the REPARO trial and Study 0214 that are relevant to the decision problem or which were used within the economic model. The outcomes are described in Table 3 and Table 4 of this ERG report. Results of other outcomes and time points measured within the studies are also available in the CSRs.

4.5.1 Corneal healing at Week 4

Corneal healing (<0.5 mm) at Week 4 was the primary outcome in the REPARO trial. The results are summarised in Table 11. The difference in the percentage of patients achieving corneal healing (<0.5 mm) between the cenegermin and vehicle arms at 4 weeks was 38.4% (97.06% CI 18.96% to 57.83%, p<0.001). This outcome was also reported as a secondary endpoint of Study 0214; no statistically significant differences between the cenegermin and vehicle arms at 4 weeks were observed (19%, 95% CI -9.0% to 47.1%, p=0.191).

Table 11 Summary of corneal healing results at Week 4 in the REPARO trial and Study 0214

Corneal healing in the ITT population, by analysis approach		REPARO		Study 0214	
		Cenegermin N=52	Vehicle N=52	Cenegermin N=24	Vehicle N=24
Corneal healing (<0.5 mm) at Week 4					
LOCF, central reading centre	Number analysed[a]	50	51	23	24
	Complete healing: n (%)	29 (58.0)	10 (19.6)	13 (56.5)	9 (37.5)
	Difference in % CH[b]	38.4 (97.06% CI 19.0 to 57.8) p<0.001		19 (95% CI -9.0 to 47.1) p=0.191	

[a] Participants without any post-baseline measurements excluded
[b] The significance level for the statistical tests is 0.0294 (adjusted according to Pocock[29]) in the REPARO trial. P values are from 2x2 Chi-squared tests.
CI=confidence interval; CS=company submission; LOCF=last observation carried forward; CH=corneal healing; ITT=intention-to-treat
Source: CS, adapted from Table 9 and Table 10

4.5.2 Corneal healing at Week 8

Corneal healing (<0.5 mm) at Week 8 was a [redacted] endpoint of Study 0214 and a secondary endpoint of the REPARO trial.

Results for the ITT population of the REPARO trial and Study 0214 for corneal healing (<0.5 mm) at Week 8 are presented in Table 12. In the primary analysis approach of both studies, corneal healing (<0.5 mm) was determined by a central reading centre and LOCF methodology was used to account for missing data. In this approach, the difference in the percentage of patients achieving corneal healing (<0.5 mm) between the cenegermin and vehicle arms at 8 weeks was 30.9% (97.06% CI 10.60% to 51.13%; p=0.002) in the REPARO trial and 40.4% (95% CI 14.2% to 66.6%; p=0.006) in Study 0214.

Table 12 Summary of corneal healing results during the controlled treatment periods in the REPARO trial and Study 0214

Corneal healing in the ITT population, by analysis approach		REPARO		Study 0214	
		Cenegermin N=52	Vehicle N=52	Cenegermin N=24	Vehicle N=24
Corneal healing (<0.5 mm) at Week 8					
LOCF, central reading centre	Number analysed[a]	50	51	23	24
	Complete healing: n (%)	37 (74.0)	22 (43.1)	16 (69.6)	7 (29.2)
	Difference in % CH[b]	30.9 (97.06% CI 10.6 to 51.1) p=0.002		40.4 (95% CI 14.2 to 66.6) p=0.006	
Investigator assessment, response available at Week 8	Number analysed[c]	[redacted]	[redacted]	[redacted]	[redacted]
	Complete healing: n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in % CH[b]	[redacted]		[redacted]	
All missing data treated as failure, central reading centre	Number analysed	[redacted]	[redacted]	[redacted]	[redacted]
	Complete healing: n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in % CH[b]	[redacted]		[redacted]	
Multiple imputation central reading centre	Number analysed[d]	[redacted]	[redacted]	[redacted]	[redacted]
	Complete healing: n (%)	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in % CH[b,e]	[redacted]		[redacted]	
Corneal healing (0 mm) at Week 8					
LOCF, central reading centre	Number analysed[a]	50	51	23	24
	Complete healing: n (%)	36 (72.0)	17 (33.3)	15 (65.2)	4 (16.7)
	Difference in % CH[b]	38.7 (97.06% CI 18.7 to 58.6) p<0.001		48.6 (95% CI 24.0 to 73.1) p<0.001	

[a] Participants without any post-baseline measurements excluded
[b] The significance level for the statistical tests is 0.0294 (adjusted according to Pocock[29]) in REPARO. P values are from 2x2 Chi-squared tests.
[c] Participants with a response available for investigator assessment at Week 8 in the REPARO trial (observed cases). Participants with a response available for investigator assessment at Week 8 with LOCF in Study 0214
[d] Observed cases (central reading centre) at Week 8
[e] Confidence Interval and p value determined by Multiple Imputation to account for missing data
CH=corneal healing; CI=confidence interval; CS=company submission; CSR=clinical study report; ITT=intention-to-treat; LOCF=last observation carried forward; OR=odds ratio
Source: CS, adapted from Table 9 and Table 10; REPARO CSR, adapted from Table 37, Table 38, Table 39. Study 0214, adapted from Text Table 17, Table 14.2-1.4, Table 14.2-1.7

While the rates of corneal healing are reported to be broadly similar for patients treated with cenegermin in both the REPARO trial and Study 0214, the EMA note that there are differences in the response rates for patients in the vehicle arms with and without methionine. At Week 8, 43.1% of patients in the vehicle arm (without methionine) of the REPARO trial had achieved corneal healing compared to 29.2% of the patients receiving vehicle (with methionine) in Study 0214. However, the EMA considered that the response rates in both trials were, nonetheless, in line with the estimated rates for vehicle used for study size and power calculations for both trials (approximately 30%).

The ERG notes that the sample size calculation used in Study 0214 specified a one-sided significance level of 5%, which was amended within the protocol and TSAP to a two-sided significance level of 10% (i.e. 90% CIs, rather than 95% CIs). The ERG notes no change in the conclusions of the [redacted] endpoints from the 90% CI; 40.4% ([redacted]; p=0.006, CSR p93) for corneal healing (<0.5 mm) and 48.6% ([redacted] p=0.006, CSR addendum p21) for corneal healing (0 mm) in Study 0214.

As stated in Section 4.3.2 and Table 7 of this ERG report, the ERG is concerned about the use of LOCF method due to the biases associated with this method,[33] and the ERG considers the multiple imputation approach used in the sensitivity analysis described by the company, which is more statistically powerful and captures the uncertainty introduced by the missing outcome data, to be the most appropriate method of handling missing data in these trials. Results of the sensitivity analyses and corneal healing (<0.5 mm) by the investigator are also presented in Table 12. The ERG notes that the results of the analyses using LOCF methodology [redacted] percentage difference between cenegermin and vehicle in both the REPARO trial and in Study 0214 when compared to the results of the sensitivity analyses. However, the ERG considers that the numerical results of the different approaches are sufficiently similar and the different analysis approaches do not lead to different conclusions regarding the comparative effectiveness of cenegermin and vehicle.

Corneal healing (0 mm) at Week 8 was also analysed in both studies at the request of the FDA (as an additional [redacted] endpoint in a protocol amendment to Study 0214 and as a post-hoc outcome of the REPARO trial). Results presented in Table 12 show that the difference in the percentage of patients achieving corneal healing (0 mm) between the cenegermin and vehicle arms at 8 weeks was 38.7% (97.06% CI 18.72% to 58.62%; p<0.001) in REPARO and 48.6% (95% CI 24.0% to 73.1%; p<0.001) in Study 0214.

Subgroup analysis by disease severity and aetiology

During the clarification process, the ERG requested subgroup data for corneal healing (<0.5 mm) for patients with Stage 2 and Stage 3 NK in the REPARO trial and in Study 0214. The number of patients with each stage of NK in the studies is presented in cenegermin arm of Study 0214. of this ERG report (Section 4.4.2). Given the small number of patients in each subgroup, the company provided pooled subgroup data from the REPARO trial and Study 0214. The ERG agrees that this approach was appropriate.

When pooling all patients who initially received cenegermin in the two studies, 25 out of 40 (63%) patients with stage 2 NK and 28 out of 33 (85%) patients with stage 3 NK achieved corneal healing (<0.5 mm) at the end of the 8 week controlled treatment period. When pooling

all patients who initially received vehicle in the two studies, 15 out of 46 (33%) patients with stage 2 NK and 14 out of 29 (48%) patients with stage 3 NK achieved corneal healing (<0.5 mm) at the end of the 8 week controlled treatment period. The ERG notes that more patients appear to achieve corneal healing with stage 3 NK than with stage 2 NK (in both treatment arms). Using the pooled data, the improvement in corneal healing for cenegermin compared with vehicle was statistically significant for patients with stage 2 NK (p=0.006) and for patients with stage 3 NK (p=0.002).

An additional post-hoc analysis was performed by the company in response to a request by the CHMP for the most representative local and systemic aetiologies. This additional analysis is presented in the EPAR and is shown in Table 13 of this ERG report. The results suggest that, with the possible exception of iatrogenic eye damage, corneal healing rates are at least as similar to those reported for the ITT population. However, the ERG notes that the number of patients in each arm is extremely small (zero in one of the arms) and no formal statistical analyses were conducted by aetiology.

Table 13 Percentage of patients with corneal healing (<0.5 mm) at Week 8 in the REPARO trial and Study 0214 by NK aetiology

NK aetiology (% and n out of N)	REPARO		Study 0214	
	Cenegermin	Vehicle	Cenegermin	Vehicle
Diabetes	75% (3/4)	50% (2/4)	Not enrolled	0% (0/1)
Dry eye	100% (6/6)	40% (2/5)	67% (2/3)	33% (1/3)
Herpes (Simplex or Zoster)	70% (7/10)	35% (6/17)	73% (8/11)	38% (3/8)
Iatrogenic eye damage	64% (7/11)	54% (7/13)	50% (3/6)	43% (3/7)
Innervation alterations[a]	75% (6/8)	29% (2/7)	100% (1/1)	0% (0/2)

a Innervation alterations" include both neurosurgical procedures and isolated diseases of the trigeminal/cranial nerves
NK=neurotropic keratitis
Source: EPAR, Table 10

Sensitivity analysis for patients who received concomitant ocular medication

The ERG notes that in the EPAR, the EMA states that, in general, prevalence, diagnosis and therapeutic approach differ between the US and Europe. Within this context, therefore, the EMA were reassured that analyses presented by the company showed that the use of concomitant medication did not affect the treatment effect of cenegermin. The analyses are not presented in the EPAR but a sensitivity analysis for corneal healing (0 mm) is presented in an addendum to the final CSR of Study 0214 (Table 6). [redacted]

[redacted]

Meta-analysis of the REPARO trial and Study 0214

The company pooled outcome data from the two trials for corneal healing to <0.5 mm and to 0 mm in the lesion area, no persistent staining elsewhere at Week 8 (central reading centre, LOCF) using the Mantel-Haenszel method of meta-analysis and reported results as odds ratios (ORs).[37] Meta-analyses were conducted with fixed-effects due to the absence of any statistical heterogeneity (I^2= 0%). The ERG considers this methodological approach to be appropriate.

Both of the pooled ORs were in favour of cenegermin compared to vehicle. The meta-analysis of corneal healing to <0.5 mm at Week 8 provided a pooled OR of 4.24 (95% CI 2.11 to 8.50; p<0.001) and the meta-analysis of corneal healing to 0 mm in the lesion area, no persistent staining elsewhere at Week 8 provided a pooled OR of 6.09 (95% CI 2.97 to 12.50; p<0.001).

4.5.3 Secondary efficacy results at Week 8

Table 14 summarises the results of the secondary efficacy outcomes of the REPARO trial and Study 0214. In addition to the outcomes relevant to the decision problem, the ERG also reports data for complete corneal clearing since this was also reported in the CS.

Table 14 Summary of secondary efficacy results at Week 8 in the REPARO trial and Study 0214

		REPARO		Study 0214	
		Cenegermin	Vehicle	Cenegermin	Vehicle
Randomised at baseline		52	52	24	24
Complete corneal clearing at Week 8 (central reading centre, LOCF)	Number analysed	42	40	22	24
	CCC: n (%)	[redacted]	[redacted]	5 (22.7%)	1 (4.2%)
	Difference in % CCC[a]	11.4 (95% CI -4.1 to 26.9) p=0.157		18.6 (95% CI -0.7 to 37.8) p=0.062	
Visual acuity: BCDVA score	Number analysed	52	52	23	24
	Baseline: mean (SE)	[redacted]	[redacted]	[redacted]	[redacted]
	Change from baseline: mean (SE)	11.9 (2.8)	6.9 (2.8)	4.5 (9.8)	4.3 (10.4)
	Treatment difference[b]	[redacted]		[redacted]	
Visual acuity: percentage of patients achieving a 15 letter gain in BCDVA score	Number analysed	52	52	[redacted]	[redacted]
	15 letter gain: n(%)	[redacted]	[redacted]	[redacted]	[redacted]
	% difference in 15 letter gain[a]	19 (95% CI -0.91 to 38.83) p=0.068		[redacted]	
Improvement in corneal sensitivity	Number analysed	[redacted]	[redacted]	[redacted]	[redacted]
	Improved: n(%)	[redacted]	[redacted]	[redacted]	[redacted]
Deterioration of NK	Number analysed	[redacted]	[redacted]	[redacted]	[redacted]
	Deteriorated: n(%)	[redacted]	[redacted]	[redacted]	[redacted]
	Difference in % deteriorated[a]	[redacted]		[redacted]	

a P values are from 2x2 Chi-squared tests
b Treatment difference for change from baseline in BCDVA calculated from an ANCOVA model with treatment and baseline BCDVA score as fixed effects
ANCOVA=analysis of covariance; BCDVA=best corrected distance visual acuity; CCC=complete corneal clearing; CI=confidence interval; CS=company submission; CSR=clinical study report; NK=neurotropic keratitis; LOCF=last observation carried forward; SE=standard error
Source: CS, adapted from Table 9, Table 10, page 49. Appendix L (p26), REPARO CSR, Table 14.2.6.3b, Table 14.2.2.1.1b, Table 14.2.2.1.2b, Table 14.2.2.4b, Table 14.2.4.1.3b, Study 0214 CSR Table 20, CSR Text Table 22, Text Table 23, company response to ERG clarification letter.

There was no significant difference between the treatment arms at Week 8 in either study in terms of the percentage of patients achieving complete corneal clearing, experiencing deterioration of NK, in the change from baseline in mean BCDVA score or the percentage of patients achieving a 15 letter gain in BCDVA score.

The ERG notes that within the CS (p49), corneal sensitivity was presented as the proportion of patients with an improvement in corneal sensitivity (i.e. frequency and percentage) in the REPARO trial and as the change from baseline in corneal sensitivity (i.e. mean difference and 95% CIs) in Study 0214. For consistency, during the clarification process, the ERG requested results for corneal sensitivity on the same scale for the two studies. In the response to the ERG clarification letter, the company re-calculated corneal sensitivity using the same algorithm for both studies and the results are presented within Table 14. Within the two studies, the proportions of patients experiencing an improvement in corneal sensitivity were

similar in the cenegermin and vehicle treatment arms. No formal statistical analysis was conducted.

The ERG also notes that, for the REPARO trial, the company reports a post-hoc analysis for deterioration (CS, Appendix L). The rationale for the post hoc analysis and/or how this differed to the original analysis is not reported. This analysis showed that [redacted] and [redacted] patients in the cenegermin and vehicle arms respectively experienced deterioration on or before Week 8.

4.5.4 Corneal healing during the extended follow up period

The disposition of patients during the extended follow-up periods of the two studies is described in Section 4.4.1 of this ERG report. The procedures within the studies for patients who deteriorated (see Table 14 of this ERG report) during the controlled treatment period, were not completely healed during the controlled treatment period or experienced a recurrence during the uncontrolled treatment period are outlined in Figure 3 of the CS.

Table 15 presents the proportions of patients who achieved corneal healing at Week 8 and who remained healed at the end of the extended follow-up period after completing treatment (i.e. 48 weeks in the REPARO trial and 24 weeks in Study 0214). Patients who were healed at Week 8 but no longer healed at 32 or 56 Weeks are considered to have had a recurrence of NK. Recurrence rates at 32 Weeks in the two trials varied from 0 to 3% in the REPARO trial and 0 to 14% in Study 0214, depending on the arm to which patients were originally randomised. At 56 weeks, recurrence rates were 3% to 5% in the REPARO trial, depending on the arm to which patients were originally randomised.

The ERG notes that the data reported in Table 15 do not include patients who received vehicle during the controlled treatment period and then cenegermin during the uncontrolled treatment period (i.e. those with a total of 64 weeks follow-up). It is however reported in the company response to the ERG clarification letter (and the EPAR) that in Study 0214, 10 patients who were initially randomised to vehicle and were not completely healed after Week 8 received cenegermin in the uncontrolled treatment period. Three (30%) of these patients were treated for recurrence during the extended follow-up period (i.e. up to Week 40).

Table 15 Summary of corneal healing results during the extended follow-up period in the REPARO trial and Study 0214

	REPARO		Study 0214	
	Cenegermin	Vehicle	Cenegermin	Vehicle
Randomised at baseline	52	52	24	24
Achieved corneal healing at Week 8: n (%)[a]	37 (71.1%)	22 (42.3%)	14 (58.3%)	7 (29.2%)
Number healed with response available at 32 weeks	31	21	14	7
Remained healed at 32 weeks, n (%)[b]	30 (96.7%)	21 (100%)	12 (85.7%)	7 (100%)
Number healed with response available at 56 weeks, n	29	21	NA	NA
Remained healed at 56 weeks, n (%)[b]	28 (96.5%)	20 (95.2%)	NA	NA

a Denominator of the percentages is the number randomised at baseline
b Denominator of the percentages is the number with the response available at each time point
c Including 10 patients initially randomised to vehicle who received cenegermin 20 µg/ml in the uncontrolled treatment period and 7 patients who did not undergo uncontrolled treatment
CS=company submission; NA=not applicable; NK=neurotropic keratitis
Source: CS, adapted from p48 and Table 20

It should be noted that these analyses are exploratory and based on the set of patients for whom response data were available; the company did not intend to formally statistically test these data according to the TSAP. In the CS (p48) the company states they are "…indicative only and do not permit firm conclusions to be drawn."

4.6 Adverse events reported in the included trials

The company presents details of AEs and deaths occurring during the controlled treatment period for the safety populations for both the REPARO trial and for Study 0214. The analyses included all data available at the time of database lock for each trial: 3 months and 4 weeks of follow-up, respectively. In this section, the ERG has only reported data for the licensed 20 µg/ml dose for cenegermin and the vehicle control arm for comparison, and AEs during the controlled follow-up periods, except where stated.

4.6.1 Overview of adverse events

An overview of AEs and deaths is presented in Table 16. Patients in both the cenegermin and vehicle arms of Study 0214 experienced higher rates of treatment emergent AEs (TEAEs) and treatment-related AEs (TRAEs) compared to patients in the respective arms of the REPARO trial.

The proportions of patients who reported a serious adverse event (SAE) or AE leading to discontinuation of study drug were similar in the cenegermin arms of the trials but were higher in the vehicle arm of Study 0214 compared to the vehicle arm of the REPARO trial. Where SAEs occurred, it is reported in the CS, Appendix F (p16) that none of the SAEs in the REPARO trial were considered related to treatment; [redacted]. It is also stated that none of the deaths were considered related to treatment (it is reported there were two deaths as a result of AEs in the REPARO trial in the text of the CS, Appendix F [p13] whereas in the accompanying Table 5, it is reported that there was only one death). It is reported in the EPAR that SAEs and AEs leading to treatment discontinuation were mostly eye-related, and mild or moderate and transient in nature.

Table 16 Number (and proportion) of patients with adverse events and deaths during the controlled treatment periods of the REPARO trial and Study 0214

Event, n (%)	REPARO			Study 0214		
	Cenegermin (N=52)*	Vehicle (N=52)	All (N=104)	Cenegermin (N=23)	Vehicle (N=24)	All (N=47)
≥1 TEAE	27 (51.9)	20 (38.5)	47 (45.2)	21 (91.3)	18 (75.0)	39 (83.0)
≥1 TRAE	9 (17.3)	10 (19.2)	19 (18.3)	10 (43.5)	8 (33.3)	18 (38.3)
≥1 SAE	9 (17.3)	5 (9.6)	14 (13.5)	3 (13.0)	4 (16.7)	7 (14.9)
Discontinuation of study drug	9 (17.3)	4 (7.7)	13 (12.5)	5 (21.7)	7 (29.2)	12 (25.5)
Deaths	1 (1.9)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)

*20 µg/ml dose only
AE=adverse event; SAE=serious adverse event; TEAE=treatment emergent adverse event; TRAE=treatment-related adverse event
Source: adapted from EPAR, Table 22 and CS, Table 14

Patients often reported multiple AEs, hence the total number of AEs experienced in the two arms of the REPARO trial were 51 in the cenegermin arm and 50 in the vehicle arm. In Study 0214, the number of AEs reported in each arm was 82 and 54 respectively.

4.6.2 Common types of adverse events

For each trial, the company has also presented details of TEAEs with an incidence rate of ≥2% by preferred term / system organ class during the controlled-treatment period (CS, Appendix F, Table 6 and Table 8) and ≥5% (CS, Table 15). Again, the incidence of TEAEs was notably higher in Study 0214 compared to the REPARO trial. Eye disorders were the most common class of AEs experienced in both arms of the REPARO trial (cenegermin: 25.0%, vehicle: 30.8%) and Study 0214 (cenegermin: 78.3%, vehicle: 58.3%). The most common type of eye disorder (as a proportion of all patients in each arm) was eye pain (REPARO trial, cenegermin: 9.6%, vehicle: 7.7%; Study 0214, cenegermin: 30.4%, vehicle: 8.3%). Reduced visual acuity was also reported as a common eye disorder in both trials (REPARO, cenegermin: 5.8%, vehicle: 3.8%; Study 0214, cenegermin: 21.7%, vehicle: 20.8%). No other type of eye disorder was reported at a frequency of ≥5% in the REPARO trial but nine other types of eye disorder were reported at a frequency of ≥5% (8.7% to 17.4%) in Study 0214.

4.6.3 Systemic adverse events

The company reports that systemic AEs were very rare in both trials. Systemic AEs were considered by the company to be unlikely to be related to the study medication, given the very limited systemic absorption of cenegermin.

4.6.4 Adverse events reported by patients who received concomitant ocular medication

In the EPAR, it is reported that in the REPARO trial, 27/30 (90%) and 21/25 (84%) patients who received concomitant ocular medication and treated with cenegermin and vehicle respectively reported an AE, a higher proportion than reported in the respective trial arms as a whole (see Table 16). The ERG notes the denominators differ to the number of patients who were reported by in the EPAR (and by the company in the CS, Appendix L) to receive these medications ([redacted] patients in the cenegermin arm and [redacted] patients in the vehicle arm). Most AEs were described as being mild-to-moderate and transient. Of the different AEs experienced by these patients, 15/71 (21%) AEs in the cenegermin arm and 28/77 (36%) in the vehicle arm were considered possibly related to study drug (cenegermin or vehicle, respectively).

In Study 0214, the ERG notes the denominator used in the EPAR for estimating the proportion of patients who received concomitant ocular medication appears to differ to the number of patients who were reported by the company to receive these medications in the CS (Appendix

D1). It is reported in the EPAR that 10 (91%) and 9 (75%) patients in the cenegermin and vehicle arms respectively reported an AE, implying these are proportions of 11 and 12 patients, respectively, while the company report that [redacted] patients in each arm received concomitant ocular medication. Nonetheless, the proportions of patients with concomitant ocular medication reported to experience an AE in the EPAR are similar to the proportion of patients who reported an AE in the trial as a whole (see Table 16). Most AEs were reported as being mild-to-moderate (7/10 [70%] and 7/9 [77.8%] respectively). The proportion of patients who received concomitant ocular medication whose AE was considered to be related to the study drug (cenegermin or vehicle, respectively) was reported to be 54% and 50% respectively.

4.6.5 Adverse events reported during the extended follow-up period

Some AE data for each trial during the extended follow-up periods are also reported in the EPAR. In the REPARO trial, 21/65 (32.3%) patients in the cenegermin arm and 11/34 (37.9%) patients in the vehicle arm reported an AE. In Study 0214, AEs were reported by 23/47 (48.9%) patients in the cenegermin arm and 14/23 (60.9%) patients in the vehicle arm. The most common class of AEs in Study 0214 were eye disorders: 9/23 (39.1%) in the cenegermin arm and 6/24 (25.0%) in the vehicle arm (equivalent data not reported for the REPARO trial). It is noted in the EPAR that these data included data for patients who received a second treatment with cenegermin due to recurrence of PED or ulcer during the follow-up and that they were consistent with safety data for the controlled periods of the trials.

4.6.6 Pooled adverse event data over all treatment periods

It is reported in the CS (and SmPC[8]) that the most common AEs (pooled) observed with cenegermin during the clinical trials were eye-related and included eye pain (11.1 %), eye inflammation (8.3 %), lacrimation increased (5.6 %), eyelid pain (5.6 %) and foreign body sensation in the eye (5.6 %). These frequencies are calculated from all NK patients exposed to cenegermin 20 µg/ml (including the controlled and uncontrolled treatment periods, as well as unscheduled treatment).

4.6.7 Comment on adverse event data

The reasons for the differences in some AE frequencies across trials are unknown. In Study 0214, eye drops issued in both arms of the trial included methionine (the formulation of cenegermin which is licensed for use in clinical practice also contain methionine). The EMA highlight that while methionine has scarcely been used in ophthalmological preparations to date, it is a very common food ingredient with no reported toxicity issues. The EMA also highlight that the company have argued that US patients and physicians tend to report AEs

more frequently than Europeans, which could be a factor (as Study 0214 was conducted in the US and the REPARO trial was conducted in Europe).

Overall, the company considers that cenegermin was well tolerated, as the majority of the SAEs and TRAEs were mild or moderate in severity, which did not require treatment discontinuation or any corrective treatment. It is noted that there were more discontinuations due to an AE in the vehicle arm than the cenegermin arm of Study 0214 but not the REPARO trial. The company argues that transient reductions in visual acuity and transient ocular pain are not necessarily a sign of an AE and can both be related to the healing process in patients with NK, reflecting improved corneal sensitivity. The ERG concurs with the company. However, the ERG also notes that approximately a fifth of patients in both trials withdrew treatment with cenegermin as a result of an AE (Table 16). Furthermore, as a proportion of all study withdrawals before 8 weeks, AEs were the most common reason given, by approximately two-thirds of patients in both trials (see Section 4.4.1, Table 8). Given the uncertainty regarding the possible effects of methionine on tolerability, the EMA have recommended that the company generate further long-term data with the methionine-containing formulation of cenegermin.

4.7 Health-related quality of life

HRQoL was measured in both trials using the European Quality of Life - 5 Dimensions Questionnaire (EQ-5D-5L), EQ-5D visual analogue scale (VAS) and national eye institute visual functioning questionnaire 25 (NEI-VFQ-25). The EQ-5D is a standardised measure of health status that provides a simple, generic measure of HRQoL. As highlighted in the CSR of Study 0214, the utility of the NEI-VFQ-25 in NK is unknown but many consider it to be the standard tool to assess vision-targeted functioning. The questionnaires were completed by patients before any ophthalmic examinations were performed at a given study visit.

Analyses of the HRQoL outcomes were conducted in the ITT populations of both trials. The analyses reported in the CS are described by the company as "further analysis" to the analyses reported in the CSRs. Data are reported for both trials separately and pooled data are also reported for EQ-5D-5L. EQ-5D-5L data were reported for patients considered to be in the following health states: 'corneal healing', 'not healed but stable' and 'not healed and deteriorating'. The pooled data were used to inform the company's economic model. Analyses reported in the CS compare only patients who had values reported at both baseline and Week 8. The data are reported in the CS (Tables 11 to 13 and pp50-56).

As highlighted by the company, the results from the EQ-5D-5L analyses are highly variable, with no consistent pattern in terms of change from baseline to Week 8 in either arm, for either trial or the pooled data, for any health state. In terms of EQ-5D VAS and NEI-VFQ-25, there were slight increases in scores for cenegermin and a slight decrease in scores for vehicle in both trials. The company notes that the baseline EQ-5D VAS and NEI-VFQ-25 scores in both arms of Study 0214 study were higher than in the REPARO trial. Regarding the least squares mean change for EQ-5D VAS and NEI-VFQ-25, no statistically significant differences between arms from baseline to Week 8 were found.

The company states that the variability of the EQ-5D-5L results may be a consequence of small patient numbers, particularly for patients in the 'not healed and deteriorating' health state. Therefore, it is argued that no robust interpretations or conclusions can be drawn from the results. The ERG concurs with the company's justification. The ERG further notes that there appear to be only minimal changes in HRQoL in either arm as measured by the EQ-5D VAS and NEI-VFQ-25 scores and patient numbers are small. The ERG concurs with the company that the apparent lack of change in HRQoL is unsurprising given that NK is, by definition, a largely asymptomatic disease (See Section 2.1, Box 1, of this ERG report).

4.8 Indirect evidence (mixed treatment comparison)

The company conducted a MTC based on very limited data and considered that the results were associated with such uncertainty that no conclusions could be drawn. Therefore, the company considered only direct evidence for cenegermin and preservative-free artificial tears (vehicle) within the cost-utility analysis presented within the CS. For this reason, the ERG provides only a brief description and critique of the MTC. Full details of the MTC approach and analysis (including trial and participant characteristics and the company's quality assessments of studies) can be found in the CS, Appendix D3 and Appendix D4.

4.8.1 Studies included in the mixed treatment comparison

From the 'clinical extension review' a total of 44 studies were considered for inclusion in the MTC (43 studies identified by the company's literature search,[19,36,38-78] which included a conference abstract for the REPARO trial;[19] while no reference for Study 0214 was identified, Study 0214 was however considered for inclusion in the MTC). Of these 44 studies, 19 studies were excluded from the MTC.[36,38,40-42,45,47,49,55,58,59,65,67-69,71,73,75,77] The ERG considers the reasons for excluding these studies to be appropriate. In total 25 studies were considered for inclusion in the MTC: three RCTs (the REPARO trial, Study 0214 and an RCT by Khokhar et al[54]), a non-randomised comparative study[74] and 21 studies with a single treatment arm.[39,43,44,46,48,50-53,56,57,60-64,66,70,72,76,78] For further information about the RCT conducted by Khokhar et al,[54] see the appendices to this ERG report, Section 9.4 of this ERG report.

4.8.2 Outcomes included in the mixed treatment comparison

The only outcome considered in the MTC was healing / epithelisation. The company notes that the REPARO trial and Study 0214 had specific definitions of healing (see Table 5 and Table 6 of this ERG report) whereas other studies within the literature did not clearly define 'healing.' Table 1 of Appendix D4 to the CS provides a summary of the data in the studies included in the MTC for the outcome of 'healing' and Table 2 of Appendix D4 to the CS outlines further details of study designs and patient populations. The company notes that poor reporting in some studies may have led to data being extracted regarding refractory NK, which could have biased the healing rates in the analyses.

4.8.3 Comparisons enabled by the mixed treatment comparison

The studies enabled a comparison of the following interventions: autologous serum eye drops, amniotic membrane transplantation, tarsorrhaphy, bandage contact lens, cenegermin and vehicle. Figure 2 of Appendix D4 to the CS illustrates a network diagram of the direct and indirect comparisons made in the MTC. In order to create links within the network between vehicle and comparators of interest, an 'external control' assumption was made in comparative

studies without a vehicle arm that the percentage of patients healed on vehicle would be 35%. This assumption was based on the number of patients healed in the vehicle arms of the REPARO trial and Study 0214 and was tested in sensitivity analyses assuming 30% or 40% of patients healed on vehicle.

4.8.4 Approaches to analysis in the mixed treatment comparison

The company took three approaches to analysis in the MTC; analysis of the three RCTs only, analysis of the four comparative studies (including the three RCTs) and analysis of all available data including single arm studies. The company used Bayesian models in the MTC, as described by Welton et al,[79] to estimate probabilities (and standard errors) of being healed on each treatment and comparative ORs and 95% credible intervals of all treatments compared to cenegermin and all treatments compared to vehicle. The company fitted fixed effects models, random effects models and random effects models with a multi-arm correction. Although the fixed effects models provided the best model fit statistically, the company presented results from the random effects models with a multi-arm correction due to the diversity of the studies and uncertainty in the results. The ERG considers this methodological approach to be appropriate.

4.8.5 Findings from the mixed treatment comparison

The results of the MTC from all three approaches and the additional sensitivity analyses to account for the assumptions of the external control showed a large amount of uncertainty and credible intervals were very wide for the majority of comparisons.

4.8.6 Comment on the indirect evidence

The ERG considers the methodological approaches attempted by the company to conduct its MTC to be appropriate. However, the ERG also agrees with the company that the data were limited, and that the uncertainty associated with the results is so large that the results are too challenging to interpret and to draw conclusions from.

4.9 Conclusions of the clinical effectiveness section

RCT evidence for the comparative effectiveness of cenegermin to vehicle has been presented from two small phase 2 trials (the REPARO trial and Study 0214) in a population of patients that is relevant to the decision problem, and for whom cenegermin is licensed (stage 2 and stage 3 NK). The ERG considers that the patients' characteristics are similar to those of patients seen in the NHS. The small size of the trials is perhaps reflective of the rarity of stage 2 and stage 3 NK in the wider population (NK being classified as an orphan disease).

Results from both trials show that at 8 weeks, cenegermin significantly improves rates of complete corneal healing when compared with vehicle. The superiority of cenegermin is demonstrated whether using the company's preferred method of analysis (LOCF) or sensitivity analyses, including the ERG's preferred method (multiple imputation approach). The trials of cenegermin show that at 8 weeks, rates of corneal healing are significantly higher in the cenegermin arm compared with vehicle. No statistically significant differences were reported between arms at 8 weeks for other relevant efficacy outcomes in either trial.

Regarding safety data, eye disorders (such as eye pain) were the most common class of AEs experienced in both arms of the trials. It is unclear why the AE frequencies differed quite markedly between trials. Nonetheless, the safety evidence presented suggest that cenegermin was well tolerated since the majority of the SAEs and TRAEs were mild or moderate in severity and did not require treatment discontinuation or any corrective treatment.

The company argues that transient reductions in visual acuity and transient ocular pain are not necessarily a sign of an AE and can both be related to the healing process in patients with NK, reflecting improved corneal sensitivity. The ERG concurs with the company.

As argued by the company, no robust interpretations or conclusions can be drawn from the HRQoL results. The ERG concurs with the company that the apparent lack of change in HRQoL is unsurprising given that NK is, by definition, a largely asymptomatic disease.

Regarding the effectiveness of cenegermin beyond 8 weeks, the majority of patients who achieved corneal healing at 8 weeks remained healed after a further 24 weeks in both studies and after a further 48 weeks in the REPARO trial. However, as stated by the company, these results can only be considered indicative. As noted by the EMA, given the uncertainty regarding the possible effects of methionine on tolerability, the EMA have recommended that the company generate further long-term safety data with the methionine-containing formulation of cenegermin since this is the formulation to be used in clinical practice. It should also be highlighted that to date, only 24 patients included in the trials were randomised to

receive this formulation of cenegermin and only a further 10 patients received this formulation in the uncontrolled treatment period.

While artificial tears are used to treat patients with stage 2 and stage 3 NK, they are often used in addition to other interventions. The company therefore conducted an MTC to compare cenegermin with other comparators. However, the results from the MTC were associated with such uncertainty that no conclusions could be drawn from the results of the MTC.

It has been argued that while currently available treatments aim to promote corneal healing, they do not address the pathophysiology/cause of the disease (corneal nerve impairment). It is argued that cenegermin, on the other hand, does address the underlying cause of the disease. The ERG does not consider that there is evidence to demonstrate this. While the evidence shows that treatment with cenegermin results in corneal healing, this outcome does not measure whether a treatment addresses the pathophysiology of the disease. Rather, corneal healing is a measure of the size of PED and/or corneal ulcer by corneal fluorescein staining. The ERG does however note that it is reported in the EPAR that NGF has been shown to play a crucial role in the pathophysiology of NK and cenegermin is a recombinant form of NGF.

It is unclear where cenegermin would be best placed in the treatment pathway for NK. However, given previous tarsorrhaphy was an exclusion criterion for trial entry into both cenegermin trials, it is anticipated that cenegermin would precede tarsorrhaphy.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured critique of the economic evidence submitted by the company in support of the use of cenegermin for the treatment of patients with NK. The two key components of the economic evidence presented in the CS are (i) a systematic review of the relevant literature and (ii) a report of the company's de novo economic evaluation. The company provided an electronic version of the economic model, developed using Microsoft Excel.

5.2 ERG critique of the company's review of cost effectiveness evidence

5.2.1 Objective of the company's systematic review

The company conducted a systematic review of the literature to identify studies that considered the cost effectiveness of treatments for NK. The company searched the following databases on 23rd and 24th August 2017: Embase, MEDLINE and MEDLINE In-Process, the Cochrane Library (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects [DARE], Health Technology Assessment database, NHS Economic Evaluation Database [NHS EED]) and EconLit. The search strategy included relevant disease terms and a cost effectiveness filter. Retrieved studies were restricted to those published in the English language. Details of the search strategies employed by the company are provided in Appendix G of the CS. Electronic database searches were supplemented by additional hand searches of reference lists of included studies, proceedings from the Association for Research in Vision and Ophthalmology (ARVO), European Association for Research in Vision and Ophthalmology (EVER), EUCornea and European Society for Cataract and Refractive Surgery (ESCRS). Searches of conference proceedings were limited to those published between 2014 and 2017. The Cost-Effectiveness Analysis (CEA) Registry, EconPapers within Research Papers in Economics (RePEc), International Network of Agencies for Health Technology Assessment (INAHTA), NIHR HTA, and the University of York Centre for Reviews and Dissemination websites were also searched for potentially relevant economic evaluations.

5.2.2 Eligibility criteria used in study selection

The eligibility criteria used by the company to facilitate study selection are described in Table 1, Appendix G of the CS and reproduced in Table 17. The ERG considers that the eligibility criteria were appropriate to the objective of the company's review of cost effectiveness evidence.

Table 17 Economic review eligibility criteria

Parameter	Inclusion criteria	Exclusion criteria
Population	Adult patients with a corneal disease	Paediatric patients with a corneal disease
Interventions	rhNGF	Intervention(s) not listed
Comparators	Preservative-free artificial tears Cacicol Therapeutic contact lenses Autologous eye serum drops Substance P and insulin-like growth factor eye drops Thymosin beta-4 eye drops Amniotic membrane transplantation Tarsorrhaphy Corneal neurotisation	Intervention(s) not listed
Outcomes	ICERs, base case and sensitivity analyses Model structure and summary (including perspective, time horizon, discounting, and model type) Assumptions underpinning model assumptions	Outcome(s) not listed
Study design	Cost-effectiveness analyses Cost-utility analyses Cost-benefit analyses Cost-minimisation analyses	Study design(s) not listed including reviews and editorials
Language restrictions	English language publications and English language abstracts of foreign language publications	Foreign language publications without an English abstract
Date of publication	Post-1995	Pre-1995
Countries/global reach	No restriction	-

5.2.3 Included and excluded studies

The company did not identify any cost effectiveness studies relevant to the final scope issued by NICE. Details of the screening process and reasons for exclusion of studies are presented in Section B.3.1 of the CS (pp 67-70) and Appendix G of the CS.

5.2.4 ERG critique of the company's cost effectiveness review

The ERG considers that the databases searched and search terms used appear to be reasonable. However, the criticisms (i.e. syntax errors and inability to search the Cochrane Library via the Ovid interface) highlighted in the clinical effectiveness review (Section 4.1.1) are also pertinent to the cost effectiveness review.

The ERG updated the company searches for the period between August 2017 and 11th January 2018 and is satisfied that that the company has not missed any relevant economic studies.

5.3 Summary and critique of the company's submitted economic evaluation

5.3.1 ERG summary of the company's submitted economic evaluation

The company has developed a de novo economic model to compare the cost effectiveness of cenegermin versus preservative-free artificial tears for patients with moderate or severe NK.

5.3.2 NICE reference case checklist

Table 18 NICE reference case checklist completed by ERG

Attribute	Reference case	Does the de novo economic evaluation match the reference case?
Decision problem	The scope developed by NICE	Partial. The company did not perform a cost effectiveness evaluation of cenegermin compared to treatments other than preservative-free artificial tears due to insufficient evidence (see Section 4.8 of this ERG report for more details)
Comparator(s)	As listed in the scope developed by NICE	Partial. The company did not perform a cost effectiveness evaluation of cenegermin compared to treatments other than preservative-free artificial tears due to insufficient evidence
Perspective costs	NHS and Personal Social Services	Partial. NHS costs only
Perspective benefits	All health effects on individuals	Yes
Form of economic evaluation	Cost effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	Yes. Set at 100 years of age for the cohort
Synthesis of evidence on outcomes	Systematic review	Yes. The company uses data from the REPARO trial and Study 0214, the only trials identified by the company's systematic review. This is appropriate
Outcome measure	Quality adjusted life years	Yes
Health states for QALY	Described using a standardised and validated instrument	Yes. EQ-5D-5L
Benefit valuation	Time-trade off or standard gamble	Yes. Time-trade off
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes. EQ-5D-5L mapped to EQ-5D-3L to generate utility values
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Sensitivity analysis	Probabilistic sensitivity analysis	Yes. A PSA was performed

EQ-5D-5L=EuroQol-5 dimension-5 levels; EQ-5D-3L=EuroQol-5 dimension-3 levels; HRQoL=health-related quality of life; QALY=quality adjusted life year; PSA=probabilistic sensitivity analysis

5.3.3 Model structure

The company developed a de novo cost effectiveness model structure in Microsoft Excel. The cost effectiveness model presented by the company comprises two-stages: a decision tree followed by a Markov model. The company states (CS, p74) that the rationale to use a decision tree followed by a Markov model was to separate the initial treatment period and healing outcome (decision tree) from maintenance treatment, recurrences and administration of further treatment options (Markov model).

Decision tree

In the decision tree, patients can experience one of four mutually exclusive health states: sustained healing, non-healed, deteriorated and dead (Figure 1). A description of the health states considered in the decision tree is provided in Table 19. Following non-healing, the cohort is assumed to transition to a standard of care (SoC) "basket" health state that accounts for average costs and utilities of subsequent non-surgical and surgical treatments. A SoC "basket" health state is also considered for the cohort that deteriorates while on initial treatment. The decision tree reflects a treatment length of 8 weeks, which represents the total duration of therapy with cenegermin. For artificial tears the treatment length in the decision tree represents the minimum duration of therapy.

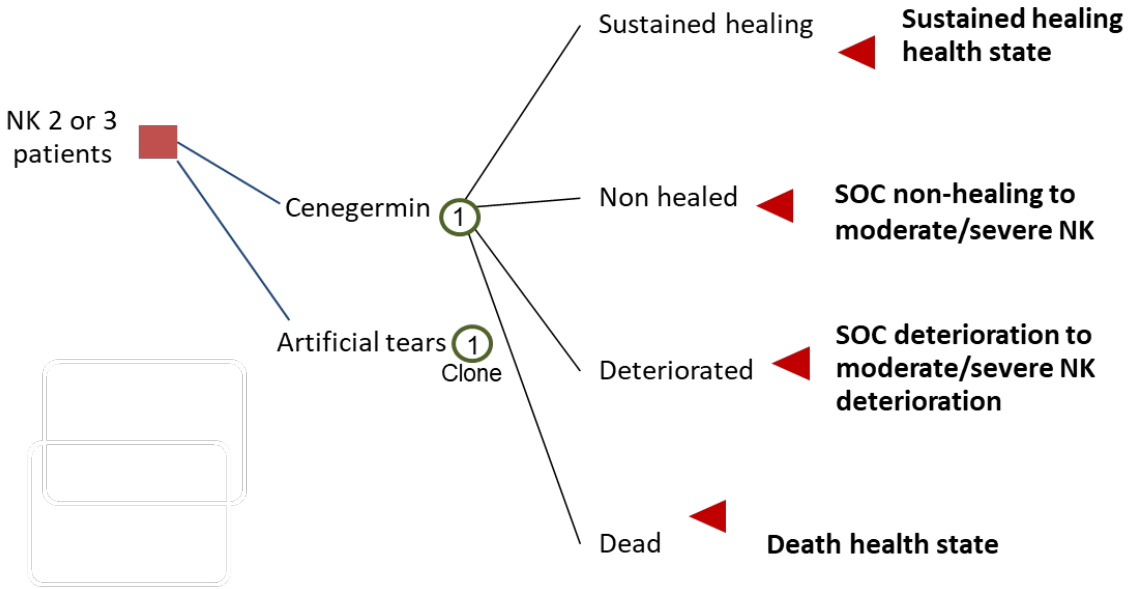

Figure 1 Company decision tree structure

NK=neurotrophic keratitis; SoC=standard of care
Source: CS, Figure 8

Table 19 Health state definitions in the decision tree

Health state	Definition
Sustained healing	Complete corneal healing (using the cenegermin trials end point of staining diameter <0.5 mm)
Non-healed	No improvement in the disease i.e. remaining in starting state (moderate or severe NK)
Deteriorated	As in the cenegermin trials - 'increase in lesion size ≥1 mm, decrease in BCDVA by >5 ETDRS letters, progression in lesion depth to corneal melting or perforation, onset of infection, or 'other' (as reported on the electronic case report form)'
Dead	As a result of all-cause general population mortality, as no disease specific fatality has been observed

BCDVA=best corrected distance visual acuity; ETDRS=Early Treatment Diabetic Retinopathy Study; NK=neurotrophic keratitis
Source: CS, p74

Markov model

At the end of the decision tree treatment pathway, the patients enter the Markov model (Figure 2) in one of four mutually exclusive health states:

- Cohort healed, entering the follow-up model in the 'sustained healing' health state
- Cohort non-healed, entering the follow-up model in the 'SoC non-healing to moderate/severe NK' health state
- Cohort deteriorated, entering the follow-up model in the 'SoC deterioration to moderate/severe NK deterioration' health state
- Cohort dead, entering the follow-up model in the 'death' health state.

A description of the health states considered in the model is provided in Table 20.

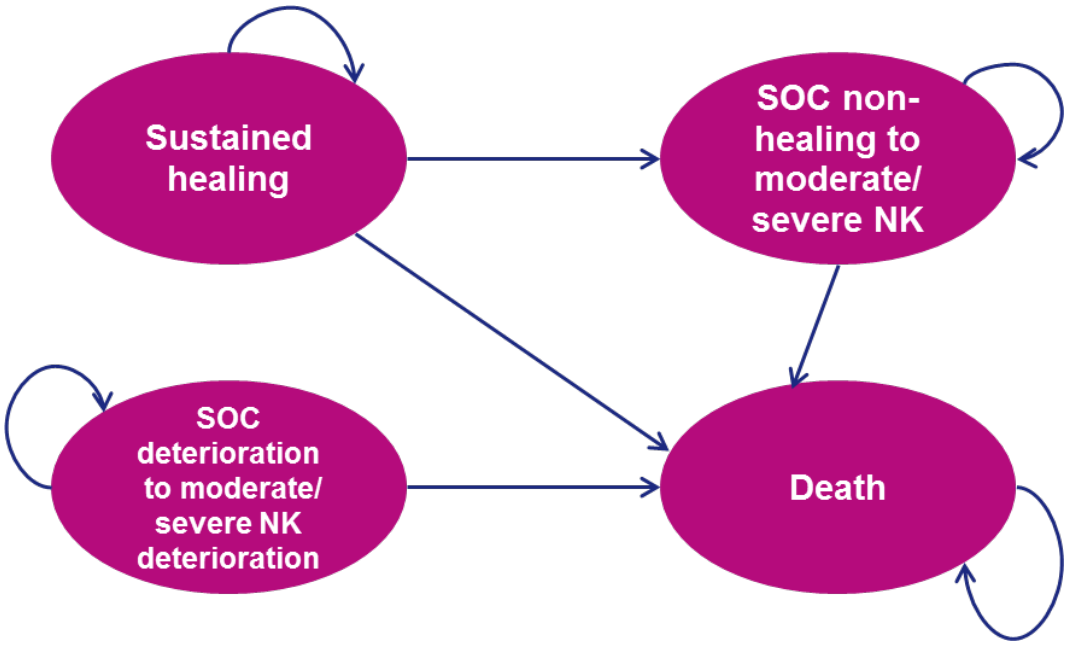

Figure 2 Company Markov model structure

NK=neurotrophic keratitis; SoC=standard of care
Source: CS, Figure 9

Table 20 Health state definitions in the Markov model

Health state	Description
Sustained healing	The epithelial defect is healed; This is the starting state for the cohort that achieved healing in the decision tree treatment model; In the artificial tears arm, the cohort in this health state continue to receive treatment over the entire time horizon of the analysis to maintain healing; The incidence of treatment related AEs is applied to the cohort receiving treatment; The cohort in this health state may experience recurrence of NK and move to SoC non-healing to moderate/severe NK. Recurrence is defined by development of persistent epithelial defect or corneal ulcer following previous healing with a given treatment.
SoC non-healing to moderate/severe NK	This state represents the average of cost and effect of all possible situations that may occur to the cohort following non-healing (or recurrence) with initial NK treatment; This is the starting state for the cohort that were not healed in the decision tree treatment model; A weighted average cost and utility of all possible treatment/non-treatment scenarios following a non-healing/recurrence with initial treatment is considered for the cohort in this health state; This is a semi-absorbing state as from here the cohort may transition to the death state only.
SoC deterioration to moderate/severe NK deterioration	This state represents the average of cost and effect of all possible situations that may occur to the cohort following NK deterioration while on initial NK treatment; This is the starting state for the cohort that had deterioration in the decision tree treatment model. A weighted average cost and utility of all possible treatment/non-treatment scenarios following an initial deterioration is considered for the cohort in this health state; This is a semi-absorbing state as from here the cohort may transition to the death state only.
Death	The cohort dies at rates following mortality in the general UK population

AEs=adverse events; NK=neurotrophic keratitis; SoC=standard of care
Source: CS, Table 17

The cycle length is set to 4 weeks, which the company claims is the minimum amount of time required to observe recurrences (CS, p78). The probability of healing, non-healing and deterioration only define the starting health state in the follow-up model, and transitions across states are based on the probability of recurrence and death. Consequently, the model considers that both the 'SoC non-healing to moderate/severe NK' and 'SoC deterioration to moderate/severe NK deterioration' health states are semi-absorbing and patients in these health states will not improve and can only transition to the death state. The only absorbing state is death based on general population mortality (age- and sex-specific), since NK is not associated with disease-specific mortality and NK treatments do not appear to increase the risk of mortality.

5.3.4 Population

The population reflected in the company model is adult patients with moderate or severe NK in line with cenegermin's licensed EMA indication. The mean baseline age of the cohort (62.6

years), the percentage of females (61.84%) and initial proportion of the cohort with stage 2 NK and stage 3 NK (57.9% and 42.1% respectively) were obtained from pooled trial data from the REPARO trial and Study 0214..

5.3.5 Interventions and comparators

Intervention

Cenegermin eye drops is implemented in the model in line with the licensed dose, i.e. 20 µg/ml solution administered by applying one drop in the affected eye six times per day over a treatment course of 8 weeks.

Comparators

Preservative-free artificial tears is the only comparator included in the cost effectiveness analysis. In the REPARO trial and Study 0214, the comparator was vehicle, which consisted of an identical preparation to cenegermin but without the active ingredient. The company states (CS, p71) that vehicle can be regarded as comparable to preservative-free artificial tears since its composition included ingredients widely used in artificial tears and other ocular lubricants (i.e. trehalose, polyethylene glycol and hydroxypropyl methylcellulose). As highlighted in Section 3.3 of this ERG report, the ERG agrees with the company. Artificial tears are continued over the life-time of the cohort in the follow-up Markov model, based on responses from a survey of clinical experts (CS, p75).

The company conducted an MTC to assess the clinical effectiveness of cenegermin versus other treatments (CS, Section B.2.9 and Appendix D4). As described in Section 4.8 of this ERG report, due to the uncertainty in the results of the MTC, the ERG considers that the inclusion of comparators other than preservative-free artificial tears in the model would also lead to uncertain results.

Standard of care

Following non-healing, recurrence of deterioration with the initial treatment, patients in the cohort transition to a SoC “basket” health state and receive different recurring treatments or combinations of treatments for the remainder of their lifetime. The SoC “basket” accounts for the average costs and utilities of subsequent non-surgical and surgical treatments. The possible treatments that were considered for moderate and severe NK and the proportion of patients that would receive each treatment by stage were derived from market research conducted by the company with 12 corneal specialists in the UK. The estimated proportion of each treatment used, by stage, is presented in the CS (Table 22) and reproduced here in Table 21. Clinical advice to the ERG is that selection of treatments for NK depend on the expertise of the clinician and the availability of the treatments.

Table 21 Proportion of each treatment used, by stage, included in SoC "basket"

Treatment	Stage 2	Stage 3 (corneal ulcer or corneal melting)	Stage 3 (corneal perforation)
Artificial tears (preservative-free)	100%	100%	89%
Autologous serum eye drops	58%	46%	21%
Amniotic membrane transplantation	4%	41%	41%
Contact lenses	31%	36%	67%
Conjunctival flap	0%	25%	13%
Permanent tarsorrhaphy	2%	12%	21%
Temporary tarsorrhaphy	8%	16%	12%
Corneal transplant	0%	8%	46%

Source: CS, Table 22

The company states (CS, p85) that the 12 clinicians surveyed confirmed that there is no established treatment algorithm and patients in the UK typically go through a series of non-surgical palliative treatments in no set order and often, one or more treatments are used concurrently. The ERG notes that although the company states that "…following nonhealing, recurrence or deterioration with the initial treatment, the cohort will receive different recurring treatments or combinations of treatments, and experience healing, non-healing, and recurrences multiple times throughout their lifetime" (CS, p79), the current model does not allow a patient receiving one of the treatments in the SoC "basket" to transition to a 'sustained healing' health state.

5.3.6 Perspective, time horizon and discounting

The company states that the cost effectiveness analysis is undertaken from the perspective of the NHS in England and Wales. The analysis excludes patients' out-of-pocket expenses, carers' costs and lost productivity derived costs. The time horizon in the base case is the lifetime of patients, set at 100 years of age for the cohort, with 5-, 10- and 20-year time horizons included as scenario analyses. Costs and benefits are discounted at a rate of 3.5% per annum.

5.3.7 Treatment effectiveness and extrapolation

Corneal healing

The probability of complete corneal healing at week 8 for cenegermin and for artificial tears was obtained from the cenegermin and vehicle (preservative-free artificial tears) arms respectively, of the pooled REPARO trial and Study 0214. For the probability of healing, the definition of complete corneal healing presented in Table 19 was used. The probability of healing with cenegermin and artificial tears was explored using alternative scenarios:

- REPARO trial only
- REPARO trial only, with the definition of healing of: greatest diameter of staining <0 mm, as per the FDA definition.

The probability of healing with cenegermin and with artificial tears is presented in the CS, Table 18 and reproduced in Table 22 of the ERG report.

Table 22 Odds of complete healing and proportion of patients with complete healing from cenegermin clinical trials

Source of data	Odds ratio vs vehicle	Proportion achieving complete corneal healing
Artificial tears		
Pooled trial data (REPARO and 0214)	N/A	38.2% (95% CI 30.5% to 45.8%)
REPARO	N/A	43.1% (95% CI 34.5% to 51.8%)
REPARO, where healing is defined as per FDA i.e. greatest diameter of staining <0 mm	N/A	33.3% (95% CI 26.7% to 40.0%)
Cenegermin		
Meta-analysis of REPARO and 0214	4.24 (95% CrI 2.11 to 8.50)	72.3% (95% CI 56.6% to 84.0%)*
REPARO	N/A	74.0% (95% CI 53.7% to 94.3%)
REPARO, where healing is defined as per FDA i.e. greatest diameter of staining <0 mm	N/A	72.0% (95% CI 52.1% to 92.0%)

CI=confidence interval; CrI=credible interval; FDA=Food and Drug Administration; N/A=not applicable
*proportion derived using healing odds for vehicle based on pooled trial data
Source: CS, Table 18

Patients were assumed to remain in the sustained healing state except if they died, or experienced a recurrence over the 5 years following treatment initiation. Thus, the treatment effect was extrapolated over a lifetime. The company claims that this is consistent with clinical expert opinion i.e., that the rate of recurrence with all treatments reduces over time and plateaus at 5 years meaning that patients that are completely healed at 5 years will likely remain completely healed indefinitely. Clinical opinion to the ERG is that there is no evidence that patients that are completely healed at 5 years will remain completely healed indefinitely.

Deterioration

The probabilities of deterioration for cenegermin and artificial tears were obtained from the pooled data from the REPARO trial and Study 0214. In the endpoints of the clinical trials, patients that had deterioration at week 8 may or may not have also experienced complete healing. However, the company considered in the model that complete healing and deterioration were mutually exclusive health states. Therefore, the company reanalysed the data to identify the proportion of patients that did not experience complete healing and did experience deterioration. The probabilities of deterioration are presented in the CS (Table 19) and reproduced in Table 23 of the ERG report.

Table 23 Probabilities of deterioration

Study	Treatment	Number of patients deteriorated	Sample size, N	% deteriorated
REPARO	Artificial tears	16	51	31.4
	Cenegermin	7	50	14.0
Study 0214	Artificial tears	[redacted]	24	[redacted]
	Cenegermin	[redacted]	23	[redacted]
Total across REPARO and Study 0214	Artificial tears	[redacted]	75	[redacted]
	Cenegermin	[redacted]	73	[redacted]

Source: CS, Table 19

Recurrence

The probability of NK recurrence refers to the reappearance of moderate/severe NK symptoms and the transition from the 'sustained healing' health state to the 'SoC non-healing to moderate/severe NK' health state. The company states (CS, p83) that data collected on recurrence during follow-up was not recorded consistently and many patients were lost to follow-up. The company's calculation of the recurrence rate is presented in the CS (pp 83-85).

The company converted the recurrence rate of [redacted] observed in the REPARO clinical trial over 48 weeks into a probability of NK recurrence per cycle (4 weeks) of [redacted], this probability is assumed to apply for the first 5 years following initial treatment on the basis of clinical expert opinion. In the company model, it is assumed that no patients experienced a recurrence event after 5 years. The recurrence rate of artificial tears was assumed to be the same as the rate for cenegermin in the model.

5.3.8 Health-related quality of life

HRQoL data were collected as part of the REPARO trial and Study 0214 and are discussed in Section 4.7 of this ERG report. No clear treatment effect or differences in EQ-5D utility values by health state were observed. The company claims (CS, pp 87-88) that patients that are non-healed may report a greater HRQoL improvement than the healed patients (score changes of 0.0197 versus 0.0117) as a consequence of improved signs of healing, such as epithelium growth over the corneal wounds which can occur with cenegermin and causes pain. Until the re-epithelisation process is complete, the growing epithelium may cause corneal sensitivity that temporarily manifests as pain and reduced visual acuity. Clinical opinion to the ERG is that the rationale presented by the company for non-healed patients having higher HRQoL than healed patients is plausible, however there is no evidence to support the company's reasoning.

The average baseline utility between the cenegermin and vehicle arms of the pooled REPARO trial and Study 0214 of 0.635 was used as the utility value at baseline for all health states. Patients in the 'SoC non-healing to moderate/severe NK' and 'SoC deterioration to

moderate/severe NK deterioration' health states are assumed to receive a SoC "basket" of non-surgical and surgical treatments. The proportions of patients that receive disfiguring surgeries and surgeries that result in unilateral blindness were obtained from the company's survey of 12 UK clinical experts. Details of the company's calculations of disutility associated with tarsorrhaphy are provided in the CS (pp 90-91). The disutilities included in the SoC "basket" and used in the model are reproduced in Table 24. No additional disutilities associated with other treatments in the SoC "basket" were incorporated in the model.

Table 24 Disutilities included in the SoC "basket"

Treatment	Disutility	Duration	Patients receiving treatment		
			Stage 2	Stage 3 (corneal ulcer or melting)	Stage 3 (corneal perforation)
Permanent tarsorrhaphy	0.205	Indefinite	2%	12%	21%
Temporary tarsorrhaphy	0.205	10 weeks	8%	16%	12%
Total annual disutility			0.008	0.030	0.048

Source: CS, Table 24

A utility decrement of 0.02 is applied when patients experience a deterioration (i.e. the first cycle of the 'SoC deterioration to moderate/severe NK deterioration' health state). The utility values used in the cost effectiveness analysis are presented in Table 25.

Table 25 Utility values used in the model

State	Utility value	Company justification
Baseline health utility used in treatment model Sustained healing health state in follow-up model	Mean=0.635 SD=0.3043	Average baseline utility between cenegermin and vehicle arms of the pooled REPARO trial and Study 0214
Non-healing health states SoC non-healing to moderate/ severe NK SoC deterioration to moderate/ severe NK deterioration	0.618	Baseline utility of 0.635 minus 0.017 surgical treatment in SoC "basket" Variability (95% CI) not reported so standard deviation was assumed to be 10% of the mean
Deterioration event	-0.02	Utility decrement observed in patients that had deteriorated at week 8, compared to baseline: pooled cenegermin and vehicle arm of the REPARO trial and Study 0214

CI=confidence interval; NK=neurotrophic keratitis; SD=standard deviation; SoC=standard of care
Source: CS, Table 25

5.3.9 Adverse events

Treatment-related AEs were considered within each health state according to NK treatment. AEs resulted in HRQoL decrements, but some AEs incurred additional costs. Treatment-related AEs with cenegermin and artificial tears were obtained from pooling data from the REPARO trial and Study 0214, with only mild or moderate AEs being observed. Eye pain was the most common AE reported in both the REPARO trial and Study 0214. The pooled incidence of eye pain used in the model following treatment with cenegermin is 7/76 (9.2%) compared to 3/76 (3.9%) following treatment with preservative-free artificial tears.

The company did not identify studies reporting health state utilities for treatment-related AEs in NK or with cenegermin or artificial tears and could not identify utility decrements for eye pain, the most common AE. Since the eye pain was mild to moderate and is expected to be part of the course of healing, this was set to zero in the base case analysis with an assumed disutility of 0.05 being used in sensitivity analysis.

5.3.10 Resources and costs

Drug costs

Cenegermin and artificial tears are both self-administered treatments and do not require treatment-specific monitoring.

The cost of Hylo-Forte (0.2%) is used in the base case analysis; clinical opinion to the company is that this is the most commonly used preservative-free artificial tears treatment. Each box of artificial tears was assumed to last 2 weeks, thus the monthly cost was assumed to be £19.00. Since in clinical practice this cost is more variable, the impact of varying the cost of artificial tears was tested in sensitivity analysis. Drug acquisition costs are presented in Table 26.

Table 26 Drug acquisition costs

Drug	Price	Quantity per box	Unit definition	Price per unit	Source
Cenegermin	£14,500	8-week course of treatment			List price
Artificial tears+ointment Hylo-Forte (0.2%)	£9.50	10	ml	£0.95	British National Formulary[80]

Source: CS, Table 26

Resource use by health state

Resource use according to each health state was estimated based on the company's survey of 12 clinical experts. The resource use by health state was assumed to consist of a number of visits to a specialist. To estimate the mean number of specialist visits per month, the company assumed that a period of hospitalisation was equivalent to 10 specialist visits. Hospitalisation was assumed to last between 10 to 14 days. Patients with sustained healing are estimated to visit a specialist less than once a month, on average. 'SoC non-healing to moderate/ severe NK' patients are estimated to visit a specialist 5.1 times per month and deteriorating patients 10 times per month. All patients are assumed to incur the resource use associated with the 'SoC non-healing to moderate/ severe NK' health state at baseline. The cost associated with specialist visits is presented in Table 27.

Table 27 Mean specialist visits by stage of NK and health state and total costs per month

Stage of NK	Sustained healing	SoC non-healing to moderate/ severe NK	SoC deterioration to moderate/ severe NK deterioration
Stage 2	0.8	3.7	6.2
Stage 3 (corneal ulcer or melting)	0.9	7.8	9.6
Stage 3 (corneal perforation)	1.0	8.0	10.0
Average	0.8	5.1	7.4
Total cost	£73.25	£444.57	£642.76

NK=neurotrophic keratitis; SoC=standard of care
Source: CS, Table 27

Standard of care basket

Treatment-related resource use is defined as all visits, examinations and medications associated with the management of patients receiving a given treatment. Clinical advice to the company is that, upon initiation of treatment with autologous serum eye drops or an amniotic membrane transplantation or tarsorrhaphy, a routine blood exam, serology test and blood microbiological culture would be conducted. The SoC "basket" is applied as a monthly cost. The cost of treatment consists of:

1. ongoing monthly treatment costs (in the case of artificial tears, autologous serum eye drops and contact lenses), which are multiplied by the duration in years to give an average cost
2. surgical costs for the remaining treatments given in the SoC "basket".

The unit costs of each treatment included in the SoC "basket" are provided in Table 28.

Table 28 Unit costs of treatments included in the SoC "basket"

Treatment/ procedure	Unit cost	Cost detail	Treatment duration	Source
Artificial tears	£19.00	2 bottles, assumed to cover 1 months' treatment	0.76 years*	British National Formulary[80]
Contact lens	£34.50	1 single lens, assumed to last the duration of treatment	0.32 years*	Limbal fir gas permeable rigid £34.50 (Lens Catalogue UK)[81]
Autologous serum eye drops	£372.26	Conservatively using cost of maintenance treatment (3-month supply)	1 year or less	Sharma et al. 2015[82]
Temporary tarsorrhaphy	£697.61	One-off surgery	0.2 years*	National Reference Cost 2015/16 - BZ46A, Minor Oculoplastics Procedures, 19 years and over[83]
Semi-permanent tarsorrhaphy	£697.61	One-off surgery	1 year or less	
Amniotic membrane transplantation	£2,789.17	One-off surgery	1 year or less	National Reference Cost 2015/16 - BZ46A, Minor Oculoplastics Procedures, 19 years and over, day case [83]
Keratoplasty	£2,851.74	One-off surgery	1 year or less	National Reference Cost 2015/16 - BZ60B, Very Complex, Cornea or Sclera Procedures, with CC Score 0-1[83]
Conjunctival flap	£1,418.24	One-off surgery	1 year or less	National Reference Cost 2015/16 - BZ64A, Intermediate, Cornea or Sclera Procedures, with CC Score 1+[83]

*Based on an average response in a survey of 12 clinical experts, weighted by number of patients
Source: CS, Table 28

The total cost per cycle for the health states receiving the SoC "basket" treatments costs is provided in Table 29.

Table 29 Cost per cycle for the health states receiving SoC "basket" treatments

Health state	Treatment costs	Costs of visit to specialist	Total cost
SoC non-healing to moderate/severe NK	£112.83	£444.57	£557.40
SoC deterioration to moderate/severe NK deterioration	£112.83	£642.76	£755.58

NK=neurotrophic keratitis; SoC=standard of care
Source: CS, Table 29

5.3.11 Cost effectiveness results

Total costs, life years gained (LYG), QALYs and incremental costs per QALY gained for the cost effectiveness comparison of treatment with cenegermin versus artificial tears are shown in Table 30. In the base case, cenegermin generates more benefits than artificial tears (+0.08 QALYs) at a decreased cost of £21,549. In the company base case, cenegermin is dominant when compared to artificial tears.

Table 30 Base case cost effectiveness results

Technologies	Total			Incremental			ICER per QALY gained
	Costs	LYG	QALYs	Costs	LYG	QALYs	
Artificial tears	£86,242	15.21	9.49	-£21,549	0	0.08	Cenegermin dominant
Cenegermin	£64,693	15.21	9.56				

LYG=life years gained; QALY=quality adjusted life year; ICER=incremental cost effectiveness ratio
Source: CS, adapted from Table 32

5.3.12 Sensitivity analyses

Deterministic sensitivity analyses

The company carried out one-way sensitivity analyses to explore the sensitivity of model results to variations in the magnitude of various model inputs. The results of the one-way sensitivity analyses are presented in Figure 13 of the CS. The results show that varying the utility of the non-healing health states in the follow-up model has the biggest effect on the company's cost effectiveness results, followed by the starting age, the discount rate and the probability of healing with cenegermin versus artificial tears. Cenegermin remained cost effective in all scenarios.

Scenario analyses

Cost effectiveness results from seven different scenarios are presented in the CS and are summarised in Table 31. Considering a time horizon of 5 years, cenegermin generates more benefits than artificial tears (+0.02 QALYs) at an increased cost of £3,139. The ICER for this scenario for the comparison of cenegermin versus artificial tears is £127,390 per QALY gained. Cenegermin is dominant when compared to artificial tears in all other scenarios investigated by the company.

Table 31 Results of scenario analysis

Technologies	Total			Incremental			ICER per QALY gained
	Costs	LYG	QALYs	Costs	LYG	QALYs	
Scenario: time horizon 5 years							
Artificial tears	£25,266	4.58	2.86	£3,139	0	0.02	£127,390
Cenegermin	£28,405	4.58	2.88				
Scenario: time horizon 10 years							
Artificial tears	£46,214	8.23	5.14	-£5,351	0	0.04	Cenegermin dominant
Cenegermin	£40,862	8.23	5.18				
Scenario: time horizon 20 years							
Artificial tears	£73,908	13.06	8.15	-£16,560	0	0.07	Cenegermin dominant
Cenegermin	£57,347	13.06	8.21				
Scenario: Recurrence rate [redacted]							
Artificial tears	£93,609	15.21	9.47	-£14,380	0	0.06	Cenegermin dominant
Cenegermin	£79,229	15.21	9.52				
Scenario: Recurrence rate of [redacted] **over lifetime rather than first 5 years only**							
Artificial tears	£90,295	15.21	9.48	-£17,605	0	0.07	Cenegermin dominant
Cenegermin	£72,690	15.21	9.54				
Scenario: EMA endpoint REPARO trial (proportions) both for cenegermin and vehicle							
Artificial tears	£82,551	15.21	9.50	-£19,147	0	0.07	Cenegermin dominant
Cenegermin	£63,403	15.21	9.57				
Scenario: FDA endpoint REPARO trial (proportions) both for cenegermin and vehicle							
Artificial tears	£89,819	15.21	9.48	-£24,873	0	0.09	Cenegermin dominant
Cenegermin	£64,946	15.21	9.56				

LYG=life years gained; QALY=quality adjusted life year; ICER=incremental cost effectiveness ratio
Source: CS, adapted from Tables 34-39

Probabilistic sensitivity analyses

The company's probabilistic sensitivity analysis (PSA) involved varying only a limited number of parameters (probabilities, proportions, utility and disutility data, costs, resource use, odds ratios and age). The cost effectiveness plane and the cost effectiveness acceptability curves for the company's base case are shown in Figure 3 and Figure 4 respectively. The PSA results suggest that cenegermin dominates artificial tears. Results of company analyses suggest that, for this treatment comparison, there is a 97.6% probability of treatment with cenegermin being cost effective at a threshold of £20,000 per QALY gained and a 97.7% probability of cenegermin being cost effective at a threshold of £30,000 per QALY gained.

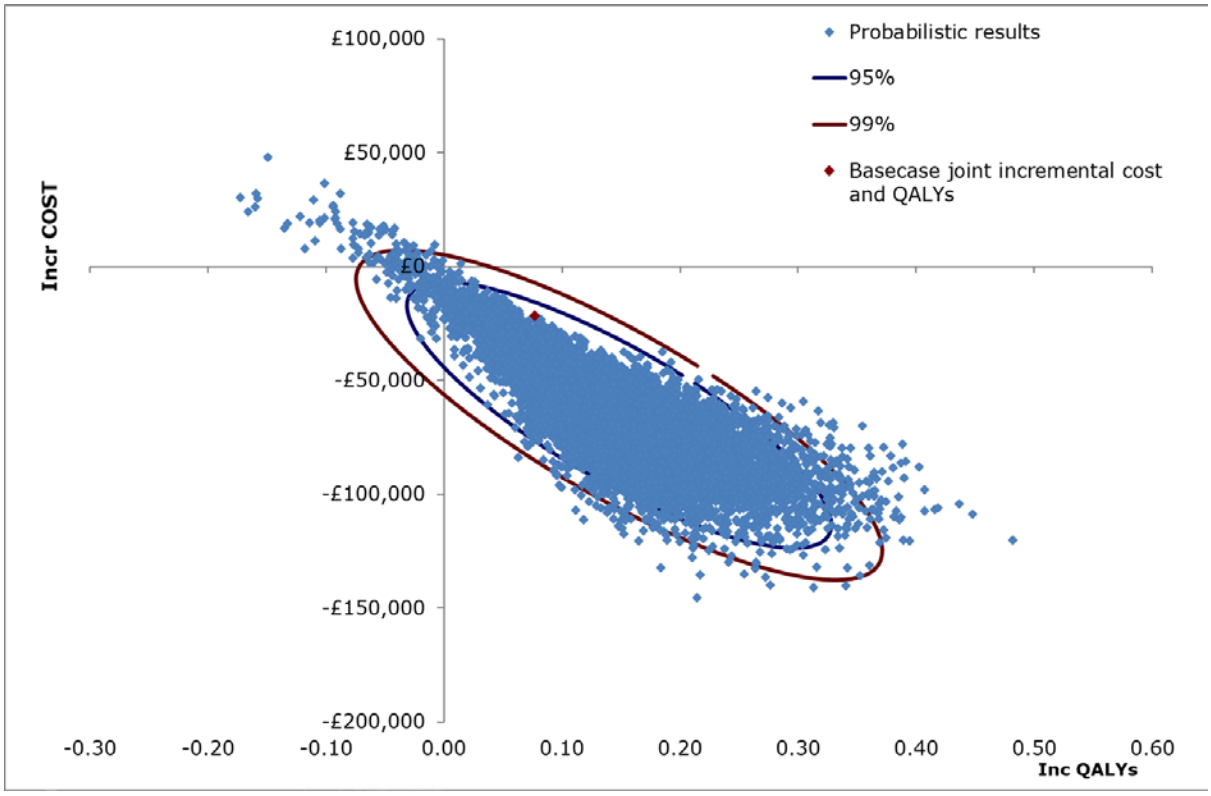

Figure 3 Cost effectiveness plane

Source: CS, Figure 11

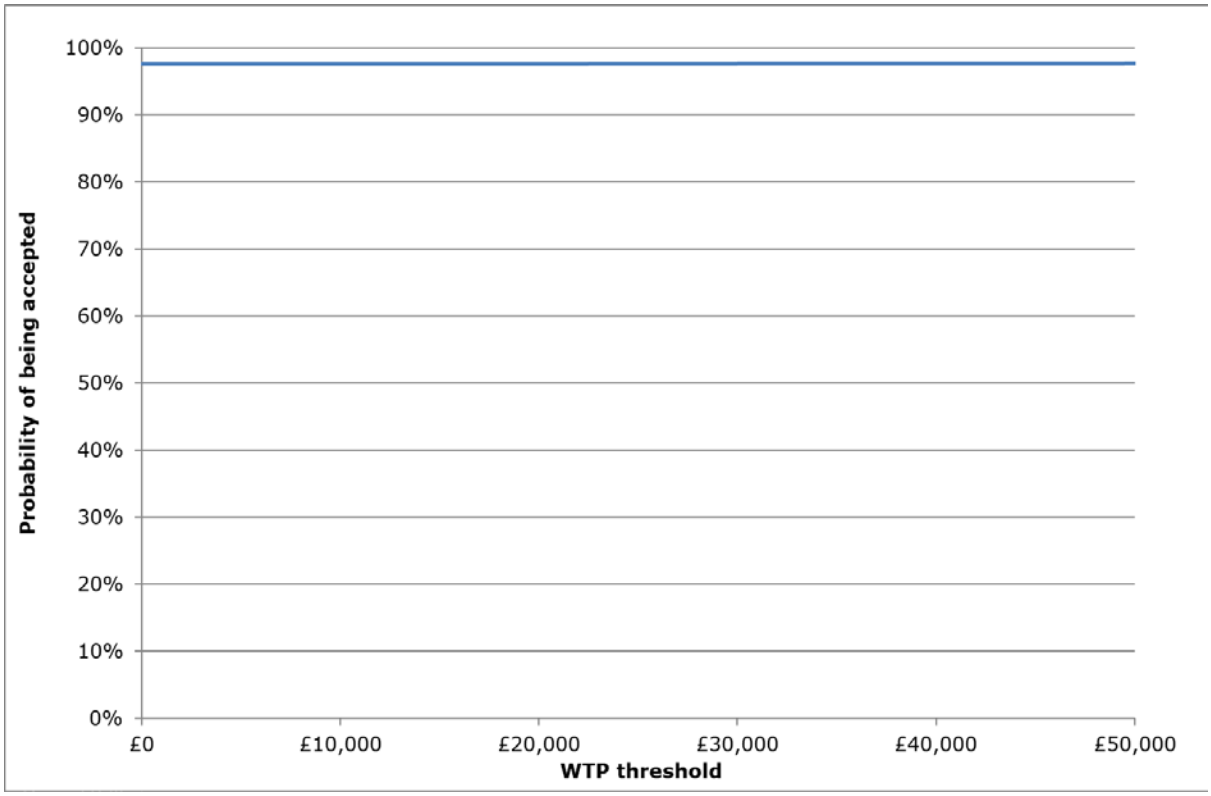

Figure 4 Cost effectiveness acceptability curve

Source: CS, Figure 12

5.4 Detailed critique of company economic model

5.4.1 Drummond checklist

Table 32 Drummond critical appraisal checklist completed by the ERG

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	
Was a comprehensive description of the competing alternatives given?	Yes	
Was the effectiveness of the programme or services established?	Yes	
Were all the important and relevant costs and consequences for each alternative identified?	No	The effectiveness of comparators to cenegermin outside of artificial tears was not established or included in the economic model
Were costs and consequences measured accurately in appropriate physical units?	Yes	
Were the cost and consequences valued credibly?	No	As patients cannot enter a healed state of the markov model after the first cycle, the model generates implausible costs associated with both treatment and clinician visits
Were costs and consequences adjusted for differential timing?	Yes	
Was an incremental analysis of costs and consequences of alternatives performed?	Yes	
Was allowance made for uncertainty in the estimates of costs and consequences?	Partial	Whilst extensive sensitivity analysis was performed, as the model did not allow movement into a sustained healing state after the first cycle the model had a structural flaw that made the analyses of uncertainty performed of limited value
Did the presentation and discussion of study results include all issues of concern to users?	Partial	The company did not provide adequate rationale for some of the assumptions made

AEs=adverse events; ERG=Evidence Review Group

5.4.2 Overview

The ERG considers that the submitted company model has a structural flaw that renders it inappropriate to inform decision making as no realistic ICER per QALY gained can be calculated. There is considerable uncertainty in the utility values used in the company model. Additionally, costs and utility values have not been incorporated in the model correctly.

5.4.3 Structural flaw in the company model

As described in Section 5.3.3, after an initial decision tree element which determines whether patients achieve sustained healing, patients enter a Markov process with three NK states: sustained healing, non-healing or deteriorating with death as an absorbing state.

In each cycle, patients can transition from the sustained healing state to a non-healing state. This is the only transition that can occur in the model apart from a transition to death. Therefore, patients cannot transition from:

- a “non-healing” or “deteriorating” state to a “sustained healing” state
- a “sustained healing” or “non-healing” state to a “deteriorating” state.

In the model, the limitations associated with health state transitions have the following implications:

- all of the treatments offered within the SoC basket are effectively assumed to be completely ineffective at moving non-healed patients or deteriorating patients to a sustained healing state
- all treatments in the “non-healing” state are 100% effective at stopping deterioration
- for patients in the deteriorating state, their NK will continue to deteriorate until death with no treatment ever halting the deterioration but the deterioration never results in removal of the diseased eye.

The ERG accepts that the modelling of NK is problematic given the limited evidence available on the natural history of the disease and on the NHS treatment pathway in the UK. The ERG acknowledges the efforts of the company to produce a simplified model to estimate the cost effectiveness of cenegermin versus artificial tears. However, the ERG considers that in simplifying the model to the point where there is no transition occurring between health states (notably back into the sustained healing state), the company has introduced a structural flaw that means the model produces implausible estimates of costs and therefore cost effectiveness results.

Costs in the model are applied as monthly costs based upon expected resource use in each of the three health states as estimated from the results of the company’s telephone survey of 12 clinicians. The survey was also used to estimate the number of specialist visits per cycle in each health state and to estimate the proportion of treatments that every patient in each health state would receive. Resource use and costs in each health state do not change over time.

The combination of the health state costing method and the model structure (i.e., keeping people in unhealed and deteriorating states until death), results in the following implausible resource use/cost estimates (calculated by the ERG from the base case of the company model):

- on average, patients receiving artificial tears will see a specialist for their NK 1,224 times over their lifetime at a total undiscounted cost of £71,993 (725 visits at a total undiscounted cost of £42,340 with cenegermin)

- the average patient receiving artificial tears will incur an undiscounted lifetime cost from amniotic membrane transplantation of £3,221 which is equivalent to every patient in the model having the procedure on average of 1.15 times. The results of the company's telephone survey of 12 clinicians suggest that no patients with sustained healing, 4% of patients with stage 2 NK and 41% with stage 3 NK, would receive amniotic membrane transplantation. These figures conflict with the amniotic membrane transplantation assumption included in the model. Similar issues of implausible treatment usage occur for other 'one-off' treatments (such as tarsorrhaphy) or treatments that would not be given continuously for the remainder of a patient's life (such as serum eyedrops)
- patients who have permanent tarsorrhaphy or amniotic membrane transplantation are assumed to incur exactly the same treatment costs and require the same number of specialist visits before and after the procedure, regardless of treatment outcome.

To address the structural flaw, the model should allow patients, as a minimum, to move to the sustained healing state in line with the efficacy gains from treatments in the SoC basket. Whilst the ERG accepts that the evidence of efficacy of other treatments compared to cenegermin is uncertain, the company's assumption that these treatments have zero efficacy gains contrasts with the findings of the company's clinician survey which asked specifically for 'complete healing' rates with different SoC treatments. As an example, clinician responses for autologous serum eye drops achieving complete healing ranged between 50% and 85%. The same clinician survey also asked clinicians for recurrence rates after treatments at 6 months, 1 year and 5 years and the proportion of patients that experienced deterioration (see Table 24 of this ERG report).

The ERG raised the importance of the structural flaw within the company model during the clarification process and requested that the company's model be restructured to produce more realistic ICERs per QALY gained. In their clarification response, the company stated that they were satisfied with the model structure and that use of the SoC basket captured the effectiveness of the treatments currently available to treat NK. In the model, patients cannot move to the 'sustained healing' state, therefore, the ERG does not agree with the company's viewpoint. All patients who are not in the 'sustained healing state' continue to receive treatments and require specialist visits in exactly the same manner at the start of the model as they do at the end of their life in the model so it is unclear in what sense the effectiveness of treatments has been captured.

The company stated, in their additional clarification response to the ERG that they had asked a clinician to estimate the likely number of specialist visits that patients receiving treatments included as part of the SoC basket would require. This was in response to the ERG raising concerns with the high number of specialist visits being estimated in the model; the clinician

survey had already asked for this information and it is unclear to the ERG why the question was asked again to a single clinician. Based upon the single clinician's response that a patient who had not healed 'may see a specialist once a week for approximately 6 months, thereafter seeing a specialist once a month' and that the proportion of patients having amniotic membrane transplantation recurrence would be around 50% over 2 years, the company estimated that the average number of specialist visits per patient in an unhealed state would be two per month (as opposed to 3.7 to 10 visits used in the base case model).

Assuming two visits per month in the "non-healed" or "deteriorating" health states means that non-healed patients in the artificial tears arm of the model will see a specialist about their NK, on average, about 450 times over their lifetime compared the initial company base case assumptions of 1,227 times. The ERG considers this high number of specialist visits is still implausible for the average patient and that the basis of the calculation is not robust. It is not clear to the ERG why amniotic membrane transplantation was chosen as the basis for this calculation and notes that the clinician said patients 'may' be seen once a week for 6 months, not that this was the case for the average patient which is required for use in the model. However, applying a value of two specialist visits per month for patients who do not have sustained healing results in cenegermin no longer being a dominant strategy compared to artificial tears, resulting instead in an ICER for cenegermin compared to artificial tears of £22,737 per QALY gained (as reported by the company in their additional clarification response to the ERG).

Given that the company had information on SoC treatment effectiveness and recurrence rates from the clinician survey (other parts of which provided the majority of the evidence to construct the model), the ERG considers that it would have been feasible for the company to construct an exploratory model with patients being allowed to move into a sustained healing state and back into a non-healing state as well as from a non-healing state to a deterioration state. The ERG considers that the company's refusal to restructure the model means that the model available is structurally flawed and is therefore unfit for informed decision making.

5.4.4 Additional model issues

In addition to the structural flaw in the company model outlined above, the ERG considers that there are issues with the utility values and costs incorporated into the model. The ERG has recalculated the ICERs per QALY gained based upon alternative cost and utility values, however, these ICERs should not be interpreted as being ERG preferred values. Rather, the ERG revised ICERs per QALY gained should be interpreted as being better estimates ONLY if the company's model structure were valid. Without creating a new economic model – which

the ERG considers to be beyond its remit – the ERG considers that none of the ICERs per QALY gained presented in the CS or in this ERG report should be considered robust.

Utility values

No statistically significant differences in EQ-5D utility values were reported in the REPARO trial and Study 0214 before and after treatment. These results can be considered to reflect the largely asymptomatic nature of NK (or the ineffectiveness of cenegermin and artificial tears at addressing the symptoms of NK that impact on HRQoL as measured by the EQ-5D). The utility values used in the model were therefore almost entirely derived from a disutility value applied for tarsorrhaphy (the same value was applied for permanent and temporary tarsorrhaphy). Consequently, this means that the utility values for the sustained healing state only differ from the non-healing and deteriorating states due to a proportion of patients without sustained healing having a disutility from undergoing permanent or temporary tarsorrhaphy.

The disutility applied for tarsorrhaphy was estimated to be 0.205. Given a baseline utility of 0.635, a patient having tarsorrhaphy would therefore have a utility of 0.43 and such a low utility value warrants strong supporting evidence. The ERG considers that the tarsorrhaphy utility decrement – based upon a disfigurement disutility from cataract (0.14) and disfigurement for unilateral blindness (0.065) – is highly speculative, poorly evidenced and likely to be inaccurate. In addition, the utility value chosen for cataract already includes an element for loss of visual acuity so the addition of a reduction in utility value for blindness may be considered as double counting. Nevertheless, blindness would only occur if the tarsorrhaphy was full and not partial (i.e. the whole eyelid was sewn together). Clinical advice to the ERG is that tarsorrhaphy tends to be partial.

Even if the utility decrements were correct, the disutilities are applied jointly and from the first cycle in the model meaning that:

- patients have a utility decrement applied for both temporary and permanent tarsorrhaphy even though the utility decrement for permanent tarsorrhaphy is applied for a whole year. This assumption only holds if patients having a temporary tarsorrhaphy do not have a permanent tarsorrhaphy in the same year
- patients having a temporary tarsorrhaphy have the disutility for the tarsorrhaphy applied every year. This is despite clinical advice to the ERG being that most patients would have a temporary tarsorrhaphy only once in their lifetime
- disutility from temporary and permanent tarsorrhaphy occurs over the entire lifetime of patients within the model even though clinical advice to the ERG is that tarsorrhaphy would only be considered in the most severe cases and after other avenues had been explored. Applying the disutility from the very start of the model therefore overestimates the lifetime QALY loss from the procedures.

The ERG considers that, given the flawed model structure, there is limited room to explore the impact of the utility values used in the model and how they have been applied on the size of the base case ICER per QALY gained. However, applying a disutility for temporary tarsorrhaphy every year is inappropriate and can be relatively easily adjusted in the company model to only apply in the first year.

Applying a disutility for temporary tarsorrhaphy only for the first year of the model results in a disutility from the procedures of 0.017 in the first year reducing to 0.009 from the second year onwards. In the company base case, the QALY gain would fall from 0.07 to 0.05 and cenegermin would remain dominant. Using the assumption of an average of two specialist visits per month for patients without sustained healing - as suggested by the company in the clarification response – the change to utility values would increase the size of the company ICER from £22,737 per QALY gained with cenegermin to £39,343 per QALY gained.

Addressing the other utility issues in the model – such as making adjustments for tarsorrhaphy not always resulting in blindness and applying the tarsorrhaphy disutility any time after the start of the model – would also reduce the size of the QALY gain from cenegermin and therefore would further increase the size of the ICER per QALY gained.

Treatment costs in SOC basket

The ERG considers that, given the current company model structure, there is nothing meaningful that can be done to adjust the model to more accurately estimate the number of specialist visits. However, the ERG considers that some changes can be made to reduce the implausible treatment costs that arise in the model due to the application of the costs of one-off treatments every cycle throughout the lifetime of a patient.

The ERG adjusted the costs in the company model so that surgical treatments would only occur in the first year. This adjustment reduced the monthly cost of treatment per patient without sustained healing (excluding the visits to specialists) from year 2 onwards from £112.82 in the company base case to £41.62. The ERG considers that this monthly cost is still likely too high as almost all of the remaining costs relate to autologous serum eye drops, which, according to clinical advice to the ERG, are unlikely to be given throughout the lifetime of the average patient.

Adjusting the monthly costs from year 2 onwards does not stop cenegermin being dominant compared to artificial tears in the company base case. However, using the assumption of two specialist visits a month, as suggested by the company in the clarification response, together

with the adjustment to monthly treatment costs would result in an ICER of £72,682 per QALY gained for cenegermin compared to artificial tears.

Mortality rates

The company has assumed that mortality rates in the model are equal to that of the general population. The mean EQ-5D-5L utility value in the pooled studies was 0.6350 (CS, Table 25). This compares to the mean EQ-5D-3L utility value for people aged 55-64 of 0.80[84] (with a starting age in the model of 63). This suggests that the patients receiving cenegermin in the clinical trials and, therefore, as a patient population as a whole, have more and/or more severe health conditions besides NK compared to the average population. The mortality rates of patients with NK are therefore, likely on average to be higher than the general population.

If a higher mortality rate than the rate adopted by the company were used in the model, there would be two effects from the lower life expectancy of patients. First, there would be less time on average that patients would be alive who had undergone tarsorrhaphy and therefore less QALYs would be lost from the procedure. Second, the average time period over which patients would be treated for NK without healing would decrease thus reducing the overall costs of SoC. These two effects would reduce the QALY gain with cenegermin and reduce the costs of artificial tears compared to cenegermin. Both effects would therefore result in an underestimate of the true ICER per QALY gained for cenegermin versus artificial tears.

The ERG has not amended the model to adjust for background mortality. However, the ERG considers that even if there were no other concerns about the validity of the company's ICERs, the assumption of equal mortality rates of NK patients to those of the general population would mean that ICERs produced by the company would be optimistic.

5.4.5 Conclusions of the ERG cost effectiveness critique

The company has produced a model that the ERG does not consider to be fit for purpose. In the company model, it is assumed that patients who do not achieve sustained healing with initial treatment with cenegermin or artificial tears never achieve sustained healing and only have palliative treatments with frequent (up to 10 times per month) visits to specialists for the rest of their lives. The ERG considers such a high number of specialist visits per month to be implausible. Furthermore, the implicit assumed zero efficacy of treatments in the SoC basket at achieving sustained healing contrasts with the company's own clinician survey.

Without restructuring and reconstructing the model, the ERG cannot present a plausible or preferred ICER per QALY gained. However, the company did suggest during the clarification process that lower estimates for the number of specialist visits for patients without sustained

healing than had been assumed in the company base case would be more appropriate and this would move cenegermin from being dominant to having an ICER of £22,737 per QALY gained compared to artificial tears. Even if the ERG was satisfied with the model structure, there were errors in the way utility values and the costs of one-off treatments were applied in the model. Making the ERG adjustments to utility values and costs, together with the company clarification suggestion about the reduced number of specialist visits would result in an ICER of £125,764 per QALY gained. Due to the model's structural weakness the ERG does not present this figure as a preferred ICER but simply as a more accurate estimate of the company base case ICER within the confines of the flawed model structure. However, this value is still likely to be an underestimate of the ICER per QALY gained for cenegermin versus artificial tears as:

- the average number of specialist visits for people initially treated with artificial tears seems implausibly high at approximately 450 over a patient's lifetime. If the value is lower than 450, the ICER per QALY gained for cenegermin would increase
- the utility decrements for tarsorrhaphy are uncertain but the values used may be too high as all patients with tarsorrhaphy are assumed to suffer unilateral blindness from the procedure when this is not the case. If the utility decrement for tarsorrhaphy is lower than assumed in the model, then the ICER for cenegermin would increase
- mortality in the model has likely been underestimated resulting in an overestimate of the QALY gain with cenegermin and an overestimate of the costs of treatment for people initially treated with artificial tears.

6 END OF LIFE CRITERIA

End of life considerations do not apply.

7 OVERALL CONCLUSIONS

7.1 Clinical effectiveness

The company has presented evidence from two small phase 2 RCTs that demonstrates that at 8 weeks, for patients with stage 2 or stage 3 NK, cenegermin results in improved corneal healing compared to vehicle. In the trials, vehicle was similar to artificial tears used in clinical practice. The population of patients in the trials have characteristics similar to those of patients seen in the NHS. AEs, particularly eye pain, are common with cenegermin but these tend to be mild or moderate in severity and do not require treatment discontinuation or any corrective treatment. Furthermore, transient eye pain is not always a sign of an AE and can be related to the healing process in patients with NK, reflecting improved corneal sensitivity. No robust interpretations or conclusions can be drawn from the HRQoL results. It should also be noted that only 24 patients included in the trials were randomised to receive the commercially available formulation of cenegermin (i.e. including methionine) and only a further 10 patients received this formulation during an uncontrolled 8 week treatment period.

While artificial tears are used to treat patients with stage 2 and stage 3 NK, they are often used in addition to other interventions. The company therefore conducted an MTC to compare cenegermin with other comparators. However, the results from the MTC were associated with such uncertainty that no conclusions could be drawn from the results of the MTC.

7.2 Cost effectiveness

Cost effectiveness results presented by the company suggest that cenegermin dominates vehicle. However, the results of the sensitivity and scenario analyses presented by the company suggest that the ICER per QALY gained could be as high as £127,390.

The ERG considers that the company has submitted a cost effectiveness model that has a major structural flaw; the model fails to allow patients to enter a ‘sustained healing’ state from ‘non-healing’ and ‘deteriorating’ states or to move into a ‘deteriorating state’ from a ‘non-healing’ state. The ERG considers that this structural flaw results in such implausible resource use assumptions that the model is not fit for purpose. The company does not agree with the ERG that that the submitted model is structurally flawed. The company considers that the submitted model is simple, is structurally sound and that the ICERs generated are informative.

Without restructuring and reconstructing the model, the ERG cannot present a plausible or preferred ICER per QALY gained. Due to the model’s structural flaw, the ERG considers a more accurate (although conservative) estimate of the company base case ICER, within the confines of the flawed model structure, to be £125,764 per QALY gained.

7.3 Implications for research

Data for the relative effectiveness of cenegermin compared with serum eye drops and amniotic membrane transplantation would be of clinical benefit.

The ERG notes the recommendation from the Royal College of Ophthalmologists statement that, given the rarity of NK, in the event of NICE approval, all patients should be entered into a national audit of outcomes.

The ERG also notes that the company has informed the EMA that a new clinical study (NGF0215) will be conducted using the commercially available formulation of cenegermin (i.e. including methionine). It is noted that this study should provide additional efficacy data on the prolonged use of cenegermin (i.e. beyond 8 weeks) and help enrich the safety database with long-term data for the commercial formulation.

The ERG considers that further data on the efficacy and safety of cenegermin by NK stage and by progressive or non-progressive disease may be informative to clinical decision making.

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9 APPENDICES

9.1 Studies of comparator treatments included in the company's systematic review

The company included 41 studies that investigated the clinical effectiveness of the comparator treatments listed in the decision problem in its systematic review.[40,43,44,48-54,56,60-62,64-67,70-77,85-99] Of these, 22 studies enrolled only patients with NK.[40,43,51,53,54,60,71,73,74,77,85-89,92-94,96-99] Nine studies were presented as conference abstracts only.[73,87,88,90-94,97] Only two studies were RCTs.[54,75]

The most common interventions examined by these studies were amniotic membrane transplantation (n=13)[43,49,50,52-54,56,61,62,64,65,72] and autologous serum eye drops (n=10).[44,48,51,60,70,73-77] Corneal healing was investigated by 30 studies,[43,44,50-54,60-62,64-66,70-72,74-77,85-89,93-96,99] including both RCTs.[54,75] The first of the RCTs was a double-masked study conducted in India that compared 31 patients randomised to umbilical cord serum therapy with 29 patients randomised to autologous serum eye drops.[75] However, only 12 patients in this study had NK (eight and four patients randomised to each treatment arm respectively). The second RCT was also conducted in India.[54] This open-label study of 30 patients with NK compared the efficacy of amniotic membrane transplantation (n=15) with 'conventional management' (n=15; tarsorrhaphy, n=11; bandage contact lens, n=4).

9.2 Studies of comparator treatments included in the company's 'clinical extension review'

The company included 42 studies which investigated the clinical effectiveness of the comparator treatments listed in the decision problem in its 'clinical extension review''.[36,38-78] Of these, 12 studies included exclusively patients with NK.[36,40,41,43,51,53,54,60,71,73,74,77] One study was presented as an abstract only.[73]

Amniotic membrane transplantation (n=16)[42,43,49,50,52-57,61,62,64,65,69,72] and autologous serum eye drops (n=14)[39,44,48,51,60,63,68,70,73-78] were the most commonly investigated interventions. Corneal healing was investigated by 33 studies,[38,39,41-46,48,50-55,57,59-66,68,70-72,74-78] including the only two RCTs of comparator treatments also included in the company's 'clinical extension review'.[54,75]

The ERG notes that not all the studies included in the 'clinical extension review' were included in the company's systematic review. Indeed, only 27 studies of comparator treatments were included in both reviews.[36,40,43,44,48-54,56,60-62,64-67,70-77] Five of the studies that were included in the company's systematic review were excluded from the 'clinical extension review' because the intervention was not deemed to be relevant.[85,88,91,95,98] It is unclear why eight other studies were excluded,[86,87,89,90,92,96,97,99] but the ERG notes that in four instances, the intervention

studied was CACICOL®.[87,92,97,100] Three studies of CACICOL were included in the systematic review,[85,88,91] but excluded from the 'clinical extension review' with the reason given for exclusion being "intervention" (CS, Table 6 of Appendix D3). Of the additional 15 studies included in the 'clinical extension review', 14 studies included fewer than five patients with NK so did not meet the inclusion criteria for the systematic review.[38,39,41,42,45,47,55,57-59,63,68,69,78] The other study included 25 patients with NK treated by temporary or permanent tarsorrhaphies;[46] it is therefore unclear why this study was excluded from the systematic review.

9.3 Studies included in the company's mixed treatment comparison

Studies considered for inclusion into the MTC were the two cenegermin trials plus 23 studies of comparator treatments included in the 'clinical extension review'.[39,43,44,46,48,50-54,56,57,60-64,66,70,72,74,76,78] Only one of the included studies of comparator treatments was an RCT.[54] This RCT is the RCT that was also included in the company's systematic review which compared the efficacy of amniotic membrane transplantation in 15 patients versus 'conventional management' (tarsorrhaphy, n=11; bandage contact lens, n=4). The other RCT could not be included in an MTC because it did not provide data for NK patients only.[75] See Section 4.8 of this ERG report for more information on the MTC conducted by the company.

9.4 Randomised controlled trial included in the company's mixed treatment comparison

Only one of the included studies of comparator treatments included in the company's MTC was an RCT.[54] In this trial, thirty patients with NK were enrolled from a cornea services centre based in New Delhi, India, from May 2001 to March 2003 to compare the efficacy of amniotic membrane transplantation (n=15) with NK versus 'conventional management' (tarsorrhaphy, n=11; bandage contact lens, n=4). The results from this trial show that at the end of 3 months follow-up, 11/15 patients (73.3%) treated with amniotic membrane transplantation had complete epithelialization and healing of corneal ulcer compared with 10/15 patients (66.7%) in the 'conventional management' arm (p=0.96).