RGN-259 for neurotrophic keratopathy

LAY SUMMARY

Neurotrophic keratitis is a condition in which the cornea, the clear front part of the eye, becomes damaged. It is caused by nerve damage which leads to ulcers forming on the cornea. It can be very difficult to treat and some patients will need eye surgery.

RGN-259 is a new drug for the treatment of neurotrophic keratitis that is given as eye drops. Some studies have suggested the RGN-259 may be helpful for people who already have quite severe damage to their eye.

If RGN-259 is licensed for use in the UK, it could be a new treatment option for patients with this condition, which could reduce the need for surgery.

NIHR HSRIC ID: 11475
TARGET GROUP

- Neurotrophic keratopathy: stage 2 and 3.

TECHNOLOGY

DESCRIPTION

RGN-259 (GBT-201; TB4; thymosin beta-4) is a synthetic version of the 43-amino-acid peptide thymosin β4 (TB4), which is a matrix metallopeptidase (MMP)-9 and MMP-1 modulator that was originally isolated from the thymus and is a wound healing agent. TB4 binds to actin and regulates its activity within cells. It promotes endothelial cell differentiation and keratinocyte migration, downregulates a number of inflammatory cytokines and chemokines, and promotes expression of laminin-5, a key component in the wound healing process. In phase III clinical trials, RGN-259 was administered as an ophthalmic 0.1% solution five times daily for four weeks.\(^a\)

RGN-259 does not currently have Marketing Authorisation in the EU for any indication.

RGN-259 is currently in phase III clinical trials for xerophthalmia. It is also in phase II trials for unspecified ulcers, wound healing, epidermolysis bullosa and corneal ulcers.

INNOVATION and/or ADVANTAGES

If licensed, RGN-259 will offer an additional treatment option for patients with stage 2 and 3 keratopathy.

DEVELOPER

RegeneRx Biopharmaceuticals.

AVAILABILITY, LAUNCH OR MARKETING

RGN-259 is a designated orphan drug in the USA. It is in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Neurotrophic keratopathy (NK) is a degenerative disease characterised by decreased corneal sensitivity and poor corneal healing resulting from impaired corneal innervation.\(^2,3\) This disorder leaves the cornea susceptible to injury and decreases reflex tearing.\(^2\) Epithelial breakdown can lead to ulceration, infection, melting, and perforation secondary to poor healing.\(^2,3\)

The most common causes of impairment of corneal sensation are viral infection (herpes simplex and herpes zoster keratoconjunctivitis), intracranial space-occupying lesions (neuroma, menigioma and aneurysms), and neurosurgical procedures that damage the

\(^a\) Company provided information.
trigeminal ophthalmic branch\textsuperscript{4,5}. Other ocular causes include ocular surface injury (chemical or thermal burns), corneal dystrophy and contact lens wear\textsuperscript{4}. Many systemic conditions are also associated with the development of corneal anaesthesia, including diabetes mellitus, multiple sclerosis and some congenital syndromes\textsuperscript{3,4,5}.

NK is classified into three stages according to severity\textsuperscript{3,4}:

- **Stage 1** – mild, non-specific signs and symptoms, characterised by corneal epithelial changes with dry and cloudy cornea.
- **Stage 2** – non-healing corneal epithelial defect, characterised by recurrent and/or persistent epithelial defects which are surrounded by poorly adherent opaque and oedematous epithelium.
- **Stage 3** – often ensues if stage 1 and 2 are not appropriately treated. Characterised by corneal ulcer with stromal involvement which may be complicated by stromal melting and progression to corneal perforation.

**NHS or GOVERNMENT PRIORITY AREA**

This topic is relevant to:


**CLINICAL NEED and BURDEN OF DISEASE**

NK is classified as an orphan disease with an estimated prevalence of less than 5 per 10,000 individuals worldwide\textsuperscript{4}. Although the epidemiology of NK has not been accurately determined, the prevalence and incidence of the disease may be estimated from epidemiological data on conditions associated with NK\textsuperscript{4}. NK develops in an average 6% of herpetic keratitis cases, which have a prevalence of 149 per 100,000 population, and in 13% of herpes zoster keratitis cases, which have a prevalence of 26 per 100,000 population\textsuperscript{2,4}. In addition, 2.8% of patients who underwent surgical procedures for trigeminal neuralgia (1.5 per 10,000 population\textsuperscript{6}) subsequently developed NK\textsuperscript{4}. The percentage of NK cases associated with other conditions, such as diabetes mellitus, multiple sclerosis, corneal dystrophy, and congenital diseases is not known.

In 2014-15, there were 2,426 hospital admissions for keratitis (ICD-10 H16) equating to 10,437 bed days and 2,569 finished consultant episodes in England\textsuperscript{7}.

The population likely to be eligible to receive RGN-259 could not be estimated from available published sources.

**PATIENT PATHWAY**

**RELEVANT GUIDANCE**

**NICE Guidance**


CURRENT TREATMENT OPTIONS

Current treatments for NK aim to prevent progression of corneal damage and to promote epithelial healing. Therapy should be promptly initiated, and is based on the clinical stage of the disease:

- **Stage 1**
  - Preservative-free artificial tears.
  - Punctual occlusion.

- **Stage 2**
  - Prophylactic antibiotic drops and preservative-free artificial tears.
  - Corneal or scleral therapeutic contact lenses.
  - Lateral tarsorrhaphy (surgical closure of the eyelids).
  - Amniotic membrane transplantation over the epithelial defect.
  - Injection of botulinum A toxin into the upper eyelid levator muscle.

- **Stage 3**
  - Prophylactic antibiotic drops and preservative-free artificial tears.
  - In cases of stromal melting, topical collagenase inhibitors such as N-acetylcysteine, tetracycline or medroxyprogesterone, may be administered.
  - Lateral tarsorrhaphy.
  - Conjunctival flap surgery.
  - Lamellar or penetrating keratoplasty.
  - Amniotic membrane transplantation.
  - Larger defects may require lamellar or penetrating keratoplasty.

EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>NCT02600429, RGN-NK-301; RGN-259 vs placebo; phase III.</th>
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<td>Sponsor</td>
<td>ReGenTree, LLC.</td>
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<tr>
<td>Status</td>
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<td>Source of information</td>
<td>Trial registry¹, manufacturer.</td>
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<td>Location</td>
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<td>Design</td>
<td>Randomised, placebo-controlled.</td>
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<tr>
<td>Participants</td>
<td>n=46; aged 18 years and older; stage 2 or 3 neurotrophic keratopathy in at least one eye; no clinically significant slit lamp findings at visit 1 that may interfere with study parameters; no significant blepharitis, meibomian gland dysfunction, lid margin inflammation or active ocular allergy that requires treatment; no lid function abnormality (such as lagophthalmos) which in the opinion of the investigator is the primary cause of the persistent epithelial defect; no diagnosis of ongoing ocular...</td>
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infection or active inflammation; no use of fluoroquinolone-containing antibiotic eye drops; no use of contact lenses within 14 days prior to visit 1; no use of immunosuppressive therapy; no uncontrolled systemic disease that interferes with study parameters.

Schedule
Randomised to RGN-259 0.1% ophthalmic solution 5 times a day; or placebo ophthalmic solution 5 times a day.

Follow-up
Active treatment for 4 wks, follow-up for approximately 6 wks (2 wks post-treatment).

Primary outcome/s
Complete healing of the persistent epithelial defect at day 29 as determined by corneal fluorescein staining.

Secondary outcome/s
Percentage of subjects achieving complete healing at 8, 15, 22, 36, 43 days as determined by corneal fluorescein staining; epithelial defect measurement and classification as stage 1, 2 or 3 using Mackie Classification; tear film break-up time at 29, 36, 43 days; ocular discomfort questionnaire at 8, 15, 22, 29, 36, 43 days; visual acuity at 8, 15, 22, 29, 36, 43 days; Other outcome measures: change in biomicroscopy using slit-lamp at 8, 15, 22, 29, 36, 43 days; corneal sensitivity using an aesthesiometer (Cochet-Bonnet); safety; change in biomicroscopy using dilated fundoscopy at 29 and 43 days; intraocular pressure at 29 and 43 days.

Expected reporting date
Study completion date reported at Aug 2016.

ESTIMATED COST and IMPACT

COST
The cost of RGN-259 is not yet known.

IMPACT - SPECULATIVE

Impact on Patients and Carers
- Reduced mortality/increased length of survival ✓ Reduced symptoms or disability
- Other □ No impact identified

Impact on Health and Social Care Services
- Increased use of existing services □ Decreased use of existing services
- Re-organisation of existing services □ Need for new services
- Other □ None identified

Impact on Costs and Other Resource Use
- Increased drug treatment costs □ Reduced drug treatment costs
- Other increase in costs □ Other reduction in costs
- Other: uncertain unit cost compared to existing treatment options. ✓ None identified

Other Issues
- Clinical uncertainty or other research question identified □ None identified
REFERENCES


