# Manuscript Details

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<th>OPHTHA_2017_2894_R1</th>
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<td><strong>Title</strong></td>
<td>Phase I Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis</td>
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<td>Case Report</td>
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<tr>
<td><strong>Corresponding Author</strong></td>
<td>Alessandro Lambiase</td>
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<td><strong>Corresponding Author's Institution</strong></td>
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<tr>
<td><strong>Order of Authors</strong></td>
<td>Stefano Bonini, Alessandro Lambiase, Paolo Rama, Isabella Filatori, Marcello Allegretti, Wendy Chao, flavio mantelli</td>
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</tbody>
</table>
Phase I Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis

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S.B.: Consultant/advisor – Dompé Farmaceutici, SpA.
A.L.: Consultant/advisor – Dompé Farmaceutici, SpA.
Financial Support: Supported by Dompé Farmaceutici SpA. The sponsor participated in the design and conduct of the study; data collection for pharmacokinetics and immunogenicity assessments; management, analysis, and interpretation of the data; and preparation and review of the manuscript. The sponsor was not involved in efficacy data collection for masked central analysis.

Trial registration: ClinicalTrials.gov identifier: NCT01756456

Appendix 1: The REPARO Study Group

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This article contains additional online-only material. The following should appear online-only:

Appendix 1 (REPARO Study Group)

Figure S1 (CONSORT diagram)

Figure S2 (PK results)
Neurotrophic keratitis/keratopathy (NK), a rare degenerative corneal disease, lacks effective pharmacologic therapies. Because NK pathology involves trigeminal nerve damage and loss of corneal innervation, nerve growth factor (NGF) is surmised to promote healing of NK. Preliminary studies with murine NGF demonstrated efficacy for treating corneal neurotrophic ulcers; however, the complex tertiary structure of NGF has complicated the production of recombinant human NGF (rhNGF) suitable for clinical development. To this end, we developed an *E. coli*-derived rhNGF formulation that demonstrated to be well tolerated and safe for topical ophthalmic use in a phase I study in healthy volunteers. Here, we report phase I results of topical rhNGF for patients with moderate-to-severe NK.

NGF0212/REPARO (Latin, “repair”) was a phase I/II randomized, double-masked, multicenter, vehicle-controlled, parallel group study (ClinicalTrials.gov identifier NCT01756456) that evaluated the safety and efficacy of rhNGF eye drops (10 or 20 µg/ml, 6 drops/day for 8 weeks) in patients with moderate (stage 2) or severe (stage 3) NK. Patients ≥18 years of age with stage 2/3 NK were enrolled according to published diagnostic criteria and inclusion/exclusion criteria described in the REPARO phase II report. Table 1 summarizes patient demographics, baseline characteristics, and prior NK treatments.
Eighteen patients (2 cohorts of 9 consecutively enrolled patients each) with stage 2 or 3 NK gave informed consent and were randomized 7:2 to rhNGF 10 μg/ml vs. vehicle (cohort A) or rhNGF 20 μg/ml vs. vehicle (cohort B). Sample size was based on clinical feasibility (i.e., no formal power calculation was performed), as phase I aimed primarily to assess the safety and systemic absorption of topical rhNGF to support proceeding with phase II, which was conducted, analyzed, and reported separately.5

Patients, investigators, and site/sponsor staff were masked to primary randomized treatment. Indistinguishable treatment kits were randomly assigned by Statistical Analysis System programmers. A clinical research organization maintained the masked database. No formal statistical testing was applied to phase I data. The study obtained institutional review board and independent ethics committee approval (detailed in the phase II report5) and complied with the Declaration of Helsinki, Code of Federal Regulations, and Good Laboratory/Clinical Practice guidelines.

Figure S1 (available at www.aaojournal.org) depicts overall study design and patient disposition, including reasons for withdrawal. The study included an 8-week controlled treatment period and a 48- or 56-week follow-up (duration determined by treatment allocation and corneal healing status during controlled treatment). In the event of treatment failure during the 8-week controlled treatment period (pre-defined as failure to achieve corneal healing, recurrence of NK after healing, or deterioration as described in the phase II report5), vehicle-treated patients were eligible to receive 8 weeks of uncontrolled rhNGF.
treatment (cohort A: 10 µg/ml; cohort B: 20 µg/ml) before continuing follow-up (total 
follow-up: 56 weeks). However, no phase I patients entered the 56-week follow-up period. 

The primary safety variable was incidence of adverse events (AEs), defined per GCP 
guidelines as any untoward medical occurrences in patients who received study treatment, 
regardless of causal or temporal association. Other safety parameters included visual 
analogue scale for ocular tolerability (described in the phase II report), best corrected 
distance visual acuity measured in Early Treatment Diabetic Retinopathy Study (ETDRS) 
letters, intraocular pressure, dilated fundus ophthalmoscopy, vital signs, hematology, and 
clinical chemistry.

Table 1 summarizes treatment-related AEs (TAEs), defined as AEs recorded by the 
investigator as having possible, probable, or highly probable relationships to study 
treatment, during controlled treatment. Eye pain and headache were the most frequently 
reported TAEs during controlled treatment, each occurring in 2 patients (28.6%) in the 
rhNGF 20 µg/ml group. TAEs reported during controlled treatment occurred in 1 of 18 
patients each. No TAEs were reported during the 48-week follow-up. No deaths occurred 
controlled treatment or follow-up, nor were there any notable trends or clinically 
significant differences over time or between treatment groups in laboratory parameters, 
vital signs, or other ocular safety assessments.

Pharmacokinetics (PK) profiling was performed as described previously. As shown in 
Figure S2 (available at [www.aaojournal.org](http://www.aaojournal.org)), only two patients had detectable serum NGF
at any time point. Of note, the patient in rhNGF 10 μg/ml group only had one positive NGF measurement during the study, and the patient in the rhNGF 20 μg/ml group had detectable serum NGF levels at all time points, even prior to initiating study treatment. Taken together, the PK results suggest individual fluctuations of endogenous NGF independent of study treatment.

Although the phase I study was not designed or powered for efficacy outcomes, corneal healing (<0.5 mm fluorescein staining in the lesion area) was assessed in clinical pictures by central readers (masked to treatment assignment and duration) at week 4 (primary endpoint) and week 8 (key secondary endpoint). At week 4, based on post-baseline last-observation-carried-forward analysis, corneal healing was achieved by 1/4 patients (25.0%) receiving vehicle, 3/7 patients (42.9%) receiving rhNGF 10 μg/ml, and 3/7 patients (42.9%) receiving rhNGF 20 μg/ml. Of patients with responses available at week 8, corneal healing was achieved by 1/2 patients (50%) receiving vehicle, 4/6 patients (66.7%) receiving rhNGF 10 μg/ml, and 6/7 patients (85.7%) receiving rhNGF 20 μg/ml. No phase I patients discontinued due to a lack of efficacy or inadequate control of NK. Prior to week 8, no patients in any treatment group experienced deterioration. At week 8, 1 patient who received rhNGF 20 μg/ml experienced a decrease in BCDVA score of >5 ETDRS letters.

The REPARO phase I study demonstrated that topical ophthalmic rhNGF (10 or 20 μg/ml), administered 6 drops/day for 8 weeks, was well tolerated in patients with stage 2/3 NK. No safety concerns arose; most AEs were ocular, mild, transient, and did not require
discontinuing or corrective treatments. Most patients had undetectable serum NGF, and systemic AEs were infrequent and mild. This is consistent with previous PK findings in healthy volunteers\textsuperscript{4} and lack of detectable systemic NGF or immunogenicity in the phase II study.\textsuperscript{5} Taken together, these results suggest unlikely systemic absorption or accumulation of rhNGF. Favorable trends in corneal healing suggest that topical ophthalmic rhNGF may be effective for treating patients with moderate-to-severe NK.
REFERENCES


Table 1. Patient demographics, baseline characteristics, prior treatments, and treatment-related adverse events* (controlled treatment period).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>rhNGF 10 μg/ml (N=7)</th>
<th>rhNGF 20 μg/ml (N=7)</th>
<th>Vehicle (N=4)</th>
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</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>61.7 (21.47)</td>
<td>52.0 (17.24)</td>
<td>64.3 (24.06)</td>
</tr>
<tr>
<td>Median (min, max)</td>
<td>67.0 (29, 80)</td>
<td>55.0 (24, 71)</td>
<td>68.5 (34, 86)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>3 (42.9)</td>
<td>4 (57.1)</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
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<td>Hispanic, Latino, or Spanish</td>
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<td>N/A</td>
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<tr>
<td><strong>Race, n (%)</strong></td>
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<tr>
<td>White</td>
<td>7 (100.0)</td>
<td>6 (85.7)</td>
<td>4 (100.0)</td>
</tr>
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<td>N/A</td>
<td>0</td>
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<td><strong>Primary NK diagnosis, n (%)</strong></td>
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<tr>
<td>Stage 2</td>
<td>3 (42.9)</td>
<td>5 (71.4)</td>
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<td>Stage 3</td>
<td>4 (57.1)</td>
<td>2 (28.6)</td>
<td>2 (50.0)</td>
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<td><strong>Underlying etiology, n (%)</strong></td>
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<td>Diabetes mellitus</td>
<td>1 (14.3)</td>
<td>2 (28.6)</td>
<td>1 (25.0)</td>
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<td>Dry eye disease</td>
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<td>Herpetic eye disease*</td>
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<td>2 (28.6)</td>
<td>2 (50.0)</td>
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<td>Neurosurgical procedure (medulloblastoma excision)</td>
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<td>1 (14.3)</td>
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<td>Cataract surgery/scleral buckle/vitrectomy</td>
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<tr>
<td>Stroke</td>
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<td><strong>Prior treatments, n (%)†</strong></td>
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<tr>
<td>Artificial tears/gels/ointments</td>
<td>1 (14.3)</td>
<td>6 (85.7)</td>
<td>3 (75.0)</td>
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<td>Preservative free artificial tears/gels/ointments</td>
<td>4 (57.1)</td>
<td>4 (57.1)</td>
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<td>Topical antibiotics</td>
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<td>Other</td>
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<td><strong>n</strong></td>
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<td>Any adverse event</td>
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<td>Muscle spasms</td>
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Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; min = minimum; max = maximum; N/A: not available (ethnicity and race were not collected in all countries); N = number of patients randomized to each treatment group at baseline; n = number of patients in each category; N' = number of adverse events reported, n' = number of patients reporting the adverse event; rhNGF = recombinant human nerve growth factor; SD = standard deviation. Percentages (%) are calculated using the number randomized to each treatment group (N) as the denominator.

*Treatment-related adverse events are those events recorded by the investigator as having a possible, probable, or highly probable relationship to study treatment.

†Includes herpes simplex, herpes zoster, and recurrent herpetic keratitis

‡Patients may have received more than one prior treatment

§Disease progression was defined as increase in lesion size ≥ 1mm; decrease in best corrected distance visual acuity (BCDVA) by >5 Early Treatment Diabetic Retinopathy Study (ETDRS) letters; progression in lesion depth to corneal melting or perforation; or onset of infection. One patient in the rhNGF 10 μg/ml group had ≥ 1mm increase in lesion size from baseline. One patient had a transient decrease in blood pressure from baseline.
Appendix 1. REPARO Study Group and Administration

STUDY INVESTIGATORS

The following principal investigators were members of the REPARO Study Group:

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- **Ludovic Couillard**, Associate Project Director
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- **Deepa Khadar**, Senior Medical Writer

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The REPARO phase I study evaluated the safety of topical ophthalmic recombinant human nerve growth factor (rhNGF), 6 drops daily for 8 weeks, in 18 patients (two cohorts of 9 consecutively enrolled patients) with neurotrophic keratitis of severity stage 2 (persistent epithelial defect) or stage 3 (corneal ulcer). Enrollment of cohort A (randomized 7:2 to 10 µg/ml rhNGF or vehicle) preceded enrollment of cohort B (randomized 7:2 to 20 µg/ml rhNGF or vehicle). Patients received 8 weeks of controlled treatment and 48 weeks of follow-up. A 56-week follow-up period was intended for vehicle-treated patients who experienced treatment failure (see text for details), and was to include an additional 8 weeks of uncontrolled treatment with 10 µg/ml rhNGF (cohort A) or 20 µg/ml rhNGF (cohort B) before continuing follow-up for 48 weeks. No patients from the phase I study entered the 56-week follow-up.
Figure S2. REPARO Phase I Pharmacokinetics.

Serum concentration of nerve growth factor (NGF) plotted over time for individual patients in the REPARO Phase I study. Blood samples were taken from patients receiving recombinant human NGF (rhNGF) or vehicle for pharmacokinetics (PK) profiling at various time points over the 8-week controlled treatment period (on days 1, 2; weeks 1, 2, 3, 4, 6; day 55; and week 8). Multiple time points (ranging from 0.5 hours pre-dose to 8 hours post-dose) were taken on days at the beginning and end of the controlled treatment period. For the purpose of these plots, measurements below the lower limit of quantification (LLQ) of 32.000 pg/ml were considered as 0 pg/ml, and only patients with measurements >LLQ are shown. In the rhNGF 10 µg/ml group (n=7, ●), one patient had a serum NGF concentration of 130.868 pg/ml (0.5 hours post dose) on day 1, then <LLQ at all other time points tested. In the rhNGF 20 µg/ml group (n=7, ◇), one patient had serum NGF concentrations >LLQ at all time points, even prior to treatment initiation (893.53 pg/ml 0.5 hours pre-dose on day 1) and ranging from 247.7 pg/ml (week 1) to 1010.7 pg/ml (week 3) during the 8-week controlled treatment period. In the vehicle group (n=4, not shown), no patients had detectable serum NGF at any time point tested.