



# Reports



## Phase I Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis

Neurotrophic keratitis/keratopathy (NK), a rare degenerative corneal disease, lacks effective pharmacologic therapies.<sup>1</sup> Because NK pathology involves trigeminal nerve damage and loss of corneal innervation, nerve growth factor (NGF) is surmised to promote healing of NK.<sup>2</sup> Preliminary studies with murine NGF demonstrated efficacy for treating corneal neurotrophic ulcers;<sup>3</sup> 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 *Escherichia coli*-derived rhNGF formulation that demonstrated to be well tolerated and safe for topical ophthalmic use in a phase I study in healthy volunteers.<sup>4</sup> 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](https://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 aged ≥18 years with stage 2 or 3 NK were enrolled according to published diagnostic criteria and inclusion/exclusion criteria described in the REPARO phase II report.<sup>5</sup> [Table 1](#) summarizes patient demographics, baseline characteristics, and prior NK treatments.

Eighteen phase I 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 versus vehicle (cohort A) or rhNGF 20 µg/ml versus vehicle (cohort B). Sample size was based on clinical feasibility (i.e., no formal power calculation was performed), because 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.<sup>5</sup>

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 report<sup>5</sup>) and complied with the Declaration of Helsinki, Code of Federal Regulations, and Good Laboratory/Clinical Practice guidelines.

[Figure S1](#) (available at [www.aaojournal.org](https://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 (predefined as failure to achieve corneal healing, recurrence of NK after healing, or deterioration as described in the phase II report<sup>5</sup>), 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 Good Clinical Practice 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<sup>5</sup>), best-corrected distance visual acuity measured in Early Treatment Diabetic Retinopathy Study 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. Treatment-related AEs reported during controlled treatment occurred in 1 of 18 patients each. No TAEs were reported during the 48-week follow-up. No deaths occurred during 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.<sup>4</sup> As shown in [Figure S2](#) (available at [www.aaojournal.org](https://www.aaojournal.org)), only 2 patients had detectable serum NGF at any time point. Of note, the patient in the rhNGF 10 µg/ml group had only 1 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 before 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 end point) and week 8 (key secondary end point). At week 4, based on postbaseline last-observation-carried-forward analysis, corneal healing was achieved by 1 of 4 patients (25.0%) receiving vehicle, 3 of 7 patients (42.9%) receiving rhNGF 10 µg/ml, and 3 of 7 patients (42.9%) receiving rhNGF 20 µg/ml. Of patients with responses available at week 8, corneal healing was achieved by 1 of 2 patients (50%) receiving vehicle, 4 of 6 patients (66.7%) receiving rhNGF 10 µg/ml, and 6 of 7 patients (85.7%) receiving rhNGF 20 µg/ml. No phase I patients discontinued because of a lack of efficacy or inadequate control of NK. Before 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 best-corrected distance visual acuity score of >5 Early Treatment Diabetic Retinopathy Study letters.

The REPARO phase I study demonstrated that topical ophthalmic rhNGF (10 or 20 µg/ml), administered 6 drops/day for

Table 1. Patient Demographics, Baseline Characteristics, Prior Treatments, and Treatment-Related Adverse Events\*

Characteristics	Recombinant Human Nerve Growth Factor		Vehicle (N=4)
	10 µg/ml (N=7)	20 µg/ml (N=7)	
Age (yrs)			
Mean (SD)	61.7 (21.47)	52.0 (17.24)	64.3 (24.06)
Median (min, max)	67.0 (29, 80)	55.0 (24, 71)	68.5 (34, 86)
Female, n (%)	3 (42.9)	4 (57.1)	2 (50.0)
Ethnicity, n (%)			
Hispanic, Latino, or Spanish	1 (14.3)	0	0
N/A	0	1 (14.3)	0
Race, n (%)			
White	7 (100.0)	6 (85.7)	4 (100.0)
N/A	0	1 (14.3)	0
Primary NK diagnosis, n (%)			
Stage 2	3 (42.9)	5 (71.4)	2 (50.0)
Stage 3	4 (57.1)	2 (28.6)	2 (50.0)
Underlying cause, n (%)			
Diabetes mellitus	1 (14.3)	2 (28.6)	1 (25.0)
Dry eye disease	1 (14.3)	0	0
Herpetic eye disease <sup>†</sup>	1 (14.3)	2 (28.6)	2 (50.0)
Neurosurgical procedure (medulloblastoma excision)	2 (28.6)	1 (14.3)	0
Ocular surgery or procedure			
Cataract surgery/scleral buckle/vitreotomy	1 (14.3)	1 (14.3)	0
Keratoplasty	1 (14.3)	0	0
LASIK	0	1 (14.3)	0
Stroke	0	0	1 (25.0)
Prior treatments, n (%) <sup>‡</sup>			
Artificial tears/gels/ointments	1 (14.3)	6 (85.7)	3 (75.0)
Preservative-free artificial tears/gels/ointments	4 (57.1)	4 (57.1)	2 (50.0)
Topical antibiotics	4 (57.1)	4 (57.1)	3 (75.0)
Therapeutic contact lens	2 (28.6)	1 (14.3)	1 (25.0)
Autologous serum eye drops	1 (14.3)	2 (28.6)	1 (25.0)
Other	0	2 (28.6)	0

TAEs (Controlled Treatment Period)	No. of Events Reported	No. of Patients (%)	No. of Events Reported	No. of Patients (%)	No. of Events Reported	No. of Patients (%)
Body system						
MedDRA preferred term						
Any AE	4	1 (14.3)	12	3 (42.9)	1	1 (25.0)
Eye disorders	3	1 (14.3)	5	3 (42.9)	1	1 (25.0)
Eye pain	0	0	2	2 (28.6)	0	0
Conjunctival hyperemia	2	1 (14.3)	0	0	0	0
Erythema of eyelid	1	1 (14.3)	0	0	0	0
Eye inflammation	0	0	1	1 (14.3)	0	0
Eye irritation	0	0	1	1 (14.3)	0	0
Foreign body sensation in eyes	0	0	0	0	1	1 (25.0)
Photophobia	0	0	1	1 (14.3)	0	0
General disorders and administration site conditions	1	1 (14.3)	3	2 (28.6)	0	0
Disease progression <sup>§</sup>	1	1 (14.3)	0	0	0	0
Fatigue	0	0	1	1 (14.3)	0	0
Instillation site pruritus	0	0	1	1 (14.3)	0	0
Irritability	0	0	1	1 (14.3)	0	0
Nervous system disorders	0	0	2	2 (28.6)	0	0
Headache	0	0	2	2 (28.6)	0	0
Cardiac disorders	0	0	1	1 (14.3)	0	0
Cardiovascular disorder <sup>  </sup>	0	0	1	1 (14.3)	0	0
Musculoskeletal and connective tissue disorders	0	0	1	1 (14.3)	0	0
Muscle spasms	0	0	1	1 (14.3)	0	0

AE = adverse event; max = maximum; MedDRA = Medical Dictionary for Regulatory Activities; min = minimum; N/A: not available (ethnicity and race were not collected in all countries); N = number of patients randomized to each treatment group at baseline; NK = neurotrophic keratitis/keratopathy; rhNGF = recombinant human nerve growth factor; SD = standard deviation; TAE = treatment-related adverse event.

Percentages (%) are calculated using the number randomized to each treatment group (N) as the denominator.

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

<sup>†</sup>Includes herpes simplex, herpes zoster, and recurrent herpetic keratitis.

<sup>‡</sup>Patients may have received >1 prior treatment.

<sup>§</sup>Disease progression was defined as increase in lesion size  $\geq 1$  mm; decrease in best-corrected distance visual acuity by  $>5$  Early Treatment Diabetic Retinopathy Study letters; progression in lesion depth to corneal melting or perforation; or onset of infection. One patient in the rhNGF 10 µg/ml group had  $\geq 1$ -mm increase in lesion size from baseline.

<sup>||</sup>One patient in the rhNGF 20 µg/ml group had a transient decrease in blood pressure from baseline.

8 weeks, was well tolerated in patients with stage 2 or 3 NK. No safety concerns arose; most AEs were ocular, mild, and 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<sup>4</sup> and lack of detectable systemic NGF or immunogenicity in the phase II study.<sup>5</sup> 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.

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