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

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

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A.L.: Consultant/advisor – Dompé Farmaceutici, SpA.

P.R.: Scientific Advisory Board, Dompé Farmaceutici, SpA.

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Trial registration: ClinicalTrials.gov identifier: NCT01756456

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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)

Report (998 of 1000 words)

Neurotrophic keratitis/keratopathy (NK), a rare degenerative corneal disease, lacks effective pharmacologic therapies.[1] Because NK pathology involves trigeminal nerve damage and loss of corneal innervation, nerve growth factor (NGF) is surmised to promote healing of NK.[2] Preliminary studies with murine NGF demonstrated efficacy for treating corneal neurotrophic ulcers[3]; 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.[4] 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.[5] 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 report[5]) 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 report[5]), vehicle-treated patients were eligible to receive 8 weeks of uncontrolled rhNGF

147 treatment (cohort A: 10 μg/ml; cohort B: 20 μg/ml) before continuing follow-up (total
148 follow-up: 56 weeks). However, no phase I patients entered the 56-week follow-up period.
149
150 The primary safety variable was incidence of adverse events (AEs), defined per GCP
151 guidelines as any untoward medical occurrences in patients who received study treatment,
152 regardless of causal or temporal association. Other safety parameters included visual
153 analogue scale for ocular tolerability (described in the phase II report[5]), best corrected
154 distance visual acuity measured in Early Treatment Diabetic Retinopathy Study (ETDRS)
155 letters, intraocular pressure, dilated fundus ophthalmoscopy, vital signs, hematology, and
156 clinical chemistry.
157
158 Table 1 summarizes treatment-related AEs (TAEs), defined as AEs recorded by the
159 investigator as having possible, probable, or highly probable relationships to study
160 treatment, during controlled treatment. Eye pain and headache were the most frequently
161 reported TAEs during controlled treatment, each occurring in 2 patients (28.6%) in the
162 rhNGF 20 μg/ml group. TAEs reported during controlled treatment occurred in 1 of 18
163 patients each. No TAEs were reported during the 48-week follow-up. No deaths occurred
164 controlled treatment or follow-up, nor were there any notable trends or clinically
165 significant differences over time or between treatment groups in laboratory parameters,
166 vital signs, or other ocular safety assessments.
167
168 Pharmacokinetics (PK) profiling was performed as described previously.[4] As shown in
169 Figure S2 (available at 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[4] and lack of detectable systemic NGF or immunogenicity in the phase II study.[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.

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

Characteristics	rhNGF 10 µg/ml (N=7)		rhNGF 20 µg/ml (N=7)		Vehicle (N=4)	
Age (years)						
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 etiology, n (%)						
Diabetes mellitus	1 (14.3)		2 (28.6)		1 (25.0)	
Dry eye disease	1 (14.3)		0		0	
Herpetic eye disease*	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/vitrectomy	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 (%)†						
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	
Treatment-related Adverse Events	**N'**	**n**	**N'**	**n**	**N'**	**n**
Body system						
MedDRA preferred term						
Any adverse event	**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‡	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§	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

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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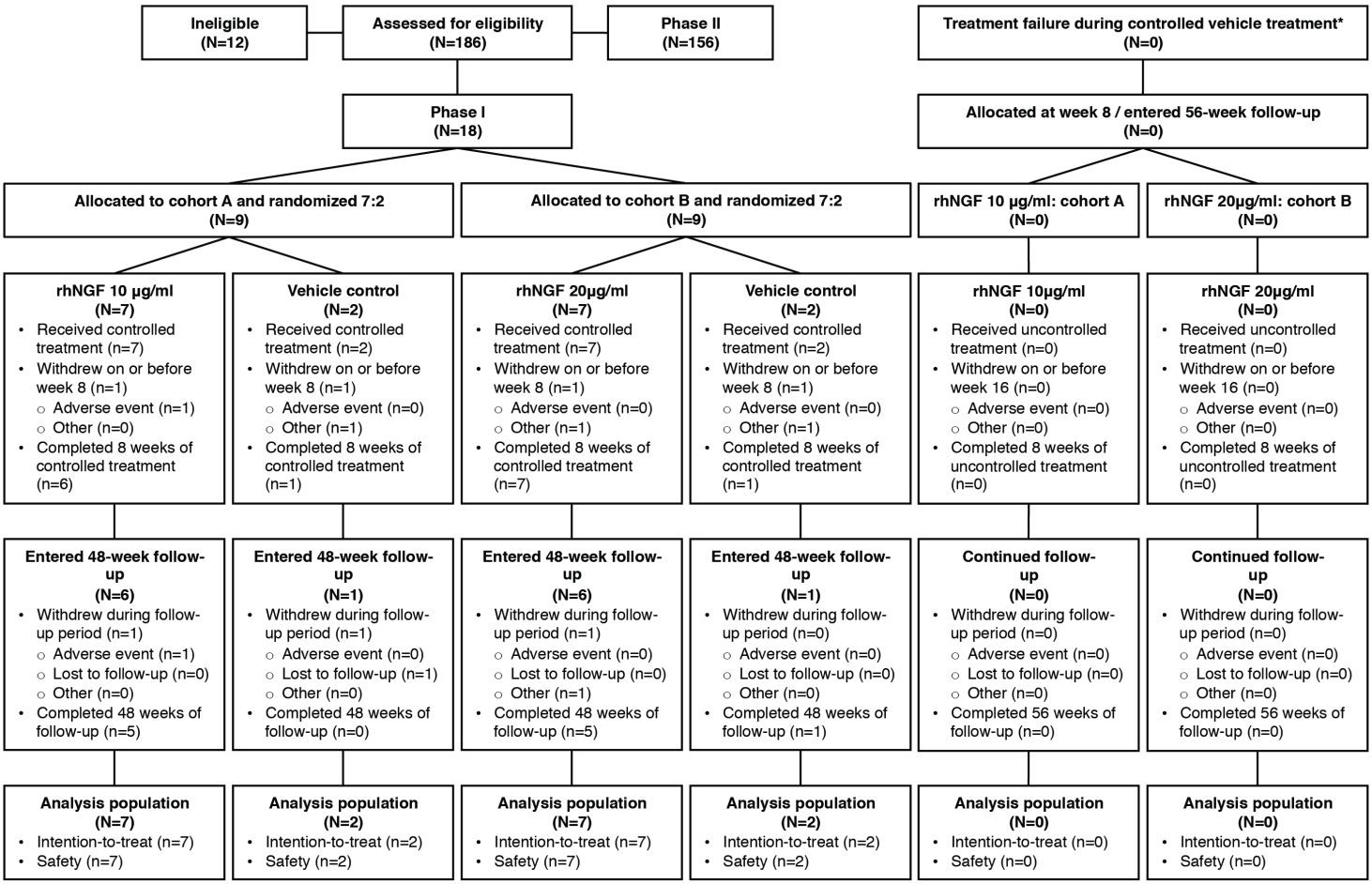
Figure S1. REPARO Phase I study design and overall patient disposition.



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.