CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761094Orig1s000

CLINICAL REVIEW(S)

Medical Officer's Review of BLA 761094
Review #2

BLA 761094	**Submission Date:**	July 19, 2018
	Receipt Date:	July 19, 2018
	Review Date:	July 23, 2018

Applicant: Dompé farmaceutici S.p.A.
Via Santa Lucia
6-20122 Milan, Italy

Applicant's Representative: Lamberto Dionigi.
Regulatory Affairs & Drug Safety Director
39-02-5838-3559

Drug: OXERVATE (cenegermin – bkbj) ophthalmic solution, 20 mcg/mL

Submitted:

Reference is made to the meeting Teleconference of 15-July-2018, in which the FDA has requested to provide information available at Dompé on the use of Oxervate in the pediatric population.

Pediatric patients exposed to Oxervate:
Dompé confirms that Oxervate is not yet approved in Europe for use in children and no clinical studies have been conducted in this population. As far as the company is aware, four (4) Neurotrophic Keratitis (NK) pediatric patients, aged from 2 to 12 years of age, have been exposed to Oxervate.

- A 6-year-old child with severe NK secondary to Stuve-Wiedmann syndrome was treated with Oxervate under "Temporary Authorization for Use" (ATU) in France. Dompé reports that the corneal ulcer was completely healed at the end of the treatment. There were signs of corneal sensitivity recovery by month 8 post-treatment.

- A 9-year-old child with NK was treated with Oxervate under ATU in France. Dompé reports that the lesion improved, but did not completely heal with the treatment. There is no other follow-up information available.

- A 12-year-old child with severe NK was treated with Oxervate under Expanded Access in the US. The patient should have recently completed the treatment, but Dompé has not received additional follow-up information thus far.

- A 2-year-old child with severe NK received off-label Oxervate treatment in Italy. Dompé reports that the lesion completely healed after 2 weeks of treatment with Oxervate. Treatment is still ongoing (July 6, 2018 was treatment Week 4).

No adverse event reports have been submitted to Dompé regarding the use of Oxervate in these patients.

Reviewer's Comments:
Studies NGF0212 and NGF0214 enrolled patients age 18 to 95 years. Dompé has submitted information on additional pediatric patients who have been treated with OXERVATE. No adverse reactions have been reported and no safety concerns revealed in the treatment of these children 2 to 12 years.

It is recommended that the OXERVATE labeling be revised to include the following statement in 8.4 Pediatric Use:

Safety and effectiveness have not been established in pediatric patients below age 2.

Rhea Lloyd, M.D.
Medical Officer

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RHEA A LLOYD
08/06/2018

WILLIAM M BOYD
08/06/2018

CLINICAL REVIEW of BLA 761094

Application Type	BLA
Application Number	761094
Priority or Standard	Priority
Submit Date	December 22, 2017
Received Date	December 22, 2017
PDUFA Goal Date	August 22, 2018
Division/Office	DTOP/OND
Reviewer Name	Rhea A. Lloyd, MD
Review Completion Date	May 11, 2018
Established/Proper Name	cenergermin ophthalmic solution, 20 mcg/mL
(Proposed) Trade Name	Oxervate
Applicant	Dompé farmaceutici S.p.A.
Dosage Form(s)	Topical ophthalmic solution
Applicant Proposed Dosing Regimen(s)	One drop in the affected eye 6 times per day at 2 hour intervals, for eight weeks
Applicant Proposed Indication(s)/Population(s)	(b) (4) neurotrophic keratitis
Recommended Regulatory Action	Approval
Recommended Indication(s)/Population(s)	(b) (4) neurotrophic keratitis.

Table of Contents

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IFU	Instructions for Use
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NGF	nerve growth factor
NK	neurotrophic keratitis
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PED	persistent epithelial defect
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
rhNGF	recombinant human nerve growth factor
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Oxervate (cenegermin ophthalmic solution) is a recombinant form of human nerve growth factor (rhNGF), an endogenous protein which is believed to be involved in the differentiation and maintenance of neurons, which acts through specific high-affinity (i.e., TrkA) and low affinity (i.e., p75NTR) nerve growth factor (NGF) receptors. NGF receptors are expressed in the anterior segment of the eye (cornea, conjunctiva, iris, ciliary body, and lens), by the lacrimal gland, and by posterior segment intraocular tissues. RhNGF is delivered as 20 mcg/mL preservative-free sterile ophthalmic solution in vials for daily use. One drop is to be administered 6 times daily, at approximately 2-hour intervals. Treatment is intended to allow restoration of corneal integrity and the recovery of visual function in neurotrophic keratitis (NK) patients.

1.2. Conclusions on the Substantial Evidence of Effectiveness

BLA 761094 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of Oxervate for the treatment of (b) (4) neurotrophic keratitis.

1.3 Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The data contained in this submission establishes the efficacy of Oxervate (cenergermin ophthalmic solution), 20 mcg/mL dosed six times daily for 8 weeks for the treatment of (b) (4) neurotrophic keratitis.

Studies NGF0212 and NGF0214 demonstrated faster healing of the corneal epithelium in patients treated with cenergermin ophthalmic solution, 20 mcg/mL than in patients treated with the cenergermin vehicle solution. To date, no long-term consequences of cenergermin ophthalmic solution administration have been identified. The most common ocular adverse event for cenergermin ophthalmic solution was eye pain.

There is a favorable benefit-risk ratio of cenergermin ophthalmic solution, 20 mcg/mL in the treatment of neurotrophic keratitis.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Neurotrophic keratitis (NK) is a degenerative corneal disease caused by impairment in the first branch of the trigeminal nerve (cranial nerve V1) which leads to a decrease or absence of corneal sensation. • Loss of corneal sensory innervation interferes with the normal corneal epithelial turnover resulting in epithelial defects which may lead to corneal stromal infection. • Persistent epithelial defects and ulcers of the cornea are sight and eye threatening.	The goal of treatment of epithelial defects is the achievement of complete healing of the corneal epithelium reducing the risk of corneal infections.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There is no FDA approved pharmacologic therapy for the treatment of NK. • Treatment options are supportive and may include therapeutic soft contact lenses, patching, topical autologous serum application, amniotic membrane grafting, tarsorrhaphy or botulinum toxin induced ptosis.	Treatment options are supportive, but do not necessarily improve the speed of healing.
Benefit	• Patients treated with Oxervate demonstrated faster resolution of epithelial defects in two clinical trials (Studies NGF0212 and NGF0214)	Faster resolution of epithelial defects results in less time at risk of corneal infections.
Risk and Risk Management	• Clinical trials were conducted in relatively small numbers of patients. The long-term safety has not been established. • Routine post-market monitoring and reporting of all adverse events are recommended to potentially identify adverse reactions not observed in clinical trials.	Routine monitoring and reporting of all adverse events are expected to be adequate to monitor for potential new adverse reactions.

2. Therapeutic Context

2.1. Analysis of Condition

Neurotrophic keratitis (NK) is a degenerative corneal disease caused by impairment in the first branch of the trigeminal nerve (cranial nerve V1) which causes a decrease or absence of corneal sensation. The cornea is one of the body's most densely innervated regions with sensory nerve endings which exert a trophic influence on the corneal epithelium. Loss of corneal sensory innervation causes a change in the levels of various neuromediators and subsequent decrease in the vitality, metabolism and mitosis of epithelial cells. In NK, the corneal epithelium becomes the primary sight of pathology because the sensory signals meant to promote epithelium repair are not received. Epithelial breakdown can lead to ulceration, melting of the stroma, and ultimately to corneal perforation.

Damage to the fifth cranial nerve may be caused by aneurysms, cerebrovascular accidents, diabetes mellitus, hereditary disorders, herpes zoster ophthalmicus, herpes simplex keratitis, leprosy, multiple sclerosis, surgical trauma, toxicity of certain topical medications, or other tumors. The most common causes of NK are herpetic corneal infections, surgery for trigeminal neuralgia, and surgery for acoustic neuroma.

2.2. Analysis of Current Treatment Options

There is no FDA approved pharmacologic therapy for the treatment of NK.

The medical standard of care is the administration of topical lubricants. For persistent epithelial defects and corneal ulceration, there is no consensus regarding medical or surgical therapies. Treatment options may include therapeutic soft contact lenses, patching, topical autologous serum application, amniotic membrane grafting, tarsorrhaphy or botulinum toxin induced ptosis.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Cenergermin, a recombinant form of human nerve growth factor (rhNGF), is a new chemical entity.

3.2. Summary of Presubmission/Submission Regulatory Activity

- Pre-IND meeting, October 22, 2012
  Non-clinical investigation plan and quality aspects of the rhNGF clinical lots were discussed.
- Orphan Designation granted June 23, 2014
  Designation Request #14-4362 for the treatment of NK (all 3 stages of NK).
- Type C guidance meeting, March 31, 2016
  Phase 2 results of study NGF0212 were presented. Among other Agency guidance, the primary efficacy endpoint acceptable to the Agency was discussed, "complete resolution of corneal staining". It was agreed that a post-hoc analysis using this endpoint would be performed. The Agency recommended writing two different statistical analysis plans for the EMA and FDA.
- Pre-BLA meeting, January 2017
- Email communication, October 2, 2017
- Email communication, October 31, 2017

3.3. Foreign Regulatory Actions and Marketing History

rhNGF was authorized for marketing in the European Union (EU) by the European Medical Agency (EMA) in July 2017. As of December 2017, rhNGF eye drops have only been marketed in Germany.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

See CDTL memorandum. No clinical integrity issues identified.

4.2. Product Quality

As detailed in the June 23, 2017, Chemistry, Manufacturing, and Controls submission, the initial development formulation was a sterile aqueous solution intended for ocular instillation, containing rhNGF at different concentrations up to 180 µg/mL. This formulation was evaluated in a Phase 1 study in healthy volunteers (Study NGF0112). The same formulation, with concentrations of rhNGF of 10 µg/ml and 20 µg/ml, was evaluated in the Phase 1/2 clinical study in patients with moderate and severe neurotrophic keratitis (NK) (Study NGF0212).

Based on a trend observed in preliminary results of the clinical study NGF0212 and on other

manufacturing considerations, (b) (4)

(b) (4)

- a Phase 2 clinical study (NGF 0214): the study was conducted using a formulation with rhNGF of 20 µg/ml in patients with moderate and severe NK.
- a Phase 1/2 clinical study (NGF 0113): the study was conducted using rhNGF of 60 µg/ml and 180 µg/ml in patients with retinitis pigmentosa;
- a Phase 2 clinical study (NGF 0213): the study was conducted using rhNGF of 20 µg/ml and 4 µg/ml (obtained by dilution of rhNGF 20 µg/ml formulation) in patients with moderate and severe dry eye;

The changes in the formulation did not appear to significantly affect the safety and efficacy of the final drug product based on the results of the clinical trials.

4.3. Clinical Microbiology

This product is not an anti-infective.

4.4. Nonclinical Pharmacology/Toxicology

The final nonclinical pharmacology/toxicology review is pending. See CDTL review for complete findings.

4.5. Clinical Pharmacology

See CDTL memorandum.

4.6. Devices and Companion Diagnostic Issues

Not applicable. There is not a companion device or diagnostic.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Study Name / Phase	Study Design	No. of Patients Randomized/ Enrolled	Study Drug Treatment Groups	Treatment Regimen	Primary Efficacy Analysis / Outcome Measures (as amended)
Controlled Studies to Support – Safety and Efficacy					
NGF0212 Phase 2 segment Module 5.3.5.1	**Study Design:** Multicenter, randomized (1:1:1), double-masked, vehicle-controlled, parallel group study in Europe **Evaluations:** Safety and efficacy of rhNGF 20 mcg/mL in patients with stage 2 or 3 NK	156	rhNGF 10 mcg/mL= 52 rhNGF 20 mcg/mL = 52 Vehicle = 52	One drop administered into the affected eye 6 times per day for 8 weeks	Complete resolution of corneal staining at Week 4 and Week 8* as determined by the central reading center.
NGF0214 Phase 2 Module 5.3.5.1	**Study Design:** Multicenter, randomized (1:1), double-masked, vehicle-controlled, parallel group study in US **Evaluations:** Safety and efficacy of rhNGF 20 mcg/mL eye drops containing methionine versus vehicle containing methionine in patients with stage 2 or 3 NK	48	rhNGF 20 mcg/mL ** = 24 Vehicle** =24	One drop administered into the affected eye(s) 6 times per day for 8 weeks	Complete resolution of corneal staining at Week 4 and Week 8* as determined by the central reading center.

Note: NGF0212 total enrollment = 174 pts. Ph. I segment = 18; Ph II segment = 156
* Endpoint added per FDA request.
** Methionine added to stabilize formulation

Study Name / Phase	Study Design	No. of Patients Randomized/ Enrolled	Study Drug Treatment Groups	Treatment Regimen	Primary Efficacy Analysis / Outcome Measures (as amended)
Safety Studies					
NGF0212 Phase 1 Module 5.3.5.1	**Study Design:** Multicenter, randomized (1:1:1), double-masked, vehicle-controlled, sequential group study in Europe **Evaluations:** Safety and PK evaluation of rhNGF 20 mcg/mL in patients with stage 2 or 3 NK	18	rhNGF 10 mcg/mL rhNGF 20 mcg/mL Vehicle	Phase 1 segment: One drop administered into the affected eye 6 times per day for 8 weeks	Safety assessments PK assessments.
NGF0213 Phase 2 Module 5.3.5.4	**Study Design:** Single-center, open-label, dose escalation study in Austria **Evaluations:** Safety and efficacy of rhNGF eye drops in patients with dry eye disease	40	Group 1: rhNGF 4 mcg/mL** Group 2: rhNGF 20 mcg/mL**	One drop administered into both eye(s) BID for 28 days	SANDE Lissamine green staining Schirmer's test type I Adverse events
NGF0113 Phase 1/2 Module 5.3.5.4	**Study Design:** Multicenter, randomized (2:2:1), double-masked, vehicle-controlled, parallel group study in Italy **Evaluations:** Safety and efficacy in patients with retinitis pigmentosa	50	rhNGF 60 mcg/mL rhNGF 180 mcg/mL rhNGF Vehicle	One drop administered into both eye(s) TID for 24 weeks	Improving or slowing deterioration of visual function

Study Name / Phase	Study Design	No. of Patients Randomized/ Enrolled	Study Drug Treatment Groups	Treatment Regimen	Primary Efficacy Analysis / Outcome Measures (as amended)
NGF0116 [a] Phase 2 Module 5.3.5.4	**Study Design:** Single center, randomized (2:1), double-masked, vehicle-controlled, parallel group study in Italy **Evaluations:** Safety and efficacy in patients with post cataract and refractive surgery	120	rhNGF 20 mcg/mL** rhNGF Vehicle	One drop administered into the affected eye 6 times per day for 8 weeks	SANDE
NGF0216 [a] Phase 2 Module 5.3.5.4	**Study Design:** Single center, randomized (2:1), double-masked, vehicle-controlled, parallel group study in the US **Evaluations:** Safety and efficacy in patients with dry eye disease	150	rhNGF 20 mcg/mL ** rhNGF Vehicle **	One drop administered into the affected eye 6 times per day for 8 weeks	SANDE
NGF0112 Phase 1 Module 5.3.3.1	**Study Design:** Multicenter, randomized, double-masked, vehicle-controlled single and multiple ascending dose study in Switzerland, UK **Evaluations:** Safety and tolerability in healthy volunteers	74	rhNGF: 0.5 – 5 mcg/mL 20 mcg/mL 60 – 180 mcg/mL rhNGF Vehicle	Single ascending dose portion: One drop only One drop q 4 hrs Multiple ascending dose portion: One drop q 4 hrs for 5 days	Serum concentration Adverse events ECGs Clinical labs Anti-therapeutic antibodies (ATAs) Ophthalmologic exams

Study Name / Phase	Study Design	No. of Patients Randomized/ Enrolled	Study Drug Treatment Groups	Treatment Regimen	Primary Efficacy Analysis / Outcome Measures (as amended)
NEMO Investigator-initiated Phase 2 Module 5.4	**Study Design:** Multicenter, randomized, double-masked, vehicle-controlled parallel group study in Italy **Evaluations:** Safety and efficacy in patients with retinitis pigmentosa associated CME	45	rhNGF 180 mcg/mL rhNGF Vehicle	One drop dosed TID	Safety and tolerability assessments

a Studies conducted using the final formulation with methionine and packaging configuration proposed for marketing.

5.2. Review Strategy

Clinical data for Studies NGF0212 and NGF0214 listed in Section 5.1 were reviewed to support safety and efficacy. Clinical data from the additional studies in Section 5.1 were reviewed as appropriate to support safety.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study NGF0212 – An 8-week Phase 1 / 2, Multicenter, Randomized, Double-masked, Vehicle-controlled Parallel-group Study with a 48- or 56-week Follow-up Period to Evaluate the Safety and Efficacy of Two Doses (10 mcg/mL and 20 mcg/mL) of Recombinant Human Nerve Growth Factor (rhNGF) Eye Drops Solution Versus Vehicle in Patients with Stage 2 and 3 of Neurotrophic Keratitis (NK)

6.1.1. Study Design

Primary Objective: To assess the safety and the efficacy of two dose regimens of rhNGF ophthalmic solution (10 mcg/mL or 20 mcg/mL; single drop in the affected eye 6 times per day) compared to vehicle, for inducing complete resolution of corneal staining (0 mm lesion size and no residual staining) in Stage 2 (persistent epithelial defect (PED)) and Stage 3 (corneal ulcer) NK patients, as measured by the central reading center assessing clinical pictures of corneal fluorescein staining.

Key Secondary Objective: A key secondary objective was to assess corneal healing (<0.5 mm lesion size) as measured by the central reading center, as agreed with FDA.

Secondary Objectives:

- Duration of corneal healing (<0.5 mm lesion size)
- Improvement in visual acuity
- Improvement in corneal sensitivity

Pharmacokinetic Objectives: To determine the pharmacokinetic (PK) profile of rhNGF and to provide data concerning the possible systemic exposure of rhNGF in Stage 2 and Stage 3 NK patients treated with rhNGF via local application to the eye.

List of Investigators

Country	Site Number	Number of randomised patients (Phase 1)	Number of randomised patients (Phase 2)	Investigator Last Name	Investigator First Name	Investigator Degree	Institution	Department	Postal Address 1	Postal Address 2	City	State	Postal/ Zip Code
Italy	(b) (6)	2	4	Rama	Paolo	Prof.	Fondazione San Raffaele del Monte Tabor.	U.O. Oculistica – Unità Cornea e Superficie Oculare, settore S piano -1.	via Olgettina 60,		Milano	Italy	20132
Italy				Ferrari	Giulio	Dr	Fondazione San Raffaele del Monte Tabor.	U.O. Oculistica – Unità Cornea e Superficie Oculare, settore S piano -1.	via Olgettina 60,		Milano	Italy	20132
Italy		2	7	Virgili Menchini	Gianni Ugo	Prof. Prof.	Azienda Ospedaliero universitaria Careggi	U.O. Oftalmologia	Largo Brambilla, 3		Florence	Italy	50124
Italy		2	4	Traverso Rolando	Carlo Enrico Maurizio	Prof. Prof.	Dipartimento di Scienze Neurologiche Oftalmologia e Genetica – Università di Genova	Clinica Oculistica – Viale Benedetto XV	Viale Benedetto XV		Genova	Italy	16132
Italy		1	9	Mastropasqua	Leonardo	Prof.	Università G. D' Annunzio	Clinica Oftalmologica - Centro regionale di Eccellenza in Oftalmologia	Via dei Vestini		Chieti	Italy	66100
Italy			14	Aragona	Pasquale	Prof.	Azienda Ospedaliero Universitaria di Messina	Università degli Studi di Messina - Dipartimento di Scienze Sperimentali Medico-Chirurgiche Specialistiche e Odontostomatologiche - Sezione di Oftlamologia - Centro di Riferimento Regionale per le Malattie della Superficie Oculare	Policlinico Universitario "G. Martino"	via Consolare Valeria 1, 9 Pad. W piano terra	Messina	Italy	98125
Italy		2	17	Bonini	Stefano	Prof.	Università Campus Biomedico di Roma	Area Specialistica di Oftalmologia	Via Álvaro del Portillo, 200		Rome	Italy	00128

Country	Site Number	Number of randomised patients (Phase 1)	Number of randomised patients	Investigator Last Name	Investigator First Name	Investigator Degree	Institution	Department	Postal Address 1	Postal Address 2	City	State	Postal / Zip Code
Italy	(b) (6)	1	5	Leonardi	Andrea	Dr.	Azienda ospedaliera di Padova	Clinica Oculistica Policlinico 7° Piano	Via Giustiniani, 2		Padova	Italy	35128
Italy			2	Fogagnolo	Paolo	Dr.	Azienda Ospedaliera San Paolo	U.O. Oculistica	Via dei Rudini 8		Milano	Italy	20142
Italy			15	Lambiase	Alessandro	Prof.	Università La Saplenza	Unità Organi di Senso, Oftalmologia	Policlinico Umberto 1	Viale del Policlinico 155	Rome	Italy	00161
Spain			4	Echevarría	Jaime	Dr.	Hospital de Cruces	Oftalmología Planta baja	Plaza de Cruces s/n		Baracalado . Vizcaya	Spain	48903
Spain		1	2	Sainz de la Maza	Maite	Dr.	Hospital Clinic de Barcelona	Oftalmología	Sabino de Arana s/n	Casa Maternidad	Barcelona	Spain	08028
Spain			6	Montero Iruzubieta	Jesus	Dr.	Cartuja Visión - Centro de Servicios Oftlamológicos de Edificio Da Vinci	Oftalmología	C/ Imagen nº 9, 5ª planta B. 41003 SEVILLA	Edificio Da Vinci	Sevilla	Spain	41003
Spain			1	Benitez del Castillo Sanchez	José M	Prof.	Hospital Clínico San Carlos	Oftalmología. Unidad de Superficie Ocular	c/ Martín Lagos, s/n	Pabellón 8, Facultad de Medicina, 5ª planta	Madrid	Spain	28040
Spain			1	Merayo Lloves	Jesus	Prof.	Instituto Oftalmológico Fernández-Vega	Oftalmología	Avenida Dres. Fernández-Vega nº 34		Oviedo, Asturias	Spain	33012
Spain			3	Fideliz de la Paz	Maria	Dra.	Centro de Oftalmologia Barraquet	Oftalmologia	C/Muntaner 314		Barcelona	Spain	08021

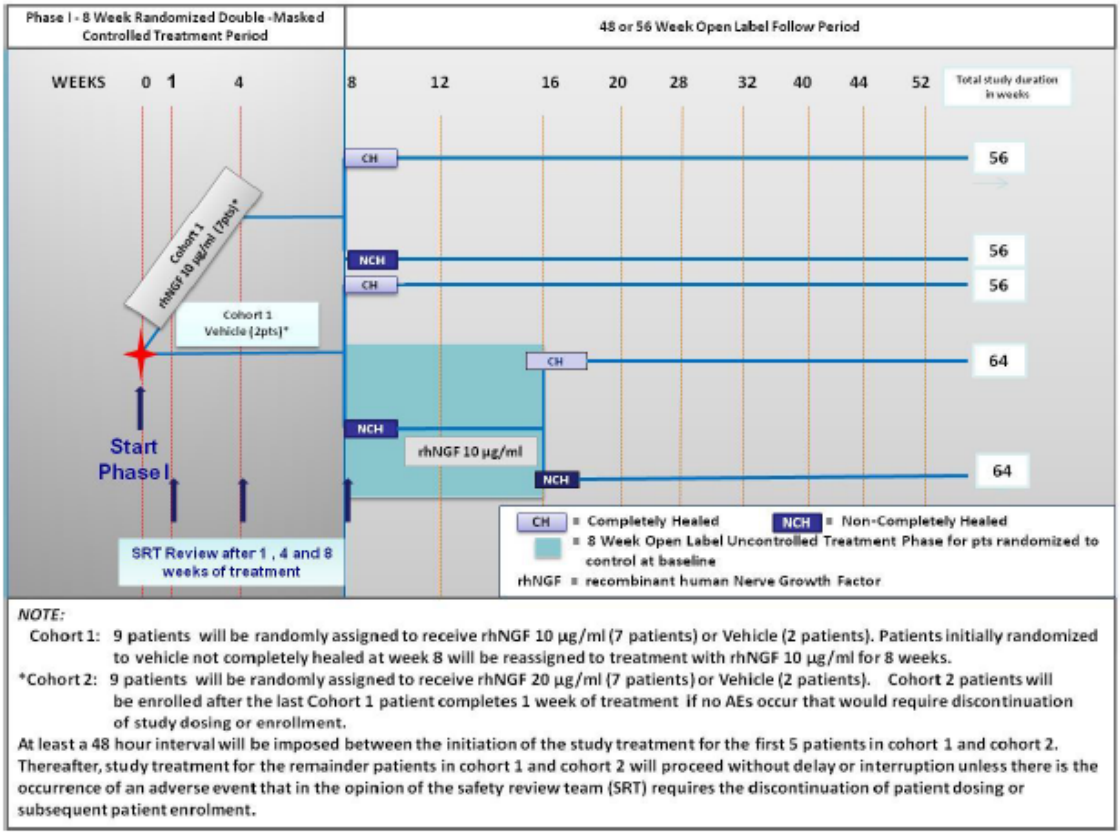
Country	Site Number	Number of randomised patients (Phase 1)	Number of randomised patients	Investigator Last Name	Investigator First Name	Investigator Degree	Institution	Department	Postal Address 1	Postal Address 2	City	State	Postal / Zip Code
Germany	(b) (6)	1		Kruse	Friedrich Eduard	Prof.	Universitätsklinikum Erlangen	Augenklinik	Schwabachanlage 6		Erlangen	Germany	91054
Germany		2	3	Cursiefen	Claus	Prof.	Universität zu Köln	Zentrum für Augenheilkunde am Universitätsklinikum Köln	Joseph-Stelzmann-Strasse 9		Köln	Germany	50924
Germany		1	11	Geerling	Gerd	Prof.	University Eye Clinic in Duesseldorf	Klinik für Augenheilkunde Heinrich-Heine-Universität Düsseldorf	Moorenstr. 5		Düsseldorf	Germany	40225
Germany			5	Böhringer	Daniel	Dr.	Universitäts-Augenklinik Freiburg		Killianstr. 5		Freiburg	Germany	79106
Germany			2	Lorenz	Katrin	Dr.	Johannes-Gutenberg-Universität Augenklinik und Poliklinik	Department of Ophthalmology,	Langenbreckstr. 1		Mainz	Germany	55131
Germany			15	Messmer	Elisabeth	PD/Dr.	Klinikum der Universität München	Augenklinik der Ludwig-Maximilians-Universtiät München	Campus Innenstadt Mathildenstrasse 8		Munchen	Germany	80336
UK		2	4	Dart	John	Prof.	Moorfields Eye Hospital	Moorfields Eye Hospital	162 City Road		London	UK	EC1V 2PD
UK			2	Figueiredo	Francisco	Prof.	Royal Victoria Infirmary	Dept. of Ophthalmology	Queen Victoria Road		Newcastle upon Tyne	UK	NE1 4LP
UK			2	Hossain	Parwez	Mr.	University of Southampton Southampton General Hospital	MP104, Eye Unit	Tremona Road		Southampton	UK	SO16 6YD
UK			1	Rauz	Saaeha	Miss	Academic Unit of Ophthalmology Birmingham and Midland Eye Centre	Dudley Road Winson Green Birmingham B18 7QH	Winson Green		Birmingham	UK	B18 7QH

Country	Site Number	Number of randomised patients (Phase 1)	Number of randomised patients	Investigator Last Name	Investigator First Name	Investigator Degree	Institution	Department	Postal Address 1	Postal Address 2	City	State	Postal / Zip Code
France	(b) (6)		3	Borderie	Vincent	Prof.	Centre Hospitalier National d'Ophtalmologie	Service d'ophtalmologie	28, rue de Charenton		Paris, Cedex 12	France	75571
France		1		Malecaze	François	Prof.	CHU Toulouse-Purpan	Service Ophtalmologie	Place Dr Baylac		Toulouse Cedex	France	31059
France			1	Creuzot Garcher Muselier	Catherine Aurore	Prof. Dr.	CHU de Dijon	Service ophtalmologie	3, rue du Faubourg Raines		Dijon	France	21000
France			2	Robert	Pierre-Yves	Prof.	CHU Dupuytren	Service Ophtalmologie	2, avenue Martin Luther King		Limoges Cedex	France	87042
France			4	Gabison	Eric	Dr.	Fondation Ophtalmologique Adolphe de Rothschild	Unité de Recherche Clinique	25 rue Manin		Paris	France	75019
Poland			4	Szaflik	Jacek P.	Prof.	SPKSO Szpital Okulistyczny ul.	Katedra i Klinika Okulistyki II Wydziału Lekarskiego Warszawskiego Uniwersytetu	Sierakowskiego 13		Warsawa	Poland	03-709
Poland			3	Wylegala	Edward	Prof.	District Railway Hospital Katowice,	Department of Ophthalmology	Panewnicka 65		Katowice	Poland	40-760

Overall Design:

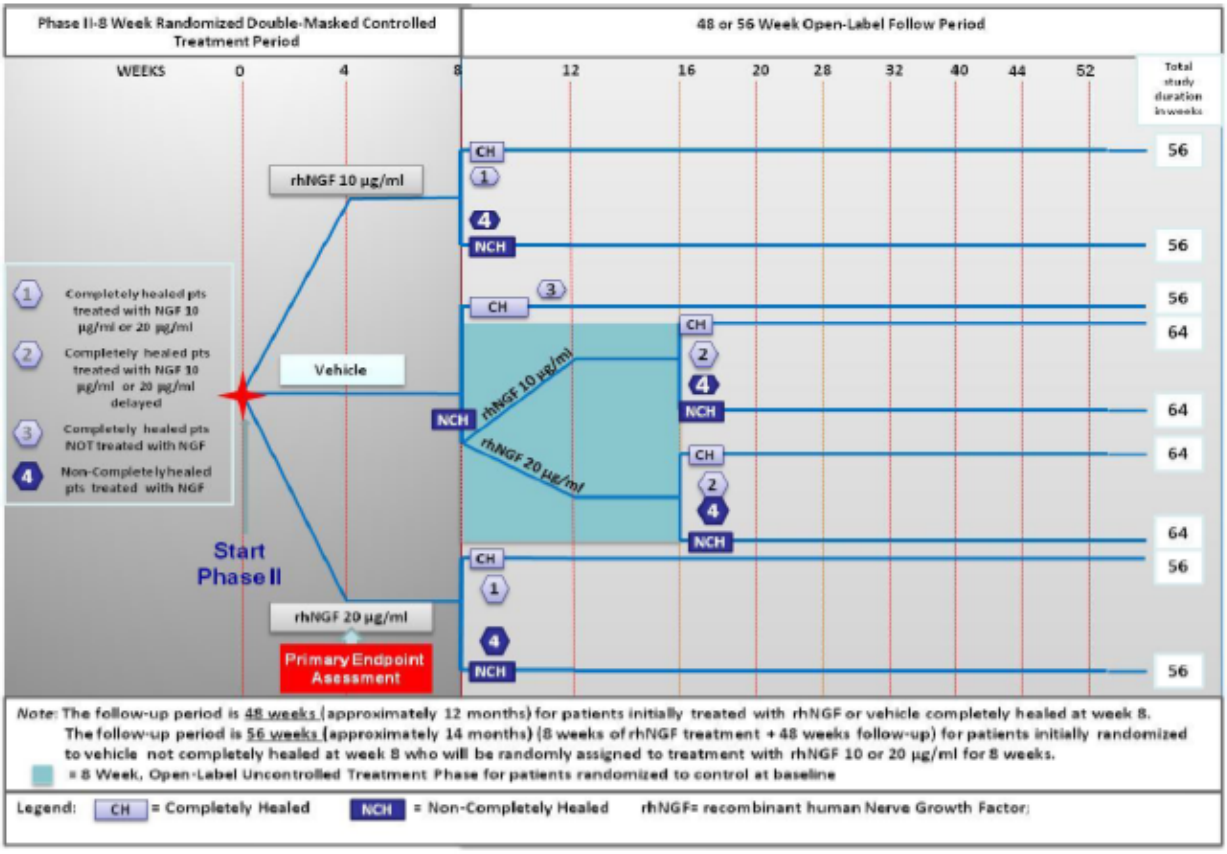
This study was an 8-week, randomized, double-masked, vehicle-controlled, parallel group study (referred to as the controlled treatment period) followed by a 48- or 56-week follow-up period. See Figure 1. The study design also consisted of a Phase I segment and Phase II segment. The design of the Phase I and Phase II segments of the NGF0212 study was identical with the exception that in the Phase I segment the two doses of rhNGF (10 mcg/mL and 20 mcg/mL) were initiated in a sequential manner, with a randomization of 7:2 (rhNGF vs. vehicle), and patients were followed with additional safety assessments and tested for PK profiling. In the Phase II segment the randomization was 1:1:1 (rhNGF 10 mcg/mL vs. rhNGF 20 mcg/mL vs. vehicle). See Figure 2.

Figure 1: Study NGF0212 – Phase I Segment



Source: CSR NGF0212 Protocol Figure 1
Key: AEs = adverse events; CH = corneal healing (<0.5 mm lesion size); µg = microgram(s); ml = milliliter(s); NCH = no corneal healing; pts = patients; rhNGF = recombinant human nerve growth factor; SRT = safety review team

Figure 2: Study NGF0212 – Phase II Segment



Source: CSR NGF0212 Protocol Figure 2
Key: CH = corneal healing (<0.5 mm lesion size); µg = microgram(s); ml = milliliter(s); NCH = no corneal healing; pts = patients; rhNGF = recombinant human nerve growth factor

Both Phase I and Phase II began with an 8-week randomized, controlled, double-masked treatment period. After the 8-week controlled treatment period, patients were assessed as completely healed (CH) or non-completely healed (NCH), and entered the 48-week or 56-week follow-up period.

The follow-up period was 48 weeks in length for the following patients:

- Those initially randomized to rhNGF (10 mcg/mL or 20 mcg/mL), regardless of whether the patient was completely healed or non-completely healed at Week 8.
- Those initially randomized to vehicle and who were completely healed at Week 8.

The follow-up period was 56 weeks in length for patients:

- Those initially randomized to vehicle and who were non-completely healed at Week 8 were treated with rhNGF during the 8-week uncontrolled treatment period (Week 8 to Week 16). At initial randomization, patients randomized to vehicle were secondarily

assigned to treatment with rhNGF (10 mcg/mL or 20 mcg/mL). Following the uncontrolled treatment period, these patients were followed for 48 weeks, such that their total follow-up period was 56 weeks in length (i.e., 8 weeks of rhNGF treatment plus 48 weeks of follow-up).

Patient Disposition After Controlled Treatment Period (Week 8)
Completely healed patients were followed during the 48-week follow-up period (Weeks 8-56) without any protocol-required study medication; however, preservative-free artificial tears (PFAT) could be prescribed as needed at the discretion of the study Investigator.

rhNGF group patients who were non-completely healed were not eligible to receive further treatment with rhNGF during the study. These patients could be treated with any non-experimental treatment for NK, at the discretion of the Investigator, while continuing to be followed until Week 56, the end of the 48-week follow-up period.

Vehicle control group patients who were non-completely healed were followed for an additional 56-week follow-up period consisting of an 8-week uncontrolled treatment period when patients were treated per their baseline randomized secondary treatment assignment (rhNGF 10 mcg/ml or 20 mcg/ml), followed by the 48-week follow-up period. At Week 16, following treatment with rhNGF, the patients were defined as completely healed or non-completely healed.

In the event that a patient progressed to deterioration (defined as an increase in the lesion size ≥1 mm, 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, onset of infection, or other evidence of deterioration) during the uncontrolled treatment period, the patient was to be discontinued from the study and treated as appropriate at the discretion of the Investigator.

Patient Disposition After Uncontrolled Treatment Period (Week 16)
Completely healed patients were followed for the 48-week follow-up period to Week 64 without any protocol-required study medication; however, PFAT could be prescribed as needed at the discretion of the study Investigator.

Non-completely healed patients were not eligible to receive additional treatment with rhNGF during the study and may have been treated, at the discretion of the Investigator, with any non-experimental treatment for NK, as needed, while continuing to be followed for an additional 48 weeks until Week 64, the end of the 56-week follow-up period.

Recurrent PED / Corneal Ulcer Treatment
In the event of a recurrent PED or corneal ulcer, at the recommendation of the study Investigator, these patients may have elected one of the following:

- To receive 1 additional course of treatment with rhNGF (1 drop 6 times a day, up to 56 days [8 weeks]) per their previously randomized treatment arm for patients randomized to active treatment, or per their secondary treatment assignment for patients randomized to vehicle control or,
- To be treated at the discretion of the study Investigator with any non-experimental treatment for NK while continuing to be followed until Week 56, the end of the 48-week follow-up period.

Study Population

Inclusion Criteria

1. Patients 18 years of age or older
2. Patients with Stage 2 (PED) or Stage 3 (corneal ulcer) neurotrophic keratitis involving only 1 eye. Patients with contralateral eye affected with Stage 1 NK could be enrolled.
3. PED or corneal ulceration of at least 2 weeks' duration refractory to one or more conventional non-surgical treatments for neurotrophic keratitis (e.g., preservative-free artificial tears, gels or ointments; discontinuation of preserved topical drops and medications that can decrease corneal sensitivity; therapeutic contact lenses).
4. Evidence of decreased corneal sensitivity (≤ 4 cm using the Cochet-Bonnet aesthesiometer) within the area of the PED or corneal ulcer and outside of the area of the defect in at least 1 corneal quadrant.
5. Best corrected distance visual acuity (BCDVA) score ≤ 75 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, (≥ +0.2 logMAR, ≤ 20/32 Snellen or ≤ 0.625 decimal fraction) in the affected eye.
6. No objective clinical evidence of improvement in the PED or corneal ulceration within the 2 weeks prior to study enrollment.
7. Only patients who satisfied all Informed Consent requirements could be included in the study. The patient and/or his/her legal representative must have read, signed and dated the Informed Consent document before any study-related procedures were performed. The Informed Consent form signed by patient and/or legal representative must have been approved by the IEC/IRB for the current study.
8. Patients must have had the ability and willingness to comply with study procedures.
9. Patients must have been eligible for the National Health Insurance (where applicable).

Exclusion Criteria

1. Patients with Stage 2 or 3 NK affecting both eyes.
2. Any active ocular infection (bacterial, viral, fungal or protozoal) or active ocular inflammation not related to NK in the affected eye.
3. Any other ocular disease requiring topical ocular treatment in the affected eye during the study treatment period. No topical treatments other than the study medications provided by the study sponsor or allowed by the study protocol could be administered in the affected eye during the study treatment periods.

4. Patients with severe vision loss in the affected eye with no potential for visual improvement in the opinion of the Investigator because of the study treatment.
5. Schirmer's test without anesthesia ≤ 3 mm/ 5 minutes in the affected eye.
6. Patients with severe blepharitis and/or severe meibomian gland disease in the affected eye.
7. History of any ocular surgery (including laser or refractive surgical procedures) in the affected eye within the three months before study enrollment. (An exception to the preceding statement was allowed if the ocular surgery was the cause of the Stage 2 or 3 NK).
8. Prior surgical procedure(s) for the treatment of NK (e.g., complete tarsorrhaphy, conjunctival flap, etc.) in the affected eye except for amniotic membrane transplantation could only be enrolled 2 weeks after the membrane had disappeared within the area of the PED or corneal ulcer or at least 6 weeks after the date of the amniotic membrane transplantation procedure. Patients previously treated with Botox (botulinum toxin) injections used to induce pharmacologic blepharoptosis were eligible for enrollment only if the last injection was give at least 90 days prior to enrollment in the study.
9. Use of therapeutic contact lenses or contact lens wear for refractive correction during the study treatment periods in the eye with NK.
10. Anticipated need for punctal occlusion during the study treatment period. Patients with punctal occlusion or punctal plugs inserted prior to the study were eligible for enrollment if the punctal occlusion was maintained during the study.
11. Evidence of corneal ulceration involving the posterior third of the corneal stroma, corneal melting or perforation in the affected eye.
12. Presence or history of any ocular or systemic disorder or condition that might have hindered the efficacy of the study treatment or its evaluation, could possibly have interfered with the interpretation of study results, or could have been judged by the Investigator to be incompatible with the study visit schedule or conduct (e.g., progressive or degenerative corneal or retinal conditions, uveitis, optic neuritis, poorly controlled diabetes, autoimmune disease, systemic infection, neoplastic diseases).
13. Any need for or anticipated change in the dose of systemic medications known to impair the function of the trigeminal nerve (e.g., neuroleptics, antipsychotic and antihistamine drugs). These treatments were allowed during the study if initiated prior to 30 days before study enrollment provided they remained stable throughout the course of the study treatment periods.
14. Known hypersensitivity to one of the components of the study or procedural medications (e.g., fluorescein).
15. History of drug, medication or alcohol abuse or addiction
16. Use of any investigational agent within 4 weeks of Baseline visit.
17. Participation in another clinical study at the same time as the present study.

18. Females of childbearing potential (those who are not surgically sterilized or post-menopausal for at least 1 year) were excluded from participation in the study if they met any 1 of the following conditions:
    a. Were currently pregnant or,
    b. Had a positive result on the urine pregnancy test at the Randomization Visit or,
    c. Intended to become pregnant during the study treatment period or,
    d. Were breast-feeding or,
    e. Not willing to use highly effective birth control measures, such as: Hormonal contraceptives – oral, implanted, transdermal, or injected and/or mechanical barrier methods – spermicide in conjunction with a barrier such as a condom or diaphragm or intra-uterine device (IUD) during the entire course of and 30 days after the study treatment periods.

Discontinued Patients

Discontinued patients were those who withdrew or were withdrawn from the study after the Randomization Visit.

- If a patient progressed to deterioration of their Stage 2 or 3 NK during the 8-week controlled treatment period, the patient's treatment was to be unmasked. Patients randomized to either dose of rhNGF were to be discontinued from the study and treated as appropriate at the discretion of the Investigator, whereas patients randomized to vehicle control were eligible to initiate treatment with rhNGF per their secondary treatment assignment, at the recommendation of the Investigator.
- If a patient progressed to deterioration during treatment with rhNGF during the 8-week uncontrolled treatment period, the patient was to be discontinued from the study.

Study Treatments

- Test product: rhNGF 10 mcg/mL (one 35 mcg drop equals to 0.35 mcg of rhNGF) and 20 mcg/mL (one 35 mcg drop equals to 0.70 mcg of rhNGF)
- Vehicle product: Ophthalmic solution of the same composition as the test product except for rhNGF.

Criteria for Evaluation

Efficacy Variables

At the Type C Meeting held with the Agency on March 31, 2016, (after the conclusion of the Study NGF0212), the FDA requested a revision in the definition of 'Completely Healed'.

> Dompe's original definition: The greatest diameter of corneal fluorescein staining in the area of the persistent epithelial defect (PED) or corneal ulcer (as measured at the baseline visit) was < 0.5 mm at the moment of assessment.
>
> Revised definition per FDA request: 'Completely Staining Free' means

- No residual fluorescein staining in the area of the corneal lesion at the moment of assessment and
- No persistent staining (i.e., not changing in shape and/or location at different time points) elsewhere in the cornea as seen in pictures taken at different time points during the study.

The applicant performed post-hoc efficacy analyses of the Phase II segment of Study NGF0212 described in the Statistical Analysis Plan Addendum 2, Version 1.0, dated July 5, 2016. To implement this re-analysis, the corneal images needed to be reassessed by the central reading center which remained masked to the patient and visit to which each image corresponded. All images were reassessed for patients who were judged to have been completely healed (Dompé definition) or had a lesion size of 0 mm at any time point, and determined the following for each patient:

- Is any residual staining present? (i.e., is there any staining outside of the lesion area?) (Yes/No)
- If residual staining is present, is the staining persistent? (where persistent indicated the staining was persistent in a specific zone of the cornea and had not cleared or changed in shape and/or location between images) (Yes/No)

There were 3 possible scenarios per patient. The table below describes the possible responses and the resultant healing status for each patient.

Residual Staining Present?	**Staining Persistent?**	**Response for Complete Healing with No Residual Staining**
No	N/A	Completely Healed*
Yes	No	Completely Healed *
Yes	Yes	Not Completely Healed**

* Result from main analysis unchanged.
** Completely Healed status from main analysis is revised to be Not Completely Healed for all time points.

All post-hoc efficacy analyses were performed using the ITT population. The analysis of the post-hoc efficacy endpoints for the Phase II segment of the study used the data for the 8-week controlled treatment period.

For the chi-square analyses of achievement of complete healing at Week 4 and Week 8, missing data were imputed using the last observation carried forward (LOCF) methodology. These analyses were also presented by imputing missing data as failures (worst case scenario), where data were considered to be missing at a given visit regardless of the reason for the missing data. All other post-hoc analyses were conducted on an observed case basis, that is, no further imputation of missing data was carried out unless expressly stated otherwise.

Safety Variables
The primary safety variable in this study was the incidence of AEs. Other safety variables included:

- Visual analogue scale (VAS) for ocular tolerability
- BCDVA
- Intraocular pressure
- Dilated fundus ophthalmoscopy
- Vital signs
- Hematology and clinical chemistry laboratory tests
- Anti-NGF antibodies
- Electroretinography (ERG), at selected sites; no outputs related to ERG were produced due to insufficient data

Pharmacokinetic (PK) Assessments
During the Phase I segment of the study, blood samples for PK profiling were collected at multiple time points from Day 1 through to the end of the 8-week controlled treatment period. During the Phase II segment of the study, PK blood samples were collected at limited time points from Day 0 through to the end of the 8-week controlled treatment period for approximately the first 50 patients only.

Pharmacokinetic Analyses
The rhNGF concentrations were summarized using descriptive statistics for continuous variables by treatment and time point for all relevant visits for Phase I and Phase II segments separately. In addition, rhNGF concentration versus time was presented on a profile plot for each patient individually, and the mean rhNGF concentration over time was presented graphically by treatment for Phase I and Phase II separately.

Interim Analysis
There was no planned interim analysis for this study.

Determination of Sample Size
Based on the only published randomized clinical study and published results of uncontrolled studies in patients treated with mammalian nerve growth factor (mNGF), a conservative estimate of 60% of patients achieving complete healing of the PED or corneal ulcer as determined by the central reading center using corneal fluorescein staining with rhNGF eye drops as compared to 30% in patients treated with the vehicle at 4 weeks was set. Using a chi-square test and a correction of α probability level for multiplicity per Pocock, the Phase II study segment needed 141 evaluable patients to have 80% power to detect such a difference. Assuming a drop-out rate from 10% to 20%, a minimum of 156 patients were expected to be randomized in the Phase II segment of the study.

Schedule of Procedures and Assessments – Phase I

Study Procedure	Randomization (Baseline) Visit	Randomized, Double-Masked, Controlled Treatment Period Visits										
	Day 0	Day 1* + 3 Days	Day 2	Wk 1*	Wk 2*	Wk 3*	Wk 4*	Wk 5*	Wk 6*	Wk 7*	Day 55[7,*]	Wk 8*
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Demographics	X											
Ocular and Systemic Medical History	X											
Previous and Concomitant Ocular And Systemic Medications	X	X	X	X	X	X	X		X		X	X
Record AEs	X	X	X	X	X	X	X		X		X	X
Determine and record patient's study medication dosing compliance			X	X	X	X	X		X			X
PK Blood Sampling		X[c]	X[c]	X[d]	X[d]	X[d]	X[d]		X[d]		X[c]	X[d]
Clinical Laboratory Tests		X[d]										X[d]
Administer Study Medication		s[h]	s[h]	p[h]	p[h]	p[h]	p[h]		p[h]		s[h]	s[h]
VAS	X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]		X[b]			X[b]
NEI-VFQ	X											X
EQ-5D	X											X
BCDVA	X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]		X[b]			X[b]
External Ocular Examination	X						X					X
Tear Film Osmolarity (Selected Sites)	X											X
Corneal Sensitivity	X				X		X		X			X
Schirmer Test Without Anesthesia	X						X					X
Slit Lamp Examination	X	X[b]	X[b]	X	X	X	X		X			X
Corneal Photo Without Fluorescein	X			[f]	[f]	[f]	X		X			X
Corneal Fluorescein Staining	X			X	X	X	X		X			X
Corneal Photo With Fluorescein	X			[f]	[f]	[f]	X		X			X
Intraocular Pressure (IOP)	X			X	X	X	X					X
Fundus Ophthalmoscopy	X				X		X					X

Schedule of Procedures and Assessments – Phase I (continued)

Investigator Global Evaluation of Efficacy							X					X
Pregnancy Test	X											X
Randomization	X											
Vital Signs	X	X[d]	X	X	X	X	X					X
Study Drug Dispensing		X[a]	X[a]	X	X	X	X	X	X	X		A[e]

Abbreviations: AE = adverse event; BCDVA = best corrected distance visual acuity; EQ-5D = EuroQol 5D; IOP = intraocular pressure; NEI-VFQ = national eye institute visual functioning questionnaire 25; PED = persistent epithelial defect; PK = pharmacokinetics; VAS = visual analogue scale; Wk = week

'X' indicates visits/assessment performed by all patients enrolled in the Phase I segment of the study during the 8-week randomized, double-masked, controlled treatment period.

[a] In the Phase I segment of the study, on the Day 1 Visit 1 vial of study medication (the sixth dose) was dispensed to the patient for self-administration and on the Day 2 Visit study drug (1 kit) was dispensed for self-administration at home if no clinically significant Adverse Events in the opinion of the Investigator were noted after the administration of the study medication in the clinic.

[b] These examinations was performed at least 15 minutes after the second and fifth doses of study medication were instilled on the Day 1 Visit, at least 15 minutes after the second dose of study medication was instilled on the Day 2 Visit and at least 15 minutes after the first dose of study medication was instilled on the Week 1, Week 2, Week 3, Week 4, Week 6 and Week 8 Visits.

[c] If PK blood sample was to be collected while the ophthalmic exam was being performed, priority was given to the PK blood sampling.

[d] PK blood samples and clinical laboratory tests, when required were collected before the administration of the first dose of study medication by the study site personnel or patient in the morning of the study visit.

[e] 'A' indicates visits/assessments only for patients randomized at baseline to the vehicle control arm for first 8 weeks of study and non-completely healed at Week 8 that entered the 56-week follow-up period and were to be treated with rhNGF from Weeks 8-16.

[f] Take corneal photo with fluorescein if slit lamp examination revealed complete healing of the PED or corneal ulcer.

[g] The Day 55-2 Days Visit was scheduled the day prior to the Week 8 Visit.

[h] On the day of the study visit the study medication was administered in the clinic by the study site personnel (s) or the patient (p).

*all the weekly visits had a window of minus 2 days where they could anticipate for eventual patient/site staff availability issue

Schedule of Procedures and Assessments – Phase II

Study Procedure	Randomization (Baseline) Visit	Randomized, Double-Masked, Controlled Treatment Period Visits							
	Day 0	Wk 1*	Wk 2*	Wk 3*	Wk 4*	Wk 5*	Wk 6*	Wk 7*	Wk 8*
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Demographics	X								
Ocular and Systemic Medical history	X								
Previous and Concomitant Ocular and Systemic Medications	X	X	X	X	X		X		X
Record AEs	X	X	X	X	X		X		X
Determine and record patient's study medication dosing compliance		X	X	X	X		X		X
VAS	X		X		X		X		X
NEI-VFQ	X								X
EQ-5D	X								X
BCDVA	X	X	X	X	X		X		X
External Ocular Examination	X				X				X
Tear Film Osmolarity (Selected Sites)	X				X				X
Corneal Sensitivity	X		X		X		X		X
Schirmer Test Without Anesthesia	X				X				X
Slit Lamp Examination	X	X	X	X	X		X		X
Corneal Photo Without Fluorescein	X	[c]	[c]	[c]	X		X		X
Corneal Fluorescein Staining	X	X	X	X	X		X		X
Corneal Photo With Fluorescein	X	[c]	[c]	[c]	X		X		X
Intraocular Pressure (IOP)	X								X
Fundus Ophthalmoscopy	X								X
Investigator global evaluation of efficacy					X				X
Confocal Microscopy (Selected Sites)	X								X
ERG (Selected Sites)	X								
Pregnancy Test	X								X
Randomization	X								
Vital Signs	X				X				X
Clinical Laboratory Tests	X								X

Schedule of Procedures and Assessments – Phase II (continued)

Blood for Anti-rhNGF Antibodies	X				X				X
PK Blood Sampling	X	X[b]		X[b]			X[b]		X[b]
Administer Study Medication		P[b]		P[b]			P[b]		P[b]
Study Drug Dispensing	X	X	X	X	X	X	X	X	A[a]

Abbreviations: AE = adverse event; BCDVA = best corrected distance visual acuity; ERG = electroretinography; EQ-5D = EuroQol 5D; IOP = intraocular pressure; NEI-VFQ = national eye institute visual functioning questionnaire 25; PED = persistent epithelial defect; PK = pharmacokinetics; rhNGF = recombinant human nerve growth factor; VAS = visual analogue scale; Wk = week

'X' indicates visits/assessment performed by all patients enrolled in the Phase II segment of the study during the 8-week randomized, double-masked, controlled treatment period.

[a]'A' indicates visits/assessments only for patients randomized at baseline to the vehicle control arm for first 8 weeks of study and non-completely healed at Week 8 that entered the 56-week follow-up period and were treated with rhNGF from Weeks 8- 16.

[b] PK blood sample was taken before the administration of the first dose of study medication by the patient (P) in the morning of the study visit.

[c]Take corneal photo with fluorescein if slit lamp examination revealed complete healing of the PED or corneal ulcer

*All the weekly visits had a window of minus 2 days where they could anticipate for eventual patient/site staff availability issues.

Schedule of Procedures and Assessments – 48-week Follow-Up Period

(Patients initially treated with rhNGF or vehicle treated patients completely healed at Week 8)						
Study Procedure	**Follow-up Period Visits**					**Early Exit Visit[b]**
	Wk 12 ± 3 Days	Wk 20 ± 7 Days	Wk 32 ± 7 Days	Wk 44 ± 7 Days	Wk 56 ± 7 Days	
Previous and Concomitant Ocular and Systemic Medications	X	X	X	X	X	X
Record AEs	X	X	X	X	X	X
(Determine and record patient's study medication dosing compliance)						‹X›
VAS	X	X	X	X	X	X
NEI-VFQ					X	X
EQ-5D					X	X
BCDVA	X	X	X	X	X	X
External Ocular Examination	X	X	X	X	X	X
Corneal Sensitivity	X	X	X	X	X	X
Schirmer Test Without Anesthesia	X				X	X
Slit Lamp Examination	X	X	X	X	X	X
Corneal Photo Without Fluorescein	c	c	c	c	c	c
Corneal Fluorescein Staining	X	X	X	X	X	X
Intraocular Pressure (IOP)	X		X		X	X
Fundus Ophthalmoscopy	X				X	X
Confocal Microscopy (Selected Sites)[a]					X[a]	X[a]
ERG (Selected Sites)					X	X
Vital signs	X				X	X
(Pregnancy test)						‹‹X››
Blood for Anti-rhNGF antibody (Only for patients enrolled in Phase II).	X					

Schedule of Procedures and Assessments – 48-week Follow-Up Period (continued)

Abbreviations: AE = adverse event; BCDVA = best corrected distance visual acuity; ERG = electroretinography; EQ-5D = EuroQol 5D; IOP = intraocular pressure; NEI-VFQ = national eye institute visual functioning questionnaire 25; PED = persistent epithelial defect; rhNGF = recombinant human nerve growth factor; VAS = visual analogue scale; Wk = week

'X' indicates visits/assessments performed by all patients treated with rhNGF and/or completely healed at Week 8 entered the 48-week follow-up period.

[a]Confocal microscopy was only performed at week 56 or Early Exit Visit in patients completely healed at Week 8 Visit; however if patient completely healed at Week 8 experienced a recurrent PED or corneal ulcer during the follow-up period confocal microscopy was also performed at the time of the recurrence.

[b] The Early Exit Visit assessments should have been completed by patients being followed in the 48-week follow-up period exiting the study prematurely after Week 8.

[c] If the investigator revealed presence of corneal neovascularization, corneal images without fluorescein were taken.

‹X› not needed if patient had not received rhNGF after Week 8 of initial treatment or had not received an additional course of rhNGF at the time of the Early Exit Visit.

‹‹X›› Not needed unless patient had not had a prior negative pregnancy test and had received or was receiving rhNGF at the time of the Early Exit Visit.

NOTE: *In the event of a recurrent PED or corneal ulcer for completely healed patients entered into the 48-week follow-up period, at the recommendation of the study Investigator, patients could elect to receive one additional course of treatment with rhNGF (6 times a day, up to 56 days) or any non-experimental treatment for NK.*

(Pregnancy test): repeat pregnancy test before the administration and after the completion of rhNGF treatment if patient had recurrent PED or corneal ulcer and elected to receive an additional course of rhNGF treatment.

(Determine and record patient's study medication dosing compliance): only during rhNGF treatment if patient had recurrent PED or corneal ulcer and elected to receive an additional course of rhNGF treatment.

Schedule of Procedures and Assessments – 56-week Follow-up Period

(Patients initially randomized to vehicle not completely healed at Week 8)														
Study Procedure	**Uncontrolled Treatment Period Visits (Only for Patients Randomized to Vehicle Control at Baseline)**								**Follow-up Period Visits#**					**Early Exit Visit[b]**
	Wk 9*	Wk 10*	Wk 11*	Wk 12*	Wk 13*	Wk 14*	Wk 15*	Wk 16*	Wk 20 ± 3 Days	Wk 28± 7 Days	Wk 40± 7 Days	Wk 52± 7 Days	Wk 64± 7 Days	
Previous and Concomitant Ocular and Systemic Medications	A	A	A	A		A		A	A	A	A	A	A	A
Record AEs	A	A	A	A		A		A	A	A	A	A	A	A
Determine and record patient's study medication dosing compliance	A	A	A	A		A		A						‹X›
VAS		A		A		A		A	A	A	A	A	A	A
NEI-VFQ								A					A	A
EQ-5D								A					A	A
BCDVA	A	A	A	A		A		A	A	A	A	A	A	A
External Ocular Examination				A				A	A	A	A	A	A	A
Tear Film Osmolarity (Selected Sites)				A				A						
Corneal Sensitivity		A		A		A		A	A	A	A	A	A	A
Schirmer Test Without Anesthesia				A				A	A				A	A
Slit Lamp Examination	A	A	A	A		A		A	A	A	A	A	A	A
Corneal Photo Without Fluorescein	[c]	[c]	[c]	A		A		A	[c]	[c]	[c]	[c]	[c]	[c]
Corneal Fluorescein Staining	A	A	A	A		A		A	A	A	A	A	A	A
Corneal Photo With Fluorescein	[c]	[c]	[c]	A		A		A						
Intraocular Pressure (IOP)				A				A	A		A		A	A
Fundus Ophthalmoscopy								A	A				A	A
Confocal Microscopy (Selected Sites)[a]								A					A[a]	A[a]
ERG (Selected sites)													A	A
Investigator Global Evaluation of Efficacy				A				A						
(Pregnancy test)								A						‹‹X››
Vital signs				A				A	A				A	A
Clinical Laboratory Tests								A						

Schedule of Procedures and Assessments – 56-week Follow-up Period (continued)

Blood for Anti- rhNGF antibody (Only for patients enrolled in Phase II)				A				A	A					
Study Drug Dispensing	A	A	A	A	A	A	A							

Abbreviations: AE = adverse event; BCDVA = best corrected distance visual acuity; ERG = electroretinography; EQ-5D = EuroQol 5D; IOP = intraocular pressure; NEI-VFQ = national eye institute visual functioning questionnaire 25; PED = persistent epithelial defect; rhNGF = recombinant human nerve growth factor; VAS = visual analogue scale; Wk = week

'A' indicates visits/assessments only for patients randomized at baseline to the vehicle control arm for first 8 weeks of study and non-completely healed at Week 8 that entered the 56-week follow-up period and was treated with rhNGF from Weeks 8- 16.

[a] Confocal microscopy was only performed at Week 64 or Early Exit Visit in patients completely healed at Week 16. If patient completely healed at Week 16 experienced a recurrent PED or corneal ulcer during the follow-up period, confocal microscopy was also performed at the time of the recurrence.

[b] The Early Exit Visit assessments should have been completed by patients being followed in the 56-week follow-up period exiting the study prematurely after Week 8.

[c] Take corneal photo with fluorescein if slit lamp examination revealed complete healing of the PED or corneal ulcer. If the investigator revealed presence of corneal neovascularization, corneal images without fluorescein were taken.

‹X› not needed if patient had not received rhNGF after Week 16 or had not received an additional course of rhNGF at the time of the Early Exit Visit.

‹‹X›› Not needed unless patient had not had a prior negative pregnancy test and had received or was receiving rhNGF at the time of the Early Exit Visit.

*All the weekly visits had a window of 2 days where they could be anticipated for eventual patient/site staff availability issue

NOTE: *In the event of a recurrent PED or corneal ulcer for completely healed patients entered into the 56-week follow-up period, at the recommendation of the study Investigator, patients could elect to receive one additional course of treatment with rhNGF (6 times a day, up to 56 days)*

(Pregnancy test): repeat pregnancy test before the administration and after the completion of rhNGF treatment if patient had recurrent PED or corneal ulcer and elected to receive an additional course of rhNGF treatment.

(Determine and record patient's study medication dosing compliance): only during rhNGF treatment if patient had recurrent PED or corneal ulcer and elected to receive an additional course of rhNGF treatment.

6.1.2. **Study Results**

Compliance with Good Clinical Practices

This study was conducted per the principles of Good Clinical Practices (GCP). Quality assurance audits were performed at 5 centers (Centers 11, 14, 22, 31, and 40) by an (b) (4) (b) (4) auditor on behalf of Dompé.

Table 6.1.2-1
Study NGF0212 Phase II –
Summary of Patient Disposition and Efficacy by Treatment for the Controlled Treatment

	Baseline Randomized Treatment		
	rhNGF 10 mcg/mL (N=52)	**rhNGF 20 mcg/mL (N=52)**	**Vehicle Control (N=52)**
Randomized at Baseline	52 (100.0%)	52 (100.0%)	52 (100.0%)
Withdrawn during the Controlled Treatment Period	7 / 52 (13.5%)	13 / 52 (25.0%)	4 / 52 (7.7%)
Completely Healed at Week 8 – ITT Population Observed Cases	30 /46 (65.2%)	34 / 42 (81.0%)	17 / 39 (33.3%)
Completely Healed at Week 8 Recurrence of PED / Corneal Ulcer during 48-wk F/U	6 / 32 (18.8%)	7 / 36 (19.4%)	2 / 17 (11.8%)

Source: NGF0212 Final Addendum CSR Table 5, Table 13, Table 14.2.1.5.3b, Table 16.2.6.1.4b

Table 6.1.2-2 Phase II – Summary of Patient Disposition, by Treatment and Overall for the Controlled Treatment Period (Baseline Randomized Treatment)

	Baseline Randomized Treatment		
	rhNGF 10 mcg/mL (N=52)	**rhNGF 20 mcg/mL (N=52)**	**Vehicle Control (N=52)**
Randomized at Baseline	**52 (100.0%)**	**52 (100.0%)**	**52 (100.0%)**
Randomized at Week 8 between 10 mcg/mL and 20 mcg/mL	**0**	**0**	**17 (33.3%)**
Withdrawn from Study	**19 (36.5%)**	**19 (36.5%)**	**14 (26.9%)**
Withdrawn during the Controlled Treatment Period [a]	7 (36.8%)	13 (68.4%)	4 (28.6%)
Withdrawn during the Uncontrolled Treatment Period [a]	0	0	1 (7.1%)
Attended Week 8 Visit	48 (92.3%)	42 (80.8%)	40 (76.9%)
Entered the 48-Week Follow-up Period	45 (86.5%)	39 (75.0%)	25 (48.1%)
Completed the Study	**33 (63.5%)**	**33 (63.5%)**	**38 (73.1%)**
Completed Study with 48-Week Follow-up Period [b]	33 (100.0%)	33 (100.0%)	22 (57.9%)
Completed Study with 56-Week Follow-up Period [b]	0	0	16 (42.1%)

	Baseline Randomized Treatment		
	rhNGF 10 mcg/mL (N=52)	rhNGF 20 mcg/mL (N=52)	Vehicle Control (N=52)
Study Populations			
Intent-to-Treat Population	52 (100.0%)	52 (100.0%)	52 (100.0%)
Lost to Follow-up	52 (100.0%)	52 (100.0%)	52 (100.0%)

Source: NGF0212 Final Addendum CSR Table 5
The denominator of percentage is the number of patients randomized at Baseline in each group, and their total.
a The denominator of percentage was the number of patients who withdrew from the study. **b** The denominator of percentage is the number of patients who completed the study.

Reviewer's Comment: *Twenty-three patients (44.2%) in the Vehicle group were not completely healed at Week 8, compared to 32 patients (62.7%) in the rhNGF 10 mcg/mL and 36 patients (72.0%) in the rhNGF 20 mcg/mL groups. Patients on Vehicle entered the 8-week uncontrolled treatment period and received either rhNGF 10 mcg/mL or 20 mcg/mL depending upon baseline secondary randomization.*

Table 6.1.2-3 Phase II – Summary of Patient Disposition by Treatment and Overall for the Uncontrolled Treatment Period (Week 8 Randomized Treatment)

	Baseline Randomized Treatment	
	rhNGF 10 mcg/mL n (%)	rhNGF 20 mcg/mL n (%)
Randomized at Week 8	**10 (100.0%)**	**13 (100.0%)**
Withdrawn from Study	**3 (30.0%)**	**4 (30.8%)**
Withdrawn after Week 8 and on or before Week 16 [a]	1 (33.3%)	0
Withdrawn during 56-week Follow-up Period (On or before Week 20) [a]	2 (66.7%)	4 (100.0%)
Attended Week 16 Visit	9 (90.0%)	13 (100.0%)
Entered the 56-Week Follow-Up Period	9 (90.0%)	13 (100.0%)
Completed the Study	**7 (70.0%)**	**9 (69.2%)**

Source: NGF0212 Final Addendum CSR Table 6
The denominator of percentage is the number of patients randomized at Week 8 in each group, and their total.
a The denominator of percentage was the number of patients who withdrew from the study.

Table 6.1.2-4 Phase II – Summary of Final Status and Reason for Withdrawal by Treatment and Overall (All Patients)

	Baseline Randomized Treatment		
	rhNGF 10 mcg/mL (N=52)	rhNGF 20 mcg/mL (N=52)	Vehicle Control (N=52)
Attended Week 20 Visit (Completed Study to 3 Month Follow-Up)	**42 (80.8%)**	**37 (71.2%)**	**43 (82.7%)**
Completed the Study to 12-month follow-up	121 (23.1%)	13 (25.0%)	15 (28.8%)
Still in Study Post Week 20 (not completed or withdrawn)	25 (48.1%)	23 (44.2%)	25 (48.1%)
Withdrawn from Study	15 (28.8%)	16 (30.8%)	12 (23.1%)
Primary Reason for Withdrawal [a]			
Adverse Event	8 (53.3%)	9 (56.3%)	2 (16.7%)
Lack of Efficacy / Inadequate Control of NK	2 (13.3%)	1 (6.3%)	1 (8.3%)
Lost to follow-up	2 (13.3%)	0	1 (8.3%)
Decision Unrelated to an Adverse Event	1 (6.7%)	1 (6.3%)	1 (8.3%)
Other	2 (13.3%)	5 (31.3%)	7 (58.3%)
Withdrawn from Study on or before Week 8 (during the controlled treatment period)	7 (13.5%)	13 (25.0%)	4 (7.7%)
Primary Reason of Withdrawal [b]			
Adverse Event	3 (42.9%)	9 (69.2%)	1 (25.0%)
Lack of Efficacy / Inadequate Control of NK	2 (28.6%)	1 (7.7%)	0
Decision Unrelated to an Adverse Event	1 (14.3%)	1 (7.7%)	1 (25.0%)
Other	1 (14.3%)	2 (15.4%)	2 (50.0%)
Withdrawn from Study after Week 8 and on or before Week 16 (during the uncontrolled treatment period) due to lack of efficacy	0	0	1 (1.9%)
Withdrawn from Study during 48-Week or 56-Week Follow-Up Period (On or before Week 20)	3 (5.8%)	2 (3.8%)	5 (9.6%)
Primary Reason of Withdrawal [d]			
Adverse Event	2 (66.7%)	0	1 (20.0%)
Lost to Follow-Up	1 (33.3%)	0	1 (20.0%)
Other	0	2 (100.0%)	3 (60.0%)
Withdrawn from Study during 48-Week or 56-Week Follow-Up Period (Post Week 20)	5 (9.6%)	1 (1.9%)	2 (3.8%)

	Baseline Randomized Treatment		
	rhNGF 10 mcg/mL (N=52)	rhNGF 20 mcg/mL (N=52)	Vehicle Control (N=52)
Primary Reason of Withdrawal [e]			
Adverse Event	3 (60.0%)	0	0
Lost to Follow-Up	1 (20.0%)	0	0
Other	1 (20.0%)	1 (100.0%)	2 (100.0%)

Source: NGF0212 CSR Table 27
Percentages are calculated using the population number in each treatment group (N) as the denominator.
a Percentages are calculated using the population number within each treatment group that withdrew from the study. **b** Percentages are calculated using the population number within each treatment group that withdrew from the study on or before Week 8. **c** Percentages are calculated using the population number within each treatment group that withdrew from the study after Week 8 and on or before Week 16. **d** Percentages are calculated using the population number within each treatment group that withdrew from the study during the 48-week or 56-week follow-up period on or before Week 20. **e** Percentages are calculated using the population number within each treatment group that withdrew from the study during the 48-week or 56-week follow-up period post Week 20.

Table 6.1.2-5 Phase II – Patient Demographics, by Treatment and Overall (Safety Population)

	rhNGF 10 mcg/mL (N=52)	rhNGF 20 mcg/mL (N=52)	Vehicle Control (N=52)
Age (years) [a]			
N	52	52	52
Mean (SD)	59.0 (17.2)	62.5 (14.0)	60.4 (16.8)
Min, Median, Max	20, 61, 87	18, 63, 95	23, 60, 91
Gender, n(%)			
Male	22 (42%)	22 (42%)	17 (33%)
Female	30 (58%)	30 (58%)	35 (67%)
Ethnicity, n(%)			
Not collected	4 (8%)	1 (2%)	6 (11%)
Hispanic, Latino or Spanish	6 (11%)	9 (17%)	5 (10%)
Not Hispanic, Latino or Spanish	42 (81%)	42 (81%)	41 (79%)
Race, n(%)			
Not collected	5 (10%)	1 (2%)	5 (10%)
White	46 (89%)	51 (98%)	45 (87%)
Black or African American	0	0	1 (2%)
Asian	1 (2%)	0	1 (2%)

Source: NGF0212 CSR Table 28
Percentages are calculated using the number of non-missing responses in each treatment group as the denominator.
a Age was recorded directly in the database and was not calculated separately.

Reviewer's Comment: *Overall, the study population had a mean age of 61 years, was majority female (61%) and white (91%). There was a slight imbalance by gender across treatment groups - rhNGF groups were 58% female and the vehicle group 67% female.*

Unscheduled Exposure to Study Treatment During the Follow-Up Period

During the follow-up period, a total of 13 patients had unscheduled exposure to study treatment following recurrence of PED or corneal ulcer, including 6 patients in the rhNGF 10 mcg/ml group and 7 patients in the rhNGF 20 mcg/ml group.

Agency Requested Efficacy Analyses (SAP Addendum 2)

Table 6.1.2-6 Post-hoc Analysis of Percentage of Patients Who Achieved Complete Healing with No Residual Staining at Week 4 and Week 8 as Determined by the Reading Center (ITT Population - LOCF)

	rhNGF 10 mcg/mL (N=52)	rhNGF 20 mcg/mL (N=52)	Vehicle Control (N=52)
Week 4 Complete Healing Achieved			
Yes	25 (49.0%)	29 (58.0%)	7 (13.7%)
No	26 (51.0%)	21 (42.0%)	44 (86.3%)
Treatment Comparison [a] (rhNGF vs. Vehicle)			
Difference in % Complete Healing	35.3%	44.3%	
97.06% CI [b]	(16.78, 53.80)	(25.80, 62.75)	
p-value [c]	<0.001	<0.001	
Week 8 Complete Healing Achieved			
Yes	32 (62.7%)	36 (72.0%)	17 (33.3%)
No	19 (37.3%)	14 (28.0%)	34 (66.7%)
Treatment Comparison [a] (rhNGF vs. Vehicle)			
Difference in % Complete Healing	29.4%	38.7%	
97.06% CI [b]	(8.82, 50.01)	(18.72, 58.62)	
p-value [c]	0.003	<0.001	

Source: NGF0212 CSR Final Addendum Table 10 and 13
Top N counts relate to the number of patients randomized to each treatment at Baseline. The significance level for the statistical tests is 0.0294 (adjusted according to Pocock).
a rhNGF 10 mcg/mL and rhNGF 20 mcg/mL were each compared against the vehicle control group. **b** Asymptotic (Wald) CI. **c** Asymptotic p-value based on Pearson statistic from Chi-Square test. Patients without a Yes/No response available at Week 4 were not considered in the Week 8 table.

Reviewer's Comment: *Complete healing with no residual staining at Week 4 was achieved by 49% of patients in the 10 mcg/mL and 58% of patients in the 20 mcg/mL rhNGF groups and 13% in the vehicle group. The treatment group differences for both rhNGF groups compared to vehicle was statistically significant at p<0.001.*

Complete healing with no residual staining at Week 8 was achieved by 63% of patients in the 10 mcg/mL and 72% of patients in the 20 mcg/mL rhNGF groups and 33% in the vehicle group. The treatment group differences for both rhNGF groups compared to vehicle was statistically significant at p=0.003 for the 10 mcg/mL rhNGF group, and p<0.001 for the 20 mcg/mL rhNGF group.

Sensitivity Analyses

Table 6.1.2-7 Post-hoc Analysis of Percentage of Patients Who Achieved Complete Healing with No Residual Staining at Week 4 and Week 8 as Determined by the Reading Center (ITT Population – Observed Cases)

	rhNGF 10 mcg/mL (N=52)	rhNGF 20 mcg/mL (N=52)	Vehicle Control (N=52)
Week 4 Complete Healing Achieved			
Yes	23 (51.0%)	28 (68.3%)	7 (16.7%)
No	24 (49.0%)	13 (31.7%)	35 (83.3%)
Total	49 (100.0%)	41 (100.0%)	42 (100.0%)
Treatment Comparison [a] (rhNGF vs. Vehicle Control)			
Difference in % Complete Healing	34.4%	51.6%	
97.06% CI [b]	(14.38, 54.32)	(31.44, 71.81)	
p-value [c]	<0.001	<0.001	
Week 8 Complete Healing Achieved			
Yes	30 (65.2%)	34 (81.0%)	17 (43.6%)
No	16 (34.8%)	8 (19.0%)	22 (56.4%)
Total	46 (100.0%)	42 (100.0%)	39 (100.0%)
Treatment Comparison [a] (rhNGF vs. Vehicle Control)			
Difference in % Complete Healing	21.6%	37.4%	
97.06% CI [b]	(-1.46, 44.72)	(15.61, 59.12)	
p-value [c]	0.046	<0.001	

Source: NGF0212 CSR Final Addendum Table 11 and – End-of-Text Table 14.2.1.3.7.3b. For ITT population - Patients with Missing Data for Any Reason Considered as Failures, NGF0212 CSR Final Addendum – Table 12 and End-of-Text Table 14.2.1.3.7.2b
Top N counts relate to the number of patients randomized to each treatment at Baseline. The significance level for the statistical tests is 0.0294 (adjusted according to Pocock).
a rhNGF 10 mcg/mL and rhNGF 20 mcg/mL were each compared against the vehicle control group. **b** Asymptotic (Wald) CI. **c** Asymptotic p-value based on Pearson statistic from Chi-Square test.
Patients without a Yes/No response available at Week 4 were not considered in the Week 4 portion of this table. Patients without a Yes/No response available at Week 8 were not considered in the Week 8 portion of this table.

Reviewer's Comment: *There was little difference between the analyses with Observed cases only and Last Observation Carried Forward at either Week 4 or Week 8. When the data was analyzed using the Patients with Missing Data for Any Reason Considered as Failures (ITT Population), the results were consistent.*

Corneal Sensitivity Results

Corneal sensitivity was evaluated using 'improvement or no change in corneal sensitivity' as the endpoint. There were no statistically significant treatment group differences in improvement in corneal sensitivity in patients who achieved complete corneal clearing at Week 4, 6, or 8.

Table 6.1.2-8 Recurrence of PED or Corneal Ulcer During Follow-Up (ITT Population)

		rhNGF 10 mcg/mL (N=62)	rhNGF 20 mcg/mL (N=65)	Vehicle Control (N=29)
Completely Healed Patients at Week 8, n		36	35	22
Completely Healed Patients at Week 8, with Recurrence (48-Week Follow-Up)	n	6 (17%)	7 (20%)	2 (10%)
	Mean (SD)	59.2 (57.37)	108.6 (80.26)	188.5 (222.74)
	Median	27.5	94.0	188.5
	Min, Max	23, 165	30, 265	31, 346
Completely Healed Patients at Week 16, n		36	35	22
Completely Healed Patients at Week 16, with Recurrence Treated with rhNGF (56-Week Follow-Up)	n	4	8	
	Mean (SD)	29.0 (--)	128.0 (175.82)	
	Median	29.0	29.0	
	Min, Max	29, 29	24, 331	

Source: NGF0212 CSR Final Addendum – End-of-Text Table 14.2.1.5.3b
Top N counts relate to the number of patients randomized to each treatment – this will be the Baseline randomized treatment for patients completely healed at Week 8 and will be the Week 8 randomized treatment for patients completely healed at Week 16.
Time to recurrence is measured in days from the end of the treatment regimen during which complete healing (according to central reading center) is achieved. Recurrence is defined as Stage 2 or Stage 3 NK after complete healing has occurred and the treatment has stopped. Only patients experiencing recurrence are considered.

Reviewer's Comment: *The recurrences for the rhNGF groups were more frequent and occurred sooner than for the vehicle, at a rate (17-20%).*

6.2. Study NGF0214 – An 8-week Phase 2, Multicenter, Randomized, Double-masked, Vehicle-controlled Parallel-group Study with a 24- or 32-week Follow-up Period to Evaluate the Efficacy of a Formulation Containing Anti-Oxidant of Recombinant Human Nerve Growth Factor (rhNGF) in 20 mcg/mL Eye Drops Solution Versus Vehicle Containing Anti-Oxidant in Patients with Stage 2 and 3 of Neurotrophic Keratitis (NK)

6.2.1. Study Design

Primary Objective: To evaluate the efficacy of the rhNGF 20 mcg/mL formulation containing anti-oxidant methionine compared to vehicle formulation containing the same amount of the anti-oxidant methionine dosed 6 times per day for 8 weeks for inducing complete healing (0 mm lesion size and no residual staining) in patients with Stage 2 (persistent epithelial defect (PED)) and Stage 3 (corneal ulcer) NK as measured by the central reading center evaluating the clinical pictures of corneal fluorescein staining.

Key Secondary Efficacy Parameter: Corneal healing (<0.5 mm lesion size) in patients with Stage 2 (PED) or Stage 3 (corneal ulcer) NK as measured by the central reading center evaluating the clinical pictures of corneal fluorescein staining.

Secondary Objectives: To assess rhNGF ophthalmic solution treatment on:

- Duration of corneal healing (< 0.5 mm lesion size)
- Improvement in visual acuity
- Improvement in corneal sensitivity
- Percentage of patients achieving complete corneal clearing defined as Grade 0 on the Modified Oxford Scale

Overall Design:
The study was designed as an 8-week randomized, double-masked, vehicle controlled parallel group study that was followed by a 24- or 32-week follow-up period. At least 48 patients were planned to be randomized in a 1:1 ratio to the rhNGF treatment arm or vehicle control arm (both containing the anti-oxidant methionine) at 11 study sites in the US. The study treatments were dosed one drop six times per day for 8 weeks. The maximum study duration was 40 weeks (approximately 10 months).

List of Investigators

Site Number	Number of randomized patients	Principal Investigator, Centre Location
(b) (6)	3	John Affeldt, MD Loma Linda University Eye Institute, Loma Linda, CA 92354
	1	Natalie Afshari, M.D., F.A.C.S Shiley Eye Center, University of California, San Diego, La Jolla, CA 92093
	6	Sophie X. Deng, M.D., PhD, Jules Stein Eye Institute, UCLA, Los Angeles, CA 90095
	5	Ladan Espandar, M.D. UPMC Eye Center, University of Pittsburgh, Pittsburgh, PA 15213
	4	C. Stephen Foster, M.D. Massachusetts Eye Research and Surgery Institution, Waltham, MA 02451
	9	Giacomina Massaro-Giordano, M.D. Scheie Eye Institute, University of Pennsylvania, Philadelphia, PA 19104
	4	Reza Dana, M.D. Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA 02114
	8	Victor L. Perez, M.D. Bascom Palmer Eye Institute, University of Miami, Plantation, FL 33324
	1	Stephen C. Pflugfelder, M.D. Baylor College of Medicine, Houston, TX 77030
	2	John Seedor, M.D. New York Eye and Ear Infirmary of Mt. Sinai, New York, NY 10003
	5	Pedram Hamrah, M.D., FACS Tufts Medical Center, Boston, MA 02111

Controlled Treatment Period

Enrolled patients were randomized at baseline in a 1:1 ratio to either vehicle or rhNGF 20 mcg/mL both formulations containing the anti-oxidant methionine. Study treatment was dosed one drop (35 mcL) six times per day. Upon enrollment, the study patients were required to discontinue all topical ophthalmic medications. Randomized patients were dispensed study medication in a refrigerated bag and were instructed to self-administer the study medication one drop six times a day starting on the day after Day 0 Visit through Week 8 of the controlled treatment period.

During the 8-week controlled treatment period patients were instructed to return to the clinic each week on Week 1 through Week 8 with the kit of study medication. During the 8-week controlled treatment phase, any patient, in the opinion of the investigator, considered to be at imminent risk of deterioration could also be treated with preservative-free topical antibiotics and/or preservative-free topical antiviral eye drops, in addition to receiving treatment with the randomized study medication.

If a patient being treated with rhNGF progressed to deterioration (defined as an increase in the lesion size ≥ 1 mm and/or decrease in BCDVA by >5 ETDRS letters and/or progression in lesion depth to corneal melting or perforation and/or onset of infection), the patient was to be discontinued from the study and treated as appropriate at the discretion of the investigator.

Uncontrolled Treatment Period

Patients Completely Healed at Week 8

Completely healed patients at Week 8 in either treatment arm were followed for an additional 24 weeks during the follow-up period. During the 24-week follow-up period (Weeks 8-32), the patients were followed without any protocol-required study medication; however, preservative-free artificial tears (not provided by the study sponsor) could be prescribed as needed at the discretion of the study investigator. In the event of a recurrent PED or corneal ulcer, patients, at the recommendation of the study investigator, could elect:

- To receive one additional course of treatment with rhNGF (one drop six times a day, up to 56 days) to be dispensed weekly, or
- To be treated at the discretion of the study investigator with any non- experimental treatment for NK while continuing to be followed until Week 32, the end of the 24 week follow up period.

Patients Randomized to rhNGF Not Completely Healed at Week 8

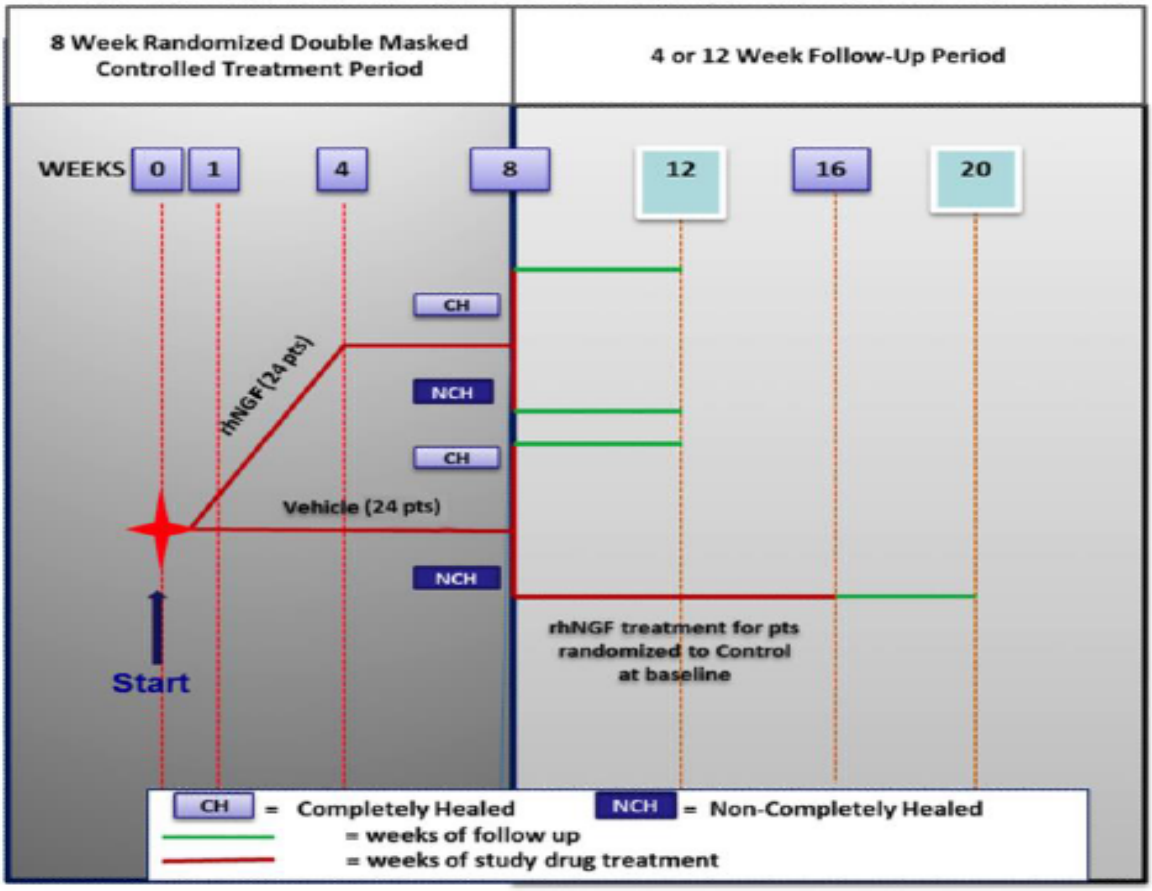
Non-completely healed patients at Week 8 who were randomized to the rhNGF group were followed for an additional 24 weeks during the follow-up period. These patients were not eligible to receive further treatment with rhNGF during the study and were treated at the discretion of the investigator with any non-experimental treatment for NK while continuing to be followed until Week 32, the end of the 24-week follow-up period.

The visit schedule for these patients was the same as for completely healed patients at Week 8.

Patients Randomized to Vehicle Not Completely Healed at Week 8

Non-completely healed patients at Week 8 who were randomized to the vehicle control group were followed for an additional 32 weeks during the follow-up period. For the first 8 weeks of the 32-week follow-up period, these patients received a course of rhNGF, one drop six times per day for eight weeks. This was the uncontrolled treatment phase visit.

If a patient being treated with rhNGF progressed to deterioration (defined as an increase in the lesion size ≥ 1 mm and/or decrease in BCDVA by >5 ETDRS letters and/or progression in lesion depth to corneal melting or perforation and/or onset of infection), the patient was to be discontinued from the study and treated as appropriate at the discretion of the investigator.



Source: CSR NGF0214 Protocol Figure 1
Key: CH = corneal healing (<0.5 mm lesion size); NCH = non-completely healed; pts = patients; rhNGF = recombinant human nerve growth factor

Study Population

Inclusion Criteria

The Inclusion Criteria were the same as in Study NGF0212 except for the following:

- Patients with Stage 2 (persistent epithelial defect, PED) or Stage 3 (corneal ulcer) neurotrophic keratitis with one or both eyes affected could be enrolled, not just patients with one eye affected.
- The requirement to be eligible for the National Health Service was not applicable.

Exclusion Criteria

The Exclusion Criteria were the same as in Study NGF0212 except for the following:

- Patients with neurotrophic keratitis in both eyes were not excluded.
- Ocular surgery was not allowed during the study treatment period and elective ocular surgery procedures were not to be planned during the follow-up period.

Statistical and Analytical Plans

An amendment to the SAP (Amendment version 1.0, 07-Jun-2016), referred to the final SAP (version 3.0), was used for the CSR. The SAP Amendment provides a detailed description of analyses performed after completion of the safety follow-up period.

Efficacy Analyses

The efficacy endpoints initially planned were revised per the FDA request in the 2016 Type C meeting. The protocol and statistical analysis plans were revised to provide for primary analysis in a separate SAP for the US FDA using the 'Completely Staining Free' primary efficacy endpoint. 'Completely Staining Free' means no residual fluorescein staining in the corneal lesion at the time of assessment and no persistent staining (i.e., not changing in shape and/or location at different time points) elsewhere in the cornea as seen in pictures taken at different timepoints during the study. Otherwise, the result is 'Not Completely Staining Free'.

Primary Efficacy Endpoint – Percentage of patients achieving complete resolution of corneal fluorescein staining (0 mm lesion size and no residual staining) of the PED or corneal ulcer determined by corneal fluorescein staining at Week 8 as assessed by the central reading center evaluating clinical pictures.

Key Secondary Variable – Percentage of patients achieving corneal healing (<0.5 mm lesion size) of the PED or corneal ulcer determined by corneal fluorescein staining at Weeks 4 and 8 of the controlled treatment period as assessed by the central reading center.

Secondary Efficacy Endpoints

- Percentage of patients experiencing corneal healing (<0.5 mm lesion size) of the PED or corneal ulcer at 4 and 6 weeks as measured by the central reading center evaluating clinical pictures
- Percentage of patients experiencing corneal healing (<0.5 mm lesion size) of the PED or corneal ulcer determined by corneal fluorescein staining at Weeks 4, 6, and 8 weeks as measured by the Investigator
- Percentage of patients with complete corneal clearing at Weeks 4, 6, and 8 defined as grade 0 on the modified Oxford scale
- Mean change in best corrected distance visual acuity (BCDVA) from Baseline to Week 8
- Percentage of patients that achieve a ≥ 15-letter gain in BCDVA at Weeks 4, 6, and 8
- Percentage of patients that achieve an improvement in corneal sensitivity as measured by the Cochet-Bonnet aesthesiometer (CBA) at 4, 6, and 8 weeks

- Percentage of patients experiencing deterioration (increase in lesion size ≥ 1 mm, decrease in BCDVA by > 5 Early Treatment Diabetic Retinopathy Study [ETDRS] letters, progression in lesion depth to corneal melting or perforation, onset of infection) in stage 2 or 3 NK from Baseline to Week 8
- Investigator global evaluation of efficacy at 4 and 8 weeks.

Safety Variables

- Adverse events
- Anti-NGF antibodies
- Hematology test, clinical chemistry test
- Vital signs
- Ocular tolerability
- Intraocular pressure
- Dilated fundus ophthalmoscopy

Interim Analyses

No interim analysis was planned.

One Eye per Patient

In the even a patient is enrolled with both eyes affected efficacy assessments from only the worse affected eye (study eye) at the time of randomization will be included in the analysis of efficacy, while safety assessments from both treated eyes will be included in the analysis of safety. The study eye was determined by the investigator and will be taken from the electronic Case Report Form (eCRF). The study eye was the worst eye and if both eyes have the same severity, it is the right eye.

Handling of Dropouts or Missing Data

For the primary analysis of the endpoint 'Completely Staining Free', patients, who discontinued before Week 4 (and who did not have a post-baseline corneal photography with fluorescein), were assumed to have been 'Not Completely Staining Free' if in the 'Corneal Photography with Fluorescein' eCRF page(s), the Investigator recorded that the 'measurements are N/A because the greatest dimension of the PED or corneal ulcer evaluated was greater than 1 mm on the slit lamp'. If no such post-baseline value was available, no imputation was performed. All other missing evaluations were imputed by the last observation carried forward (LOCF) up to and including the 8 Week visit.

Efficacy Analyses

Chi Square Test

Completely Staining Free was analyzed after 8 weeks of treatment with a 2x2 Chi-square test. If, for whatever reason, any Chi square analysis specified above is not possible (e.g. cell counts less than 5), then a Fisher's exact test was performed instead.

Sensitivity Analyses

To explore the effect of early terminations (i.e., before week 4), a sensitivity analysis was performed repeating the analysis on observed cases. In addition, the primary analysis was repeated for Week 8 but patients progressing to deterioration of their stage 2 or 3 NK (patients recording 'Yes' to 'progression' on the 'Patient Status' eCRF page) during the 8-week controlled treatment were considered as 'Not Completely Staining Free'. As further sensitivity analyses, 'Completely Staining Free' was analyzed firstly by imputing missing data as failures, and secondly, by using the multiple imputation method for missing data considering all patients in the ITT. Furthermore, a sensitivity analysis was performed using tipping point methodology.

Compliance with Good Clinical Practices

The applicant arranged for independent quality assurance audits to be conducted at Sites 3, 5, 6, 9 and the (b) (4) Office. During the study, the following breaches of GCP and of the study protocol were identified:

- Site 04 at the UPMC Eye Center University of Pittsburgh inadvertently unmasked patient (b) (6) and then circulated the unmasking information amongst two blinded study team members: the Project Manager and the Lead Clinical Research Associate (CRA, study monitor). Per the site's IRB requirements, the unmasking of the patient was not reported to the site IRB, as the unmasking did not affect the safety of the patient. Study staff were retrained on un-masking procedures. Patient (b) (6) was in the Follow-Up phase at time of unmasking and was included in the Intent-to-treat (ITT) Population.

- In March 2016, Site 09, at the University of Miami, Florida, was temporarily suspended by their IRB for GCP non-compliance. The IRB lifted the suspension in May 2016 after corrective measures were implemented. The site was subsequently audited by a Dompé consultant. An additional sensitivity analysis was introduced to investigate the effect of data from this site to primary efficacy conclusion. Results of these can be found in CSR Section 11.4.1.1. The sensitivity analysis is deemed to confirm that there were no differences to the conclusions of the study with and without data from site 09 patients.

- In August 2016, there was a need to query and correct data entered in the clinical database after it was soft locked on 14-Jun-2016 prior to the main objective analysis. The request to unlock the database came after ongoing review identified incomplete and incorrect data from site 04. The root cause analysis performed by (b) (4) identified inadequate source data verification performed by the CRA (study monitor) assigned to sites 04 and 06. Immediate actions to ensure the reliability of all data in the database included further monitoring queries and correction of data from sites 04 and 06. Upon this investigation, it was confirmed that the remaining sites had data that was complete and correct. The full CAPA plan was defined and implementation will be completed by October 2016. Duplication of data, affecting the sites 04, 05, 06 and 09 was also a reason for unlocking the database.

Study Plan: Treatment Period

Study Procedures	Randomization (Baseline) Visit	Randomized, Double-Masked, Controlled Treatment Period Visits							
	Day 0	Wk 1 - 2 Days	Wk 2 - 2 Days	Wk 3 - 2 Days	Wk 4 - 2 Days	Wk 5 - 2 Days	Wk 6 - 2 Days	Wk 7 - 2 Days	Wk 8 - 2 Days
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Demographics	X								
Ocular and Systemic Medical history	X								
Previous and Concomitant Ocular and Systemic Medications	X	X	X	X	X		X		X
Record AEs	X	X	X	X	X		X		X
Determine and record patient's study medication dosing compliance		X	X	X	X	X	X	X	X
VAS	X		X		X		X		X
NEI-VFQ	X								X
EQ5D	X								X
BCDVA	X	X	X	X	X		X		X
External Ocular Examination	X				X				X
Tear Film Osmolarity (Selected Sites)	X				X				X
Corneal Sensitivity	X		X		X		X		X
Schirmer Test Without Anesthesia	X				X				X
Slit Lamp Examination	X	X	X	X	X		X		X
Corneal Photo Without Fluorescein	X	[2]	[2]	[2]	X		X		X
Corneal Fluorescein Staining	X	X	X	X	X		X		X
Corneal Photo With Fluorescein	X	[2]	[2]	[2]	X		X		X
Intraocular Pressure (IOP)	X								X
Fundus Ophthalmoscopy	X								X
Investigator global evaluation of efficacy					X				X
Confocal Microscopy (Selected Sites)	X								X
Pregnancy Test	X								X
Randomization	X								
Vital Signs	X				X				X
Clinical Laboratory Tests	X								X
Evaluation of Anti-rhNGF Antibodies	X				X				X
Study Drug Dispensing	X	X	X	X	X	X	X	X	A[1]

[1] 'A' indicates visits/assessments only for patients randomized at baseline to the vehicle control arm for first 8 weeks of study and non-completely healed at Week 8 that entered the 24-week follow-up period and were treated with rhNGF from Weeks 8- 16.
[2] Corneal photo was to be taken without and with fluorescein if SLE revealed the PED or corneal ulcer to be < 1 mm before Week 4 Visit

Study Plan: 24-Week Follow-Up Period (Patients initially treated with rhNGF or vehicle completely healed at week 8)

Study Procedures	Follow-up Period Visits			Early Exit Visit[2]
	Wk 12 ± 3 Days	Wk 20 ± 7 Days	Wk 32 ± 7 Days	
Previous and Concomitant Ocular and Systemic Medications	X	X	X	X
Record AEs	X	X	X	X
VAS	X			X
NEI-VFQ	X			X
EQ5D	X			X
BCDVA	X			X
External Ocular Examination	X	X	X	X
Corneal Sensitivity	X	X	X	X
Schirmer Test Without Anesthesia	X			X
Slit Lamp Examination	X	X	X	X
Corneal Fluorescein Staining	X	X	X	X
Intraocular Pressure (IOP)	X		X	X
Fundus Ophthalmoscopy	X			X
Confocal Microscopy (Selected Sites)[1]	X[1]			X[1]
Vital signs	X			X
Evaluation of Anti-rhNGF Antibodies	X			X
Clinical Laboratory Tests	X			X

[1]Confocal microscopy was only to be performed at week 12 or Early Exit Visit in patients completely healed at week 8 Visit however if patient completely healed at week 8 experienced a recurrent PED or corneal ulcer during the follow-up period confocal microscopy was also performed at the time of the recurrence.
[2] The Early Exit Visit assessments were to be completed by patients being followed in the 24-week follow-up period exiting the study prematurely after week 8.
NOTE: In the event of a recurrent PED or corneal ulcer for completely healed patients entered into the 24-week follow-up period at the recommendation of the study investigator patients could elect to receive one additional course of treatment with rhNGF (six times a day, up to 56 days) or any non-experimental treatment for NK.

Study Plan: 32 Week Follow-Up Period (Patients initially randomized to vehicle not completely healed at week 8)

Study Procedures	Uncontrolled Treatment Phase Visits (Only for Patients Randomized to Vehicle Control at Baseline)								Follow up Visits			
	Wk 9 -2 Days	Wk 10 -2 Days	Wk 11 -2 Days	Wk 12 - 2 Days	Wk 13 - 2 Days	Wk 14 - 2 Days	Wk 15 -2 Days	Wk 16± 2 Days	Wk 20± 3 Days	Wk 28± 7 Days	Wk 40± 7 Days	Early Exit Visit[2]
Previous and Concomitant Ocular and Systemic Medications	A	A	A	A		A		A	A	A	A	A
Record AEs	A	A	A	A		A		A	A	A	A	A
Determine and record patient's study medication dosing compliance	A	A	A	A	A	A	A	A				‹X›
VAS		A		A		A		A	A			A
NEI-VFQ								A	A			A
EQ5D								A	A			A
BCDVA	A	A	A	A		A		A	A			A
External Ocular Examination				A				A	A	A	A	A
Tear Film Osmolarity (Selected Sites)				A				A				
Corneal Sensitivity		A		A		A		A	A	A	A	A
Schirmer Test Without Anesthesia				A				A	A			A
Slit Lamp Examination	A	A	A	A		A		A	A			A
Corneal Photo Without Fluorescein	[3]	[3]	[3]	A		A		A				
Corneal Fluorescein Staining	A	A	A	A		A		A	A	A	A	A
Corneal Photo With Fluorescein	[3]	[3]	[3]	A		A		A				
Intraocular Pressure (IOP)				A				A	A		A	A
Fundus Ophthalmoscopy								A	A			A
Confocal Microscopy (Selected Sites)[1]								A	A			A[1]
Investigator Global Evaluation of Efficacy				A				A				
(Pregnancy test)								A				‹‹X››
Vital signs				A				A	A			A
Clinical Laboratory Tests								A				
Evaluation of Anti- rhNGF antibody				A				A	A			A
Study Drug Dispensing	A	A	A	A	A	A	A					

'A' indicates visits/assessments only for patients randomized at baseline to the vehicle control arm for first 8 weeks of study and non-completely healed at Week 8 that entered the 32 week follow-up period and be treated with rhNGF from Weeks 8-16.
[1]Confocal microscopy was only to be performed at Week 20 or Early Exit Visit in patients completely healed at Week 16. If patient completely healed at Week 16 experienced a recurrent PED or corneal ulcer during the follow-up period confocal microscopy was also to be performed at the time of the recurrence.
[2]The Early Exit Visit assessments were to be completed by patients being followed in the 32week follow-up period exiting the study prematurely after Week 8.
[3]Corneal photo to be taken with fluorescein if SLE revealed the PED or corneal ulcer to be < 1 mm before Week 12 Visit.
‹X› not needed if patient had not received rhNGF after Week 16 or had not received an additional course of rhNGF at the time of the Early Exit Visit.
‹‹X›› Not needed unless patient had not had a prior negative pregnancy test and had received or was receiving rhNGF at the time of the Early Exit Visit.
NOTE: In the event of a recurrent PED or corneal ulcer for completely healed patients entered into the 24-week follow-up period at the recommendation of the study investigator patients could also elect to receive one additional course of treatment with rhNGF (six times a day, up to 56 days).
(Pregnancy test): test repeated before the administration and after the completion of rhNGF treatment if patient had recurrent PED or ulcer and elected to receive an additional course of rhNGF treatment.

6.2.2 Study Results

Patient Disposition

Table 6.2.2-1

Study NGF0214 - Summary of Patient Disposition and Efficacy by Treatment

	rhNGF 20 mcg/mL (N=24)	Vehicle Control (N=48)
Randomized at Baseline	24 (100.0%)	24 (100.0%)
Withdrawn during the Controlled Treatment Period	6 / 24 (25.0%)	9 / 24 (37.5%)
Completely Healed at Week 8 – ITT Population (Observed Cases)	14 / 24 (77.8%)	3 / 24 (21.4%)
Completely Healed at Week 8 Recurrence of PED / Corneal Ulcer during 48-wk F/U	2 / 14 (14.3%)	0 / 3 (0.0%)

Source: NGF0214 Final Addendum CSR Text Table 1, Text Table 3, Text Table 9

Table 6.2.2-2 Summary of Patient Disposition (All Patients)

	rhNGF 20 mcg/mL n (%)	Vehicle Control n (%)	Total n(%)
Screened			52
Screening Failures [a]			4 (7.7%)
Randomized [a]	**24**	**24**	**48 (92.3%)**
ITT Population [a]	**24 (100.0%)**	**24 (100.0%)**	**48 (92.3%)**
Did not receive study drug	1 (4.2%)	0	1 (2.1%)
Discontinued during Controlled Treatment Period [b]	6 (25.0%)	9 (37.5%)	15 (31.3%)
Completed Controlled Treatment Period	18 (75.0%)	15 (62.5%)	33 (68.8%)
Completely healed at Week 8 [b, c]	14 (58.3%)	7 (29.2%)	21 (43.8%)
Not completely healed at Week 8 [b, c]	4 (16.7%)	8 (33.3%)	12 (25.0%)
Patients retreated for recurrence [b]	2 (8.3%)	3 (12.5%)	5 (10.4%)

Source: NGF0214 CSR Addendum, Text Table 1

a The percentages are calculated based on screened patients. **b** Percentages are calculated based on the ITT Population.

c Vehicle patients completely healed at Week 8 move into the 24-week follow-up period (as do all rhNGF patients), while vehicle patients not completely healed at Week 8 enter Uncontrolled Treatment Period with rhNGF for 8 weeks before entering a 24-week follow-up period. Further 6 vehicle patients [redacted] (b) (6) entered Uncontrolled Treatment Period after premature termination before Week 8.

Reviewer's Comment: *One patient in the rhNGF treatment group* [redacted] (b) (6) *was randomized and immediately discontinued and was never treated. No postbaseline data was documented for this patient. In the vehicle group, seven patients were not completely healed at Week 8 and entered the uncontrolled treatment phase* [redacted] (b) (6) *One patient* [redacted] (b) (6) *was considered as not completely healed at Week 8, but did not enter*

uncontrolled treatment period upon discretion of the investigator.

Table 6.2.2-3 Reasons for Discontinuation by Treatment (ITT Population)

	rhNGF 20 mcg/mL N=24 n (%)	Vehicle N=24 n (%)
Completed Controlled Period	18 (75.0%)	15 (62.5%)
Completed Follow-up Period	15 (62.5%)	16 (66.7%)
Reason for Early Discontinuation of Controlled Period		
Adverse Event	4 (16.7%)	3 (12.5%)
Other	2 (8.3%)	6 (25.0%)

Source: NGF0214 CSR Table 14.1-1.2
Percentages are based on the ITT Population. Subjects should only have one reason for not completing the study.
Ongoing after Controlled Period are subjects who completed the controlled period but have not yet completed (or discontinued from the follow-up period.) Six patients (b) (6) of the Vehicle Group terminated the Controlled Period prematurely and continued directly into the Uncontrolled Treatment Period.

Reviewer's Comment: *Most patient discontinuations during the controlled period were due to adverse events. The 'Other' category included one patient in the rhNGF group (b) (6) who was worried about her treated eye after she had experienced an adverse event (possible ocular infection) and withdrew from the study; the other (b) (6) had uncontrolled intraocular pressure and glaucoma specialist recommended patient not to participate in the study.*

Table 6.2.2-4 Protocol Deviations (ITT Population)

Protocol Deviation	rhNGF 20 mcg/mL N=24 n (%)	Vehicle N=24 n (%)
Failure to comply with SAE reporting requirements	1 (4.2%)	0 (0.0%)
Failure to comply with essential study procedures	10 (41.7%)	7 (29.2%)
Failure to comply with inclusion/exclusion criteria	4 (16.7%)	9 (37.5%)
Failure to comply with protocol specific masking procedures	0 (0.0%)	1 (4.2%)
Failure to comply with the procedures for obtaining informed consent	2 (8.3%)	2 (8.3%)
Failure to comply with the trial medication	1 (4.2%)	1 (4.2%)
Use of a prohibited concomitant medication during the controlled treatment period	7 (29.2%)	3 (12.5%)

Source: NGF0214 CSR Table 14.1-2
Counting is on a per-patient basis. If a patient reports the same deviation repeatedly, it is counted only once.

Reviewer's Comment: *Failure to comply with essential study procedures was the most frequent protocol deviation.*

Table 6.2.2-5 Patient Demographics, by Treatment and Overall (Safety Population)

	rhNGF 20 mcg/mL N=24	Vehicle Control N=24
Age (years)		
N	24	24
Mean (SD)	65.9 (13.85)	64.5 (14.15)
Min, Median, Max	33, 67, 94	35, 65, 92
Gender, n(%)		
Male	10 (42%)	9 (37%)
Female [a]	14 (58%)	15 (63%)
Race, n(%)		
Asian	1 (4%)	0
Black or African American	3 (13%)	2 (8%)
Native Hawaiian or Other Pacific Islander	0	1 (4%)
White	20 (83%)	20 (83%)
Other	0	1 (4%)
Ethnicity, n(%)		
N/A	4 (17%)	4 (17%)
Hispanic, Latino or Spanish	0	1 (4%)
Not Hispanic, Latino or Spanish	20 (83%)	19 (79%)

Source: NGF0214 CSR Addendum Text Table 12

Reviewer's Comment: *Demographics were balanced across treatment groups. The mean patient age was approximately 65 and the majority of patients were female.*

Table 6.2.2-6 Summary of Neurotrophic Keratitis History (ITT Population)

	rhNGF 20 mcg/mL N=24	Vehicle Control N=24
Time Since Initial Diagnosis of NK (months)		
N	24	24
Mean (SD)	31.1 (108.34)	33.0 (73.83)
Min, Median, Max	0, 4, 535	0, 13, 366
Time Since Initial Diagnosis of NK Stage 2 or 3, months		
Mean (SD)	7.5 (14.51)	7.9 (8.59)
Min, Median, Max	0, 3, 71	0, 4 28
Current Classification of NK, n (%)		
Stage 1	0	0
Stage 2	15 (62.5%)	18 (75.0%)
Stage 3	9 (37.5%)	6 (25.0%)

Source: NGF0214 CSR Text Table 13 Percentages are based on ITT Population.

Summary of Medical History Occurring ≥ 15% of Patients (Safety Population)
Source: NGF0214 CSR Table 14.1-5

Reviewer's Comment: *Cataracts, meibomian gland dysfunction and dry eye were the most common conditions in patient past medical history.*

Nearly all patients had a history of other eye disorders (100% in the rhNGF group and 96% in the vehicle group]. The most common were cataract (87% and 63%, respectively), meibomian gland dysfunction (83%; 58%), dry eye (74%; 42%) and blepharitis (48%; 33%). Many had undergone surgical procedures on the eye (78% and 79%), mainly intraocular lens implant (30%; 17%), amniotic membrane graft (22%; 13%), and cataract operation (13% and 21%).

Other common disorders were systemic hypertension (57% in the rhNGF group, 54% in the vehicle group), ophthalmic herpes simplex (39% and 21%, respectively), anxiety (35% and 21%), depression (26% and 17%), hypercholesterolemia (22% and 25%), diabetes mellitus (13% and 4%), gastroesophageal reflux disease (13% and 21%), drug hypersensitivity (30% and 38%), rosacea (22% only in the rhNGF group) and asthma (22% only in the rhNGF group).

Overall, treatment groups were not balanced with respect to medical history, with a preponderance of specific disorders between groups.

Concomitant Medications
Nearly all patients received concomitant medication during the Controlled Treatment Period: 100% of patients in the rhNGF group and 96% of the patients in the vehicle group. The most common were: artificial tears (26% and 29%), acyclovir (39% and 21%), moxifloxacin hydrochloride (30% and 21%), and prednisolone acetate (17% and 13%).

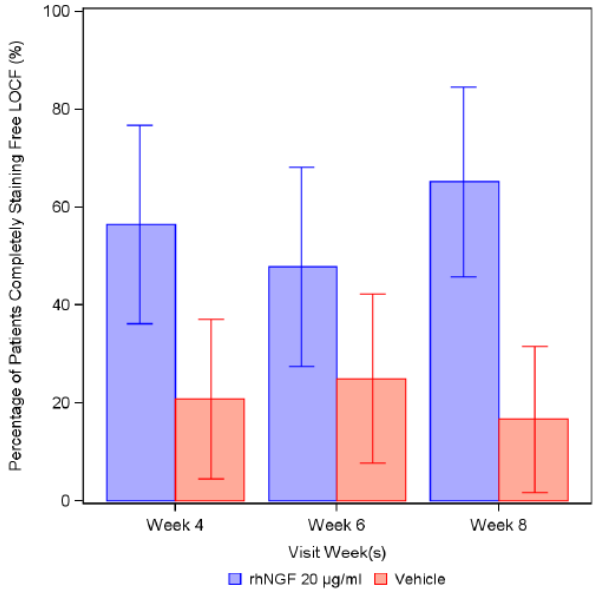
Table 6.2.2-7
Primary Efficacy Analysis of Completely Staining Free Eyes at Week 8 as Determined by the Reading Center (LOCF, ITT Population)

	rhNGF 20 mcg/mL N=23 n (%)	Vehicle N=24 n (%)
Week 8		
Completely Staining Free	15 (65.2%)	4 (16.7%)
Not Completely Staining Free	8 (34.8%)	20 (83.3%)
Treatment Comparison [a] (rhNGF vs. Vehicle Control)		
Difference in % Complete Healing	48.6%	
95% CI [b]	(24.0, 73.1)	
p-value [c]	<0.001	

Source: NGF0214 CSR Addendum Table 14.2S-0.1
"Completely Staining Free" means that corneal fluorescein staining in the area of the PED or corneal ulcer measured at the baseline visit is absent at the moment of assessment. Otherwise the result is "Not Completely Staining Free". This central reader evaluation is only provided for the study eye. All missing evaluations are imputed by the LOCF until last observed visit. If a Patient discontinued before Week 4, then "Not Completely Staining Free" is imputed, if investigator's assessment indicates a PED > 1 mm.
Patients with no post-baseline data are assumed missing and excluded from analyses.
a p-value is from a 2x2 Chi-squared test.

Reviewer's Comment: *A significant difference between groups was demonstrated in complete healing.*

Figure 6.2.2-1 Summary of Completely Staining Free as Determined by Central Reading Center. LOCF by Visit with Treatment (ITT Population)



Source: NGF0214 CSR Addendum Figure 14.2S-0.1
The confidence intervals shown are 95% confidence intervals. Confidence interval is calculated based on one-sample proportions test using the normal approximation for the Binomial theory.

Sensitivity Analyses

Table 6.2.2-8 Primary Efficacy Analysis of Completely Staining Free Eyes as Determined by the Reading Center (Observed Cases, ITT Population)

	rhNGF 20 mcg/mL N=24 n (%)	Vehicle N=24 n (%)
Week 4		
Completely Staining Free	13 (68.4%)	5 (27.8%)
Not Completely Staining Free	6 (31.6%)	13 (72.2%)
Difference in % Complete Healing **(rhNGF vs. Vehicle Control)**	40.6%	
95% CI	(11.2, 70.1)	
p-value [a]	0.013	
Week 6		
Completely Staining Free	11 (57.9%)	6 (46.2%)
Not Completely Staining Free	8 (42.1%)	7 (53.8%)
Difference in % Complete Healing **(rhNGF vs. Vehicle Control)**	11.7%	
95% CI	(-23.3, 46.8)	
p-value [a]	0.513	
Week 8		
Completely Staining Free	14 (77.8%)	3 (21.4%)
Not Completely Staining Free	4 (22.2%)	11 (78.6%)
Difference in % Complete Healing **(rhNGF vs. Vehicle Control)**	56.3%	
95% CI	(27.5, 85.2)	
p-value [a]	0.002	

Source: NGF0214 CSR Addendum Table 14.2S-0.2
"Completely Staining Free" means that corneal fluorescein staining in the area of the PED or corneal ulcer measured at the baseline visit is absent at the moment of assessment. Otherwise the result is "Not Completely Staining Free". This central reader evaluation is only provided for the study eye. **a** p-value is from a 2x2 Chi-squared test.

Reviewer's Comment: *Five fewer patients were evaluated at Week 6 than Week 4 contributing to the lack of a statistically significant difference at Week 6, even though the difference between groups was significant at Weeks 4 and 8.*

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The data from two (NGF0212 and NGF0214) studies contained in this submission establishes the efficacy of cenergermin ophthalmic solution, 20 mcg/mL dosed 6-times daily (every 2 hours) for 8 weeks for the treatment of (b) (4) neurotrophic keratitis.

8. Review of Safety

8.1. Safety Review Approach

The review focuses on the Primary Safety Pool defined by Dompé as the Safety population.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The total of patients and subjects exposed to rhNGF in the clinical program is 553. Of these, 177 were Stage 2 or 3 NK patients, which includes 36 NK patients who received rhNGF in the uncontrolled periods of studies NGF0212 and NGF0214. Fifty-eight (58) healthy volunteers were exposed to rhNGF in a Phase 1 study (NGF0112). Overall, 1 or 2 drops (from 1 to 6 times daily) were administered in the eye(s) at doses from 0.5-180 mcg/mL for a treatment duration ranging from one day up to 24 weeks.

In four studies with treatment periods of ≥8 weeks, 291 patients received a rhNGF formulation containing methionine in concentrations at or above that proposed for marketing (≥20 mcg/mL rhNGF). Twenty-three (23) patients received 180 mcg/mL rhNGF for 4 weeks in the NEMO investigator-initiated study; 10 of the patients originally randomized to 4 weeks of rhNGF had a cystoid macular edema (CME) recurrence during the study and received additional 4 weeks with active treatment. A total of 301 patients were exposed to the rhNGF formulation proposed for marketing (≥20 mcg/mL rhNGF for ≥8 weeks).

Table 8.2.1-1: List of Clinical Studies with rhNGF Eye Drops – Safety Database

Code Phase (status) Location	Key objectives	Countries	Group	Doses	Subjects randomized/ uncontrolled or rescue treated[a]	Safety database for rhNGF[b]
NGF0112 Phase I (completed) Module 5.3.3.1	Safety, PK, dose escalation (formulation without methionine)	Switzerland, UK	Healthy volunteers	0.5-5 µg/ml 20 µg/ml 60-180 µg/ml Vehicle **Total**	6 21 31 16 **74**	58
NGF0212 Phase I segment (completed) Module 5.3.5.1	Safety, PK, dose escalation (formulation without methionine)	Italy, France, UK, Germany, Spain, Hungary, Portugal, Belgium, Poland	Stage 2-3 NK	10 µg/ml 20 µg/ml Vehicle **Total**	7 7 4 **18**	141
NGF0212 Phase II segment (completed) Module 5.3.5.1	Safety, efficacy, PK, dose-ranging (formulation without methionine)	Italy, France, UK, Germany, Spain, Hungary, Portugal, Belgium, Poland	Stage 2-3 NK	10 µg/ml 20 µg/ml Vehicle **Total**	52/10[a] 52/13[a] 52 **156/23**[a]	
NGF0214 Phase II (completed) Module 5.3.5.1	Safety and efficacy (formulation with methionine – planned for marketing)	United States	Stage 2-3 NK	20 µg/ml Vehicle **Total**	24/13[a] 24 **48/13**[a]	36[c]
NGF0213 Phase II (completed) Module 5.3.5.4	Supportive for safety only (formulation with methionine – planned for marketing)	Austria	Moderate-severe dry eye	4 µg/ml 20 µg/ml **Total**	20 20 **40**	40
NGF0113 Phase I/II (completed) Module 5.3.5.4	Supportive for safety only (formulation with methionine – planned for marketing)	Italy	Retinitis pigmentosa	60 µg/ml 180 µg/ml Vehicle **Total**	20 20 10 **50**	40

Code Phase (status) Location	Key objectives	Countries	Group	Doses	Subjects randomized/ uncontrolled or rescue treated[a]	Safety database for rhNGF[b]
NGF0116 Phase II (completed) Module 5.3.5.4	Supportive for safety only (formulation with methionine – planned for marketing)	Italy	Post-refractive surgery	20 µg/ml Vehicle **Total**	120 60 **180**	115[d]
NGF0216 Phase II (completed) Module 5.3.5.4	Supportive for safety only (formulation with methionine – planned for marketing)	United States	Dry eye	20 µg/ml Vehicle **Total**	100 50 **150**	100
NEMO Investigator - initiated (completed) Module 5.4	Supportive for safety only (formulation with methionine – planned for marketing)	Italy	Retinitis pigmentosa and cystoid edema	180 µg/ml Vehicle **Total**	23 22 **45**	23[e]
Total # of subjects enrolled in all rhNGF studies to date						**761**
Total # of subjects exposed to rhNGF (any concentration) in all studies to date						**553**
Total # of NK patients exposed to rhNGF (any concentration, with or without methionine)						**177**

Sources: CSR NGF0112, CSR NGF0212, CSR NGF0214, CSR NGF0213, CSR NGF0113, CSR NGF0116, CSR NGF0216; NEMO abstract (Rama et al, abstract).

[a] These numbers include NK patients who were initially randomized to vehicle and were rescue treated with rhNGF according to the study protocol (i.e., if patient had deterioration of stage 2 or 3 NK during the 8 weeks of controlled treatment, or did not achieve corneal healing [<0.5 mm lesion size] within 8 weeks of treatment).

[b] The column "Safety database" includes only patients actually exposed to rhNGF (any concentration).

[c] In NGF0214, Only 23 of 24 patients randomized to primary rhNGF treatment received study medication

[d] In NGF0116, Only 115 of 120 patients randomized to primary rhNGF treatment received study medication [e] NEMO Report (Rama et al, abstract).Only 10 patients randomized to rhNGF received 4+4 weeks of treatment

Table 8.2.1-2: Duration of Exposure - Primary Safety Pool

	NGF0212		NGF0214	
	Vehicle	**rhNGF 20 mcg/mL**	**Vehicle+M**	**rhNGF+M 20 mcg/mL**
Duration of Exposure during Controlled Treatment Period- Exposure (Days)				
N	52	52	24	23
Mean (SD)	47.3 (16.0)	46.2 (16.2)	42.8 (18.7)	46.2 (16.5)
Median (Range)	55.0 (1-61)	55.0 (1-58)	55.0 (5-59)	54.0 (3-57)
Duration of Exposure during Uncontrolled Treatment Period- Exposure (Days)				
	Vehicle then rhNGF 20 mcg/mL		**Vehicle+M then rhNGF+M 20 mcg/mL**	
N	13		13	
Mean (SD)	49.0 (13.2)		42.7 (19.7)	
Median (Range)	49.0 (13-76)		53.0 (6-60)	

M= methionine

Reviewer's Comment: *The mean duration of exposure to rhNGF 20 mcg/mL was 46 days during the controlled treatment period and 42 – 49 days during the uncontrolled treatment period.*

Table 8.2.1-3: Safety Database for rhNGF Ophthalmic Solution Planned Marketing Formulation [a]

Study	NGF0214	NGF0113	NGF0116	NGF0216	NEMO	
Condition treated	**Stage 2-3 NK**	**Retinitis pigmentosa**	**Post-refractive surgery**	**Dry eye**	**Retinitis pigmentosa and cystoid macular edema**	**TOTAL**
rhNGF concentration(s) (formulated with methionine)	20 mcg/ml	60 mcg/ml, 180 mcg/ml	20 mcg/ml	20 mcg/ml	180 mcg/ml	N/A
Regimen, drops per day	6	3	6	6	3	N/A
Eyes treated	1 or 2	2	1 or 2	2	2	N/A
Treatment duration, weeks	8	24	8	8	4 (+ 4 wks, as needed)	N/A
Total # patients randomized to rhNGF or vehicle	48	50	180	150	45	473
Randomized to primary rhNGF treatment	24	40	120	100	23	307
Received primary or rescue rhNGF treatment	36	40	115	100	23	314
Total # patients exposed to ≥20 mcg/ml rhNGF (treatment planned for≥8 weeks) [b]	36	40	115	100	10[b]	301

Sources: CSR NGF0214, CSR NGF0113, NGF0116, NGF0216; NEMO abstract (Rama et al, abstract)
Key: CSR = clinical study report; µg = microgram(s); ml = milliliter(s); NK= neurotrophic keratitis; rhNGF = recombinant human nerve growth factor
[a] Database includes patients (any condition) randomized to the planned rhNGF concentration or higher (≥20 mcg/mL rhNGF with methionine) for the full clinical course of four or eight weeks or more
[b] In the NEMO study only10 patients randomized to rhNGF received 4+4 weeks of treatment

Reviewer's Comment: *The total number of patients exposed to rhNGF with methionine 20 mcg/mL or higher during the clinical development is 301.*

8.2.2. **Relevant characteristics of the safety population:**

The safety population is representative of the population that the drug product is intended to treat.

8.2.3. **Adequacy of the safety database:**

The safety database is adequate with respect to size, duration of exposure, duration of treatment, patient demographics, and disease characteristics.

8.3. **Adequacy of Applicant's Clinical Safety Assessments**

8.3.1. **Issues Regarding Data Integrity and Submission Quality**

This submission was of sufficient quality to allow for a substantive review. No issues related to data quality or data integrity were identified in this review.

8.3.2. **Categorization of Adverse Events**

Adverse events for the 8-week controlled treatment period are included. When significant or notable differences in adverse events occurred during the 24- to 56-week follow-up period, those adverse events are included. Adverse events were categorized as ophthalmic and systemic.

8.3.3. **Routine Clinical Tests**

Routine ophthalmic examination assessments were conducted on all subjects including visual acuity assessments, corneal photography, manifest refractions, confocal microscopy (a subset of subjects), corneal sensitivity testing, slit lamp examination, and dilated fundus examinations. Clinical laboratory tests (hematology and serum chemistry parameters) were performed at the beginning and end of the trials. Anti-drug antibody levels were also evaluated. Heart rate and blood pressure were checked at Baseline, Week 4, and Week 8.

8.4. **Safety Results**

8.4.1. **Deaths**

During the controlled treatment period in Study NGF0212, one patient (b) (6) death due to progression of lung cancer was reported in the rhNGF 20 mcg/mL. No deaths were reported during the controlled treatment period in Study NGF0214. During the follow-up period, six patient deaths were reported in Study NGF0212 and one patient death in Study NGF0214.

Table 8.4.1-1 Deaths

Patient Number / Treatment Group	Age/ Gender	Significant Medical History	Cause of Death
Study NGF0212			
(b) (6) Vehicle	87 M	COPD, chronic renal disease, ischemic cardiac disease, atrial fibrillation	Respiratory failure
rhNGF 10 mcg/mL	76 M	Cardiomyopathy, lung disease	Heart failure
rhNGF 10 mcg/mL	80 F	Hypercholesterolemia, hypertriglyceridemia	Heart attack
rhNGF 10 mcg/mL	83 M	Diverticulitis, pulmonary fibrosis, pulmonary hypertension, hypertension, atrial fibrillation, cardiac arrhythmia, dyspnea	Cardiac arrhythmia, dyspnea
rhNGF 10 mcg/mL	37 F	Ehlers-Danlos syndrome – vascular, Type 4. Carotid cavernous fistula, femoral artery dissection	Aortic dissection, aortic rupture, hemorrhagic shock
rhNGF 20 mcg/mL	68 M	Type I diabetes mellitus, right leg amputation, hypertension, poor global status.	Respiratory failure
Study NGF0214			
(b) (6) rhNGF 20 mcg/mL	68 M	Type II diabetes mellitus, hypertension, hypercholesterolemia, myocardial infarction	Cause not specified.

Reviewer's Comment: *The cardiovascular deaths which occurred during the study are consistent with the age and past medical history of the patients enrolled.*

8.4.2. Serious Adverse Events

Table 8.4.2-1 Incidence of Serious Adverse Events during the Controlled Treatment Period – Study NGF0212 (Safety Population)

Patient Number / Treatment Group	Serious Adverse Event	Outcome
Phase I		
(b) (6) Vehicle	Corneal ulcer extension	Hospitalization, amniotic membrane transplantation after pannectomy
rhNGF 10 mcg/mL	Corneal ulcer extension/ corneal edema	Resolved with topical abx, dexamethasone, bandage CLs
Phase II		
Vehicle	Corneal ulcer extension	Resolved with rhNGF 10 mcg/mL treatment
Vehicle	Corneal lesion progression, decreased VA	Resolved with rhNGF 20 mcg/mL treatment
Vehicle	Cornea lesion progression	Resolved with rhNGF 20 mcg/mL treatment
Vehicle	Corneal edema/ HSV immune reaction	Resolved with abx
Vehicle	Corneal lesion progression	Resolved (tx not reported)
Vehicle	Corneal lesion progression	Resolved with rhNGF 20 mcg/mL treatment
rhNGF 10 mcg/mL	Corneal ulcer extension	Resolved with rhNGF 20 mcg/mL treatment
rhNGF 10 mcg/mL	Corneal endothelial inflammation	Resolved with topical corticosteroids

Patient Number / Treatment Group	Serious Adverse Event	Outcome
(b) (6) rhNGF 10 mcg/mL	Respiratory distress, myocardial infarction, diverticulitis	Resolved with hospitalization.
rhNGF 20 mcg/mL	Endothelial graft rejection	Oral prednisone treatment/ Resolved
rhNGF 20 mcg/mL	Hypopyon	Discontinued tx, oral corticosteroids/ Resolved
rhNGF 20 mcg/mL	Aortic dissection	Hospitalized
rhNGF 20 mcg/mL	Corneal ulcer progression	Study drug discontinued/ Patient died (lung cancer progression)
rhNGF 20 mcg/mL	Corneal perforation	Resolved with hospitalization/ keratoplasty
rhNGF 20 mcg/mL	Vertigo	Hospitalized, resolved.
rhNGF 20 mcg/mL	Venous thrombosis	Anticoagulation, resolved.
rhNGF 20 mcg/mL	Renal colic	Hospitalized, resolved.
rhNGF 20 mcg/mL	Corneal lesion progression	Multiple interventions, resolved.

Table 8.4.2-2 Incidence of Serious Adverse Events during the Controlled Treatment Period – Study NGF0214 (Safety Population)

Patient Number / Treatment Group	SAE	Outcome
(b) (6) Vehicle	Corneal lesion progression	Resolved with rhNGF 20 mcg/mL treatment
Vehicle	Corneal lesion recurrence after healing	Resolved with rhNGF 20 mcg/mL treatment
Vehicle	Cornea lesion progression	Resolved with rhNGF 20 mcg/mL treatment
Vehicle	Ventral hernia S/P nephrectomy	Surgical repair after chemotherapy during follow-up.
rhNGF 20 mcg/mL	Syncope	Resolved without treatment
rhNGF 20 mcg/mL	Descemetocele with aqueous leakage	Withdrawn from study. Cyanoacrylate glue, keratoplasty and tarsorrhaphy.
rhNGF 20 mcg/mL	Corneal lesion progression	Additional topical medications, resolved.

Reviewer's Comment: *During the treatment periods in Studies NGF0212 and NGF0214, serious adverse events of corneal lesion progression occurred in 11 vehicle group patients and 6 rhNGF group patients. Serious adverse events reported for both studies were generally consistent with the underlying condition and patient population.*

8.4.3. **Dropouts and/or Discontinuations Due to Adverse Effects**

Table 8.4.3-1 Incidence of Adverse Events Leading to Discontinuation of Study Drug

Controlled Treatment Period				
	Phase II segment NGF0212		**NGF0214**	
System Organ Class/ Preferred Term	**Vehicle (N=52)**	**rhNGF 20 µg/ml (N=52)**	**Vehicle + methionine (N=24)**	**rhNGF 20 µg/ml + methionine (N=23)**
Patients with at least 1 adverse event n (%)	4 (7.7%)	9 (17.3%)	7 (29.2%)	5 (21.7%)
Cardiac disorders	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Arrhythmia	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Eye disorders	3 (5.8%)	6 (11.5%)	4 (16.7%)	3 (13.0%)
Corneal epithelium defect	0 (0.0%)	0 (0.0%)	1 (4.2%)	0 (0.0%)
Corneal neovascularization	1 (1.9%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Corneal thinning	0 (0.0%)	0 (0.0%)	2 (8.3%)	1 (4.3%)
Eye inflammation	0 (0.0%)	1 (1.9%)	0 (0.0%)	1 (4.3%)
Eye pain	0 (0.0%)	2 (3.8%)	0 (0.0%)	0 (0.0%)
Hyphema	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
Keratitis	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Visual acuity reduced	2 (3.8%)	2 (3.8%)	1 (4.2%)	0 (0.0%)
General disorders and administration site conditions	3 (5.8%)	2 (3.8%)	3 (12.5%)	2 (8.7%)
Disease progression	3 (5.8%)	2 (3.8%)	3 (12.5%)	2 (8.7%)
Immune system disorders	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Corneal graft rejection	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Injury, poisoning and procedural complications	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
Aqueous humor leakage	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
nvestigations	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Blood pressure increased	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Malignant neoplasm progression	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Nervous system disorders	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Headache	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)

Source: 2.7.4 Summary of Clinical Safety Table 25

Reviewer's Comment: *During the treatment period, 'disease progression' was the most common adverse event leading to discontinuation in both studies. The second leading cause of discontinuation was 'reduced visual acuity' in Study NGF0212 and 'corneal thinning' in Study NGF0214. Each of these terms indicate that the course of the underlying disease has not been*

improved. During the uncontrolled treatment period, one patient in the rhNGF 20 mcg/mL group in Study NGF0214 withdrew due to an unrelated 'eye disorder'.

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

Table 8.4.4-1 Adverse Events Pooled by Treatment Arm during the Controlled Treatment Period by System Organ Class, or by Preferred Term Occurring in ≥ 2% of Patients per Treatment Arm (Primary Safety Pool – Safety Population)

Body System MedDRA Preferred Term	NGF0212 + NGF0214 Vehicle (+/- M) n%		NGF0212 + NGF0214 rhNGF (+/- M) n%	
	n=76		n=75	
Any Adverse Event	38	50.0%	48	64.0%
Eye disorders	30	39.5%	31	41.3%
Cataract	0	0.0%	3	4.0%
Corneal deposits	0	0.0%	3	4.0%
Corneal epithelium defect	3	4.0%	3	4.0%
Corneal graft rejection	1	1.3%	2	2.7%
Corneal thinning	2	2.6%	2	2.7%
Eye inflammation	2	2.6%	4	5.3%
Eye irritation	5	6.6%	0	0.0%
Eye pain	6	7.9%	12	16.0%
Foreign body sensation	1	1.3%	2	2.7%
Lacrimation increased	2	2.6%	4	5.3%
Ocular discomfort	3	4.0%	2	2.7%
Ocular hyperemia	2	2.6%	5	6.7%
Photophobia	3	4.0%	2	2.7%
Vision blurred	3	4.0%	0	0.0%
Visual acuity reduced	7	9.2%	8	10.7%
Gastrointestinal disorders	2	2.6%	2	2.7%
General disorders and administration site conditions	13	17.1%	6	8.0%
Disease progression	10	13.2%	5	5.3%
Sensation of foreign body	2	2.6%	2	2.7%
Infections and infestations	4	5.3%	11	14.7%
Injury, poisoning and procedural complications	2	2.6%	3	4.0%
Investigations	3	4.0%	5	6.7%
Intraocular pressure increased	2	2.6%	4	5.3%
Musculoskeletal and connective tissue disorders	0	0.0%	3	4.0%
Nervous system disorders	4	5.3%	6	8.0%
Headache	4	5.3%	3	4.0%
Skin and subcutaneous disorders	1	1.3%	2	2.7%
Pooling of Like-Terms				

Body System MedDRA Preferred Term	NGF0212 + NGF0214 Vehicle (+/- M) n%		NGF0212 + NGF0214 rhNGF (+/- M) n%	
Ocular discomfort = Eye irritation, Foreign body sensation in eyes, Ocular discomfort, Sensation of foreign body	11	1.4%	6	0.1%
Blurred vision = Visual acuity reduced, Vision blurred	10	13.2%	8	10.7%

Source: 2.7.4 Summary of Clinical Safety Table 17, Integrated NGF0212 and NGF0214 Analysis Report Table1.3.2.1

Reviewer's Comment: *The highlighted adverse events occurred more frequently in the rhNGF 20 mcg/mL +/- methionine groups than in the vehicle +/- methionine groups including if only 1 patient experienced the adverse event.*

The adverse events which occurred more frequently in the rhNGF 20 mcg/mL +/- methionine groups than in the vehicle +/- methionine groups, and occurred in more than 1 patient are cataract, corneal deposits, corneal graft rejection, eye inflammation, eye pain, foreign body sensation, lacrimation increased, ocular hyperemia, visual acuity reduced and intraocular pressure increased.

These adverse events were consistent with the underlying disease process in neurotrophic keratitis and with healing of a corneal defect/ulcer. The Safety populations of Study NGF0212 - Phase II and Study NGF0214 included 89 patients over the age of 65 years. Thus, the incidence of 'cataract' is not unexpected.

In Table 8.4.4-1, similar preferred terms were pooled creating new pooled ocular discomfort and blurred vision terms. Pooling of these terms demonstrates that these events did not occur more frequently in the rhNGF 20 mcg/mL +/- methionine groups than in the vehicle +/- methionine groups.

It is recommended that adverse event labeling include the following terms: corneal deposits, eye inflammation, eye pain, lacrimation increased, ocular hyperemia, and intraocular pressure increased.

Table 8.4.4-2 Systemic Adverse Events during the Treatment Period

Study Period: Controlled Treatment				
	Phase II segment NGF0212		**NGF0214**	
Body System MedDRA Preferred Term	**Vehicle (N=52)**	**rhNGF 20 mcg/ml (N=52)**	**Vehicle + M (N=24)**	**rhNGF 20 mcg/ml + M (N=23)**
General disorders and administration site conditions, n (%)	7 (13.5%)	2 (3.8%)	6 (25.0%)	4 (17.4%)
Chest pain	0 (0.0%)	0 (0.0%)	1 (4.2%)	0 (0.0%)
Disease progression	6 (11.5%)	2 (3.8%)	4 (16.7%)	2 (8.7%)
Instillation site pain	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sensation of a foreign body	0 (0.0%)	0 (0.0%)	2 (8.3%)	2 (8.7%)
Paresthesia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
Syncope	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
Infections and infestations, n (%)	2 (3.8%)	7 (13.5%)	2 (8.3%)	4 (17.4%)
Conjunctivitis bacterial	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Corneal abscess	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Eye infection intraocular	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
Gastroenteritis	1 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hordeolum	0 (0.0%)	0 (0.0%)	1 (4.2%)	0 (0.0%)
Influenza	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Lower respiratory tract infection	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Nasopharyngitis	1 (1.9%)	2 (3.8%)	0 (0.0%)	0 (0.0%)
Ophthalmic herpes zoster	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
Respiratory tract infection	0 (0.0%)	0 (0.0%)	1 (4.2%)	0 (0.0%)
Upper respiratory tract infection	0 (0.0%)	1 (1.9%)	0 (0.0%)	0 (0.0%)
Urinary tract infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
Vulvovaginal mycotic infection	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
Nervous system disorders n (%)	2 (3.8%)	2 (3.8%)	2 (8.3%)	4 (17.4%)
Diabetic neuropathy	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
Dizziness	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
Headache	2 (3.8%)	2 (3.8%)	2 (8.3%)	1 (4.3%)
Paresthesia	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)
Syncope	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.3%)

Source: 2.7.4 Summary of Clinical Safety, Table 27, Table 28, Table 29
M= methionine

Reviewer's Comment: *There were no significant differences between groups in systemic safety.*

8.4.5. **Laboratory Findings**

No notable trends or clinically significant changes over time or between treatment groups were observed in hematology and serum chemistry parameters.

8.4.6. **Vital Signs**

No clinically significant changes from Baseline or notable differences between treatment groups were observed for any vital signs measurements.

8.4.7. Electrocardiograms (ECGs)

Electrocardiograms were not performed during either Study NGF0212 or Study NGF0214. Electrocardiograms which were performed in a Phase 1 study in healthy volunteers did not demonstrate any significant effect.

8.4.8. QT

QT studies were not performed during the clinical development of rhNGF.

(b) (4)

8.5. Analysis of Submission-Specific Safety Issues

The rhNGF drug product administered in Studies NGF0212 and NGF0214 was a preservative-free solution packaged in (b) (4) vials which were closed with a stopper and a (b) (4) cap. (b) (4) Each vial contained (b) (4) rhNGF. (b) (4) These steps were completed 6 times per day for the 8-week treatment period.

The data from Studies NGF0212 and NGF0214 contained in this submission establishes the efficacy of cenergermin ophthalmic solution 20 mcg/mL dosed six times per day for the treatment of neurotrophic keratitis using the product configuration described above.

Since the conclusion of the above clinical studies, the applicant designed a new multi-dose delivery system. (b) (4), the new system includes a multi-dose vial which contains the six treatments for a day. (b) (4) The new multi-dose delivery system includes the following:

- (b) (4) vial with stopper and a flip-off cap
- (b) (4) Vial Adapter (b) (4)
- Disposable Pipettes (to withdraw and instill single drops from the vial)
- Disinfectant (b) (4)

The new procedure with the multi-dose vials includes the following:

- The vial is uncapped using the flip-off cap.
- The adapter is positioned on the vial by piercing the vial stopper without opening the vial.

- Each dose is withdrawn (6 times per day)
  - After cleaning (b) (4) the adapter with a disinfectant (b) (4), a pipette is attached to the port.
  - The dose is withdrawn into the pipette.
  - The pipette is unscrewed and the drop delivered to the eye.
  - The pipette is then discarded.

Thus, multiple doses per day (e.g., six drops per day) are to be withdrawn from the vial and dispensed with special single-use delivery devices (pipettes), so that the patient can use only one single vial per day.

This multi-dose delivery configuration described in the proposed OXERVATE labeling has been used by patients in two clinical studies - Study NGF0116 (Module 5.3.5.4) and Study NGF0216 (Module 5.3.5.4).

> Study NGF0116 was a Phase 2, single-center, randomized, double-masked, vehicle-controlled, parallel group preliminary efficacy and safety study of rhNGF 20 mcg/mL ophthalmic solution administered 6 times daily for 8 weeks to improve corneal innervation in patients who underwent cataract and corneal refractive surgery in Italy. This study enrolled 180 post-operative patients (120 in rhNGF and 60 in vehicle groups). Treatment compliance with self-administration of the drug product from the multi-dose vials (as measured by self -administration and diary information) was 96% in the rhNGF group and 98% in the vehicle group.
>
> Study NGF0216 was Phase 2, single-center, randomized, double-masked, vehicle-controlled, parallel group efficacy and safety study of rhNGF 20 mcg/mL ophthalmic solution administered 6 times daily for 8 weeks for the treatment of patients with dry eye in the US. This study enrolled 150 patients (100 in rhNGF and 50 in vehicle groups). Treatment compliance with self-administration of the drug product from the multi-dose vials (as measured by patient diary and control of weekly boxes) was 80% - 120% in 87% in the rhNGF group and 77% in the vehicle group.

Reviewer's Comment: *It is expected that all components required for Oxervate self-administration (e.g., multi-dose vials, adapters, sterile wipes, pipettes) be included in the Oxervate box at the time it is dispensed.*

8.6. Safety Analyses by Demographic Subgroups

Safety analyses by demographic subgroups were performed in the Subgroup Integrated Safety Pool. It comprises safety data from the Phase I and Phase II segments of NGF0212 (controlled treatment only: 20 µg/ml and vehicle control groups only) and the entire safety population from the controlled treatment segment of study NGF0214.

Phase I subjects treated in the 20 mcg/mL cohort of Study NGF0212 were included in the Subgroup Integrated Pool to increase the denominator for demographic subset safety analyses thereby providing additional robustness to these evaluations.

No significant differences in adverse events were identified related to age (< 65 and ≥ 65 years of age) or gender. Because of the low numbers of patients of different races, it is difficult to discern differences or commonalities in adverse events.

Additionally, no significant differences in adverse events were noted based on disease severity (Stage 2 NK or Stage 3 NK), punctal occlusion, etiology, or concomitant medications.

8.7. Specific Safety Studies/Clinical Trials

None.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Because of the negligible systemic absorption of rhNGF ophthalmic solution after topical administration, no carcinogenicity studies were conducted.

8.8.2. Human Reproduction and Pregnancy

This drug has not been tested in pregnant women.

8.8.3. Pediatrics and Assessment of Effects on Growth

(b) (4)

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Oxervate is not a narcotic and does not have abuse potential.

8.9. Safety in the Postmarket Setting

The 4-Month Safety Update was submitted on April 19, 2018. European marketing authorization for rhNGF 20 mcg/mL for the treatment of neurotrophic keratitis in adults was granted in July 2017. The product has been marketed as Oxervate in Germany as of November 2017, and in Italy and the United Kingdom in early 2018.

A total of 55 8-week treatment supply kits have been distributed as of the end of March 2018. Thirty-one patients have received an 8-week treatment supply of Oxervate under early access programs in the European Union and Switzerland. No serious adverse events were reported and no new safety signals were identified as of March 21, 2018.

An ongoing clinical study, NGF0314, studying rhNGF 180 mcg/mL (with methionine) for the treatment of glaucoma has limited safety data. Masked study data does not suggest any new safety signals.

8.10. Integrated Assessment of Safety

The safety database contained in this submission establishes the safety of rhNGF 20 mcg/mL dosed 6 times daily for 8 weeks.

9. Advisory Committee Meeting and Other External Consultations

No Advisory Committee Meeting was held for this application.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

See the labeling recommendations in Section 13.3.

11. Risk Evaluation and Mitigation Strategies (REMS)

No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events.

12. Postmarketing Requirements and Commitments

There are no recommended Post-marketing Requirements or Phase 4 Commitments.

13. Appendices

13.1. References

A literature search conducted by this reviewer failed to identify any literature references which were contrary to the information provided or referenced by the applicant in this application for this indication.

13.2. Financial Disclosure

Clinical Investigator Financial Disclosure
Review Template

Application Number: BLA 761094
Submission Date(s): December 22, 2017
Applicant: Dompé farmaceutici S.p.A
Product: Oxervate (cenergermin ophthalmic solution), 20 mcg/mL

Reviewer: Rhea A. Lloyd, MD
Date of Review: January 31, 2018
Covered Clinical Studies (Name and/or Number):
NGF0212
NGF0214

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: Study NGF0212: 11 investigators Study NGF0214: 42 investigators with 96 sub-investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

13.3. Labeling Review

Following is the applicant's draft labeling submitted on March 2, 2018, with recommended revisions.

28 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RHEA A LLOYD
06/11/2018

WILLIAM M BOYD
06/11/2018