14-4362

FILE COPY

Creative Regulatory Solutions, LLC

RECEIVED
APR 25 2014
Office of Orphan Products Development

April 23, 2014

Director
Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32-5271
Silver Spring, Maryland 20993-0002

RE: Request for Orphan Drug Designation for Recombinant Human Nerve Growth Factor for the Treatment of Neurotrophic Keratitis

Dear Director:

In accordance with 21 CFR 316.20, we are hereby submitting, in duplicate, on behalf of Dompe s.p.a., an Orphan Drug Designation Request for recombinant human nerve growth factor ocular drops for the treatment of neurotrophic keratitis. As required, copies of all references cited in the document have been enclosed. References have been provided in alphabetical order using numbered tabs. A bibliography follows the Orphan Drug Designation Request showing the tab number with the associated reference. The submission contains a single volume containing the formal orphan drug designation request, followed by the bibliography and copies of the references. An original and a photocopy of the Orphan Drug Designation Request have been enclosed.

Should you have any questions, please feel free to contact the undersigned by telephone at (862) 397-4534 or by e mail at bmccormack@creativeregulatory.com.

Sincerely,

Robert McCormack, PhD.
Regulatory Affairs Consultant

Enclosure:

References Removed
on 6/24/14
by

Creative Regulatory Solutions, LLC
14 Edinburgh Drive
Randolph, NJ 07869 USA

Tel: 862-397-4534
Fax: 862-397-4535

DOMPE S.P.A

Orphan Drug Designation Request

RECOMBINANT HUMAN NERVE GROWTH FACTOR FOR THE TREATMENT OF NEUROTROPHIC KERATITIS

4/23/2014

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Ach	Acetylcholine
DNA	Deoxyribose nucleic acid
ELISA	Enzyme-linked immunosorbent assay
HCP	Host cell protein
IEX-HPLC	Ion exchange- high performance liquid chromatography
IV	Intravenous
LAL	Limulus amebocyte lysate
LASIK	Laser in situ keratomileusis
LC-MS	Liquid chromatography-mass spectrometry
LNGFR	Low-affinity nerve growth factor receptor
mNGF	Murine nerve growth factor
NAION	Non-arteritic anterior ischemic optic neuropathy
NGF	Nerve growth factor
NK	Neurotrophic keratitis
NOAEL	No observed adverse effect level
PED	Persistent epithelial defect
rhNGF	Recombinant human nerve growth factor
RP	Retinitis pigmentosa
rpHPLC	Reverse phase high performance liquid chromatography
RT–PCR	Real time polymerase chain reaction
SC	Subcutaneous
SCG	Superior cervical ganglia
SDS-PAGE	Sodium dodecyl sulphate polyacrylamide gel electrophoresis
SE-HPLC	Size exclusion high performance liquid chromatography
SP	Substance P

1 ORPHAN DESIGNATION REQUEST

Dompé S.p.A. (Dompé) requests orphan drug designation for recombinant human nerve growth factor (rhNGF) for the treatment of neurotrophic keratitis (NK).

2 SPONSOR AND PRODUCT INFORMATION

SPONSOR INFORMATION

Sponsor Name and Address:

Dompé s.p.a.
Via S. Martino 12-12/A, 20122 Milan, Italy
Phone: +39 02 583831; Fax: +39 02 58383324

US Resident Agent:

Sponsor Contact/Regulatory Affairs:

Lamberto Dionigi, M.Sc.
Regulatory Affairs & Drug Safety Director
Dompé s.p.a.
Via S. Martino 12-12/A, 20122 Milan, Italy
Phone: +39 366 901 8586; Fax: +39 02 5844 9644
E-mail lamberto.dionigi@dompe.it

Sponsor Representative:

Robert J McCormack, PhD
Regulatory Affairs Consultant
Dompé US Agent
14 Edinburgh Drive
Randolph, NJ 07869
Phone: 862 397 4534; Fax: 862-397-4535
E-mail: bmccormack@creativeregulatory.com

DRUG PRODUCT INFORMATION

Product Name:

Recombinant human nerve growth factor (rhNGF)

Manufacturer:

Current rhNGF (drug substance and drug product) is manufactured by the sponsor at its production facilities in L'Aquila, Italy.

3 DESCRIPTION OF RARE DISEASE OR CONDITION

Neurotrophic keratitis (NK) is a degenerative corneal disease that follows a partial or total impairment of trigeminal innervation, leading to a reduction (hypoesthesia) in or loss (anesthesia) of corneal sensitivity (Semeraro et al, 2013).

Etiopathogenesis

The trigeminal ophthalmic branch has two reflex arcs: one motor arc, regulating the opening and closing of the eyelids, and one autonomic arc, regulating the lacrimal gland, Meibomian gland and goblet cell secretion. The integration of these two reflex arcs ensures the stability of the tear film and, together with related neurotrophic factors (neurotrophins), the vitality of the epithelium and stroma. The impairment of sensory innervation causes a reduction in the lacrimation reflex and the vitality, metabolism and mitosis of epithelial cells, with subsequent deficiency in epithelial repair, stromal and intracellular edema, loss of microvilli, and abnormal development of the basal lamina.

The study of NK has directed the attention of researchers to the role of neurotransmitters such as substance P (SP), calcitonin gene-related peptide, neuropeptide Y, vasoactive intestinal peptide, galanin, methionine-enkephalin, catecholamine, and acetylcholine (Ach). Studies have shown a decrease in SP and Ach resulting from injury to the corneal nerves, the ability of SP alone to stimulate the synthesis and growth of corneal epithelial cells, and epithelial proliferation *in vitro* by SP, cholecystokinin gene-related peptide and Ach.

NK can be the expression of systemic or ocular congenital or iatrogenic diseases resulting from damage to the fifth cranial nerve (Table 3-1).

Table 3-1: Etiopathogenesis of neurotrophic keratitis (Semeraro et al, 2013)

Infections	Herpes simplex Herpes zoster Leprosy
Corneal pathologies	Chemical burns Contact lens wear Surgeries Laser-assisted *in situ* keratomileusis Corneal incision Lamellar and penetrating keratoplasty Dystrophies Lattice Granular
Topical medications	Anesthetics Timolol Betaxolol Trifluridine Sulfacetamide
Cranial nerve V palsy	Trigeminal neuralgia surgery Neoplasm Aneurysm Facial trauma Congenital iley-Day syndrome Möbius corneal hypoesthesia
Systemic diseases	Diabetes Vitamin A deficiency Multiple sclerosis
Miscellaneous	Increasing age Adie's syndrome

The most common causes of loss of corneal sensitivity are herpes keratitis, chemical burns, long-term use of contact lenses, corneal surgery, ablative procedures for trigeminal neuralgia, and surgical procedures for reduction of jaw fractures. Other less frequent causes are space-occupying intracranial masses (e.g., schwannoma, meningioma and aneurysms) that can lead to compression of the nerve and reduce corneal sensitivity. Systemic diseases that may compromise trigeminal function are diabetes, multiple sclerosis and leprosy. NK may also be a complication of radiation therapy. Congenital causes, such as the Ridley-Day syndrome, anhidrotic ectodermal dysplasia, Moebius syndrome, Goldenhar syndrome, and congenital corneal anaesthesia, are very rare.

Classification

NK can be classified into 3 stages according to the Mackie classification (Table 3-2).

Table 3-2: Classification of neurotrophic keratitis (from Semeraro et al, 2013)

Stage 1	Punctate epithelial keratopathy Decreased tear film break-up time Rose bengal staining of inferior palpebral conjunctiva Dellen Gaule spots Stromal scarring
Stage 2	Epithelial defect Stromal swelling Surrounding rim of loose epithelium Anterior chamber reaction (rare)
Stage 3	Corneal ulcer Stromal lysis Perforation

The first stage is characterized by punctate keratitis, epithelial hyperplasia, stromal scarring, and corneal neovascularization.

The second stage is characterized by a persistent epithelial defect, usually in the paracentral area, of oval shape with the horizontal axis surrounded by an irregular, oedematous, opaque epithelium capable of spontaneous detachment. A reaction in the anterior chamber or sterile hypopyon is rarely seen. At this stage, the mechanism of loss of the corneal epithelium is similar to that of recurrent erosions, promoted by reduced lubrication of the corneal surface and by the abnormal corneal epithelium.

In the third stage, there is stromal involvement that appears as a stromal corneal ulcer and stromal oedema and infiltrates; this may result in perforation and/or corneal thinning due to stromal melting.

While Stage 1 is a mild condition that in most cases can be managed by continuous lubrification or therapeutic contact lenses, in Stages 2 and 3 the corneal epithelial defect or ulcer is persistent, with significant risk of corneal perforation and vision loss. Stages 2 and 3 are usually refractory to any treatment, and often surgery is the only option for the patient.

This marked difference between Stage 1 and Stages 2-3 might suggest that clinical manifestations might be induced by different mechanisms.

Diagnosis and symptoms

Diagnosis is based on a detailed medical history to investigate all possible risk factors, followed by a careful examination of the ocular and periocular area, including the globe and ocular adnexa.

Previous episodes of redness and eye pain or the presence of cutaneous blistering or scarring suggest previous herpetic infections. A history of corneal surgery, trauma, abuse of topical anesthetics, long-term use of topical medications, chemical burns, or contact lens abuse may be contributory. Long-term use of eye drops such as timolol, betaxolol, sulfacetamide sodium, or diclofenac can cause a loss of corneal sensitivity, as can the abuse of topical anaesthetics. Corneal hypoesthesia can sometimes occur in advanced stromal dystrophies such as latex or granular dystrophies. Any neurological signs or symptoms or expression of fifth cranial nerve disease such as brain tumors, vascular accidents and thromboangiitis obliterans should be explored. A history of previous surgical resection of an acoustic neuroma may suggest an iatrogenic trigeminal nerve injury. The presence of hearing problems may indicate intracranial tumors such as neuromas of the eighth cranial nerve, especially when the fifth and seventh cranial nerves are involved. A history of long-term therapy with neuroleptics, antipsychotics and antihistamines should be investigated, as should a history of diabetes mellitus, because reduction in corneal sensitivity in diabetes increases with the duration of the disease.

The symptoms reported by the patient vary depending on the degree of corneal anesthesia, but usually, the patient complains of a red eye and a slight reduction in visual acuity. The corneal sensitivity test is the basic examination and can be performed by touching the central and peripheral cornea with a Cochet-Bonnet aesthesiometer, which locates and quantifies the loss of corneal sensitivity by recording the patient's response to the touch of a nylon thread (less than 5 mm in thread length is regarded as clinically significant corneal hyposensitivity); a less sensitive test is the response to a touch with the tip of a cotton swab. In general, the severity of NK is related to the severity of corneal sensory impairment. The disease is usually unilateral, but if it is bilateral, there will also be a reduction in blinking as well as reduced tear production due to lack of the afferent arm of the lacrimation reflex. Fluorescein, rose bengal

and lissamine green stains show a reduction in tear break-up time and formation of geographic dry spots and corneal and/or conjunctival epithelial defects. It is useful to perform a careful examination of the eyelids, including eyelid edges, positions and motility, to rule out exposure keratitis and diagnose blepharitis, which is often associated with NK.

Microbiological examination of large, persistent epithelial defects must be performed to exclude bacterial, fungal or viral infections. The combination of an afferent pupillary defect and hypoesthesia must be studied to rule out intraconal orbital nerve injury. A reduction in accommodation can indicate damage to the motor ciliary nerve of the ciliary ganglion. Iris atrophy is often an expression of a previous herpetic keratouveitis or a lepromatous lesion. NK should be suspected in all patients who have a discrepancy between reported symptoms and ocular signs or in patients who have a decreased frequency of eyelid closure.

Current therapy

While NK is frequently asymptomatic, especially at Stage 1, intervention is indicated to prevent deterioration which may ultimately lead to corneal ulcer (Stage 3) and perforation, an ocular emergency associated with loss of integrity of the eye and potentially catastrophic visual sequelae.

In stage 1 disease, treatment can be restricted to simple measures. All topical medications and systemic therapies such as neuroleptics, antipsychotics and antihistamines that can cause NK should be discontinued. The ocular surface can be preserved through the use of artificial tears without preservatives every 2–4 h and a lubricant ointment at bedtime. The goal at this stage is to improve the quality of the corneal epithelium, prevent an epithelial breakdown and preserve corneal transparency. Comorbidities such as exposure keratitis or limbal deficiency worsen the prognosis and should be treated before beginning [treatment of] NK symptoms (Semeraro et al, 2013).

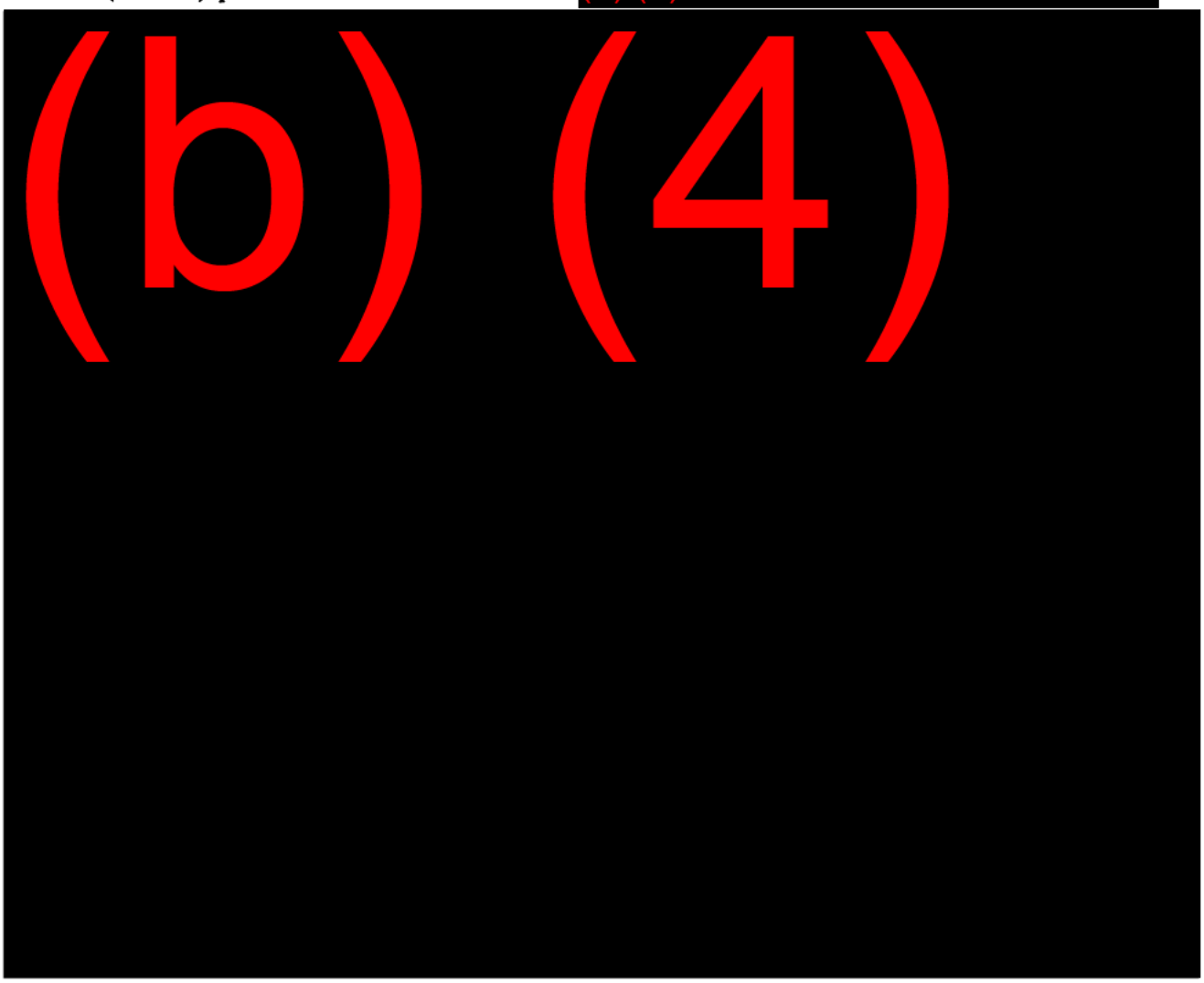
In stage 2 and 3 disease, however, more aggressive treatment is warranted. In stage 2 the aim is to avoid the development of a corneal ulcer and promote healing of the epithelial defect, while in stage 3 it is to prevent corneal thinning and perforation (Semeraro et al, 2013). It is in these stage 2 and 3 cases that a role for rhNGF is foreseen.

4 DESCRIPTION OF THE DRUG AND SCIENTIFIC RATIONALE

4.1 Characterization and Description of Drug

Drug Substance

The biological product under development is a recombinant human form of nerve growth factor (rhNGF) produced in *Escherichia coli*. (b) (4)



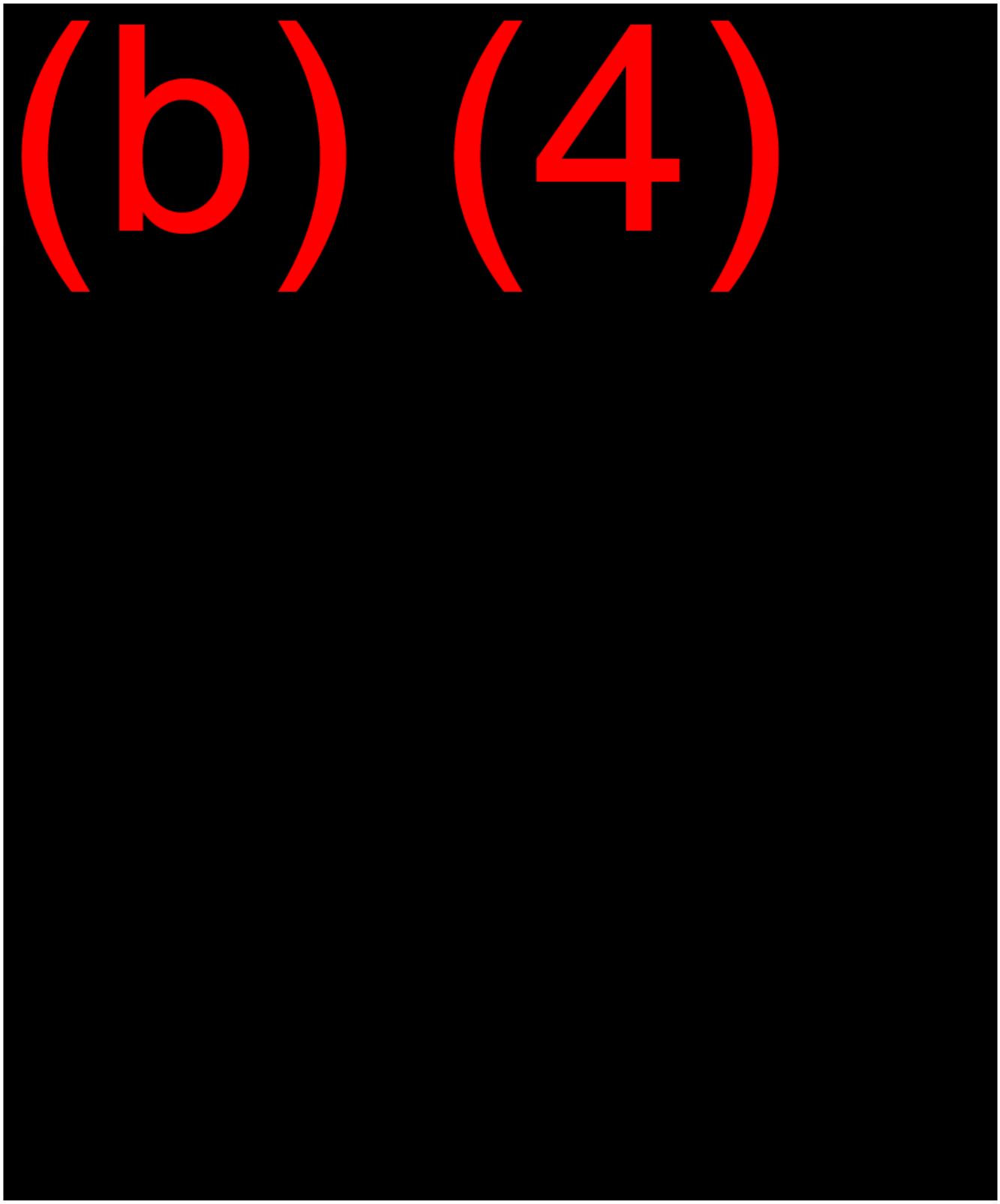
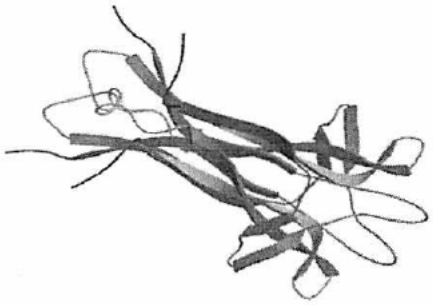

(b) (4)

Figure 4.1-2: Representation of the non-covalent dimer of rhNGF



The molecular formula has been derived by translating the experimentally determined nucleotide acid sequence to the predicted amino acid sequence of rhNGF and is $C_{583}H_{908}N_{166}O_{173}S_8$.

The calculated molecular weight of rhNGF is 13,266 Daltons.

Assays to be used for protein characterization are summarised in the table below:

Table 4.1-1: Assays for protein characterization

(b) (4)

Drug Product

rhNGF drug product is a sterile liquid administered topically in the form of eye drops. (b) (4)

Table 4.1-2: Excipients in the formulation

Function	Excipient	Concentration range
(b) (4)	(b) (4)	(b) (4)
	HPMC	
	L-methionine	
	PEG 6000	
	Trehalose dihydrate	
	Mannitol	
	(b) (4)	

The primary packaging being tested consists of a (b) (4)

The qualitative and quantitative composition of the drug product intended for commercial use in NK patients is given in Table 4.1-3.

Table 4.1-3: Composition of drug product

Constituent	Function	0.02mg/mL (% w/v)
rhNGF	API	0.002
Trehalose dihydrate		(b) (4)
Mannitol		
Na_2HPO_4 anhydrous NaH_2PO_4 dihydrate		
Hydroxypropylmethyl cellulose		
PEG 6000		
L-methionine		
WFI up to		

The drug product will be manufactured in accordance with GMP under environmental and process aseptic conditions to obtain a final sterile drug product.

4.2 Rationale for use of rhNGF in NK

NGF is a polypeptide discovered in the early 1950s by Rita Levi-Montalcini, who received the 1986 Nobel Prize in Physiology or Medicine for the discovery, along with her colleague Stanley Cohen. It is essential for the survival and growth of sympathetic and sensory neurons and for differentiation of neurons in the central nervous system.

NGF binds with at least two classes of receptors:

- TrkA, a transmembrane tyrosine kinase.
- p75 LNGFR (low-affinity nerve growth factor receptor), often abbreviated as p75NTR.

Binding of NGF to the high-affinity tyrosine kinase receptor TrkA results in phosphorylation of the enzyme, which leads to the activation of the PI 3 Kinase, ras, and PLC signalling pathways.

As opposed to TrkA, p75NTR plays a somewhat less clear role in NGF biology. Some researchers have shown this receptor serves as a "sink" for neurotrophins. Cells that express both p75NTR and Trk receptors might, therefore, have a greater activity, since they have a higher "microconcentration" of NGF (Reichardt, 2006).

NGF exerts its effects on neuron survival through modulation of expression of the well-established Bcl-2 gene family, a rise in Bcl-2:Bax ratio being accompanied by enhanced cell survival while a fall in this ratio signals apoptosis.

Rationale for the use of rhNGF

The human cornea is the most densely innervated surface tissue in the body. Marfurt et al (2010) showed that around 70 nerve bundles enter the cornea at the corneoscleral limbus and then give rise through repetitive branching to a moderately dense midstromal plexus and a dense subepithelial plexus. It is therefore not surprising that NGF is an important cytokine in corneal tissue.

Lambiase et al (2000) found that under normal physiological conditions, human and rat corneas produced and stored NGF. ELISA showed that NGF was present in normal human corneas at a concentration of 1154 ± 376 pg/mg and in the rat at a concentration of 388 ± 121

pg/mg. RT–PCR and in situ hybridization for NGF mRNA and NGF immunohistochemistry indicated that NGF was produced by epithelium, keratocytes, and endothelium in humans and rats. Rat corneal epithelium, keratocytes, and endothelium all expressed immunopositivity for TrkA.

In the same publication, these authors report that, in corneal organ culture, cells of the epithelium, keratocytes, and endothelium of normal human corneas bind radiolabeled NGF. Monitoring the rate of healing after creation of a 3-mm-diameter epithelial lesion revealed the healing process of the wounded area (7.1 mm^2) and a marked NGF presence within 24 hours.

As a third element of their work, the same authors used an animal model of epithelial debridement in which healing was initiated after 4 hours and completed within 24 hours. Time-course studies showed that the corneal lesion induced a progressive increase of NGF levels, reaching the highest value at 48 hours (3010 ± 284 pg/mg; $p < 0.01$). Thereafter, NGF concentrations progressively decreased, arriving at baseline values (706 ± 123 pg/mg; $p > 0.05$) 7 days after induction of the lesion.

Fourthly, this team investigated the effects of exogenous NGF and of NGF antibodies in the debrided eyes of the *in vivo* model. NGF treatment accelerated healing of the epithelium when compared with saline-treated eyes. This significant difference was confirmed by ANOVA (repeated measures per treatment: $p=0.0001$) and post-hoc comparisons ($p<0.05$). Four hours after creation of the lesion, the NGF-treated cornea showed a reduction of wound area, with 59% of the cornea de-epithelialized, while the control eyes showed no sign of healing. The time to complete healing was 10 ±1 hours in NGF-treated eyes versus 16 ±2 hours in the control eyes. In contrast, topical treatment with anti-NGF antibody immediately after epithelial debridement caused a significant delay in healing.

The specific role of NGF-mediated effects on corneal nerves was further elucidated by Joo et al (2004) who conducted a prospective double-masked study comparing the effect of topical NGF with balanced salt solution on corneal sensitivity after laser *in situ* keratomileusis (LASIK) in rabbits. Preoperative and postoperative corneal sensitivities were assessed using a Cochet-Bonnet esthesiometer. Eyes that were treated with topical NGF demonstrated an earlier and faster recovery of corneal sensitivity after LASIK ($p=0.007$). A statistically significant difference in corneal sensitivity was found between the topical NGF and control group postoperatively at 2 ($p=0.01$), 3 ($p=0.03$), and 4 ($p=0.03$) weeks. The authors conclude that topical NGF had beneficial effects in the early recovery of corneal sensitivity.

Two publications report encouraging results when using murine NGF in patients with NK.

Lambiase et al (1998) studied 12 patients (14 eyes) with severe corneal neurotrophic ulcers associated with corneal anesthesia who were treated with topical nerve growth factor 10 times daily for two days and then 6 times daily until the ulcers healed. Treatment continued for 2 weeks after the ulcers healed, and the patients were then followed for up to 15 months. The evolution of the corneal disease during treatment and follow-up was evaluated by slit-lamp examination, photography, fluorescein-dye testing, and tests of corneal sensitivity and best corrected visual acuity. Corneal healing began 2 to 14 days after the initiation of treatment with nerve growth factor, and all patients had complete healing of their corneal ulcers after 10 days to 6 weeks of treatment. Corneal sensitivity improved in 13 eyes, and returned to normal in 2 of the 13 eyes. Corneal integrity and sensitivity were maintained during the follow-up period (range, 3 to 15 months). Best corrected visual acuity increased progressively during treatment and follow-up in all patients. There were no systemic or local side effects of treatment.

Bonini et al (2000) also evaluated the efficacy of NGF in a prospective, non-comparative, interventional case series involving 45 eyes of 43 consecutive patients with moderate (stage 2, n=17) to severe (stage 3, n=28) neurotrophic keratitis unresponsive to other nonsurgical therapies. After a 10-day washout with preservative-free artificial tears, the eyes were treated with murine NGF (200 mg/ml) every 2 hours for 2 days followed by one drop six times daily until the ulcer healed. A maintenance dose of one drop NGF (100 mg/ml) was administered four times daily for the 2 weeks subsequent to ulcer healing. All patients had complete resolution of the persistent epithelial defect (with or without an ulcer) after 12 days to 6 weeks of treatment with NGF. Patients affected by both stages of the disease had both improved corneal sensitivity and visual acuity ($p<0.001$). No significant differences were observed in the time to complete corneal healing between stage 2 and stage 3 patients. Hyperemia and mild and transient ocular and periocular pain were side effects reported during the first days of treatment. No relapse of the disease was observed during the follow-up period, with the exception of three patients with trigeminal nerve resection, who required a single retreatment.

The use of rhNGF in humans is currently under evaluation. In a masked efficacy analysis of the Phase 1 segment of an ongoing Phase 1/2 study, in which 14 patients are receiving rhNGF and 4 patients are receiving vehicle, corneal lesions were completely healed in 73% of

patients, while lesion size increased in only one patient who received placebo (open label treatment of this patient with rhNGF resulted in complete healing of the corneal lesion).

4.3 Nonclinical data

4.3.1 Pharmacology

A summary of completed *in vitro* pharmacology studies is presented in the table below:

Table 4.3.1-1: Summary of Applicant's completed *in vitro* pharmacology studies

Study Type	Species cell type	No. of animals per sex	Dose, route, concentration	Dosing regimen	Results	Reference
Cell proliferation assays	Human TF-1 cells	n/a	0.3 pM - 6.76 nM rhNGF and mNGF	n/a	rhNGF was more active than mNGF regarding proliferation of human TF-1 cells.	Study A1130 Non-GLP
	Rabbit SIRC cells	n/a	0.3 pM - 13.52 nM rhNGF and mNGF	n/a	Rabbit SIRC cells are responsive to mNGF, but not to rhNGF.	Study A1131 Non-GLP
Binding and competition assay on human TrkA receptor	HEK293 cells	n/a	10 different concentrations of rhNGF and mNGF. Reference standard at 13nM	n/a	rhNGF has greater affinity for human TrkA receptor than mNGF (Ki = 3.7 nM vs 6.2 nM.	Study A1226/E Non-GLP

The biological activity of rhNGF produced in *E. coli* has been assessed *in vitro* by proliferation of human TF1 cells. TF1 is a human erythroleukemic cell line expressing NGF receptors. NGF induces dose-dependent proliferation of TF1 cells. The results of this study (study A1130) show that rhNGF was more active (approximately 10 fold) than murine NGF in the human TF1 cell proliferation assay.

A summary of completed *in vivo* pharmacology studies is presented in the table below:

Table 4.3.1-2: Summary of Applicant's completed *in vivo* pharmacology studies

Study Type	Species cell type	No. of animals per sex	Dose, route, concentration	Dosing regimen	Results	Reference
Safety pharmacology (modified Irwin test)	Rat	Male (n=83) and female (n=83) Wistar rats	5 µl of 0.2, 0.8 or 1.2 mg/mL rhNGF by topical ocular route	3 x daily	rhNGF had no effect on appearance, behaviour, reflexes, respiration, locomotor activity or grip strength.	Study Harlan D39098 - A1129BPL/E GLP study
Superior cervical ganglia hypertrophy test	Rat	Male Sprague-Dawley rats n=18	1, 10 & 20 µg rhNGF or mNGF by SC route	1 x daily	Both rhNGF and mNGF increased SCG weight dose-dependently. A direct correlation between increase in SCG weight and extent of neuronal tissue was observed.	Study M1109 Non-GLP
Retinitis pigmentosa model	Rat	Male and female RCS rats n=95	5 µg rhNGF by intravitreal injection 5 µg mNGF by intravitreal injection 6 µg rhNGF by topical route	Single injection Single injection 3 x daily for 20 days	rhNGF protected against photoreceptor degeneration.	Study M1212 GLP study

Activity *in vivo* of rhNGF was assessed by comparing it with murine native NGF in the superior cervical ganglion growth assay [Study Report M1109]. This study was designed to determine the biological activity of different forms of NGF (mNGF, Genentech-developed rhNGF and company-developed rhNGF, indicated as "rhNGF-Anabasis") using the superior cervical ganglia (SCG) assay, a sensitive and well-established assay of NGF activity. The SCG is a tissue composed of about 30,000 neurons and it is one of the tissues most sensitive to NGF action, in particular during pre- and post-natal development.

The study was conducted in newborn female rats. Each litter was culled to 7 female pups and each pup was treated with a different sample to avoid unspecific variability. Animals at post-

natal age 7 days received daily subcutaneous injections of 10 µg/g body weight in 50 µl of solution (10 mM KP + 150 mM NaCl, pH 7.2) for 5 consecutive days. They were then sacrificed in order to assess effects on SCG.

The effects of mNGF, rhNGF-Anabasis and Genentech-developed rhNGF on SGC were all comparable, while vehicle had no effect (see Table 4.3.1-3). Untreated controls also showed no effect. A direct correlation between increase in SCG weight and extent of neuronal tissue was observed. As a result, it was concluded that the effects on retinal protein and mRNA levels shown by Lenzi are transferable from mNGF to rhNGF (Lenzi et al, 2005).

The data collected are summarized in the table below:

Table 4.3.1-3: Results of comparison of biological activity of different NGF preparations

Treatment	Effect on superior cervical ganglia*	Body weight (g)	
		Before treatment	End of treatment
1. Mouse NGF	(b) (4)		
2. rh-proNGF-Anabasis			
3. rhNGF-Genentech/Roche			
4. rhNGF-Anabasis			
5. rh-Propeptide			
6. 10mM KP			
7. non-injected			

* +++ comparable to mouse NGF;

++ low effect;

- no effect

4.3.2 Pharmacokinetics

Pharmacokinetics following short-term ocular administration, 4-weeks ocular administration and systemic (IV and SC) administration are shown in Tables 4.3.2-1, 4.3.2-2 and 4.3.2-3 below:

Table 4.3.2-1: Summary of completed short-term ocular pharmacokinetic studies

Type of Study / Species	Dose / Route / Frequency	Comments	Reference
Male (n=12) and female (n=12) Wistar rats	5µl of 0.2, 0.4, 0.6, 0.8 & 1.2 mg/mL rhNGF by topical ocular route (both eyes) 3 x at 3-hour intervals in 1 day.	Minimal systemic exposure after ocular administration at low dose. Disproportionately greater systemic exposure at the higher doses used in toxicology studies.	Study Harlan D39087 - A1122/E Non-GLP
Male (n=1) and female (n=1) New Zealand Rabbits	30µl of 0.2, 0.4, 0.6, 0.8 & 1.2 mg/mL rhNGF by topical ocular route (both eyes) 3 x at 3-hour intervals in 1 day.	Systemic exposure following topical ocular administration is marginal and not dose proportional.	Study D39043 -A1119/E Non-GLP
Male Han Wistar rats	5µl of 0.8 mg/mL rhNGF twice in one day (3 hours apart).	Intact corneas: Serum concentrations were below the limit of detection at both 2 and 4 hours after first treatment. Abraded corneas: Serum levels were 0.179-0.266 ng/mL at 2 hours (after one administration) and 0.188 – 0.676 ng/mL at 4 hours (after 2 administrations).	Study A1215 Non-GLP
Male Han Wistar rats	5µl of 0.8 mg/mL rhNGF (with and without chlorbutanol) 3 times in one day (3 hours apart).	Intact corneas: No clinical signs. Abraded corneas: Marginal increases in scores and findings, but without relationship to time. Observations assigned to chance. Ophthalmoscopy: No treatment-related abnormalities in any group.	Study M1202 Non-GLP

Table 4.3.2-2: Summary of completed 4-week ocular pharmacokinetic studies

Type of Study / Species	Dose / Route / Frequency	Comments	Reference
Male (n=83) and female (n=83) Wistar rats	5µl of 0.6, 0.8 or 1.2 mg/mL rhNGF by topical ocular route (both eyes) 3 x per day.	rhNGF exposure increased more than dose-proportionally in male rats. For female rats, exposure approached dose-proportionality. After 4 weeks repeated dosing rhNGF exposure was decreased or stable as compared with Day 1 (AUC Week4/Day1 ratio 0.3-0.98; therefore no observed accumulation).	Study Harlan D39098 -A1129BPL/E GLP study
Male (n=16) and female (n=16) New Zealand White rabbits	30µl of 0.6, 0.8 or 1.2 mg/mL rhNGF by topical ocular route (both eyes) 3 x per day.	Data were highly variable and with exposure levels frequently below the lower limit of quantitation (indicating very low exposure). No toxicokinetic conclusions could be drawn regarding the gender and time dependency	Study Harlan D39065 -A1138BPL/E GLP study
New Zealand White rabbit Male (n=13) Female (n=13)	30µl of 0.6, or 1.2 mg/ml rhNGF by topical ocular route (right eye) 3 x per day for 58 days	Very low or levels below the limit of quantification of rhNGF were found in almost all animals.	Study IrisD23I27212 A1302BPL/E GLP study
New Zealand White rabbits Males (n= 15)	30µL 3 x per day, 3 hours apart for 14 days topical ocular route (right eye) .Doses: 1.2 (or 1.36) mg/mL rhNGF+ 0.25 (or 0.125) mg/mL L-methionine 1.2 (or 1.36) mg/mL rhNGF+ 1 (or 0. 5) mg/mL L-methionine 1.2 mg/mL rhNGF+ 1 mg/mL L-methionine	At day 1 and 14: plasma levels very low or below the limit of quantification of rhNGF,	Study Iris D23I07113 (Harlan Study Phase D79565) Dompé Study: A1314BPL/E

Table 4.3.2-3: Summary of completed IV and SC pharmacokinetic studies

Type of Study / Species	Dose / Route / Frequency	Comments	Reference
IV studies			
Male (n=12) and female (n=12) Wistar rats	0.3 & 1.2 mg/kg rhNGF with 3-day washout between administrations.	$t_{½}$ = 3-4 hours. Cl = 5.25 – 7.51 mL/h/kg. V_{ss} = 0.362 – 0.538 L/kg	Study Harlan D39076 - A1121BPL/E GLP study
Male (n=1) and female (n=1) New Zealand Rabbits	0.3, 0.6, 1.2 & 2.4 mg/kg rhNGF with 3-day washout between administrations.	$t_{½}$ = 4.3 – 6.3 hours. Cl = 1.33 – 2.34 mL/min/kg (male) and 1.87 – 5.13 mL/min/kg (female). V_{ss} = 0.0303 – 0.148 L/kg (male) and 0.0657 – 0.164 L/kg (female).	Study Harlan D39054 - A1120BPL/E GLP study

Type of Study / Species	Dose / Route / Frequency	Comments	Reference
Wistar rats Male (n = 17)	eye drop: 0.8 mg/mL, three times a day for 3 days subcutaneous: 1 mg/kg once a day for 3 days blood collected from sublingual and tail vein	Day 1 (eye drop) Sublingual Cmax: 9.2 ng/mL; Tmax: 4 h; AUCt: 56.4 ng/h/mL Tail vein Cmax: 0.10 ng/mL; Tmax: 8 h; AUCt: 0.26 ng/h/mL Day 3 (eye drop) Sublingual Cmax: 4.2 ng/mL; Tmax: 8 h; AUCt : 47.4 ng/h/mL Tail vein Cmax : 0.07 ng/mL; Tmax: 4 h; AUCt: 0.37 ng/h/mL Day 1 (subcutaneous) Sublingual Cmax: 69.5 ng/mL; Tmax: 8 h; AUCt: 838 ng/h/mL Tail vein Cmax: 174 ng/mL; Tmax: 2 h; AUCt: 1597 ng/h/mL Day 3 (subcutaneous) Sublingual Cmax: 73.5 ng/mL; Tmax; 2 h; AUCt : 277 ng/h/mL Tail vein Cmax: 173 ng/mL; Tmax: 2 h: AUCt: 555 ng/h/mL Eye drop dosing: PK profile similar on days 1 and 3 Subcutaneous dosing: concentrations on day 3 decreased faster than on day 1 Eye drop administration: concentrations after tail vein sampling lower than after sublingual sampling. Subcutaneous administration: concentrations after tail vein sampling higher than after sublingual sampling.	Study Harlan D69586. M1301 BPL GLP study
SC studies			

Type of Study / Species	Dose / Route / Frequency	Comments	Reference
Wistar rats Male (n= 15) Female (n = 15r)	Subcutaneous 50 and 100 µg/animal/day for 8/26 weeks	**Day 1: 50 µg/animal/day** C_{max} (ng/mL): 94.24 (M); 123.65 (F) T_{max} (h): 4 (M); 2 (F) AUC_{0-t} (ng.h/ml): 580.90(M); 766.48 (F) **Day 29: 50 µg/animal/day** C_{max} (ng/mL): 38.28 (M); 74.73 (F) T_{max} (h): 2 (M); 2 (F) AUC_{0-t} (ng.h/ml): 190.05 (M); 302.82 (F) **Day 61: 50 µg/animal/day** C_{max} (ng/mL): 161.67 (M); 271.45 (F) T_{max} (h): 2 (M); 2 (F) AUC_{0-t} (ng.h/ml): 893.27 (M); 1110.36 (F) **Day 89: 50 µg/animal/day** C_{max} (ng/mL): 176.46 (M); 190.20 (F) T_{max} (h): 4 (M); 4 (F) AUC_{0-t} (ng.h/ml): 671.25 (M); 885.73 (F) **Day 176: 50 µg/animal/day** C_{max} (ng/mL): 100.04 (M); 109.83 (F) T_{max} (h): 2 (M); 2 (F) AUC_{0-t} (ng.h/ml): 441.79 (M); 513.05 (F) **Day 1: 100 µg/animal/day** C_{max} (ng/mL): 191.41 (M); 283.84 (F) T_{max} (h): 4 (M); 4 (F) AUC_{0-t} (ng.h/ml): 1010.59 (M); 1358.61 (F) **Day 29: 100 µg/animal/day** C_{max} (ng/mL): 150.09 (M); 280.70 (F) T_{max} (h): 2 (M); 6 (F) AUC_{0-t} (ng.h/ml): 764.11 (M); 1952.63 (F) **Day 61: 100 µg/animal/day** C_{max} (ng/mL): 204.67 (M); 311.20 (F) T_{max} (h): 2 (M); 4 (F) AUC_{0-t} (ng.h/ml): 967.61 (M); 1783.26 (F) **Day 89: 100 µg/animal/day** C_{max} (ng/mL): 279.58 (M); 688.24 (F) T_{max} (h): 6 (M); 4 (F) AUC_{0-t} (ng.h/ml): 1563.16 (M); 3507.90 (F) **Day 176: 100 µg/animal/day** C_{max} (ng/mL): 247.17 (M); 284.71 (F) T_{max} (h): 2 (M); 2 (F) AUC_{0-t} (ng.h/ml): 926.89 (M); 1642.42 (F) Exposure in females slightly higher than in males at both doses. These differences on the exposure decreased or disappeared when dose is normalized to body weight. Accumulation ranged between 0.3 to 1.5.	Study D68304 GLP study

Type of Study / Species	Dose / Route / Frequency	Comments	Reference
90-days subcutaneous toxicity study New Zealand White rabbits Male (n= 12); Female (n =12)	Subcutaneous 100 and 200 µg/animal once per day for 13 weeks	**Day 1: 100 µg/animal/day** C_{max} (ng/mL): 2.34 (M); 2.97 (F) T_{max} (h): 2 (M); 4 (F) AUC_{0-t} (ng.h/ml): 17.49 (M); 18.60 (F) **Day 87: 100 µg/animal/day** C_{max} (ng/mL): 4.18 (M); 10.26 (F) T_{max} (h): 2 (M); 4 (F) AUC_{0-t} (ng.h/ml): 23.65 (M); 47.64 (F) **Day 1: 200 µg/animal/day** C_{max} (ng/mL): 4.69 (M); 4.84 (F) T_{max} (h): 4 (M); 2 (F) AUC_{0-t} (ng.h/ml): 38.71 (M); 31.86 (F) **Day 87: 200 µg/animal/day** C_{max} (ng/mL): 7.85 (M); 8.53 (F) T_{max} (h): 2 (M); 4 (F) AUC_{0-t} (ng.h/ml): 20.49 (M); 81.94 (F) Significant inter-animal variability in plasma levels. Accumulation ranged between 0.5-1.4 in males and 2.6 in females.	Harlan D68326 M1305BPL GLP study

Pharmacokinetics have been assessed by IV and SC routes in rats and rabbits at single ascending doses up to 2.4 mg/kg and with repeated doses up to 200 µg/animal. The topical ocular route has also been studied at concentrations of up to 1.2 mg/mL administered 3 times per day for (a) 1 day only in rats and rabbits in an ascending dose regimen, and (b) 4 weeks in rats and rabbits. Pharmacokinetics has also been evaluated in rats with intact and abraded corneas following topical ocular administration of 0.8 mg/mL twice a day with a 3-hour interval. An ELISA specific and validated analytical method was used to determine the concentrations of rhNGF in serum in the conducted toxicokinetic studies.

After 4-week repeated administration, rhNGF exposure tended to be decreased or to be stable compared with day 1: the AUC_{0-t} Week 4 / Day 1 ratios ranged between 0.30 and 0.98. No accumulation of the test item was therefore observed.

The studies showed that there is a minor systemic absorption dose proportional or hyperproportional in rat following eye drop administration, and very minimal or absent systemic absorption in rabbits following eye drop administration.

Following eye drop treatment with rhNGF in rats with abraded cornea, low levels of rhNGF could be found in serum.

The pharmacokinetic profile, after IV administration, showed a biphasic profile, with rather parallel terminal phases: the terminal half-life ($t_{½}$), ranged between 3.0 and 6.3 hours. The first descending phase was very rapid, leading to eventual uncertainty in the determination of C_{max} and AUC_{0-t}.

As the serum concentrations following IV administration are again several orders of magnitude greater than those following ocular administration, this exposure provides a very high safety margin for the clinical use of the rhNGF.

Subcutaneous administration for 26 weeks in the rat did not result in accumulation but one out of 6 animals treated with 50 µg/animal/day and 3 out of 6 animals treated with 100 µg/animal/day developed binding antibodies, indicating that there is an immunogenic potential of rhNGF in the rat when administered daily subcutaneously.

After repeated subcutaneous administration in the rabbit high variability in rhNGF concentrations was observed in half of the treated animals, possibly due to the fact that the animals showed anti-drug antibodies. Five out of 8 animals treated with 100 µg/animal and 12 out of 14 animals treated with 200 µg/animal developed binding antibodies when treated with rhNGF, further suggesting that there is an immunogenic potential of rhNGF in the rabbit when administered daily by the subcutaneous route.

4.3.3 Toxicology

The completed toxicology studies are summarised in Tables 4.3.3.1 and 4.3.3.2 below:

Table 4.3.3-1: Summary of completed systemic toxicology studies

Study Type	Species Cell type	No. of animals Sex	Dose (mg/kg) Route Concentration	Dose frequency	Results	Reference
Single dose						
Single ascending IV dose Single SC dose	Wistar rat	Male (n=12) Female (n=12)	0.3, 0.6, 1.2 & 2.4 mg/kg by IV route. 2.4 mg/kg by SC route.	Single dose with 3 day washout between each administrations (IV) Single dose (SC)	NOAEL (IV) = 2.4 mg/kg NOAEL (SC) = 2.4 mg/kg	Study Harlan D39076 - A1121BPL/E GLP study
Single ascending IV dose Single SC dose	New Zealand Rabbit	Male (n=1) Female (n=1)	0.3, 0.6, 1.2 & 2.4 mg/kg by IV route. 2.4 mg/kg by SC route.	Single dose with 3 day washout between each administrations (IV) Single dose (SC)	NOAEL (IV) = 2.4 mg/kg NOAEL (SC) = 2.4 mg/kg	Study Harlan D39054 - A1120BPL/E GLP study
Repeated dose						
Combined 8/26 weeks subcutaneous toxicity study	Han Wistar rat	Male (n= 151); Female (n= 151)	50 and 100 µg/animal by SC route	Daily for 8 or 26 weeks with a 2/4-Week Recovery Period	NOAEL of 100 µg/animal in both males and females.	Harlan D68304 M1306BPL GLP study
90-day subcutaneous toxicity study	New Zealand White rabbits	Male (n= 18); Female (n =18)	100 and 200 µg/animal by the SC route	Once per day for 90 days	NOAEL: 200 µg/day both males and females.	Harlan D68326 M1305BPL GLP study

Table 4.3.3-2: Summary of completed ocular toxicology studies

Study Type	Species Cell type	No. of animals Sex	Dose (mg/kg) Route Concentration	Dose frequency	Results	Reference
Short-term (1 day) topical ocular dosing	Wistar rat	Male (n=12) Female (n=12)	5 µl of 0.2, 0.4, 0.6, 0.8 & 1.2 mg/mL rhNGF by topical ocular route (both eyes).	3 x at 3-hour intervals in 1 day.	NOAEL = 1.2 mg/mL (6 µg per eye).	Study Harlan D39087 - A1122/E Non-GLP
Short-term (1 day) topical ocular dosing	New Zealand Rabbit	Male (n=1) and Female (n=1)	30 µl of 0.2, 0.4, 0.6, 0.8 & 1.2 mg/mL rhNGF by topical ocular route (both eyes).	3 x at 3-hour intervals in 1 day.	NOAEL = 1.2 mg/mL (36 µg per eye).	Study D39043 - A1119/E Non-GLP
4-week ocular toxicity study	Wistar rat	Male (n=83) and Female (n=83)	5 µl of 0.6, 0.8 or 1.2 mg/mL rhNGF by topical ocular route (both eyes).	3 x per day.	NOAEL = 1.2 mg/mL (6 µg per eye 3 x daily).	Study Harlan D39098 - A1129BPL/E GLP study
4-week ocular toxicity study	New Zealand White rabbits	Male (n=16) and Female (n=16)	30 µl of 0.6, 0.8 or 1.2 mg/mL rhNGF by topical ocular route (both eyes).	3 x per day.	NOEL = 1.2 mg/mL (18 µg per eye 3 x daily).	Study Harlan D39065 - A1138BPL/E GLP study
2-month tolerance/toxicity study	New Zealand White rabbits	Male (n=12) Female (n=12)	30 µl of 0.6, or 1.2 mg/mL rhNGF by topical ocular route (right eye).	3 x per day.	NOEL = 1.2 mg/ml (18 µg 3 x daily).	Study D23I27212 A1302 BPL/E GLP study Draft Audited Report
8/26-week ocular toxicity study	Han Wistar rat	Male (n=114) Female (n=114)	5 µl of 0, 0.6, 0.8 or 1.2 mg/mL rhNGF by topical ocular route (both eyes).	3 x per day, 3 hours apart.	NOEL = 5 µl of 1.2 mg/mL rhNGF per eye 3 times daily (36 µg per animal per day).	Study Accelera 0472-2011 A1129BPL/E GLP study Draft Audited Report

Study Type	Species Cell type	No. of animals Sex	Dose (mg/kg) Route Concentration	Dose frequency	Results	Reference
5-day preliminary ocular tolerance study with methionine	New Zealand White rabbits	9 males or females	30 µl of 1.2 mg/ml rhNGF and 0.25 or 1 mg/ml methionine by topical ocular route (right eye)	Multiple administrations per day as follows: • 5 x within 20 minutes on Day 1. • 2 x on Day 2 (8 hours apart). • 4 x on Day 3 (2.5 hours apart). • 6 x on Day 4 (1.5 hours apart). 8 x on Day 5 (every hour).	No apparent treatment-related effects (either systemic of local to the eyes).	Iris D23I07013 Non-GLP
14-day ocular tolerance study with methionine	New Zealand White rabbits	9 males or females	30 µl of 1.2 mg/ml rhNGF and 0.25 or 1 mg/ml methionine by topical ocular route (right eye)	3 x per day, 3 hours apart.	No apparent treatment-related effects (either systemic of local to the eyes).	Iris D23I07113 A1314 BPL/E GLP study Draft report

In all completed studies the assigned NOAEL was the highest administered dose:

- 2.4 mg/kg (IV and subcutaneous routes) in both rats and rabbits.
- 1.2 mg/mL (topical ocular route) in both rats and rabbits.

These ocular doses comprised:

- 6 µg rhNGF/administration/eye in the rat.
- 36 µg rhNGF/administration/eye in the rabbit.

4.4 Clinical trials

Completed study: Protocol NGF0112

The initial clinical trial in humans of Dompé's topical ophthalmic formulation of rhNGF (Protocol NGF0112; Ferrari et al, Biodrugs 2013;) was completed in March 2013. This trial was designed to evaluate the safety profile, pharmacokinetics and immunogenicity of rhNGF topical ophthalmic solution after single and multiple fractioned doses in healthy volunteers.
A total of 73 healthy male and female volunteers were enrolled. Eligible subjects were between 18 and 60 years of age with good systemic health, an unremarkable systemic and ocular past medical history, a BCDVA of 20/20 or better (≥83 ETDRS letters), normal anterior segment on external and slit lamp examination and normal posterior segment on fundus examination in both eyes. The study subjects were also required to be on no concomitant ocular or systemic treatment.

Study subjects were screened within 20 days of enrolment (Day -20 to Day -1) and eligible subjects who provided written informed consent were assigned to one of three phases of the study.

- *Part 0:*

  A total of 9 subjects (3 subjects per dose) were treated in a randomly selected eye with one drop of placebo (the rhNGF vehicle) administered once and the fellow eye was treated with one drop of rhNGF administered once at one of 3 concentrations:

  - 0.5 µg/mL (0.0175 µg of rhNGF).

  - 5 µg/mL (0.175 µg of rhNGF).

  - 20 µg/mL (0.7 µg of rhNGF).

- *Part A (single ascending dose portion):*

  A total of 24 subjects were treated with rhNGF administered TID for 1 day at one of 3 concentrations. Six (6) subjects were treated with each of 3 concentrations of rhNGF in a randomly selected eye and the fellow eye was treated with placebo. Two (2) subjects per dose group were treated with placebo in both eyes. The concentrations of rhNGF tested were:

- 20 μg/mL (0.7 μg of rhNGF, total daily dose 2.1 μg).

- 60 μg/mL (2.1 μg of rhNGF, total daily dose 6.3μg).

- 180 μg/mL (6.3 μg of rhNGF, total daily dose 18.9 μg).

- *Part B (multiple ascending dose portion):*

  A total of 40 subjects were treated with rhNGF administered TID for 5 days at one of 3 concentrations. In Group 0M twelve (12) subjects were treated with rhNGF and four with placebo. In Groups 1M, 2M & 3M, nine (9) subjects were treated with each of 3 concentrations of rhNGF in a randomly selected eye and the fellow eye was treated with placebo. In addition, 3 subjects per dose group were treated with placebo in both eyes.

  - Group 0M: 20 μg/mL (0.7 μg of rhNGF, total daily dose 2.1 μg per day for 5 days).

  - Group 1M: 20 μg/mL (0.7 μg of rhNGF, total daily dose 2.1 μg per day for 5 days).

  - Group 2M: 60 μg/mL (2.1 μg of rhNGF, total daily dose 6.3 μg per day for 5 days).

  - Group 3M: 180 μg/mL (6.3 μg of rhNGF, total daily dose 18.9 μg for 5 days).

Plasma samples were obtained over a 3-day period for Part A and over an 8-day period for Part B. Samples were taken before dosing, after the first dose and after last administration of the investigational drug for determination of rhNGF pharmacokinetics.

Samples for the evaluation of rhNGF immunogenicity were obtained before treatment and approximately 30 days after the end of dosing both in Part A and Part B.

Safety evaluation at each study visit (in all 3 parts of the study) consisted of a complete ophthalmic examination (slit lamp and fundus examination, plus BCDVA), ECG, vital signs, urinalysis, clinical chemistry and hematology laboratory testing.

There were no serious adverse events or adverse events of special interest (sight threatening events) reported during the Study NGF0112. Multiple doses of rhNGF eye drops were safe and well tolerated when given as a single 35 μL drop into eye at a concentration of up to the maximum 180μg/ml. There were no clinically significant findings in the physical examinations performed and no clinically significant changes in ECG, vital signs, or clinical laboratory findings were observed in all study cohorts. Also there was no evidence of systemic absorption or immunogenicity in both Part A and Part B cohorts.

Serum concentrations of rhNGF were found to be significantly different from basal levels in only 6 subjects, 2 each at 20, 60, and 180 µg/mL. These changes were sporadic and varied from positive to negative values, suggesting an individual physiological fluctuation rather than a treatment-related absorption.

Ongoing study: Protocol NGF0212

The primary objective of this Phase 1/2 clinical study is to assess the safety and the efficacy of two dose regimens (10 µg/ml or 20 µg/ml 6 times a day) of rhNGF eye drops solution compared to vehicle for inducing complete healing of Stage 2 (PED) and Stage 3 (corneal ulcer) neurotrophic keratitis (NK) as assessed by the investigator using corneal fluorescein staining. The study population consists of adult patients diagnosed with stage 2 (persistent epithelial defect: PED) and stage 3 (corneal ulcer) NK refractory to one or more conventional non-surgical treatments.

The study had a Phase 1 segment and a Phase 2 segment conducted sequentially as an 8 week, randomized, double-masked, vehicle controlled, parallel group study each followed by a 48 or 56 week open-label follow-up period. In the Phase 1 segment of the study, two concentrations of rhNGF (10 and 20 µg/ml) have been evaluated in a sequential fashion in 2 groups of patients. The duration (48 weeks or 56 weeks) and treatment administered during the open-label follow-up period is determined for each individual patient based on the initial randomized treatment received and the healing (completely healed or non-completely healed) of the PED or corneal ulcer as determined by the study investigator at the conclusion of the Phase 1 or 2 segment of the study.

At Week 8, all completely healed patients from any of the three treatment arms and not-completely healed patients following treatment with rhNGF will enter the 48 week open-label follow-up period. Non-completely healed patients initially randomized to the vehicle control arm will enter the 56 week open-label follow-up period. During the first 8 weeks of the 56 week open-label follow up period, patients randomized to vehicle control at baseline will receive open-label rhNGF. At Week 16 all patients completing the open-label treatment phase will be followed for an additional 48 weeks without any protocol-required study medication until the end of the open label follow-up period.

The first patient to be enrolled in the study was included on 29th January 2013 and 18 patients have now been enrolled into the Phase 1, thus completing the Phase 1 segment of the study. Recruitment into the Phase 2 segment is continuing.

Results of the recently completed Phase 1 segment: 18 patients (7 males, 11 females, mean age of 62) with NK caused by diabetes (4), previous ocular surgeries (4), ocular herpes zoster (2) or simplex (3) infection, neurosurgery (3), others (2) were included in the study. No significant changes of vital signs and blood values were observed during treatment. Thirty-seven adverse events (AEs) were recorded and 3 required discontinuation of study drug (2 in group A and 1 in group B). Thirteen AEs were possibly related to the study drug. Among the 5 serious AEs observed, only 1 (enlargement of PED) was possibly related to the study drug. According to the protocol, this patient was unmasked and found to be in the placebo group. Visual acuity was decreased in 2 patients, and ameliorated in 11 at the end of treatment.

Masked efficacy analysis of the Phase 1 segment showed that NGF was well tolerated according to VAS scores. Corneal lesions completely healed in 73% (71% in group A and 75% in group B), corneal sensitivity increased in 33% in both groups and Schirmer values increased in 39% of the patients (33% in group A and 44% in group B).

These initial results show that rhNGF eye drops are safe and well-tolerated. No significant systemic or ophthalmic complications were observed.

5 REQUEST FOR DESIGNATION FOR SAME DRUG FOR SAME RARE DISEASE OR CONDITION

Not applicable - there is no rhNGF authorised for the treatment of NK in the US.

6 DEVELOPMENT FOR A SUBSET OF PERSONS WITH DISEASE OR CONDITION

Not applicable.

7 REGULATORY STATUS AND MARKETING HISTORY

7.1 Investigational or Marketing Experience or Withdrawal in Other Countries

rhNGF is not marketed in any country and has never previously been marketed and/or withdrawn. In addition, no application to market rhNGF has ever been filed in any country.

At present rhNGF is under development for the treatment of neurotrophic keratitis (b) (4) (b) (4) No application to conduct a clinical trial with rhNGF has ever been refused in any country.

No adverse regulatory action has been taken against rhNGF in any country.

7.2 Other Relevant INDs

None.

8 DISEASE PREVALENCE

Estimation of the prevalence of NK is particularly challenging and resulted in the paucity of published epidemiological data.

Searches of the PubMed database with the following search strings failed to return any relevant papers:

- (neurotrophic keratitis[Title/Abstract]) AND prevalence[Title/Abstract]
- (neurotrophic keratitis[Title/Abstract]) AND incidence[Title/Abstract]
- (neurotrophic keratopathy[Title/Abstract]) AND prevalence[Title/Abstract]
- (neurotrophic keratopathy[Title/Abstract]) AND incidence[Title/Abstract]

This has been confirmed by Semeraro and co-workers whose comprehensive 2013 review of the condition states explicitly that "*Epidemiological data on NK have not been reported in the literature*".

The only option available is to examine the frequency with which NK arises as a complication of its underlying causes. This approach was pioneered by Alessandro Lambiase and Marta Sacchetti in an international ocular surface disease book chapter written in 2013 (Lambiase & Sacchetti, 2013), the relevant paragraphs of which are reproduced below:

> "NK is a rare disease with an estimated prevalence of <5 per 10,000 individuals. No data are available in the literature on the epidemiology of NK. However, the prevalence and incidence of NK may be extrapolated from its causes. Specifically, NK complicated herpetic keratitis in 4.4-8.0% of cases (Labetoulle et al, 2005). Based on an average NK prevalence of 6% of all cases of herpetic keratitis (the prevalence of herpetic keratitis is 149/100,000), the NK prevalence can be estimated as 0.89/10,000. Similarly, the prevalence of NK from herpes zoster keratitis (HZO) may be calculated as 0.33/10,000 by applying an average NK prevalence of 12.8% to the estimated prevalence of HZO (26/100,000) (Dworkin et al, 2007). NK had been reported to be a complication of various surgical procedures for trigeminal neuralgia, at a percentage ranging from 0.6 to 5% (mean value 2.8%), depending on the procedure (Bhatti & Patel, 2005). As the prevalence of trigeminal neuralgia has been reported at 1.5/10,000, the NK prevalence can be estimated as 0.2/10,000.

> The prevalence of NK caused by other conditions, such as diabetes, multiple sclerosis, acoustic neuroma, and congenital disorders, cannot be estimated because no data are available in the literature. Therefore, the final prevalence of NK within the population of Europe can be estimated at <1.6/10,000."

It may be noted that the prevalence values estimated for herpetic keratitis, HZO and surgical procedures sum to 1.42/10,000 while the text cites an overall NK prevalence of "<1.6/10,000". It may be assumed that the difference of 0.18/10,000 represents an allowance for the cases secondary to conditions such as diabetes, multiple sclerosis, acoustic neuroma and congenital disorders, no data being available for even indirect estimates of these.

The sponsor has sought, as far as possible, to confirm the calculations reported by Lambiase & Sacchetti and to set them in a US context.

Herpetic keratitis

Young et al (2010) retrospectively reviewed the records of all 394 Olmsted County, Minnesota residents diagnosed with ocular HSV from 1976 through 2007. These authors comment in their paper that:

> "We estimated an age and sex-adjusted annual incidence rate of 9.2 per 100,000 population new cases of keratitis and 11.8 per 100,000 of any ocular HSV. Labetoulle and co-investigators prospectively surveyed eye care providers in France and found an incidence of 13.2 per 100,000 person-years for new cases of herpes keratitis."

This suggests that the prevalence of herpetic keratitis in the US is very similar to that recorded for France by Labetoulle et al (2005) and used by Lambiase & Sacchetti as the basis for their calculations. No case of NK appears on the list of diagnoses in the Young et al paper, which is consistent with the rarity of the condition.

Herpes zoster ophthalmicus

Borkar et al (2013) from the University of California, San Francisco reviewed the electronic medical records of Kaiser Permanente Hawaii for 2006 and 2007 and identified 134 cases of HZO in this population of 217 061 people. The overall incidence of 30.9 per 100 000 person-years (95% confidence interval [CI], 25.9-36.6) is compatible with the prevalence of 26/100,000 reported by Dworkin et al, 2007 and used by Lambiase & Sacchetti in their calculations.

In a series of cases of HZO from the Mayo Clinic (Liesegang, 1985), 15 of 94 patients (16%) developed NK – a similar proportion to the 12.8% used by Lambiase & Sacchetti.

Surgical procedures for trigeminal neuralgia

Katusic et al (1990) studied the incidence of trigeminal neuralgia in Rochester, Minnesota, for the period from 1945 through 1984 and calculated an overall crude incidence rate per 100,000 of 4.3 for both sexes combined. The age-adjusted (to total 1980 US population) rate for women (5.9) was significantly higher than that for men (3.4). As the number of episodes varied from 1 to 11, and the length of an episode varied from 1 day to 4 years, precise conversion to a prevalence rate is problematic, but these US statistics are consistent with the trigeminal neuralgia prevalence of 1.5/10,000 used in the calculations of Lambiase & Sacchetti.

The paper by Bhatti & Patel (2005) used by Lambiase & Sacchetti as the source for the frequency with which NK had been reported to be a complication of various surgical procedures for trigeminal neuralgia originates from the University of Florida and is based on US data.

Other causes

Dompé has been unable to identify any published literature reporting the prevalence of NK in patients with diabetes, multiple sclerosis, acoustic neuroma or congenital diseases. It is therefore impossible to confirm or refute the assumption made by Lambiase & Sacchetti that these pathologies contribute to no more than 0.18/10,000 of the overall prevalence of NK. The paucity even of individual case reports does, however, make this figure plausible.

Total prevalence in the US

If the Lambiase & Sacchetti estimate of the prevalence of NK (<1.6/10,000) is applied to the US population of 317.5 million (US Census Bureau, February 4, 2014) a total prevalence of 50,800 US residents is obtained. While there is clearly a considerable margin of error in this estimate, it is reassuring to observe that this total represents only approximately a quarter of the regulatory ceiling for orphan designation.

On December 31, 2013, the drug Thymosin beta 4 received an Orphan Drug Designation in US for "Treatment of patients with neurotrophic keratopathy".

9 SPONSOR STATEMENT

The Sponsor, Dompé, is the real party in interest of the development of rhNGF and of the intended or actual production and sales of the product.

10 REFERENCES

Bhatti MT, Patel R. Neuro-ophthalmic considerations in trigeminal neuralgia and its surgical treatment. Curr Opin Ophthalmol. 2005;16(6):334-40.

Bonini S, Lambiase A, Rama P et al. Topical treatment with nerve growth factor for neurotrophic keratitis. Ophthalmology 2000;107:1347–1352.

Bonini S, Rama P, Olzi D, Lambiase A. Neurotrophic keratitis. Eye 2003; 17: 989–995.

Borkar DS, Tham VM, Esterberg E et al. Incidence of herpes zoster ophthalmicus: results from the Pacific Ocular Inflammation Study. Ophthalmology. 2013;120(3):451-6

Dworkin RH, Johnson RW, Breuer J et al. Recommendations for the management of herpes zoster. Clin Infect Dis. 2007;44 Suppl 1:S1-26.

Ferrari M, Mantelli F, Sacchetti M et al Safety and Pharmacokinetics of Escalating Doses of Human Recombinant Nerve Growth Factor Eye Drops in a Double-Masked, Randomized Clinical Trial. BioDrugs DOI 10.1007/s40259-013-0079-5

Joo, M-J, Yuhan, KR, Hyon JY et al. The effect of nerve growth factor on corneal sensitivity after laser in situ keratomileusis. Arch Ophthalmol. 2004;122:1338-1341.

Katusic S, Beard CM, Bergstralh E, Kurland LT. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945-1984. Ann Neurol. 1990; 27(1):89-95.

Labetoulle M, Auquier P, Conrad H et al. Incidence of herpes simplex virus keratitis in France. Ophthalmology 2005;112(5):888-95.

Lambiase A, Rama P, Bonini S et al. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. N Engl J Med 1998;338:1174-80.

Lambiase A, Manni L, Bonini S et al. Nerve growth factor promotes corneal healing: structural, biochemical, and molecular analyses of rat and human corneas. Invest Ophthalmol Vis Sci. 2000;41:1063–1069.

Lambiase A, Sacchetti M in Benitez-del-Castillo JM, Lemp MA (Eds) Ocular Surface Disorders JP Medical, London, 2013.

Lenzi L, Coassin M, Lambiase A et al (2005). Effect of exogenous administration of nerve growth factor in the retina of rats with inherited retinitis pigmentosa. Vision Research 45: 1491-1500.

Liesegang TJ. Corneal complications from herpes zoster ophthalmicus. Ophthalmology1985; 92(3):316-24.

Marfurt CF, Cox J, Deek S, Dvorscak L. Anatomy of the human corneal innervation. Experimental Eye Research 2010;90:478-492.

Reichardt L.F. Neurotrophin-regulated signalling pathways. Phil. Trans. R. Soc. B (2006) 361, 1545–1564.

Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. Clinical Ophthalmology 2014; 8: 571–579.

Semeraro F, Forbice E, Romano V et al. Neurotrophic Keratitis. Ophthalmologica 2013; DOI: 10.1159/000354380.

Sinigaglia F. Phase I/II Dose-Ranging, Randomized Clinical Trial of Recombinant Human Nerve Growth Factor in the Treatment of Neurotrophic Keratitis: Preliminary Results. ARVO 2014, Presentation Number 4690 - A0315.

Young RC, Hodge DO, Liesegang TJ, Baratz KH. The incidence, recurrence and outcomes of herpes simplex virus eye disease in Olmsted County, Minnesota, 1976 through 2007: The impact of oral antiviral prophylaxis. Arch Ophthalmol. 2010; 128(9): 1178–1183.

Orphan Drug Designation Request for rhNGF in the Treatment of Neurotropic Keratitis

Bibliography

Tab #1 - Bhatti MT, Patel R. Neuro-ophthalmic considerations in trigeminal neuralgia and its surgical treatment. Curr Opin Ophthalmol. 2005;16(6):334-40.

Tab #2 - Bonini S, Lambiase A, Rama P et al. Topical treatment with nerve growth factor for neurotrophic keratitis. Ophthalmology 2000;107:1347–1352.

Tab #3 - Bonini S, Rama P, Olzi D, Lambiase A. Neurotrophic keratitis. Eye 2003; 17: 989–995.

Tab #4 - Borkar DS, Tham VM, Esterberg E et al. Incidence of herpes zoster ophthalmicus: results from the Pacific Ocular Inflammation Study. Ophthalmology. 2013;120(3):451-6

Tab #5 - Dworkin RH, Johnson RW, Breuer J et al. Recommendations for the management of herpes zoster. Clin Infect Dis. 2007;44 Suppl 1:S1-26.

Tab #6 - Ferrari M, Mantelli F, Sacchetti M et al Safety and Pharmacokinetics of Escalating Doses of Human Recombinant Nerve Growth Factor Eye Drops in a Double-Masked, Randomized Clinical Trial. BioDrugs DOI 10.1007/s40259-013-0079-5

Tab #7 - Joo, M-J, Yuhan, KR, Hyon JY et al. The effect of nerve growth factor on corneal sensitivity after laser in situ keratomileusis. Arch Ophthalmol. 2004;122:1338-1341.

Tab #8 - Katusic S, Beard CM, Bergstralh E, Kurland LT. Incidence and clinical features of trigeminal neuralgia, Rochester, Minnesota, 1945-1984. Ann Neurol. 1990; 27(1):89-95.

Tab #9 - Labetoulle M, Auquier P, Conrad H et al. Incidence of herpes simplex virus keratitis in France. Ophthalmology 2005;112(5):888-95.

Tab #10 - Lambiase A, Rama P, Bonini S et al. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. N Engl J Med 1998;338:1174-80.

Tab #11 - Lambiase A, Manni L, Bonini S et al. Nerve growth factor promotes corneal healing: structural, biochemical, and molecular analyses of rat and human corneas. Invest Ophthalmol Vis Sci. 2000;41:1063–1069.

Tab #12 - Lambiase A, Sacchetti M in Benitez-del-Castillo JM, Lemp MA (Eds) Ocular Surface Disorders JP Medical, London, 2013.

Tab #13 - Lenzi L, Coassin M, Lambiase A et al (2005). Effect of exogenous administration of nerve growth factor in the retina of rats with inherited retinitis pigmentosa. Vision Research 45: 1491-1500.

Tab #14 - Liesegang TJ. Corneal complications from herpes zoster ophthalmicus. Ophthalmology1985; 92(3):316-24.

Tab #15 - Marfurt CF, Cox J, Deek S, Dvorscak L. Anatomy of the human corneal innervation. Experimental Eye Research 2010;90:478-492.

Tab #16 - Reichardt L.F. Neurotrophin-regulated signalling pathways. Phil. Trans. R. Soc. B (2006) 361, 1545–1564.

Tab #17 - Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. Clinical Ophthalmology 2014; 8: 571–579.

Tab #18 - Semeraro F, Forbice E, Romano V et al. Neurotrophic Keratitis. Ophthalmologica 2013; DOI: 10.1159/000354380.

Tab #19 - Sinigaglia F. Phase I/II Dose-Ranging, Randomized Clinical Trial of Recombinant Human Nerve Growth Factor in the Treatment of Neurotrophic Keratitis: Preliminary Results. ARVO 2014, Presentation Number 4690 - A0315.

Tab #20 - Young RC, Hodge DO, Liesegang TJ, Baratz KH. The incidence, recurrence and outcomes of herpes simplex virus eye disease in Olmsted County, Minnesota, 1976 through 2007: The impact of oral antiviral prophylaxis. Arch Ophthalmol. 2010; 128(9): 1178–1183.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32-5271
Silver Spring, MD 20993

April 29, 2014

Robert J. McCormack, PhD
Regulatory Affairs Consultant
Creative Regulatory Solutions, LLC
14 Edinburgh Drive
Randolph, NJ 07869

Dear Dr. McCormack:

This letter acknowledges receipt of your orphan drug designation request submitted on behalf of Dompé s.p.a., pursuant to section 526 of the Federal, Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) for the following:

Name: Recombinant Human Nerve Growth Factor Ocular Drops

Disease or Condition: Treatment of neurotrophic keratitis.

Date of request: April 23, 2014

Date of receipt: April 25, 2014

Designation reference number: 14-4362

We will correspond with you after we have completed our review of the request. Please note that your drug or biologic product will not be eligible for designation if you submitted a new drug application (NDA) or biologics license application (BLA) for this drug, for this indication before submitting this designation request.

All communications concerning the request should be identified with the above reference number. If you have any questions, please call me at 301-796-8685 or alternatively at 301-796-8660.

Sincerely yours,

Mary L. Grice -S

Digitally signed by Mary L. Grice -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Mary L. Grice -S, 0.9.2342.19200300.100.1.1=1300019770
Date: 2014.04.29 12:32:51 -04'00'

Designation Coordinator

Review of a Request for Orphan Drug Designation

Designation Number: 2014-4362

Date Received by FDA: April 25, 2014
Date Received by Reviewer: June 4, 2014
Date Review Completed: June 11, 2014

Product: Generic name: recombinant human nerve growth factor (rhNGF) ocular drops

Trade name: not available

Sponsor: Dompe SPA
Via S. Martino 12-12/A
Milan, 20122
Italy

US Resident Agent: Robert J McCormack, PhD
Regulatory Affairs Consultant
14 Edinburgh Drive
Randolph, NJ 07869

Manufacturer: L'Aquila, Italy is the current manufacturer of the drug product and substance.

Proposed Designation: Treatment of neurotrophic keratitis.

Regulatory Status: The sponsor states that rhNGF is being studied for use in the treatment of neurotrophic keratitis and other ocular diseases, and is not approved or had any marketing applications filed in any country.

RegeneRx Biopharmaceuticals received orphan drug designation for thymosin beta 4 for use in the treatment of patients with neurotrophic keratopathy (application# 13-4166) in December 2013.

Disease Background: Neurotrophic keratitis (keratopathy) is a degenerative corneal disease caused by damage to the trigeminal nerve that results in corneal epithelial breakdown, impairment of healing, and development of corneal ulceration, melting, and perforation. Patients experience a reduction or total loss of corneal sensation. The most frequent cause of neurotrophic keratitis is from herpetic keratitis and from lesions or surgeries that compress the trigeminal nerve or ganglion. Other diseases or conditions that can cause neurotrophic keratitis include chemical burns, physical injuries, corneal dystrophy, diabetes, multiple sclerosis, congenital syndromes and leprosy[1,2].

Diagnosis is based on patient history, clinical findings and a corneal sensitivity evaluation. Staging of neurotrophic keratitis is by the Mackie classification: Stage 1 disease consists of superficial punctate keratopathy, epithelial hyperplasia and

irregularity, stromal scarring, and superficial neovascularization; Stage 2 is characterized by a persistent epithelial defect with smooth and rolled edges, and Descemet's membrane folds and stromal swelling; and Stage 3 is typified by corneal ulcer, stromal melting and perforation[1,2].

Treatment of neurotrophic keratitis begins immediately after diagnosis in order to prevent progression and to promote epithelial healing. Stage 1 and 2 neurotrophic keratitis is treated by administration of artificial tears in order to improve the corneal surface. All other topical eye medications should be discontinued. Stage 2 disease may also require the use of corneal or scleral therapeutic contact lenses in order to prevent the development of corneal ulcers. Surgical procedures such as tarsorrhaphy or amniotic membrane transplantation can be used for unresponsive cases. Stage 3 neurotrophic keratitis is treated by surgical procedures including tarsorrhaphy and conjunctival flap to improve corneal healing. Small perforations can be treated by application of cyanoacrylate glue followed by a soft bandage contact lens while larger perforations could require corneal transplant surgery[1,2].

Hypothesis for Clinical Superiority: Not applicable.

Medically Plausible Subset Analysis: Not applicable.

Population Estimate: The prevalence of neurotrophic keratitis caused by the most frequent causes, herpetic keratitis and as a complication of surgical procedures for trigeminal neuralgia, has been estimated to be 1.6 per 10,000. The prevalence of neurotrophic keratitis from other ocular and systemic conditions cannot be estimated as no data is available in the literature. Therefore, the overall prevalence of neurotrophic keratitis as a result of all conditions is estimated to be < 5 per 10,000[1,2].

Rationale for Use: The sponsor states that NGF is a cytokine essential for the survival and growth of sympathetic and sensory neurons that are found in innervated tissues such as the cornea. NGF exerts its effect on neuron survival through modulation of expression of the Bcl-2 gene family.

The sponsor provides two publications that describe the efficacy of topical murine NGF in the treatment of patients with neurotrophic keratitis in two clinical studies [3,4]. The first was an uncontrolled study in which 12 patients (14 eyes) with severe neurotrophic corneal ulcers associated with corneal anesthesia (i.e. stage 3 neurotrophic keratitis) were treated with the murine NGF 10 times daily for two days and then 6 times daily until the ulcers healed. Treatment continued for 2 weeks after the ulcers healed, and the patients were then followed for up to 12 months. The evolution of the corneal disease during treatment and follow-up was evaluated by slit-lamp examination, photography, fluorescein-dye testing, and tests of corneal sensitivity and best corrected visual acuity. Corneal healing began 2 to 14 days after the initiation of treatment with NGF, and all patients had complete healing of their corneal ulcers after 10 days to 6 weeks of treatment. Corneal sensitivity improved in 13 eyes, and returned to normal in 2 of the 13 eyes. Corneal integrity and sensitivity were maintained during the follow-up period (range, 3 to 12 months). Best corrected visual acuity increased progressively during treatment and follow-up in all patients. There were no systemic or local side effects of

treatment[3]. The second study prospective controlled study to evaluate the efficacy of topical murine NGF in 45 eyes (43 patients) with stage 2 (17 eyes) to stage 3 (28 eyes) neurotrophic keratitis unresponsive to other nonsurgical therapies. After a 10-day washout with artificial tears, patients received murine NGF (200 microg/ml) every 2 hours for 2 days followed by one drop six times daily until the ulcer healed. A maintenance dose of one drop NGF (100 microg/ml) was administered four times daily for the 2 weeks subsequent to ulcer healing. All patients had a complete resolution of the persistent epithelial defect (with or without an ulcer) after 12 days to 6 weeks of treatment with NGF. Patients affected by both stages of the disease demonstrated both improved corneal sensitivity and visual acuity ($P<0.001$). No significant differences were observed in the time to complete corneal healing between stage 2 and stage 3 patients. Hyperemia and ocular and periocular pain were side effects reported during the first days of treatment. No relapse of the disease was observed during the follow-up period, with the exception of three patients with trigeminal nerve resection, who required a single retreatment[4].

The sponsor notes that the use of rhNGF is currently under evaluation. The sponsor's initial study, completed in 2013, was designed to evaluate the safety profile, pharmacokinetics (PK), and immunogenicity of single and multiple does of rhNGF in 73 healthy volunteers. The sponsor is currently conducting a Phase 1/2 placeb0-controlled clinical study to assess the safety and efficacy of two dose regimens (10μg/ml or 20μg/ml) of rhNGF six times daily versus placebo for inducing complete healing of stage 2 or 3 neurotrophic keratitis refractory to non-surgical therapy (REPARO study). The Phase 1 segment was recently completed in 18 patients (7 men and 11 women) with neurotrophic keratitis resulting from diabetes (4), previous ocular surgeries (4), ocular herpes (2), herpes simplex infection (3), neurosurgery complication (3) and other (2) who received either one of the two doses of rhNGF or placebo. The sponsor notes that a masked efficacy analysis showed that NGF was well tolerated and that corneal lesions completely healed in 73% of patients. The Phase 2 portion of the study is now enrolling.

Discussions and Conclusions: The sponsor has provided adequate prevalence information to show that the prevalence of neurotrophic keratitis is less than 200,000 in the US. Neurotrophic keratitis is a degenerative corneal disease caused by damage to the trigeminal nerve that results in corneal epithelial breakdown, impairment of healing, and development of corneal ulceration, melting, and perforation. The prevalence of neurotrophic keratitis caused by the most frequent causes of trigeminal nerve damage, herpetic keratitis and a complication of surgery for trigeminal neuralgia, has been estimated to be 1.6 per 10,000. The prevalence of neurotrophic keratitis from other ocular and systemic conditions cannot be estimated as no data is available in the literature; however, the overall prevalence of neurotrophic keratitis as a result of all conditions is estimated to be < 5 per 10,000[1,2]. Therefore, the overall prevalence would currently be 159,100, assuming that the prevalence is no more than 5 per 10,000 and a current US population estimate of 318.2 million[5].

The sponsor has provided adequate scientific rationale to support orphan drug designation. The proposed product rhNGF is an eye drop consisting of the recombinant form of human NGF. NGF is a cytokine essential for the survival and growth of sympathetic and sensory neurons that are found in innervated tissues such as the cornea.

NGF exerts its effect on neuron survival through modulation of expression of the Bcl-2 gene family. The sponsor provides two publications that describe the efficacy of topical murine NGF in the treatment of patients with neurotrophic keratitis in two clinical studies [3,4]. Both studies showed that topical NGF could heal the corneas, improve cornea integrity and sensitivity, and improve vision in patients with neurotrophic keratitis. The use of rhNGF is currently under clinical evaluation. The initial PK study in healthy volunteers was completed in 2013. The sponsor is currently conducting a Phase 1/2 placebo-controlled clinical study to assess the safety and efficacy of two dose regimens (10µg/ml or 20µg/ml) of rhNGF six times daily versus placebo for inducing complete healing of stage 2 or 3 neurotrophic keratitis refractory to non-surgical therapy (REPARO study). The Phase 1 segment was recently completed in 18 patients, and although still blinded, the corneal lesions completely healed in 73% of patients. The Phase 2 portion of the study is now enrolling.

Recommendation: It is recommended the recombinant human nerve growth factor be designated as an orphan drug for use in the treatment of neurotrophic keratitis. The prevalence of patients with neurotrophic keratitis in the US is currently less than 200,000, and is approximately 159,100.

Erica K. McNeilly, R.Ph.
Health Science Administrator

Concur: _____ Date: 6/16/2014

Henry H. Startzman III, M.D.
Director, Orphan Drug Designation Program
Office of Orphan Products Development

1. Sacchetti A, Lambiase A. Diagnosis and management of neurotrophic keratitis. Clinical Ophthalmology 19 March 2014.

2. Lambiase A, Sacchetti A in Benitez-del-Castillo JM, Lemp MA (Eds). Ocular Surface Disorders. Chapter 26, Neurotrophic Keratitis. JP Medical, London, 2013.

3. Lambiase A, Rama P, Bonini S, et al. Topical treatment with nerve growth factor for corneal neurotrophic ulcers. N Eng J Med 1998; 338(17):1174-80.

4. Bonini S, Lambiase A, Rama P, et al. Topical treatment with nerve growth factor for neurotrophic keratitis. Ophthalmology 2000; 107(7):1347-51.

5. US Census Bureau. http://www.census.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32- 5271
Silver Spring, MD 20993

JUN 2 3 2014

Robert J. McCormick, PhD
Regulatory Affairs Consultant
14 Edinburgh Drive
Randolph, NJ 07869

Re: Designation request # 14-4362
Dated: April 23, 2014
Received: April 25, 2014

Dear Dr. McCormick:

This letter responds to your request submitted on behalf of Dompé s.p.a. for orphan-drug designation of recombinant human nerve growth factor (rhNGF) for "treatment of neurotrophic keratitis."

Pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb), your orphan-drug designation request of recombinant human nerve growth factor (rhNGF) is granted for *treatment of neurotrophic keratitis*. Please be advised that it is the active moiety or principal molecular structural features of the drug[1] and not the formulation of the drug that is designated.

If your drug receives marketing approval for an indication broader than what is designated, it may not be entitled to exclusive marketing rights under section 527 (21 U.S.C. 360cc). Therefore, prior to submission of your marketing application, we request that you compare the drug's orphan designation with the proposed marketing indication and submit additional information to amend the orphan-drug designation if warranted. 21 CFR 316.26.

If the same drug is approved for the same orphan indication before you obtain marketing approval of your drug, you will have to demonstrate that your drug is clinically superior to the already approved same drug in order to obtain orphan-drug exclusivity. Failure to demonstrate clinical superiority over the already approved same drug will result in your drug not receiving orphan-drug exclusivity. 21 CFR 316.34(c).

[1] The term "drug" in this letter includes drug and biological products.

You must submit to the Office of Orphan Products Development a brief progress report of drug development within 14 months after this date and annually thereafter until marketing approval. 21 CFR 316.30.

Please notify this Office within 30 days of submitting a marketing application for the drug's designated use. Once your marketing application is approved, please contact Stephanie Donahoe, RPh, MPH, at 301-796-8681 or alternatively at 301-796-8660 to assess eligibility for orphan-drug exclusivity.

If you have questions regarding the development of your designated product, please feel free to contact Erica McNeilly, RPh at 301-796-8679 or alternatively at 301-796-8660. Congratulations on obtaining your orphan-drug designation.

Sincerely,

Hy H. Stanford III for Gayatri R. Rao

Gayatri R. Rao, MD, JD
Director
Office of Orphan Products Development

cc:

OOPD/File # 14-4362
OOPD/CHRON

History:
J. Fritsch 6/20/14
E. McNeilly
G. Rao

DESIGNATION GRANTED

FDA U.S. FOOD & DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Office of Orphan Products Development

Exclusivity Memorandum

Date:	9/5/2018
From:	Norris Asare, Designation Program Coordinator
Through:	Roberta Szydlo, Health Science Administrator RS 9/10/18 Henry Startzman III, MD, Director, Orphan Drug Designation Program HNS 9/13/2018
To File #:	14-4362
Name of drug or biologic:	OXERVATE™ (cenegermin-bkbj)
Orphan designation:	Treatment of neurotrophic keratitis
Designation date:	6/23/2014
Sponsor name:	Dompé S.p.A.
BLA #:	761094
Approval date:	8/22/2018
Approved indication:	OXERVATE™ (cenegermin-bkbj) ophthalmic solution 0.002% is indicated for the treatment of neurotrophic keratitis.

Is the approval within scope of designation?	**Yes ☒ No ☐**		
Comments:	Approval of cenegermin-bkbj for the treatment of neurotrophic keratitis is within the scope of orphan drug designation #14-4362 for treatment of neurotrophic keratitis.		
Has the same drug or biologic been previously approved?	**Yes ☐ No ☒**	**Is the drug or biologic a New Molecular Entity (NME) or New Biological Entity (NBE)?**	**Yes ☒ No ☐**
Comments:	Per DARRTS, this is a new molecular (biological) entity and Drugs@FDA confirms this is the first approval for cenegermin-bkbj. Therefore, cenegermin-bkbj is a new biological entity.		
Has the same drug or biologic already been approved for the same disease or condition?	**Yes ☐ No ☒**		
Comments:	The FDA News Release dated August 22, 2018 notes that this is the first approval of a drug indicated for the treatment of neurotrophic keratitis. Furthermore, pages 3 and 4 of the Deputy Office Director, Deputy Division Director, and Cross-Discipline Team Leader (CDTL) Review dated 8/22/18 indicates that prior to approval of BLA 761094, there was no FDA approved pharmacologic therapy for the treatment of neurotrophic keratitis.		
Superiority:	**Yes ☐ No ☐ Not applicable ☒**		
Comments:	There is no need to demonstrate superiority since there is no other same biologic approved for the indication that is the subject of this exclusivity.		
Recommendation:	Approval is within scope of orphan drug designation. The same biologic has not been previously approved for the same disease or condition. Therefore, the sponsor is eligible for orphan exclusivity for OXERVATE™ (cenegermin-bkbj) *indicated for the treatment of neurotrophic keratitis.*		

U.S. FOOD & DRUG
ADMINISTRATION

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32-5271
Silver Spring, MD 20993

SEP 2 4 2018

Creative Regulatory Solutions, LLC
14 Edinburgh Drive
Randolph, NJ 07869

Attention: Robert J. McCormack, PhD
US Agent for Dompé S.p.A
bmccormack@creativeregulatory.com

Re: Orphan-drug designation #14-4362

Dear Dr. McCormack:

This letter refers to your orphan drug cenegermin-bkbj which was designated pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) on June 23, 2014, for "treatment of neurotrophic keratitis." We also refer to the letter from the Center for Drug Evaluation and Research dated August 22, 2018, granting marketing approval of your Biologics License Application for OXERVATE™ (cenegermin-bkbj) *indicated for the treatment of neurotrophic keratitis.*

This letter is to inform you that as the first sponsor of this drug to obtain marketing approval for this indication, Dompé S.p.A is entitled to seven years of orphan-drug exclusive approval pursuant to section 527 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360cc). The seven-year exclusive approval began on August 22, 2018, the date of approval of the Biologics License Application (BLA 761094). The scope of orphan-drug exclusive approval is described under 21 CFR 316.31.

As the holder of exclusivity, the sponsor is required to assure the availability of sufficient quantities of this drug to meet the needs of patients. Failure to do so could result in the withdrawal of the drug's exclusive approval as stipulated under 21 CFR 316.36(b).

Congratulations on obtaining orphan-drug exclusivity. Should you have any questions regarding this exclusivity, please contact Norris Asare at 301-796-7329 or alternatively at 301-796-8660.

Sincerely,

Debra Y. Lewis, OD, MBA
Acting Director
Office of Orphan Products Development