CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761094Orig1s000

SUMMARY REVIEW

Deputy Office Director, Deputy Division Director, and Cross-Discipline Team Leader Review of BLA 761094

Date	August 14, 2018
From	Peter Stein, M.D., Wiley A. Chambers, M.D., William M. Boyd, M.D.
Subject	Deputy Office Director, Deputy Division Director, and Cross-Discipline Team Leader Review
BLA #	761094
Applicant	Dompé farmaceutici S.p.A.
Date of Submission	December 22, 2017
PDUFA Goal Date	August 22, 2018
Proprietary Name	Oxervate
Established or Proper Name	cenegermin-bkbj
Dosage Form(s)	topical ophthalmic solution
Proposed Dosing Regimen(s)	One drop in the affected eye 6 times per day at 2 hour intervals, for eight weeks
Regulatory Action	Approval
Proposed Indication(s)/Population(s)	Treatment of neurotrophic keratitis (b) (4) (b) (4)

1. Summary

Cenegermin, a recombinant form of human nerve growth factor (rhNGF). Cenegermin has been granted the Fast Track, Breakthrough Therapy, and Orphan designations by the FDA.

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. Studies NGF0212 and NGF0214 demonstrated that more patients with neurotrophic keratitis had complete healing of the corneal epithelium when treated with cenegermin ophthalmic solution, 20 mcg/mL than when treated with the cenegermin vehicle solution. To date, no long-term safety issues with cenegermin ophthalmic solution administration have been identified. The most common ocular adverse event for cenegermin ophthalmic solution was eye pain at the time of instillation.

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

2. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

BLA 761094 Benefit-Risk Integrated Assessment

The data contained in this submission establishes the efficacy of Oxervate (cenegermin 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 that more patients had complete healing of the corneal epithelium when treated with cenegermin ophthalmic solution, 20 mcg/mL than with the vehicle solution. To date, no long-term safety issues with cenegermin ophthalmic solution administration have been identified. The most common ocular adverse event for cenegermin ophthalmic solution was eye discomfort/pain after instillation of the product.

There is a favorable benefit-risk ratio of cenegermin 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 infections. • 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.
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, or tarsorrhaphy.	Treatment options are supportive, but do not necessarily improve the speed of healing.
Benefit	• A greater number of patients treated with Oxervate demonstrated resolution of epithelial defects in two clinical trials. In Study NGF0212, 72% of patients in the Oxervate group compared to 33% in the vehicle group had complete resolution. In Study NGF0214, 65% of patients in the Oxervate group compared to 17% in the vehicle group had resolution.	Use of the product resulted in a greater number of patients with resolution of their epithelial defects putting them at reduced 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 monitoring and reporting of all adverse events are expected to be adequate to monitor for potential new adverse reactions.

3. Background

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. 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 a variety of mechanisms including but not limited to aneurysms, cerebrovascular accidents, diabetes mellitus, hereditary disorders, herpes zoster ophthalmicus, herpes simplex keratitis, leprosy, multiple sclerosis, or surgical trauma. The most common causes of NK are herpetic corneal infections, surgery for trigeminal neuralgia, and surgery for acoustic neuroma.

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 physical or surgical therapies. Treatment options may include therapeutic soft contact lenses, patching, or tarsorrhaphy. These treatment options are supportive but do not necessarily improve the speed of healing.

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.

Synopsis of Presubmission/Submission Regulatory Activity

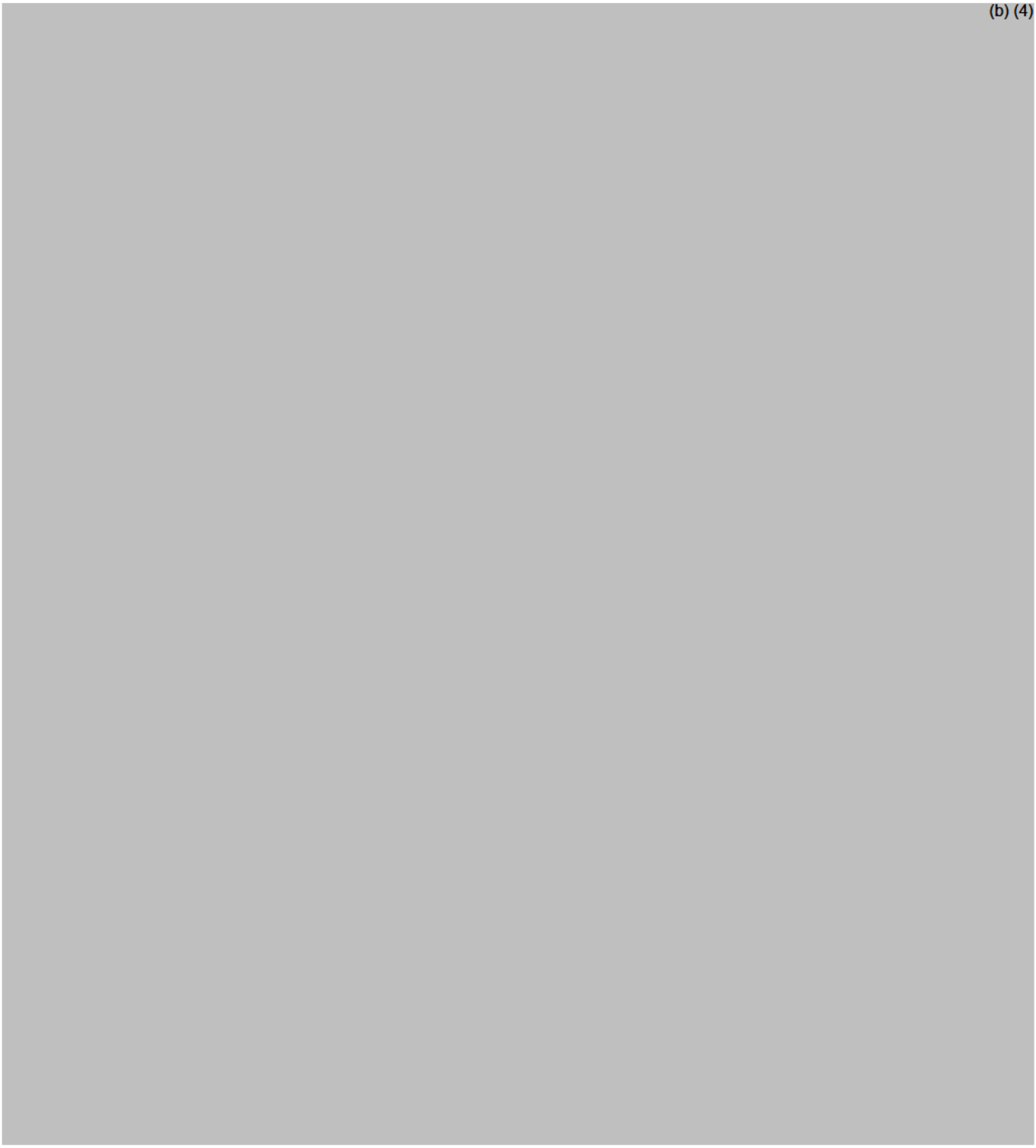
- Pre-IND meeting, October 22, 2012
  Non-clinical investigation plan and quality aspects of the rhNGF clinical lots were discussed.
- Orphan Designation granted June 23, 2014
  Designation Request #14-4362 for the treatment of NK (all 3 stages of NK).
- Type C guidance meeting, March 31, 2016
  Phase 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 (if necessary) writing two different statistical analysis plans for the EMA and FDA.
- Pre-BLA meeting, January 2017

4. Product Quality

Drug Substance

The specifications of rh-NGF Drug Substance for commercial manufacture are presented.

(b) (4)



Drug Product

rhNGF drug product is a sterile preservative-free ophthalmic solution containing 0.02 mg/mL of rhNGF drug substance. The drug product is packaged in multi-dose (b) (4) vials closed with a rubber stopper and an aluminum seal with a polypropylene flip-off.

Each vial contains 1.0 ml of solution. Seven multi-dose vials are packaged in a cardboard box with the leaflet. Each box is provided in combination with a kit of delivery system devices, including one vial-adapter, disposable pipettes (used to withdraw from the vial and administer one ocular drop), and disinfectant wipes.

Immediately before use, the flip-off is removed from the vial and a vial-adapter is connected to the glass vial. The vial is then ready for use. To administer the product, a special pipette able to deliver rhNGF solution drops of (b) (4) µL is attached to the vial adapter. The liquid transfer is secured (b) (4)

Composition of Drug Product

Ingredient	mg/mL	Function
rhNGF	0.02*	Active
Trehalose dihydrate	47.03	(b) (4)
Mannitol	12.22	
Na_2HPO_4 anhydrous	2.87	
$Na_2H_2PO_4$ dihydrate	1.22	
Hypromellose	1.00	
Macrogol 6000 (PEG 6000)	10.00	
L-methionine	0.01	
HCl	(b) (4)	pH Adjuster
NaOH		pH Adjuster
(b) (4)		(b) (4)
WFI	q.s. to 1 mL	
(b) (4)		

Source: Module 3.2.P.1

Drug Product Specification

TEST	ACCEPTANCE CRITERIA
Appearance of solution	Clear and colourless solution, practically free of visible particles
pH	7.0-7.4
Osmolality of solution (Osmol/Kg)	280-320 mOsm/Kg
Identity by Reverse Phase HPLC	Presence of rhNGF
Particulate contamination: sub-visible particles	(b) (4)
rhNGF Concentration (mg/mL) by RP-HPLC	(b) (4) mg/mL
Purity and impurities by RP-HPLC	NLT (b) (4)
	Specified imp (b) (4) NMT (b) (4)% (NMT (b) (4)% at release)
	Specified imp. (b) (4) NMT (b) (4)%
	Single expected unknown imp. NMT (b) (4)% (≤LOQ)
	No new impurity## at or above (b) (4)% (LOD)
	Total unknown impurity NMT (b) (4)%
Container Closure Integrity test	Pass or Fail
Potency (TF-1 proliferation bioassay)	(b) (4)% of reference material
Sterility	Sterile
L-Methionine	NLT (b) (4) of nominal concentration (b) (4)% at release)
Purity by SE-HPLC	NLT (b) (4)% of main peak Single Low and High molecular weight species NMT (b) (4)%
Purity by SDS-PAGE Silver Stained, Reduced	Comparable to Reference Material profile. No new band
Purity by SDS-PAGE Silver Stained, Non-Reduced	Comparable to Reference Material profile. No new band

corresponding to a protein content of (b) (4) This value will be introduced in the release CoA starting from the next industrial batches produced after the MA.
except for the following "expected" unknown imp. (b) (4)

Source: Module 3.2.P.5.1

Methionine

Based on a trend observed in preliminary results of the clinical study NGF0212 and on other manufacturing considerations, (b) (4)

(b) (4)

- Clinical study (NGF 0214): the study was conducted using a formulation with rhNGF of 20 µg/ml in patients with moderate and severe NK.

- Clinical study (NGF 0113): the study was conducted using rhNGF of 60 µg/ml and 180 µg/ml in patients with retinitis pigmentosa;

- 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.

Drug Product Container Closure

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.

After clinical studies, NGF0212 and NGF0214 were conducted, 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 was used by patients in two clinical studies - Study NGF0116 and Study NGF0216.

Clinical Study NGF0216 was conducted in patients with dry eyes. The dosing schedule of Study NGF0216 was the same as proposed for the treatment of neurotrophic keratitis. While Study NGF0216 did not demonstrate a statistically significant difference between groups (i.e., no effect due to cenegermin), the study demonstrated a clinically significant difference in corneal and conjunctival staining scores consistent with the effect that would be expected with successful administration of an aqueous vehicle. This study demonstrated successful use of the delivery system.

Based upon instructions for use that appear understandable, experience in Study NGF0216 where dose administration appeared successful, marketing of the configuration in Europe and no reported adverse events related to the dose administration, it is concluded that sufficient information is available to support the approval of this product in its proposed dosing configuration for the intended population of patients with neurotrophic keratitis.
From the Office of Biotechnology Products Integrated Quality Assessment (IQA) Review dated 8/7/2018:

Product Overview and Summary

Oxervate (cenegermin) is an *E. coli* expressed 118 KDa recombinant human Nerve Growth Factor (NGF) proposed for the treatment of neurotrophic keratitis. Oxervate is active as a non-covalent homodimer. Oxervate is provided as an ophthalmic solution in a multiple dose vial.

Reference Materials

The Applicant committed to establish post-marketing a two-tier reference standard system for (b) (4) A protocol for periodic monitoring of reference standards was reviewed and found acceptable. (b) (4) The current commercial reference standard RS 0615 is acceptable because it was adequately qualified for potency and protein concentration.

(b) (4)

(b) (4)

[redacted]

The Clinical team has reviewed and discussed the memorandum quoted above. While there are theoretical concerns of immunogenicity, they have not been demonstrated to occur in any ophthalmologically administered product to date. Potential reasons may include the lack of systemic exposure, the lack of blood vessels on the corneal surface and the relatively immunoprivileged characteristics of the eye. The recommended paragraph has therefore not been included in the labeling. Routine clinical care of patients treated with Oxervate would be expected to include monitoring for ocular inflammation.

Establishment Information

Overall Recommendation: Approval					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Manufacture and release of MCB and WCB. DS manufacture, release, packaging and stability testing. Manufacture, release and stability testing of the reference standard. DP analytical control testing (Western Blot, SDS-Page, SE-HPLC and Potency testing), DP secondary packaging (commercial pack), DP QP batch release, and DP stability testing (HPLC, Potency and SDS-Page testing).	Dompé farmaceutici Via Campo Di Pile, L'Aquila, Abruzzo, Italy 67100	3004216297	VAI requested	(b) (4)	Approval
DRUG PRODUCT					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacture, DP primary packaging (Packaging in Single-Units), DP analytical control testing (except Western Blot, SDS-Page, SE-HPLC, Potency testing), and DP stability testing (except HPLC, SDS-Page and Potency testing).	(b) (4)	3004110157	District File Review	Drug product facility inspection waived. See waiver memo.	Approval

CMC Post-Marketing Commitments

Post-marketing commitments were submitted to enhance the control strategy of the product to better ensure robust process control and product performance over time regarding: completion of real time shipping validation studies under worst case conditions; leachables assessment at release in the final DP container closures to confirm the risk assessment conclusions; (b) (4) development of a two tier RS system; enhancements to the potency assay; revision of the bioburden assay to use a 10 ml test volume; and to conduct endotoxin method qualification using two additional DS batches. The Oxervate DS and DP manufacturing processes and controls are acceptable.

1- To perform a leachable study to evaluate leachables from the manufacturing process and the container closure system in OXERVATE (cenegermin) drug product. The analysis will be performed using one drug product lot analyzed at release. Appropriate methods will be used to detect, identify, and quantify organic non-volatile, volatile and semi-volatile species, and metals. Complete data and the risk evaluation for potential impact of leachables on product safety and quality will be provided in the final study report.

2- To perform real time shipping validation studies to support the stability of OXERVATE (cenegermin) drug product vials shipped from the DP manufacturing site in Italy to the US. The shipping study should evaluate product quality before and after shipping using worst case shipping conditions of distance, duration, temperature, mode of transportation and vibration. The study should be performed with drug product manufactured with a process representative of the commercial process, same formulation and packaged in the same container closure system as that proposed for commercial batches. The final study report(s) will be submitted in accordance with 21 CFR 601.12.

3- To establish a two-tiered reference material system for OXEVATE, comprised of primary and secondary (working) reference materials prepared from lot(s) representative of production and clinical materials. The final study report(s) will be submitted in accordance with 21 CFR 601.12.

4- To conduct structure-function studies to better understand whether all critical aspects of NGF biological function relevant to receptor binding are adequately controlled by the current TF-1 cell based assay, that only assesses NGF activity through binding the TrkA.

5- To implement a control reference material for the potency assay to improve control over the assay variability and provide additional assurance that the RS is performing as expected during routine potency testing. The potency assay control material should perform within established acceptance criteria relative to the reference standard. The final study report(s) will be submitted in accordance with 21 CFR 601.12.

6- To conduct the bioburden test with a 10-mL sample volume. The revised bioburden method should be qualified using three batches of in-process intermediates and bulk drug substance.

7- To conduct the endotoxin method qualification using two additional batches of the bulk drug substance.

8- Provide the shipping validation summary report for drug product distribution to the US, performed in the actual shipping lanes under worst-case conditions (summer). (b) (4)

Office of Product Quality Recommendation
The Office of Product Quality, CDER, recommended approval of STN 761094 for Oxervate (cenegermin) manufactured by Dompé farmaceutici S.p.A. The data submitted in this application are adequate to support the conclusion that the manufacture of Oxervate is adequately-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

5. Nonclinical Pharmacology/Toxicology

From the original Nonclinical Pharmacology/Toxicology Review dated 8/6/2018:

Nerve Growth Factor (NGF) is member of the neurotrophin family and controls the differentiation, regeneration and the survival of sympathetic and sensory neurons of vertebrates. Receptors for NGF include TrkA and the low-affinity nerve growth factor receptor p75. Nerve growth factor receptors have been found on the normal and abnormal cornea and conjunctiva. In vitro, NGF has been shown to induce proliferation and differentiation of rabbit corneal epithelial cells. In humans and in experimental animal models, both corneal and conjunctival layers (epithelial, stromal and endothelial cells) show the ability to produce and release NGF, and express TrkA and p75.

The ocular toxicity of recombinant human nerve growth factor (rhNGF) has been evaluated in rats and rabbits. Recombinant human nerve growth factor (also known as cenegermin) was not associated with adverse ocular toxicity following daily topical administration in rats and rabbits for periods up to 26-weeks and 125-days, respectively; at a rat dose corresponding to 3.8-fold the MRHOD and rabbit dose corresponding to 23-fold the MHROD.

The systemic toxicity of rhNGF was evaluated in rats and rabbits after subcutaneous or ocular administration. Immunogenic response to rhNGF (a heterologous protein in animals) was reported in multiple studies following administration of rhNGF. In three of the pivotal toxicology studies, administration of rhNGF in females was associated with ovarian findings (Rabbit: 90-day subcutaneous administration and 2-month ocular administration; Rat: 26-week ocular administration). Findings included persistent estrus, ovarian follicular cysts, atrophy/reduction of corpora lutea, and changes in ovarian weight at doses ≥119-fold the MRHOD. The Applicant proposes that the observed ovarian findings in animals are consistent with mechanism of action. While plausible, no empirical data was provided to directly support that supposition.

In reproductive toxicity studies, rhNGF did not produce effects on fertility or postnatal development in offspring. Following daily subcutaneous administration of rhNGF during the period of organogenesis, a slight increase in post-implantation loss (embryofetal resorption) was observed in rats and rabbits at all doses (≥42 µg/kg/day or 267-fold MRHOD); cardiovascular

anomalies were observed in rabbits at 83 µg/kg/day (534-fold MRHOD) and hydrocephaly and ureter anomalies were observed in rats at 267 µg/kg/day (1709-fold MRHOD).

Fetal malformations were not observed at doses ≤42 µg/kg/day (267-fold MRHOD). In parental rats and rabbits, an immunogenic response to cenegermin was observed in all reproductive toxicity studies. Given that cenegermin is a heterologous protein in animals, this response may not be relevant to humans.

6. Clinical Pharmacology

From the original Clinical Pharmacology review dated 5/24/2018:

Information on extent of systemic exposure to cenegermin following repeated topical ocular dosing of the proposed to-be-marketed cenegermin eye drops has not been provided by the Applicant. The proposed to-be-marketed drug product is a sterile aqueous ophthalmic solution containing 20 µg/mL of cenegermin and 0.001% w/v of methionine (b) (4). However, the Clinical Pharmacology information provided by the Applicant in support of this BLA is from the clinical studies that were conducted with the drug product without methionine. Complete details on the available pharmacokinetic (PK) information from the drug product without methionine is summarized in the Clinical Pharmacology review of an IND submission (SDN-33) under IND 115892 (DARRTS Review date 01/30/2017). Because the Clinical Pharmacology information contained in this submission is not from the proposed to-be-marketed drug product, the Clinical Pharmacology review of this information has been not included in their memorandum.

The Applicant has agreed to provide the requested PK information and submitted the interim clinical study report from the Phase 1 PK study in June 2018. Because the requested PK information in support of this BLA is anticipated to arrive too close to the BLA review goal date, the Clinical Pharmacology Review Team recommended a Post Marketing Commitment (PMC).

Note: The Applicant has agreed to the following PMC language and milestones:

PMR/PMC Set 3460-1
PMR/PMC Description
PMC to conduct a clinical study to determine the extent of systemic exposure to cenegermin following repeated topical ocular dosing of the final to-be-marketed formulation of OXERVATE containing methionine.

PMC Schedule Milestones
Draft Protocol Submission: 01/2018
Final Protocol Submission: 01/2018
Study/Trial Completion: 06/2018
Interim /Other: 06/2018
Final Report Submission: 01/2019

7. Clinical/Statistical- Efficacy

From the original Medical Officer Review dated 6/11/2018:

Clinical data for Studies NGF0212 and NGF0214 were reviewed to support efficacy.

Study NGF0212

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.'

Dompé's original definition was: 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.

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
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.

Study NGF0214

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.

Efficacy Summary Statement

The data from two (NGF0212 and NGF0214) studies contained in this application establishes the efficacy of cenegermin ophthalmic solution, 20 mcg/mL dosed 6-times daily (every 2 hours) for 8 weeks for the treatment of (b) (4) neurotrophic keratitis. The use of the to-be-marketed multi-dose delivery configuration described in the proposed Oxervate labeling is supported by two clinical studies - Study NGF0116 (Module 5.3.5.4) and Study NGF0216 (Module 5.3.5.4). See the Medical Officer's review dated 6/11/2018, Section 8.5, page 74.

8. Safety

From the original Medical Officer Review dated 6/11/2018:

Safety Database

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

Code Phase (status) Location	Key objectives	Countries	Group	Doses	Subjects randomized/ uncontrolled or rescue treated[a]	Safety database for rhNGF[b]
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
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 8.2.1-3: 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 weeks, 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

The total number of patients exposed to rhNGF with methionine 20 mcg/mL or higher during the clinical development is 301.

Deaths

Study	Patient Population	rhNGF doses	Treatment Duration	Subjects exposed to rhNGF	Deaths
112	Healthy volunteers	0.5 to 180 µg/mL	5 days	58	0
212	Neurotropic keratitis	10 and 20 µg/mL	8 weeks	141*	8
214	Neurotropic keratitis	20 µg/mL	8 weeks	36*	1
213	Dry eye syndrome	4 and 20 µg/mL	4 weeks	40	0
113	Retinitis pigmentosa	60 and 180 µg/mL	24 weeks	40	0

*These numbers include also neurotrophic keratitis patients who were initially randomized to vehicle and were subsequently randomized to rhNGF.

Patient Number / Treatment Group	**Age/ Gender**	**Significant Medical History**	**Cause of Death**	**Time relationship to treatment**
Study NGF0212				
(b) (6) rhNGF 20 mcg/mL **Case ID** (b) (6)	67 ♂	Lung Cancer	Progression of Lung Cancer	Died during treatment
(b) (6) Vehicle Case ID (b) (6)	87 ♂	COPD, chronic renal disease, ischemic cardiac disease, atrial fibrillation	Respiratory failure	Vehicle treatment
(b) (6) rhNGF 10 mcg/mL Case ID (b) (6)	76 ♂	Cardiomyopathy, lung disease	Heart failure	Died 8 months after completing treatment
(b) (6) rhNGF 10 mcg/mL Case ID (b) (6)	80 ♀	Hypercholesterolemia, hypertriglyceridemia	Heart attack	Died 11 months after completing treatment
(b) (6) rhNGF 10 mcg/mL Case ID (b) (6)	83 ♂	Diverticulitis, chronic renal dysfunction, pulmonary fibrosis, pulmonary hypertension, arterial hypertension, myocardial infarction, atrial fibrillation, dyspnea	Cardiac arrhythmia, dyspnea	Died 2 weeks after second course of treatment
rhNGF 10 mcg/mL Case ID (b) (6)	70 ♂	Pulmonary fibrosis, Berger's disease, squamous cell carcinoma, kidney transplant	Progression of squamous cell carcinoma	Died during treatment
(b) (6) rhNGF 10 mcg/mL Case ID (b) (6)	37 ♀	Ehlers-Danlos syndrome – vascular, Type 4. Carotid cavernous fistula, femoral artery dissection	Aortic dissection, aortic rupture, hemorrhagic shock	Died 3 months after completing treatment
(b) (6) rhNGF 20 mcg/mL Case ID (b) (6)	68 ♂	Type I diabetes mellitus, right leg amputation, hypertension, poor global status.	Respiratory failure	Died 1 year after completing treatment
Study NGF0214				
(b) (6) rhNGF 20 mcg/mL Case ID (b) (6)	68 ♂	Type II diabetes mellitus, hypertension, hypercholesterolemia, myocardial infarction	Cause of death not forwarded to applicant despite repeated requests.	Died 5 months after completing treatment.

The cardiovascular, cancer and respiratory deaths which occurred during the study are consistent with the age and past medical history of the patients enrolled. Most events occurred well after the treatment had been completed. The investigator, applicant, and FDA's clinical team have concluded that the investigational product was unlikely to have contributed to the death of these patients.

Serious Adverse Events

Incidence of Serious Adverse Events during the Controlled Treatment Period

Patient Number / Treatment Group	Serious Adverse Event	Outcome
Study NGF0212		
	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 antibiotic, 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 antibiotic
Vehicle	Corneal lesion progression	Resolved (treatment 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
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 treatment, 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.
Study NGF0214		
(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.

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.

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

Body System MedDRA Preferred Term	NGF0212 + NGF0214 Vehicle (+/- M) n%		NGF0212 + NGF0214 rhNGF (+/- M) n%	
	n=76		n=75	
Any Adverse Event	38	50%	48	64%
Eye disorders	30	39%	31	41%
Cataract	0	0%	3	4%
Corneal deposits	0	0%	3	4%
Corneal epithelium defect	3	4%	3	4%
Corneal graft rejection	1	1%	2	3%
Corneal thinning	2	3%	2	3%
Eye/Ocular inflammation	2	3%	4	5%
Eye irritation	5	7%	0	0%
Eye pain	6	8%	12	16%
Foreign body sensation	1	1%	2	3%
Lacrimation increased (tearing)	2	3%	4	5%
Ocular discomfort	3	4%	2	3%
Ocular hyperemia	2	3%	5	7%
Photophobia	3	4%	2	3%
Vision blurred	3	4%	0	0%
Visual acuity reduced	7	9%	8	11%
Gastrointestinal disorders	2	3%	2	3%
General disorders and administration site conditions	13	17%	6	8%
Disease progression	10	13%	5	5%
Sensation of foreign body	2	3%	2	3%
Infections and infestations	4	5%	11	15%
Injury, poisoning and procedural complications	2	3%	3	4%
Intraocular pressure increased	2	3%	4	5%
Musculoskeletal and connective tissue disorders	0	0%	3	4%
Nervous system disorders	4	5%	6	8%
Headache	4	5%	3	4%
Skin and subcutaneous disorders	1	1%	2	3%
Pooling of Like-Terms				
Ocular discomfort = Eye irritation, Foreign body sensation in eyes, Ocular discomfort, Sensation of foreign body	11	14%	6	8%
Blurred vision =Visual acuity reduced,Vision blurred	10	13%	8	11%

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

(b) (4), methionine was added to the formulation. Study NGF0212 had been conducted without methionine in the formulation. Study NGF0214 was conducted with the formulation to be marketed including methionine. 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 safety profile comparing the formulations with and without methionine was

reviewed. No significant differences in safety were noted in either the drug product formulation or the vehicle due to the presence of methionine.

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 2 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, ocular inflammation, eye pain, foreign body sensation, ocular hyperemia and tearing.

See the discussion on methionine in Section 4 Product Quality of this review. The changes in the formulation related to methionine did not appear to significantly affect the safety (or efficacy) of the final drug product based on the results of the clinical trials.

Systemic Adverse Events

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%)	2 (4%)	6 (25%)	4 (17%)
Chest pain	0	0	1 (4%)	0
Disease progression	6 (12%)	2 (4%)	4 (17%)	2 (9%)
nstillation site pain	1 (2%)	0	0	0
Sensation of a foreign body	0	0	2 (8%)	2 (9%)
Paresthesia	0	0	0	1 (4%)
Syncope	0	0	0	1 (4%)
Infections and infestations, n (%)	2 (4%)	7 (13%)	2 (8%)	4 (17%)
Conjunctivitis bacterial	0	1 (2%)	0	0
Corneal abscess	0	1 (2%)	0	0
Eye infection intraocular	0	0	0	1 (4%)
Gastroenteritis	1 (2%)	0	0	0
Hordeolum	0	0	1 (4%)	0
nfluenza	0	1 (2%)	0	0
Lower respiratory tract infection	0	1 (2%)	0	0
Nasopharyngitis	1 (2%)	2 (4%)	0	0
Ophthalmic herpes zoster	0	0	0	1 (4%)
Respiratory tract infection	0	0	1 (4%)	0
pper respiratory tract infection	0	1 (2%)	0	0
rinary tract infection	0	0	0	1 (4%)
Vulvovaginal mycotic infection	0	0	0	1 (4%)
Nervous system disorders n (%)	2 (4%)	2 (4%)	2 (8%)	4 (17%)
Diabetic neuropathy	0	0	0	1 (4%)

Dizziness	0	0	0	1 (4%)
Headache	2 (4%)	2 (4%)	2 (8%)	1 (4%)
Paresthesia	0	0	0	1 (4%)
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

There were no significant differences between groups in systemic safety and therefore none will be included in the package insert.

9. Advisory Committee Meeting

The application did not raise any new efficacy or safety issues. Complete clearing of the cornea surface is a well-established clinical endpoint. The observed and/or reported adverse events were consistent with the disease and/or are commonly evaluated in clinical trials of ocular surface conditions. There were no issues that were thought to benefit from a discussion at an advisory committee meeting.

10. Pediatrics

Dompé farmaceutici S.p.A. received orphan-drug designation of recombinant human nerve growth factor (rhNGF) for "treatment of neurotrophic keratitis" on 6/23/2014. The application is therefore exempt from the PREA requirements for pediatric studies.

From a clinical prospective, the human cornea has reached full growth and maturation by the age of 2 years. There is no clinical difference between pediatric patients with neurotrophic keratitis and adult patients with neurotrophic keratitis. The Agency would extrapolate efficacy established in adults to pediatric patients. During a teleconference of 7/15/2018, the Division requested that Dompé provide any available information on the use of Oxervate in the pediatric population. Dompé confirmed that Oxervate is not yet approved in Europe for use in children, and while no formal clinical studies had been conducted in the pediatric population, at least four neurotrophic keratitis (NK) pediatric patients, aged from 2 to 12 years of age, had been treated with Oxervate through temporary authorizations for use.

- 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).

Dompé was not aware of any adverse events reported with the use of Oxervate in these pediatric patients (age 2-12 years).

Studies NGF0212 and NGF0214 enrolled patients age 18 to 95 years, establishing efficacy extrapolatable to pediatric patients because the cornea is mature, the disease condition is the same in adults and pediatric patients and the drug product would be expected to have the same clinical effect. Dompé has submitted clinical safety information on additional pediatric patients who have been treated with OXERVATE to support safety in this rare condition.

OXERVATE labeling will be revised to include the following statement in Section 8.4:

Pediatric Use: The safety and effectiveness of OXERVATE have been established in the pediatric population. Use of OXERVATE in this population is supported by evidence from adequate and well controlled trials of OXERVATE in adults with additional safety data in pediatric patients from 2 years of age and older.

11. Other Relevant Regulatory Issues

BIOSTATISTICS
Per the original Biostatistics review dated 6/3/2018:

The applicant conducted two randomized, double-blinded, 8-week vehicle controlled, superiority studies (NGF0212 and NGF0214). These two studies shared similar study designs, with the main difference being that Study NGF0212 compared two concentrations of rhNGF (10 µg/mL and 20 µg/mL) to the vehicle, while Study NGF0214 compared only the proposed dose, rhNGF 20 µg/mL, to the vehicle. Additionally, Study NGF0212 was conducted in Europe, while Study NGF0214 was conducted in the US.

The original protocol-defined primary endpoint in both studies was the percentage of subjects with **complete healing of the cornea**, defined as the lesion size < 0.5 mm as determined by the reading center. Lesion size was measured as the maximum diameter of the corneal fluorescein staining in the area of the lesion. This primary endpoint was evaluated at Week 4 in Study NGF0212 and Week 8 in Study NGF0214. However, FDA did not accept this primary endpoint. The FDA-recommended primary endpoint is the percentage of subjects with **complete resolution of corneal staining**, defined as 0 mm in lesion size and no residual staining as determined by the reading center.

Both studies showed statistically significant efficacy results favoring the rhNGF groups for the FDA-recommended primary endpoint at Weeks 4 and 8 (Table above). For example, in Study NGF0212, the percentage of subjects with complete resolution of corneal staining at Week 8 was 72% in the rhNGF 20 µg/mL group and 33.3% in the vehicle group, with a treatment difference of 38.7% (95% confidence interval [CI]: 20.7%, 56.6%). In Study NGF0214, the percentage of subjects with complete resolution of corneal staining at Week 8 was 65.2% in the rhNGF 20 µg/mL group and 16.7% in the vehicle group, with a treatment difference of 48.6% (95% CI: 24%, 73.1%).

Efficacy Results for the FDA-Recommended and Protocol-Defined Primary Endpoints in Studies NGF0212 and NGF0214 (ITT; LOCF)

Endpoint	Study	Visit	rhNGF 10 µg/mL	rhNGF 20 µg/mL	Vehicle	rhNGF 10 µg/mL vs. Vehicle	rhNGF 20 µg/mL vs. Vehicle
			n/N (%)	n/N (%)	n/N (%)	Difference (95% CI)	Difference (95% CI)
FDA-recommended	NGF0212	Week 4	25/51 (49%)	29/50 (58%)	7/51 (13.7%)	35.3% (18.6%, 52%)	44.3% (27.7%, 60.9%)
		Week 8	32/51 (62.7%)	36/50 (72%)	17/51 (33.3%)	29.4% (10.9%,47.9%)	38.7% (20.7%, 56.6%)
	NGF0214	Week 4	-	13/23 (56.5%)	5/24 (20.8%)	-	35.7% (9.7%, 61.7%)
		Week 8	-	15/23 (65.2%)	4/24 (16.7%)	-	48.6% (24%, 73.1%)
Protocol-defined	NGF0212	Week 4	28/51 (54.9%)	29/50 (58%)	10/51 (19.6%)	35.3% (17.8%,52.8%)	38.4% (20.9%, 55.9%)
		Week 8	38/51 (74.5%)	37/50 (74%)	22/51 (43.1%)	31.4% (13.3%,49.5%)	30.9% (12.6%, 49.1%)
	NGF0214	Week 4	-	13/23 (56.5%)	9/24 (37.5%)	-	19% (-9%, 47.1%)
		Week 8	-	16/23 (69.6%)	7/24 (29.2%)	-	40.4% (14.2%, 66.6%)

Source: Addendum to NGF0212 Clinical Study Report (CSR), Tables 10 and 13; Summary of Clinical Efficacy, Table 6; NGF0212 CSR, Tables 14.2.1.1.1b, 14.2.1.3.2b; NGF0214 CSR, Table 14.2-1.1; and 95% CIs in Study NGF0212 were calculted by the reviewer (in blue)
Note: ITT (Intent-to-Treat) population included all randomized subjects. Missing data was imputed using the last post-baseline observation carried forward (LOCF) method. Subjects with only baseline primary measurements were not imputed and were excluded from the primary analysis.

Both studies also showed statistically significant efficacy results favoring the rhNGF groups for the protocol-defined primary endpoint. In Study NGF0212, treatment with both doses of rhNGF resulted in a significant higher percentage of subjects achieving complete healing of the cornea as compared to the vehicle at Weeks 4 and 8. In Study NGF0214, treatment with rhNGF 20 µg/mL resulted in a significant higher percentage of subjects who achieved complete healing of the cornea as compared to the vehicle at Week 8.

FINANCIAL DISCLOSURE

The Applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.* There were no investigators with disclosable financial interests/arrangements (Form FDA 3455). There is no evidence to suggest that any of the investigators/sub-investigators had any financial interests or arrangements with the Applicant.

OSI

A routine Office of Scientific Investigations (OSI) audit was requested. The Division did not request audits for European sites (i.e. Study NGF0212).

Per the OSI review dated 5/18/2018:

The Applicant submitted this BLA to support the use of Oxervate (cenegermin ophthalmic solution) for treatment of neurotrophic keratitis. An inspection was requested for the following protocol in support of this application:

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) 20 mcg/ml, eye drops solution versus vehicle containing anti-oxidant in patients with Stage 2 and 3 Neurotrophic Keratitis."

This study took place in 11 sites in the United States, beginning May 1, 2015, and ending August 6, 2016. A total of 48 subjects were randomized.

Study site #6 was inspected between February 28 and March 9, 2018. The clinical investigator was Giacomina Massaro-Giordano, MD, located at 51 N 39th Street, Philadelphia, PA 19104. At this site for Protocol NGF0214, 9 subjects were screened, 9 were enrolled, 1 subject discontinued (early termination), and 8 subjects completed the study. Records reviewed during the inspection included, but were not limited to, all informed consent forms for enrolled subjects; all enrolled subject records and source documents for primary and secondary efficacy endpoint data available at the study site; all enrolled subject records and source documents for eligibility, adverse events (including serious adverse events), and protocol deviations; test article accountability; training records; and regulatory documents.

The secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events. Of note, the primary efficacy endpoint was based on corneal photographs that were forwarded to a central reading facility for evaluation, and the sites were blinded to the results. Therefore, verification of the primary efficacy endpoint was not feasible during this inspection.

A Form FDA 483, Inspectional Observations, was issued at the conclusion of the inspection for:

(1) Failure to conduct the investigation in accordance with the signed statement of investigator and investigational plan:

> Specifically, one subject failed to meet the inclusion criteria. At screening, subject (b) (6) had a Schirmer Test measurement of 3 mm for the right eye. According to the protocol, the measurement must be greater than 3 mm for 5 minutes to qualify for the study.

(2) Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation:

> Specifically, six subjects at this site missed the following scheduled assessments, or the assessments were performed late.

Although regulatory violations were noted at this site, the findings are not likely to significantly impact data reliability. Otherwise, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

DRISK
Per the Division of Risk Management (DRISK) review was completed on 7/11/2018.

The Applicant did not submit a proposed REMS or risk management plan with this application. The risks associated with Oxervate are localized to the eye, of mild to moderate severity, and Oxervate has demonstrated efficacy for treatment of a vision threatening eye disease, neurotrophic keratitis. Based on the available data, the benefit-risk profile is favorable therefore, DTOP and DRISK agree that a REMS is not necessary for Oxervate for the treatment of neurotrophic keratitis to ensure that the benefits outweigh the risks.

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of originally proposed proprietary name, Oxervate, and granted conditional acceptance on 3/27/2018. Their proprietary name risk assessment did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional.

DMEPA notified the applicant that the nonproprietary name, cenegermin-bkbj, was conditionally acceptable for the Oxervate product on 7/18/2018.

DMEPA completed a labeling review of the originally submitted USPI, Instructions for Use (IFU), Patient Package Insert/Patient Leaflet (PPI) and carton/container labeling on 7/23/2018. They also completed a review of a human factors study found in Module 5.3.5.4. of the application (Protocol Number 16.031: Clinical investigation, controlled, cross-over, to assess the non-inferiority of the Pipette delivery system versus Hylo-Comod® in instilling eye drops). DMEPA found that the human factors (HF) validation study results were not acceptable; there was insufficient data to conclude that the user interface supports the safe and effective use of the product.

This human factors study was not utilized by the Review Division to determine the adequacy of the Oxervate to-be-marketed delivery system kit. All components required for Oxervate self-administration (e.g., multi-dose vials, adapters, sterile wipes, pipettes) are included in the Oxervate delivery system carton at the time it is dispensed. Per 21 CFR 200.50, this delivery system is regulated as drug. See the Medical Officer's review dated 6/11/2018, Section 8.5, page 74, for an extensive description of the multi-dose delivery configuration described in the proposed Oxervate labeling which has been used by patients in two clinical studies - Study NGF0116 (Module 5.3.5.4) and Study NGF0216 (Module 5.3.5.4).

Note: Study NGF0216 evaluated the safety and efficacy of rhNGF eye drops at 20 μg/mL concentration administered six times daily for 8 weeks in patients with dry eye (rhNGF versus vehicle). Both treatment arms demonstrated statistically improvement is in the Symptom Assessment in Dry Eye (SANDE) score and corneal and conjunctival staining scores; this demonstrates that both treatment arms had their respective treatment effectively delivered to the cornea by the to-be-marketed multi-dose delivery configuration.

Although there is limited experience with the to-be-marketed multiuse vials in patients with NK, all of the following items mitigate the concern regarding the new presentation and support a conclusion that the benefit of approval making this drug available to these patients outweighs the risk:

- the effective product delivery with the system kit in Studies NGF0216 and NGF0116
- the reasonably clear instructions for use
- commercial use of the product in this configuration in Europe.

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DMPP and OPDP
The Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) completed a joint review dated 7/3/2018 of the Patient Package Insert (PPI) and Instructions for Use (IFU). In that review, OPDP provided comments for the USPI and the carton and container labeling.

OBP LABELING
The Office of Biotechnology (OBP) Labeling Reviewer completed a review of the original labels and labeling submitted on December 22, 2017, and found them **not** acceptable from a labeling perspective. The Labeling Reviewer provided suggested edits which were incorporated into the Division's substantially complete labeling.

12. Labeling

The labeling that will be approved for BLA 761094 Oxervate (cenegermin-bkbj) ophthalmic solution for the treatment of neurotrophic keratitis is included below.

(b) (4)

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

Vial label

(b) (4)

13. Regulatory Action

BLA 761094 Oxervate (cenegermin-bkbj) ophthalmic solution will be approved for the treatment of neurotrophic keratitis. There are no recommended postmarketing risk evaluation and management strategies (i.e., REMS) for this drug product. There are no additional proposed risk management actions except the usual postmarketing collection and reporting of adverse experiences associated with the use of the drug product.

The following post-marketing commitments, agreed to by the applicant, will be included in the approval letter:

1) **PMC 3460-1**

PMC Description
PMC to conduct a clinical study to determine the extent of systemic exposure to cenegermin following repeated topical ocular dosing of the final to-be-marketed formulation of Oxervate containing methionine.

Draft Protocol Submission: 01/2018
Final Protocol Submission: 01/2018
Study/Trial Completion: 06/2018
Interim /Other: 06/2018
Final Report Submission: 01/2019

2) PMC 3460-2

PMC Description
To conduct the endotoxin method qualification using two additional batches of the bulk drug substance.

Final Report Submission: 12/31/2021

3) PMC 3460-3

PMC Description
To conduct the bioburden test with a 10 mL sample volume. The revised bioburden method should be qualified using three batches of in-process intermediates and bulk drug substance.

Final Report Submission: 12/31/2021

4) PMC 3460-4

PMC Description
Provide the shipping validation summary report for drug product distribution to the US, performed using actual shipping lanes under worst-case conditions (summer).

Final Report Submission: 8/31/2018

5) PMC 3460-5

PMC Description
To perform a leachable study to evaluate leachables from the manufacturing process and the container closure system in Oxervate (cenegermin-bkbj) drug product. The analysis will be performed using one drug product lot analyzed at release. Appropriate methods will be used to detect, identify, and quantify organic non-volatile, volatile and semi-volatile species, and metals. Complete data and the risk evaluation for potential impact of leachables on product safety and quality will be provided in the final study report.

Final Report Submission: 12/31/2019

6) PMC 3460-6

PMC Description
To perform real time shipping validation studies to support the stability of Oxervate (cenegermin-bkbj) drug product vials shipped from the DP manufacturing site in Italy to the US. The shipping study should evaluate product quality before and after shipping using worst-case shipping conditions of distance, duration, temperature, mode of transportation and vibration. The study should be performed with drug product manufactured with a process representative of the commercial process, same formulation and packaged in the same container closure system as that proposed for commercial batches.

Final Report Submission: 10/31/2019

7) PMC 3460-7

PMC Description
To establish a two-tiered reference material system for Oxervate, comprised of primary and secondary (working) reference materials prepared from lot(s) representative of production and clinical materials.

The final study report(s) will be submitted in accordance with 21 CFR 601.12.

Final Protocol Submission: 12/31/2018
Final Report Submission: 1/31/2019

8) PMC 3460-8

PMC Description
To conduct structure-function studies to better understand whether all critical aspects of NGF biological function relevant to receptor binding are adequately controlled by the current TF-1 cell based assay, that only assesses NGF activity through binding the TrkA.

Final Report Submission: 9/30/2019

9) PMC 3460-9

PMC Description
To implement a control reference material for the potency assay to improve control over the assay variability and provide additional assurance that the RS is performing as expected during routine potency testing. The potency assay control material should perform within established acceptance criteria relative to the reference standard.

The final study report(s) will be submitted in accordance with 21 CFR 601.12.

Final Report Submission: 12/31/2019

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/

WILLIAM M BOYD
08/20/2018

WILEY A CHAMBERS
08/22/2018

PETER P STEIN
08/22/2018