16.1.1 Protocol and Protocol Amendments

The latest version of the protocol used during the study is provided in this section. Previous versions of the protocol are available on request.

Protocol NGF0118 Version 2 dated 08-August-2019

Dompé

Study Protocol: NGF0118

CLINICAL STUDY PROTOCOL

Title: A 4 week, Phase II, multicenter, randomized, double-masked, vehicle-controlled, parallel group study with 12 weeks of follow-up to evaluate safety and efficacy of recombinant human Nerve Growth Factor (rhNGF) eye drops solution versus vehicle in patients with moderate to severe dry eye (DE).

Study Number:	NGF0118
IND:	115892
Investigational Product:	rhNGF
Phase of the study:	II
Protocol Version - Date:	**Version No. 2.0 – 08/AUG/2019** **As per Final Amendment no. 1 – 08/AUG/2019**

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Study Protocol: NGF0118

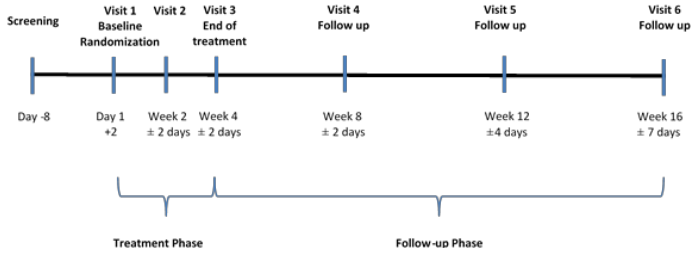
DESCRIPTION OF CHANGES

Version	Modification	Date of Revision	Application
1.0	**Final Version**	***22-JAN-2018***	**NA**
1.1	**Section 5.2.1.4 - line N° 5:** typing error "merked" modified as **"marked"** **Section 5.3 – 7th paragraph:** typing error "……pipettes (6 per vial) and disinfectant wipes (6 per vial)**"** modified as **"……pipettes (1 per vial) and disinfectant wipes (1 per vial)"**	***23-JAN-2018***	**NA**
1.2	**Section 5.2.1.1 –** typing error **"**NIMP Primary Packaging, Single Pane Label For Single Vial (Blink® Tears)" has been modified as "NIMP **Secondary** Packaging, Single Pane Label For Single Vial (Blink® Tears)" **Section 5.2.1.1 –** add the following line to the labels of NIMP: "For clinical trial use only" **Section 5.2.1.4** – label, line 7 – typing error "Batch <vvvv>/" has been modified as "Batch <vvvv>". **Section 5.2.1.4** – label, line 9 (Subj. Screening # S☐☐☐☐☐) and 10 (Subj. Randomization # R☐☐☐☐☐) has been modified as line 9: Unique Patient N° ☐☐-☐☐☐ according CRO randomization procedure. **Section 5.1.1** - "Administration route" typing error "Ophthalmic" has been modified as "Ocular". **Section 5.1.2** – "Pharmaceutical form" – "Sterile buffered acqueous solution" has been modified as "Eye drops Sterile buffered acqueous solution". **Section 5.1.2** - "Administration route" typing error "Ophthalmic" has been modified as "Ocular".	***04-FEB-2019***	**Submitted to FDA on 20FEB2019**
1.3	Dr. Pier Adelchi Ruffini, as Global Head Clinical Development and Beth Butler, as Clinical Development Manager, have been added as part of Dompé team. **Section 4.1** – IC N° 5 "Best corrected distance visual acuity (BCDVA) **score of ≥ 0.1 decimal units** in both eyes at the time of study enrolment" has been modified as "Best corrected distance visual acuity (BCDVA) **score of ≥ 0.1 decimal units (20/200 Snellen value)** in both eyes at the time of study enrolment". **Section 7.1.3 –** typing error "Number of **drop out** due to worsening in symptom scores (SANDE) and/or NEI score ≥ 50% assessed at week 2" has been modified as "Number of **patients experienced** a worsening in	***13-MAR-2019***	

	symptom scores (SANDE) and/or NEI score ≥ 50% assessed at week 2. **Section 6.1 and 6.2 –** information about the check and collection of patient's diary has been added. **Section 5.1.1 and 6.2** — the following sentence has been added "*The patient, only if strictly needed, can administer additional drops and must document in the patient's diary the n° of additional drops administered for each eye*". **Section 5.3** – typing error, the following sentence has been deleted "[…] *in a refrigerated bag. The refrigerated bag will be used to ensure that the medications will maintain refrigeration temperatures during transport to the patient's home."* **Section 6** – a definition of First Patient In has been added. **Section 8.2 –** typing error in numbering the visit. **Section 2 – "**Check and retrieval of patient's diary" has been added. **Section 6.3.1** – *"Disease progression or worsening"* has been added as primary reason of discontinuation. **Section 5.4.2 –** typing error, from "**The exact time** of study drug administration […]" has been corrected to "**Information about the study drug administration** […]". **Section 5.2.1.** – added information about the coloured vials.		
2.0	**<u>General</u>** *The typing errors have been corrected in all text where present.* *The sections have been re-numbered where necessary.* *The table of contents has been updated.* *The list of abbreviations and definition of terms has been updated*. **<u>Section 1</u> Study Centers:** *the sentences has been modify as follows*: "8-**12** study sites in US" **<u>Section 1</u> Number of Patients:** *the section is modified as follows:* **"Eligible patients will be randomized in a 1:1:1 ratio to either rhNGF eye drops solution 20 µg/ml TID (~100 patients) or rhNGF eye drops solution 20 µg/ml BID plus vehicle eye drop solution SID (~100 patients) or vehicle eye drop solution TID (~100 patients). Randomization will be stratified according to absence/presence of a documented diagnosis of Primary Sjögren's Syndrome to ensure balanced assignment across treatment groups proportional assignment. A minimum 60 patients (20 per group) with Primary Sjögren's Syndrome should be included. The enrollment of patients will be scheduled in order to assure an inclusion of approximately 240 patients without Primary Sjögren's Syndrome diagnosis and at least 60 patients with Primary Sjögren's Syndrome.**" **Section 1. Inclusion criteria #7:** *the following criteria has been modified deleting:"IEC."*	***08-AUG-2019***	**Will be Submitted to FDA with mid of August 2019**

	Section 1. Main Inclusion criteria: *the following criteria has been added as number **9***: "**Primary Sjögren's Syndrome Patients:** • **Patients with a documented diagnosis of Primary Sjögren's Syndrome according to the American-European Consensus Group Sjögren's Syndrome Criter ia (Appendix 3; must meet either 4 out of 6 total criteria OR 3 out of 4 signs). Note: Subjects who are on systemic (oral) therapy for the treatment of Sjögren's Syndrome must be on stable systemic treatment defined as the same treatment for the immediately prior 90 days**" **Section 1 Exclusion criteria #4**: *the sentence as been modified as follows:* "History of severe systemic allergy or **severe** ocular allergy (including seasonal conjunctivitis) or chronic conjunctivitis and/or keratitis other than dry eye" **Section 1: Main Exclusion criteria #8** – *The criteria has been modified as follows:* "Patient had a serious adverse reaction or significant hypersensitivity to any drug or chemically related compounds or had a clinically significant allergy to drugs, foods, amide local anesthetics or other materials including commercial artificial tears**, in particular commercial artificial tears containing carboxymethylcellulose (CMC)** (in the opinion of the investigator)." **Section 1: Main Exclusion criteria #9** – *bullet point - b.has been modified as follows* "b. have a positive result at the urine pregnancy test (**Screening/Baseline Day 1**) or," **Section 1: Exclusion criteria #15**: *the criteria is modified as follows:* "15. Participation in a clinical trial with a new active substance during the past ~~6 months~~ **60 days**" **Section 1: Duration of Study:** a *time window is specified for the wash-out period*: "**Wash-out period (from day -8 to day-1):** 7+**2** days with no further treatment except commercially available preservative free artificial tears. ***NB:*** **the wash-out should not be less than 7 days** **Section 1 Study population:** *The following sentence has been added:* **"At least 60 out of 300 patients with a documented diagnosis of Primary Sjögren's Syndrome"** **Section 1: Safety Endpoint:** *has been modifies as follows:* "**Incidence and frequency of Treatment-emergent adverse events (TEAEs), assessed throughout the study.** **Section: 1: Statistical Methods:** *The first paragraph has been modified as follows:* **"The data collected in this study will be summarized using number of observations, mean, standard deviation (SD), median, minimum, and maximum values for quantitative variables, and frequencies for qualitative variables."**		

	The second paragraph has been modified as follows:"1) **Statistical Methods - Efficacy analysis** **Primary endpoints** will be analyzed using analysis of variance **including only the treatment as main factor** followed by pre-planned comparisons from Vehicle and rhNGF dosages according to Williams procedure. **In addition, the primary endpoint will be summarized using descriptive statistics for continuous variables by treatment and visit. The change from baseline value will also be summarized for all post-baseline visits.** **An explorative sensitivity analyses of primary endpoint will be conducted including in the analysis of variance the absence/presence of diagnosis of Primary Sjögren's Syndrome and its interaction with treatments as covariates. If the interaction term is statistically significant (at the 0.10 level given its explorative nature), the treatment effects within patients with and without Primary Sjögren's Syndrome will be provided."** *The following paragraph has been added as third paragraph* **"Secondary endpoints will be presented with the appropriate descriptive statistics and inferential statistics appropriate for the nature of variable analyzed will be done in order to test treatment effect."** **Section: 2.** *The second column title has been modified as follows:*"V***isit 1 Baseline Day 1****"* **Section: 2.** *In the last line of schedule the following specification has been added:* **"*)** visit window of +2 days;" **Section 2.**– *line Ocular and Systemic Medical History*: Delete **"X"** on colum Visit 1 Baseline Day 1. **Section 3.1** – the section has been modified as follows: "The study objective is to assess the efficacy and safety of rhNGF when administered as eye drops to patients with moderate to severe dry eye **and to exploratively evaluate the preliminary efficacy data also in a group of dry eye patients with diagnosis of Primary Sjögren's Syndrome (14)**" **Section 3.2** – *the first sentecce has been nodified as follows:* "This study will be performed at 8/**12** study centers located in the USA**"** **Section 3.3** – the section has been modified to specify the time window for the wash-out: second sentence "Patients will be evaluated at screening visit (day -8), baseline (day 1+**2**), …." Second paragraph "…free artificial tears for a period of 7 days **- 9 days as maximum** (day -8 to day -1+**2**) until the baseline visit (day 1). At the end of the wash out period (day -8 to day -1+**2**),…" **Section: 3.3** *The last paragraph has been modified as follows:* "Following the completion of the **double-blind treatment patients will**		

	be followed up for safety assessments for an additional 12 weeks post treatment and will be evaluated at the end of the safety follow-up period. During the safety follow-up period patients will not use further treatment except preservative free artificial tears provided by the Sponsor three times daily (morning, afternoon, evening).” **Section: 3.3 figure 1** *has been modified to specify a time window for the wash-out period.*  **Section: 4:** *The following paragraphs will be added:* “**The safety and efficacy of rhNGF eye drops will be investigated also in a specific subgroup of patients with hyposecretive dry eye, i.e., patients with dry eye due to primary Sjögren's syndrome (2, 14). To gain information on the safety and efficacy of rhNGF in this subgroup of patients at least sixty (60) patients with a documented diagnosis of Primary Sjögren's Syndrome are out of 300 total patients are needed. It should be noted that patients with this type of dry eye could have already been enrolled based on the inclusion/exclusion criteria of the previous version of the study protocol. This amendment is applied only to set a minimum prespecified number of patients with Primary Sjögren's Syndrome. The nature of the resulting statistical analysis in this subgroup of patients will be explorative.** **Including at least y 60 subjects with documented diagnosis of Primary Sjögren's Syndrome within the total sample size (20%) will have no impact on the initial assumptioms concerning sample size for the following reasons:** • **The previous study (NGF0216), on which sample size assumptions have been based (see section 9.1), reports a similar prevalence of patients with Primary Sjögren's Syndrome in their medical history (~25% in the FAS population).** • **As dry eye due to Sjogren’s syndrome is a hyposecretive form of the disease, the primary endpoint is appropriate for both the whole study population and the subgroup with Sjögren's syndrome”**		

	• **As anticipated, the same patients could have already been enrolled based on the previously applied and approved inclusion/exclusion criteria** **Section 4.1 Inclusion criteria:** *the following criteria has been added as number 6:* "**Subjects with a diagnosis of Primary Sjögren's Syndrome according the American-European Consensus Group Sjögren's Syndrome Criter ia (Appendix 3; must meet either 4 out of 6 total criteria OR 3 out of 4 signs). Note: Subjects who are on systemic (oral) therapy for the treatment of Sjögren's Syndrome must be on stable systemic treatment defined as the same treatment for the immediately prior 90 days."** **Section 4.1 Inclusion criteria**: *general: the numbering of the inclusion criteria is revised accondingly.* **Section 4.2 Exclusion criteria**: *general: the numbering of the exclusion criteria is revised accondingly.* **Section 4.2 Exclusion criteria #4**: *to better explain the sentence has been modified as follows:* "History of severe systemic allergy or **severe** ocular allergy (including seasonal conjunctivitis) or chronic conjunctivitis and/or keratitis other than dry eye" **Section 4.2 Exclusion criteria #9** – *bullet point - b. has been modify as follows:* "b. have a positive result at the urine pregnancy test (**Screening/Baseline Day 1**) or," **Section 4.2 Exclusion criteria #15**: *the sentence as been modified as follows:* "Participation in a clinical trial with a new active substance during the past **60 days** *The following section has been added as section* "**4.3: ELIGIBLE EYE *Process for determining the eligible eye:* assuming that all the inclusion/exclusion criteria are met in both eyes, the worse eye (eligible eye) will be determined at the baseline visit using a stepladder approach, as follows:** 1. **Schirmer's Test (since this is the primary endpoint)-Worse eye determined as eye with lower Schirmer I score. If Schirmer I score is the same in both eyes, worse eye will be determined by NEI score (cornea+conjunctival staining).** 2. **NEI score (cornea+conjunctival staining).** **If all of the above are identical, determination of the worse eye will be based on the Investigator's judgement, then simply use the right eye as the eligible eye."** **Section 4 -** *general: the numbering of the section are revised*		

	accondingly **Section 4.4 RANDOMISATION – [page 28]** *The following paragraphs have been modified as follows:* "Eligible patients will be randomized **in a 1:1:1 ratio** to either rhNGF eye drops solution 20 µg/ml TID (~100 patients) or rhNGF eye drops solution 20 µg/ml BID plus vehicle eye drop solution SID (~100 patients) or vehicle eye drop solution TID **(**~100 patients)." **Randomization will be stratified according to absence/presence of a documented diagnosis of Primary Sjögren's Syndrome to ensure** balanced assignment across treatment groups**.** Each randomized patient will be allocated with randomization number, according to the **stratified** randomization list. Drop outs after randomization will not be replaced." *The following paragraph have been add as last paragraph:* **"The enrollment of patients will be scheduled in order to assure an inclusion of approximately 240 patients wthout Primary Sjögren's Syndrome diagnosis and at least 60 patients with Primary Sjögren's Syndrome. "** **Section 4.5 MASKING** *The third paragraph has been modified as follows:* "**The investigator will be provided with an access, password protected, to the RAVE Randomization and Trial Supply Management system (RAVE RSTM) so only in case of a medical emergency the Investigator can open the treatment allocation for a specific patient.** **Besides also Dompé Pharmacovigilance contact person will be provided with an access, password protected, to the RAVE Randomization and Trial Supply Management system (RAVE RSTM) so if required by the Pharmacovigilance activities the Pharmacovigilance contact person can open the treatment allocation for a specific Patient**." **Section 6.1** **Screening visits - Procedure/Assessments:** *The sentence* following sentence *has been deleted*: "Ocular and Systemic Medical History" **Screening visits - Procedure/Assessments:** *The sentence" Previous ocular and systemic medication" as bben mofided as follows:* **"previous ocular and systemic medication (prior to start the study)"** *The sentence regarding the ocular surface staining has been modified to better clarify the test to be performed*: **"**Ocular surface staining (NEI score **- corneal and conjunctival fluorescein staining)**" **Visit 1 baseline - Procedure/Assessments:**		

	The sentence" Ocular and systemic medication" as bben mofided as follows: **"Previous ocular and systemic medication (prior to start the study"** *The sentence regarding the ocular surface staining has been modified to better clarify the test to be performed:* **"**Ocular surface staining (NEI score **- corneal and conjunctival fluorescein staining)"** *The order of the procedure has been revised to clarify that the patient elegiliby should be performed after the ocular the systemic and ocular assessment:* The following procedures will be performed (order below is mandatory): ➢ Pregnancy test for female patients of childbirth potential ➢ Ocular and systemic medical history ➢ Previous ocular and systemic medications **(prior to the treatment)** ➢ Ocular examination of both eyes: • Assessment by SANDE questionnaire • Assessment by IDEEL questionnaire • Assessment by EQ-5D-3L questionnaire • Assessment of best corrected distance visual acuity (BCDVA) • External Ocular Examination • Schirmer test I (without anesthesia) • Slit-lamp examination (SLE) to assess the eyelid (Meibomian glands), eyelid (erythema), eyelid (edema), lashes, conjunctiva erythema, lens, iris, anterior chamber, corneal horizontal diameter • TFBUT • Ocular surface staining (NEI score – **corneal and conjunctival fluorescein staining**) • Schirmer test II (with anesthesia) • Laser scanning confocal microscopy to assess goblet cells density (only selected sites) • Corneal endothelium and stroma evaluation (only the sites having a confocal microscope will do this type of evaluation) ➢ **Patient eligibility: Inclusion/exclusion criteria evaluation** ➢ **Randomization** ➢ **Study drug dispensation** ➢ **Preservative free artificial tears dispensation** ➢ AE collection **Visit 2 Week 2 - Procedure/Assessments** *The sentence regarding the slit-lamp examination as been modified as follows*: Slit-lamp examination (SLE) to assess the eyelid (Meibomian glands), eyelid (erythema), eyelid (edema), lashes, conjunctiva erythema, lens, iris, anterior chamber, **corneal horizontal diameter.** The sentence regarding the ocular surface staining has been modified to better clarify the test to be performed: **"**Ocular surface staining (NEI score **- corneal and conjunctival fluorescein staining)"**		

	Visit 3 Week 4 - Procedure/Assessments *The sentence regarding the slit-lamp examination as been modified as follows*:Slit-lamp examination (SLE) to assess the eyelid (Meibomian glands), eyelid (erythema), eyelid (edema), lashes, conjunctiva erythema, lens, iris, anterior chamber, **corneal horizontal diameter.** *The sentence regarding the ocular surface staining has been modified to better clarify the test to be performed*: **"**Ocular surface staining (NEI score - **corneal and conjunctival fluorescein staining)"** **Section 6.2:** **Visit 4 Follow up Week 8 - Procedure/Assessments** **Visit 5 Follow up Week 12 - Procedure/Assessments** **Visit 6 Follow up Week 16 - Procedure/Assessments** *The following sentences has been modified as follows:* "Slit-lamp examination (SLE) to assess the eyelid (Meibomian glands), eyelid (erythema), eyelid (edema), lashes, conjunctiva erythema, lens, iris, anterior chamber, **corneal horizontal diameter.** *The following sentences has been modified as follows:* **"**Ocular surface staining (NEI score - **corneal and conjunctival fluorescein staining)"** **Section 6.3.2. Discontinuation procedures [page 49]** *The last bullet point has been modified as follows:* "record in the eCRF any follow-up if the patient is withdrawn for an AE. **AE's should be followed until resolution**." **Section 7.1.3.:** *The last bullet point has been modified as follows:* "Change from baseline in goblet cells density **Vs week 4."** The following section has been added as section **7.1.5** **"7.1.5. Stratification according to absence /presence of Primary Sjögren's Syndrome** • **The primary, secondary, explorative and safety endpoints (see 7.1.1, .7.1.2 7.13 & 7.1.4) will be also evaluated within each stratification subgroup (absence/presence of Primary Sjögren's Syndrome).** **Section 9:** *The first paragraph has been modified has follows:* "**The data collected in this study will be summarized using number of observations, mean, standard deviation (SD), median, minimum, and maximum values for quantitative variables, and frequencies for qualitative variables."** **Section 9.1.:** *The second paragraph, first bullet point has been modified as follows:*"**The probability level (α) for one-sided test is set at 0.025 (see table 12.1.2 at page 298 in Chow et al., 2008) and the power level at approximately 90%."** *The following paragraph has been added as last paragraph:*		

	"**The inclusion of approximately 60 subjects with documented diagnosis of Primary Sjögren's Syndrome within the planned 300 patients will have no impact on the initial study assumptions (Standard Deviation of 10.78 and DELTA of 5.3 mm) because the patients could have been enrolled based on the previous criteria on which sample size was based. Moreover, a similar prevalence of patients with Primary Sjögren's Syndrome has already been reported in the NGF0216 medical history (~25% of patient the FAS population).**" **Section 9.2.** *The first paragraph has been modified as follows:* "**The Screened Population will consist of all patients with the signature of the informed consent, the assignment of a PID number and regardless the completion of all the screening procedures**." *The second paragraph has been modified as follows:* "**The Eligible Population will consist of all patients with all inclusion/exclusion criteria met. Otherwise the patientspatient will be defined as screening failure."** **Section 9.3.** *The formula has been implemented has follows*: **Overall compliance** $= 100 * \frac{(\text{Number of vials dispensed} - \text{Number of unused vials returned})}{3 * (Numbers\ of\ days\ on\ treatment)}$ **Compliance for the eligible eye** $= 100 * \frac{(\text{Number of drops administered to the eligible eye})_{„}}{3*(Numbers\ of\ days\ on\ treatment)}$ **Section 9.4.1.:** *The first paragraph has been modified has follows:* "**The Enrolled Set will consist of all patients who signed the ICF. This analysis set will be used for demographic, baseline and background characteristics."** *The second paragraph has been modified as follows:****Safety Population*** **- The Safety Population (SAF) will consist of all randomized patients who took at least one dose of IP. This analysis set will be used for the safety analysis. Patients will be analyzed according to the treatment received."** *The third paragraphhas been modified has follows:* "***Full Analysis Set*** **- Full Analysis Set (FAS) will consist of all randomized patients who took at least one dose of IP and who have at least one post-baseline efficacy measurement for the primary endpoint. This analysis set will be used for the primary efficacy analysis. Patients will be analyzed according to the randomized treatment."** *The fourth paragraph has been modified as follows:*		

	"Per Protocol Set* - "Per Protocol Set (PP) will consist of all patients in the FAS who fulfil the study protocol requirements in terms of investigational medicinal product intake and collection of primary efficacy data and with no major deviations that may affect study results. This analysis set will be used for supportive efficacy analysis. Patients will be analyzed according to the treatment received.** **Each patient will be coded by the Syneos Health statistician as valid or not valid for the Enrolled Set, SAF, FAS and PP."** **Section 9.4.3.:The third bullet point has been modified as follows:* "**major deviation from** inclusion/exclusion criteria (eligibility violations)." **Section 9.4.4.:** *The paragraph has been modified as follows:* **"Demographic and baseline characteristics will be descriptively summarized per treatment group according to their nature."** **Section 9.5.:** *The paragraph has been modified as follows::* **"Primary endpoint will be analyzed using analysis of variance including only the treatment as main factor followed by pre-planned comparisons from Vehicle and rhNGF dosages according to Williams procedure.In addition, primary endpoint will be summarized using descriptive statistics for continuous variables by treatment and visit. The change from baseline value will also be summarized for all post-baseline visits.** **An explorative sensitivity analysis of primary endpoint will be conducted including in the analysis of variance the absence/presence of diagnosis of Primary Sjögren's Syndrome and its interaction with treatments as covariates. If the interaction term is statistically significant (at the 0.10 level given its explorative nature), the treatment effects within patients with and without Primary Sjögren's Syndrome will be provided.** **Secondary endpoints will be presented by means of appropriate descriptive statistics.** **Changes from baseline in global SANDE score, Schirmer test II, NEI scales, TFBUT, IDEEL, PGIC and EQ-5D-3L scores 4 will be analyzed in a similar manner as the Change from baseline in Schirmer test I (primary endpoint) in order to test treatment effect.** **Difference between treatment groupsgroup (Each active dose vs Placebo), in the percentage of patients who experienced a worsening in SANDE scores and/or NEI score will be tested using a chi-square test.** **Explorative endpoints will be summarized by means of appropriate descriptive statistics. Any statistical testing will be descriptive in nature.**		

	Additional details on the analyses will be provided in the statistical analysis plan." **Section 9.5.1:** *The send and third paragraphs have been modified from:* **"Treatment-emergent** AEs are all events occurring or worsening after the first dose of the IMP**.** **Treatment-emergent** AEs will be summarized by treatment group. The number and percentage of patients with any AE and the number of TEAEs will be tabulated by SOC and PT, seriousness, relationship to treatment and severity. **Individual AEs will be listed in patient data listings."** A new section has been added: **"Section 9.5.3 Subgroup analysis** **Sub-group analyses of primary, secondary and explorative endpoints will be performed on patients with the Sjögren's syndrome for explorative purpose. Statistical details will be reported in the SAP"** **Section 13:Reference 2:** *The reference has been updated as follows* TFOS DEWS II REPORT. Ocul Surf 2017; 15(3):269-283 **Section 13:** *the following reference has been added:"*14. Vitali C, Bombardieri S, Jonsson R, *et al.* Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002; 61:554–558. **Section 14.1:** *the following sentence hasebeen modify as follows: "*Elisa Greco, Clinical Research **Specialist"** *The following section 14.3 has been added: "***Appendix 3 American-European Consensus Criteria for Sjögren's Syndrome"**		

CONTACT INFORMATION

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Table of Contents

List of Abbreviations and Definitions of Terms

ADR	Adverse Drug Reaction
AE	Adverse Event
BCDVA	Best Corrected Distance Visual Acuity
BID	Bis in die
CFR	Code of Federal Regulations
CMC	Carboxymethylcellulose
CRA	Clinical Research Associate
CRO	Contract Research Organization
DE	Dry Eye
DHHS	Department of Health and Human Services
DNA	Deoxyribonucleic
DSUR	Development Safety Update Report
e-CRF/CRF	Electronic/Case Report Form
EDC	Electronic Data Capture
EMA	European Medicine Agency
EQ-5D-3L	EuroQol group 5 Dimensions 3 Level
ETDRS	Early Treatment Diabetic Retinopathy Study
ETV	Early Termination Visit
FAS	Full Analysis set
FDA	Food and Drug Administration
FPI	First Patient In
FPFV	First Patient First Visit
FU	Follow Up
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDEEL	Impact of Dry Eye on Everyday Life
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IUD	Intra Uterine Device
LNGFR	Low-affinity NGF receptor

LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for regulatory activities
NEI	National Eye Institute
NIMP	Non Investigational Medicinal Product
NK	Neurotrophic Keratitis
PI	Principal Investigator
PID	Patient Identification number
PGIC	Patient global Impression of Change
PP	Per Protocol Population
PT	Preferred term
p75NTR	p75 neurotrophin receptor
rhNGF	recombinant human Nerve Growth Factor
RP	Retinitis pigmentosa
SAE	Serious Adverse Event
SAF	Safety population
SANDE	Symptom Assessment in Dry Eye
SAP	Statistical Analysis Plan
SD	Standard Deviation
SID	Semel in die
SLE	Slit-lamp examination
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Advers Event
TFBUT	Tear Film Break-Up Time
TID	Tris in die
TrkA	Tropomyosin receptor kinase A
Vs	Versus
§	Section

1. STUDY SYNOPSIS

CLINICAL STUDY SYNOPSIS:	
Study Number	NGF0118
Title of Study	A 4 weeks, Phase II, multicenter, randomized, double-masked, vehicle-controlled, parallel group study with 12 weeks of follow-up to evaluate safety and efficacy of recombinant human Nerve Growth Factor (rhNGF) eye drops solution versus vehicle, in patients with moderate to severe dry eye (DE).
IND N°	115892
Study Centers (Country)	8-12 study sites in US
Development Phase	Phase II
Objective	The primary objective of this study is to assess the efficacy and safety of rhNGF eye drops at 20 µg/ml concentration administered two or three times daily for 4 weeks in patients with moderate to severe dry eye. The trial is designed to perform dose ranging.
Study Design and Methodology	This is a phase II, multicenter, randomized, double masked, parallel arm, vehicle-controlled trial.
Number of Patients	Eligible patients will be randomized in a 1:1:1 ratio to either rhNGF eye drops solution 20 µg/ml TID (~100 patients) or rhNGF eye drops solution 20 µg/ml BID plus vehicle eye drop solution SID (~100 patients) or vehicle eye drop solution TID (~100 patients). Randomization will be stratified according to absence/presence of a documented diagnosis of Primary Sjögren's Syndrome to ensure balanced assignment across treatment groups. A minimum of 60 patients (20 per group) with Primary Sjögren's Syndrome should be included. The enrollment of patients will be scheduled in order to assure an inclusion of approximately 240 patients without Primary Sjögren's Syndrome diagnosis and at least 60 patients with Primary Sjögren's Syndrome.
Main Inclusion criteria **1.** Male or female aged ≥ 18 years **2.** Patients with moderate to severe dry eye characterized by the following clinical features: a. Corneal and/or conjunctival staining with fluorescein using National Eye Institute (NEI) grading system > 3	

b. SANDE questionnaire >25 mm
c. Schirmer test I (without anaesthesia) >2mm <10 mm/5 minutes
d. Tear film break-up time (TFBUT) < 10 seconds in the worse eye

3. The same eye (eligible eye) must fulfill all the above criteria
4. Patients diagnosed with dry eye at least 6 months before enrolment (current use or recommended use of artificial tears for the treatment of Dry Eye)
5. Best corrected distance visual acuity (BCDVA) score of ≥ 0.1 decimal units (20/200 Snellen value) in both eyes at the time of study enrolment
6. If a female of childbearing potential, have a negative pregnancy test
7. Only patients who satisfy all Informed Consent requirements may be included in the study. The patient and/or his/her legal representative must read, sign and date the Informed Consent document before any study-related procedures are performed. The Informed Consent form signed by patients and/or legal representative must have been approved by the IRB for the current study
8. Patients must have the ability and willingness to comply with study procedures.
9. Primary Sjögren's Syndrome Patients:
   - Patients with a documented diagnosis of Primary Sjögren's Syndrome according the American-European Consensus Group Sjögren's Syndrome Criteria (Appendix 3; must meet either 4 out of 6 total criteria OR 3 out of 4 signs). Note: Subjects who are on systemic (oral) therapy for the treatment of Sjögren's Syndrome must be on stable systemic treatment defined as the same treatment for the immediately prior 90 days.

Main exclusion criteria

1. Inability to speak and understand the local language sufficiently to understand the nature of the study, to provide written informed consent, and to allow the completion of all study assessments;
2. Evidence of an active ocular infection, in either eye
3. Presence of any other ocular disorder or condition requiring topical medication during the entire duration of study
4. History of severe systemic allergy or severe ocular allergy (including seasonal conjunctivitis) or chronic conjunctivitis and/or keratitis other than dry eye
5. Intraocular inflammation defined as Tyndall score >0
6. History of malignancy in the last 5 years
7. Systemic disease not stabilized within 1 month before Screening Visit (e.g. diabetes with glycemia out of range, thyroid malfunction..) or judged by the investigator to be incompatible with the study (e.g. current systemic infections) or with a condition incompatible with the frequent assessment required by the study
8. Patient had a serious adverse reaction or significant hypersensitivity to any drug or chemically related compounds or had a clinically significant allergy to drugs, foods,

amide local anesthetics or other materials including commercial artificial tears, in particular commercial artificial tears containing carboxymethylcellulose (CMC) (in the opinion of the investigator) **9.** Females of childbearing potential (those who are not surgically sterilized or post-menopausal for at least 1 year) are excluded from participation in the study if they meet any one of the following conditions: a. are currently pregnant or, have a positive result at the urine pregnancy test (Screening/Baseline Day 1) or, intend to become pregnant during the study treatment period or, are breast-feeding or, are not willing to use highly effective birth control measures, such as: hormonal contraceptives - oral, implanted, transdermal, or injected - and/or mechanical barrier methods - spermicide in conjunction with a barrier such as a condom or diaphragm or IUD - during the entire course of and 30 days after the study treatment periods **10.** Any concurrent medical condition, that in the judgment of the PI, might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the patient's well-being **11.** Use of topical cyclosporine, topical corticosteroids or any other topical drug for the treatment of dry eye in either eye within 30 days of study enrolment **12.** Contact lenses or punctum plug use during the study (previous use not an exclusion criteria but must be discontinued at the screening visit) **13.** History of drug addiction or alcohol abuse **14.** Any prior ocular surgery (including refractive palpebral and cataract surgery) if within 90 days before the screening visit **15.** Participation in a clinical trial with a new active substance including medical devices during the past 60 days **16.** Participation in another clinical trial study at the same time as the present study	
Test/Reference Product, Dosage and Mode of Administration	Test product is **rhNGF 20 µg/ml**; reference product is **vehicle**. Test and reference will be instilled in both eyes according to the following scheme: **Group 1:** one drop of rhNGF 20 µg/ml will be instilled in both eyes three times daily (every 6-8 hours, e.g. 7:00 am, 02:00 pm; 09:00 pm). **Group 2**: one drop of rhNGF 20 µg/ml will be instilled in both eyes two times daily plus one drop (40 µL) of vehicle will be instilled in both eyes once daily (every 6-8 hours, e.g. 7:00 am, 02:00 pm; 09:00 pm). NB: rhNGF will be instilled in the morning and in the evening while the vehicle will be instilled in the afternoon.

	Group 3: vehicle eye one drop will be instilled in both eyes three times daily (every 6-8 hours, e.g. 7:00 am, 02:00 pm; 09:00 pm). The IMP will be provided in a monthly box containing 28 daily boxes. Each daily box contains three marked vials one for each administration (e.g. 1- Morning, 2- Afternoon and 3- Evening). Together with the IMP monthly box, the patients will be provided with a sufficient number of pipette and adaptors to be used for the administration of the IMP.
Duration of Study	Patients will be evaluated at screening visit (day -8), baseline (day 1+2), week 2 (day 14±2), week 4 (day 28±2) or early exit and week 8 (day 56±2), 12 (day 84±4) and 16 (day 112±7) weeks of follow-up. **Screening Visit (day -8):** all procedure for inclusion will be performed. **Wash-out period (from day -8 to day-1):** 7 +2 days with no further treatment except commercially available preservative free artificial tears. ***NB: the wash-out should not be less than 7 days*** **Treatment:** eligible patients will be randomized 1:1:1 and treated for 4 weeks with either rhNGF eye drops 20 µg/ml TID, rhNGF eye drops 20 µg/ml BID and vehicle SID or vehicle TID. During the treatment period only the experimental IMP is allowed. But, if strictly needed, the patient can use commercially available preservative free artificial tears, provided by Sponsor. **Follow up:** 12 weeks post treatment with no further treatment except commercially available preservative-free artificial tears provided by the Sponsor three times daily. The patient, only if strictly needed, can administer additional drops and must document in the patient's diary the n° of additional drops administered for each eye.Maximum total study duration: 17 weeks.
Study population	Male and female with moderate to severe dry eye will be included. A total of 300 patients will be enrolled. At least 60 out of 300 patients with a documented of Primary Sjögren's Syndrome should be included .
Primary Efficacy Endpoint	**Primary end-point**: 1. Change from baseline in Schirmer I test (without

	anesthesia) Vs week 4.
Secondary Efficacy Endpoints	**Secondary end-points:** 1. Change from baseline in Symptoms questionnaire (SANDE) scores for severity and frequency Vs week 4; 2. Change from baseline in Schirmer II test (with anesthesia) Vs week 4; 3. Change from baseline in Cornea and conjunctiva vital staining with fluorescein (National Eye Institute [NEI] scales) Vs week 4; 4. Change from baseline in Tear Film Break-Up Time (TFBUT) Vs week 4 5. Number of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score ≥ 50% assessed at week 4; 6. Quality of life (Impact of Dry Eye on Everyday Life (IDEEL) questionnaire; 7. Patient global Impression of change (PGIC); 8. EQ-5D-3L.
Exploratory Endpoints	1. Correlation between sign and symptom scores; 2. Proportion and frequency of preservative free artificial tears use (n° drops/day) during the treatment period; 3. Frequency of preservative free artificial tears use (n° drops/day) during the follow up period. 4. Change from baseline in Schirmer I test (without anesthesia) Vs week 2; 5. Change from baseline in Symptoms questionnaire (SANDE) scores for severity and frequency Vs week 2; 6. Change from baseline in Cornea and conjunctiva vital staining with fluorescein (National Eye Institute [NEI] scales) Vs week 2; 7. Change from baseline in Tear Film Break-Up Time (TFBUT) Vs week 2; 8. Number of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score ≥ 50% assessed at week 2; 9. Change from baseline in goblet cells density Vs week

	4.
Safety Endpoint	1. Incidence and frequency of Treatment-emergent adverse events (TEAEs), assessed throughout the study.
Statistical Methods	The data collected in this study will be summarized using number of observations, mean, standard deviation (SD), median, minimum, and maximum values for quantitative variables, and frequencies for qualitative variables. **1) Efficacy analysis** **Primary endpoints** will be analyzed using analysis of variance including only the treatment as main factor followed by pre-planned comparisons from Vehicle and rhNGF dosages according to Williams procedure. In addition, primary endpoint will be summarized using descriptive statistics for continuous variables by treatment and visit. The change from baseline value will also be summarized for all post-baseline visits. An explorative sensitivity analysis of primary endpoint will be conducted including in the analysis of variance the absence/presence of diagnosis of Primary Sjögren's Syndrome and its interaction with treatments as covariates. If the interaction term is statistically significant (at the 0.10 level given its explorative nature), the treatment effects within patients with and without Primary Sjögren's Syndrome will be provided. It will be summarized using descriptive statistics for continuous variables by treatment and visit. The change from baseline value will also be summarized for all post-baseline visits. **Secondary endpoints** will be presented with the appropriate descriptive statistics and inferential statistics appropriate for the nature of variable analyzed will be done in order to test treatment effect. **Explorative endpoints** will be summarized by means of appropriate descriptive statistics. Any statistical testing will be descriptive in nature. **2) Safety analysis** **AEs**

	Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT), using the Medical Dictionary for Regulatory Activities (MedDRA). Individual AEs will be listed in patient data listings. AEs will be summarized by treatment group. The number and percentage of patients with any AE and the number of TEAEs will be tabulated by SOC and PT, seriousness, relationship to treatment and severity. **3) Quality of life analysis** Data recorded in the questionnaires of quality of life will be presented with appropriate descriptive statistics and processed with appropriate inferential test.

2. SCHEDULE OF EVALUATIONS

Study procedures	**Screening (Day-8)**	**Visit 1 Baseline Day 1***	**Visit 2 Week 2**	**Visit 3 End of treatment Week 4[a]**	**Visit 4 follow-up Week 8[a]**	**Visit 5 follow-up Week 12[b]**	**Visit 6 follow-up Week 16[c]**
Informed Consent	X						
Inclusion/Exclusion Criteria	X	X					
Pregnancy Test	X	X					X
Randomization		X					
Demographics	X						
Ocular and Systemic Medical History	X						
Previous Ocular And Systemic Medications	X	X					
SANDE	X	X	X	X	X	X	X
IDEEL	X	X		X	X	X	X
EQ-5D-3L	X	X		X	X	X	X
PGIC				X	X	X	X
BCDVA	X	X	X	X	X	X	X
External Ocular Examination	X	X	X	X	X	X	X
Schirmer test I	X	X	X	X	X	X	X
Slit Lamp Examination	X	X	X	X	X	X	X
TFBUT	X	X	X	X	X	X	X
Fluorescein staining (NEI scale)	X	X	X	X	X	X	X
Schirmer test II		X		X			X
Confocal microscopy to assess goblet cells density [d]		X		X			X
Corneal endothelium and stroma evaluation as per confocal microscopy [e]		X		X			X
Study drug dispensation		X[f]					
Verify patient study medication dosing compliance				X			
Concomitant Ocular And Systemic Medications			X	X	X	X	X
Frequency of preservative free artificial tears use (n° drops/day)			X[g]	X[g]	X[h]	X[h]	X[h]
Check and retrieval of patient's diary			X[i]	X	X	X	X
Record AEs	X	X	X	X	X	X	X

Study procedures	Screening (Day-8)	Visit 1 Baseline Day 1*	Visit 2 Week 2	Visit 3 End of treatment Week 4[a]	Visit 4 follow-up Week 8[a]	Visit 5 follow-up Week 12[b]	Visit 6 follow-up Week 16[c]
***)** visit window of +2 days; **a)** Visit window of ± 2 days; **b)** Visit window of ± 4 days; **c)** Visit window of ± 7 days; **d)** only selected sites; **e)** Only the sites having a confocal microscope will do this type of evaluation; **f)** a monthly box will be given to the patients; **g)** During the treatment period patients can use, if strictly needed, the preservative free artificial tears; **h)** During the follow up period it is allowed to use the preservative free artificial tears**; i)** During the visit 2, week 2, the PI or a delegate must only check if the patient has correctly completed the diary.							

2.1. BACKGROUND INFORMATION

2.1.1. Nerve Growth Factor - Overview

Nerve growth factor (NGF) is a polypeptide essential for the survival and growth of sympathetic and sensory neurons, and for differentiation of neurons in the central nervous system. It binds with at least two classes of receptors: high-affinity tropomyosin receptor kinase A (TrkA), a transmembrane tyrosine kinase, and low-affinity NGF receptor (LNGFR), also known as p75 neurotrophin receptor (p75NTR).
NGF and TrkA are expressed in the anterior segment of the eye (iris, ciliary body, lens, cornea and conjunctiva), and NGF is released in the aqueous humor. Several pieces of experimental evidence suggest that NGF affects all tissues of the anterior ocular segments, playing a crucial role in the physiopathology of several anterior ocular segment diseases.

2.1.2. Chemical And Formulation Data

As recombinant human NGF (rhNGF) production in mammalian cells does not achieve adequate yields, a manufacturing process based on the use of recombinant Escherichia coli (E. coli) has been developed. However, because the biological activity of NGF relies on the formation of three disulfide bonds, and because disulfide bonds cannot occur in the reducing cytosol, the purification and renaturation of NGF produced in E. coli is problematic. Based on the knowledge that the prosequence increases the yield and rate of refolding of NGF, we have developed a manufacturing process starting from proNGF. After expression of proNGF in E. coli, the insoluble protein is isolated in the form of insoluble inactive aggregates (inclusion bodies), solubilized in a strong denaturing agent and subsequently converted into the natural conformation, which is determined by the disulfide bridges present in the natural NGF. Biologically active rhNGF is finally obtained by splitting off the prosequence by enzymatic cleavage. The deoxyribonucleic acid (DNA) sequence of human proNGF has been optimized for E coli expression (codon adjustment) and two changes in the furin cleavage site, R101V and K103A, have been introduced. These two changes are important

to ensure a homogeneous rhNGF preparation during the process with the mature protein starting with serine 105.

2.1.3. Rationale for rhNGF therapy in patients with dry eye

Dry eye is a chronic inflammatory condition of the ocular surface with severe symptoms and visual impairment, leading to worse efficiency to perform duties for an average of 184 work days and resulting in an average loss of productivity estimated in 5,000USD per year per patient (1).

Dry eye results from systemic diseases (Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, Stevens-Johnson syndrome, thyroid disease, Bell's palsy), ocular conditions (Meibomian gland dysfunction, blepharitis, ocular rosacea, corneal dystrophies), elective surgeries (refractive surgery, blepharoplasty), eyelid conditions (lagophthalmos, entropion/ectropion), cranial surgeries, side effects of drugs (antihistamines, diuretics, beta-blockers), ocular injuries and burns, chemotherapy and radiation, aging, menopause, etc. (2).

Dry eye pathogenesis is multifactorial; however, a number of common mechanisms can be identified: (i) chronic inflammation of the conjunctiva; (ii) decrease of ocular surface sensitivity; (iii) impairment of quantity of tears and/or quality of the tear film, including tear film hyperosmolarity; (iv) changes of conjunctival epithelium with squamous metaplasia and decrease of goblet cells density; (v) corneal epithelium damage.

Until now, treatment has been limited to the use of artificial tears to temporarily improve lubrication of the ocular surface, or the use of steroids to decrease the inflammatory reaction. However, chronic use of steroids is associated with severe complications such as cataract and glaucoma (2). Cyclosporine eye drop therapy for dry eye patients has been approved in the United States but not in Europe. This drug seems to affect only inflammation and tear film production, without any effect on ocular surface sensitivity or the corneal epithelium. On the other hand, experimental and clinical evidence suggests that NGF may affect all the pathogenic mechanisms of dry eye, potentially restoring ocular surface homeostasis (3).

Indeed, several studies have shown that NGF is involved in the regulation of tear film production. In fact, NGF, TrkA and p75, as well as other neurotrophins (NTs) and related receptors, are expressed by the rat lacrimal gland tissue; moreover, NGF has been quantified in human tears, indicating that NGF is basally released by the lacrimal gland (4,5,6). These data suggest that NGF may play a role in the maintenance of the tear film and in its alterations in drying ocular surface diseases. Specifically, considering that NGF potentially affects all the components of the ocular surface (cornea, conjunctiva, lacrimal gland, and sensory innervation), it might play an important role during dry eye disease. In line with this hypothesis: 1) NGF eye drop administration in a dog experimental model of dry eye increases tear production, conjunctival goblet cell density and corneal transparency (7, 2), an increased tear concentration of NGF has been reported in patients affected by keratoconjuctivita sicca

(8;9), NGF stimulates glycoconjugate secretion by conjunctival goblet cells, without affecting cell proliferation (10).

2.2. A SUMMARY OF CLINICAL DATA

rhNGF has been already studied in healthy volunteers and in different subject populations.
In the completed Phase I study in healthy volunteers (study NGF0112), a total of 58 subjects (out of 74 enrolled) were treated with single and multiple dose of different concentrations of rhNGF eye drops showing a good safety profile.
Furthermore, a Phase I/II multicenter, double-masked, vehicle controlled study to evaluate the safety and efficacy of rhNGF at 10 and 20 µg/mL six times a day in 174 patients with stage 2 and 3 of Neurotrophic Keratitis NK (study NGF0212) was completed in 2015 demonstrating that rhNGF was very well tolerated and effective in patients with NK. A successful confirmatory study (NGF0214) was completed in 2016 and marketing authorization for rhNGF 20 µg/mL eye drops has been granted by EMA in July 2017 for treatment of moderate to severe NK.
In addition to NK, rhNGF eye drops have been evaluated in a Phase I/II study in retinitis pigmentosa (RP) patients at the doses of 60 and 180 µg/mL (NGF0113), and in a phase I/II study in glaucoma at the dose of 60µg/mL (NGF0314). An open arm, uncontrolled study showed that 4 weeks treatment with rhNGF eye drops at 20 µg/mL and 4 µg/mL concentrations was safe and effective in improving symptoms, corneal staining and tear function in patients with severe dry eye disease as compared to baseline (NGF0213). These results prompted to the conduction of two additional phase II RCTs in patients with dry eye disease (NGF0216) and in patients with ocular discomfort symptoms following refractive surgery (NGF0116) which confirmed the favourable tolerability profile of rhNGF eye drops at a concentration of 20 µg/mL up to 6 times daily for 8 weeks.
In the double-masked vehicle-controlled Phase II study NGF0216 no major differences were observed in term of efficacy when comparing the two regimens (6 vs. 2 times/day) and treatment durations (8 vs. 4 weeks) in a subset of patients with similar characteristics (hyposecretive dry eye with Schirmer test <10mm/5min).
The results of these two studies in dry eye disease patients, as well as the results on reflex tear secretion obtained in the neurotrophic keratitis trials NGF0212 and NGF0214, suggest that the rhNGF may be a safe and effective treatment for patients with hyposecretive dry eye disease.
In all studies rhNGF was well tolerated and the reported ocular AEs were generally transient and mostly mild and moderate in intensity during the controlled treatment period and the follow-up period.
Only moderate and transient ocular AEs possibly related to rhNGF administration were reported.
In the Phase I study in healthy volunteers of Japanese ethnicity (study NGF0117) a total of 30 subjects were enrolled. 20 subjects were treated with single dose of rhNGF (formulation containing L-methionine as excipient) at concentration 20 µg/mL and a total of 10 subjects were treated with placebo. During the studyno adverse events occurred. Single and multiple doses of rhNGF delivered

topically as eye drops were safe and well tolerated by healthy subjects of Japanese ethnicity. No clinically important changes in ECG were observed after dosing with rhNGF. There was no apparent relationship between treatment and plasma rhNGF levels, and this study did not give any indication for an immunogenic potential of rhNGF in humans after ophthalmic treatment.

2.3. STUDY RATIONALE

The data reported above, together with the evidence of rhNGF eye drop effectiveness in the treatment of patients affected by corneal epithelial defects and ulcers, make rhNGF a strong candidate for the treatment of dry eye disease (11, 12, 13).

As part of the development plan, the present study was designed in order to evaluate the efficacy and safety of rhNGF eye drops 20 µg/mL in patients with moderate to severe dry eye.

For additional information regarding the development of rhNGF, please consult the current IB.

2.3.1. Risk assessment/benefit evaluation

The study is considered a low risk interventional trial. It is conducted with a dose of medicinal product already tested and already authorized in some European countries and recently by FDA for NK treatment.
The study is conducted in severe to moderate dry eye, a disease not approved, however 2 preliminary clinical studies were already conducted in patients with dry eye demonstrating that rhNGF is very well tolerated in this condition.
The risk of this study is comparable to the risk of the standard of care, in fact the dose proposed in this protocol is rhNGF 20 µg/mL three drops per day (both eyes), which is well below the dose approved for the treatment of NK (rhNGF 20 µg/mL six drops/eye per day).
Considering what is discussed above no particular safety risks are foreseen with respect to the safety profile of the marketed product (OXERVATE® 20 µg/mL).

The patients with dry eye participating in this study may potentially benefit from the application of rhNGF for 28 days.

The following potential study risks were evaluated:

1) Participant well-being e.g.- risk-benefit balance - burden of study visits
2) Lifestyle requirements- Study specific procedures which carry risk -additional to standard care (es: week of run in)
3) Complexity of study procedures
4) Education, training, experience and resources of all investigator site staff in GCP and study procedures

5) Manufacture and distribution of the product(s), storage at the study site (e.g. availability of Frezeer at the study sites).

The details will be described in the Risk Management Plan.

2.3.2. Description of the Investigational Product

The investigational medicinal product (IMP) consists of a sterile isotonic solution for ocular administration, containing rhNGF 20 µg/mL (containing L-methionine as excipient) as drug substance.

The matching placebo vehicle consists of a sterile isotonic solution (containing L-methionine as excipient).

Further information are given in paragraph 5.

3. OVERALL STUDY DESIGN AND INVESTIGATIONAL PLAN

3.1. STUDY OBJECTIVES

The study objective is to assess the efficacy and safety of rhNGF when administered as eye drops to patients with moderate to severe dry eye and to exploratively evaluate the preliminary efficacy data also in a group of dry eye patients with diagnosis of Primary Sjögren's Syndrome(14).

3.2. STUDY ADMINISTRATIVE STRUCTURE

This study will be performed at 8-12 study centers located in the USA. At each study center, the Principal Investigator (PI) will be responsible for ensuring that the investigation is conducted according to the signed Investigator agreement, the protocol, GCP guidelines, and local regulations.

The PI at each study center will be responsible for the management of the study, which will consist of maintaining the study file and the patient records, corresponding with the IRB, and completing the case report forms (eCRFs) and reporting SAEs within 24 hours of initial awareness.
The PI is responsible for supervising any individual or party to whom the investigator delegates trial related duties and functions conducted at the trial site.
If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

3.3. OVERALL STUDY DESIGN

This is a phase II, multicenter, randomized, double masked, vehicle controlled, parallel group study designed to perform dose ranging and evaluate efficacy of rhNGF eye drops at 20 µg/mL concentration administered two or three times daily for 4 weeks in patients with moderate to severe dry eye.
Patients will be evaluated at screening visit (day -8), baseline (day 1+2), week 2 (day 14±2), week 4 (day 28±2) or early withdrawal and week 8 (day 56±2), week 12 (day 84±4), week 16 (day 112±7) of follow up.

During the screening (day -8) all procedures for inclusion will be performed. From the day of screening the patients will stop any kind of further treatment, except commercially available preservative free artificial tears for a period of 7 days and 9 days as maximum (day -8 to day -1+2) until the baseline visit (day 1). At the end of the wash out period (day -8 to day -1+2) , patients meeting the entry criteria for this study will be randomized 1:1:1 and treated for 4 weeks with either rhNGF eye drops 20 µg/mL TID, rhNGF eye drops 20 µg/mL BID and vehicle SID or vehicle TID.

During the 4 weeks of masked treatment only the administration of IMP it is allowed. Nevertheless, if strictly needed, the patient can take preservative free artificial tears (provided by the Sponsor). The use (n° drops/day) of preservative free artificial tears will be clearly documented in a patient's diary and in the eCRF.

Following the completion of the double-blind treatment patients will be followed up for safety assessments for an additional 12 weeks post treatment and will be evaluated at the end of the safety follow-up period. During the safety follow-up period patients will not use further treatment except preservative free artificial tears provided by the Sponsor three times daily (morning, afternoon, evening).
The use of preservative free artificial tears will be clearly documented in a patient's diary and in the eCRF.
The total duration of the study is 17 weeks.

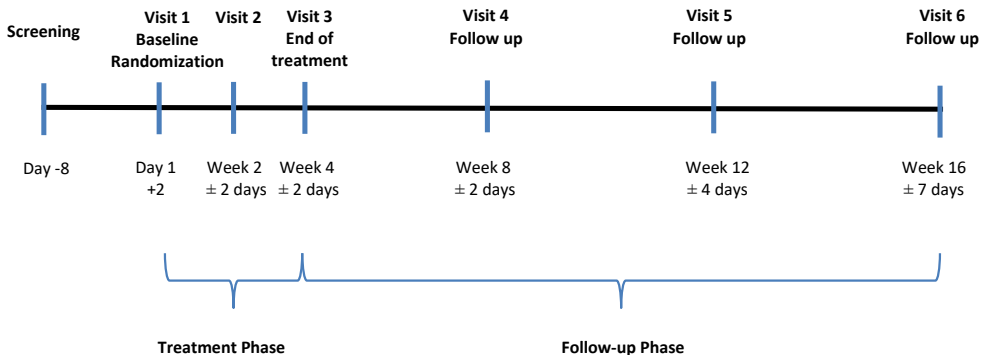

Figure 1:Study duration

3.3.1. Rationale for Selection of dose, control group and treatment schedule in the study

The dose proposed in this study (rhNGF 20 µg /mL) has already been tested both in heathy volunteers for five consecutive days (NGF0112 and NGF0117) and in patients affected by several ocular surface diseases, including dry eye.

rhNGF 20 µg /mL (one drop in each eye six times daily for 8 weeks), was also tested in the Phase I/II of the NK studies (NGF0212 and NGF0214), dry eye (NGF0216) and in patients after cataract and refractive surgery (NGF0116).

rhNGF 20 µg/mL administered two times daily, demonstrated to be safe and well tolerated (NGF0213) will also ensure the lubrification of the ocular surface in the present study where the use of artificial tears will be not allowed during the treatment period.

Higher doses of rhNGF (up to 180 µg /mL) were administrated to patients with diseases of the back of the eye, such as retinitis pigmentosa (Study NGF0213) for up to 168 days.

The 20 µg/ml concentration of rhNGF is well sustained by the current manufacturing process and is the lowest used in a commercial formulation.

A dose regimen of 2 or 3 drops per day of rhNGF eye drops and a treatment duration of 4 weeks have been selected based on the results of the previous clinical trials described above.

The administration of a total of 3 drops per day for all the study arms has been chosen to guarantee to patients randomized to the vehicle arm to have the minimum amount of lubrication that is compatible with symptoms' relief. A double-blind study design was adopted to minimize systematic bias. Randomization is expected to minimize patient selection bias and increase baseline comparability between treatment groups. The use of placebo control is critical to the study design for, providing an accurate estimate of the additive benefit of pharmacotherapy.

The use of the drug's vehicle as placebo helps in making the latter as indistinguishable from the rhNGF solution.

Patients with insufficient therapeutic response, tolerability issues, or worsening of symptoms may be discontinued at any time during the study.

4. SELECTION OF STUDY POPULATION

Male and female ≥ 18 years with moderate to severe dry eye will be included. A total of 300 patients will be enrolled.
The safety and efficacy of rhNGF eye drops will be investigated also in a specific subgroup of patients with hyposecretive dry eye, i.e., patients with dry eye due to primary Sjögren's syndrome (2, 14). To gain information on the safety and efficacy of rhNGF in this subgroup of patients at least sixty (60) patients with a documented diagnosis of Primary Sjögren's Syndrome are out of 300 total patients are needed. It should be noted that patients with this type of dry eye could have already been enrolled based on the inclusion/exclusion criteria of the previous version of the study protocol. This amendment is applied only to set a minimum prespecified number of patients with Primary Sjögren's Syndrome. The nature of the resulting statistical analysis in this subgroup of patients will be explorative.
Including at least y 60 subjects with documented diagnosis of Primary Sjögren's Syndrome within the total sample size (20%) will have no impact on the initial assumptioms concerning sample size for the following reasons:

- The previous study (NGF0216), on which sample size assumptions have been based (see section 9.1), reports a similar prevalence of patients with Primary Sjögren's Syndrome in their medical history (~25% in the FAS population).
- As dry eye due to Sjogren's syndrome is a hyposecretive form of the disease, the primary endpoint is appropriate for both the whole study population and the subgroup with Sjögren's syndrome.
- As anticipated, the same patients could have already been enrolled based on the previously applied and approved inclusion/exclusion criteria.

4.1. INCLUSION CRITERIA

To be eligible for inclusion into this study, each patient must fulfil the following inclusion criteria:

1. Male or female aged ≥ 18 years
2. Patients with moderate to severe dry eye characterized by the following clinical features:
    a. Corneal and/or conjunctival staining with fluorescein using National Eye Institute (NEI) grading system > 3
    b. SANDE questionnaire >25 mm
    c. Schirmer test I (without anaesthesia) >2 mm <10 mm/5 minutes
    d. Tear film break-up time (TFBUT) < 10 seconds in the worse eye
3. The same eye (eligible eye) must fulfill all the above criteria

4. Patients diagnosed with dry eye at least 6 months before enrolment (current use or recommended use of artificial tears for the treatment of Dry Eye)

5. Best corrected distance visual acuity (BCDVA) score of ≥ 0.1 decimal units (20/200 Snellen value) in both eyes at the time of study enrolment

6. If a female of childbearing potential, have a negative pregnancy test

7. Only patients who satisfy all Informed Consent requirements may be included in the study. The patient and/or his/her legal representative must read, sign and date the Informed Consent document before any study-related procedures are performed. The Informed Consent form signed by patients and/or legal representative must have been approved by the IRB for the current study

8. Patients must have the ability and willingness to comply with study procedures.

9. Primary Sjögren's Syndrome Patients:
   - patients with a documented diagnosis of Primary Sjögren's Syndrome according the American-European Consensus Group Sjögren's Syndrome Criteria (Appendix 3; must meet either 4 out of 6 total criteria OR 3 out of 4 signs). Note: Subjects who are on systemic (oral) therapy for the treatment of Sjögren's Syndrome must be on stable systemic treatment defined as the same treatment for the immediately prior 90 days.

4.2. EXCLUSION CRITERIA

Patients who meet any of the following criteria are NOT eligible for inclusion in the study:

1. Inability to speak and understand the local language sufficiently to understand the nature of the study, to provide written informed consent, and to allow the completion of all study assessments

2. Evidence of an active ocular infection, in either eye

3. Presence of any other ocular disorder or condition requiring topical medication during the entire duration of study

4. History of severe systemic allergy or severe ocular allergy (including seasonal conjunctivitis) or chronic conjunctivitis and/or keratitis other than dry eye

5. Intraocular inflammation defined as Tyndall score >0

6. History of malignancy in the last 5 years

7. Systemic disease not stabilized within 1 month before Screening Visit (e.g. diabetes with glycemia out of range, tyroid malfunction..) or judged by the investigator to be incompatible with the study (e.g. current systemic infections) or with a condition incompatible with the frequent assessment required by the study

8. Patient had a serious adverse reaction or significant hypersensitivity to any drug or chemically related compounds or had a clinically significant allergy to drugs, foods, amide local anesthetics or other materials including commercial artificial tears, in particular commercial artificial tears containing carboxymethylcellulose (CMC) (in the opinion of the investigator)

9. Females of childbearing potential (those who are not surgically sterilized or post-menopausal for at least 1 year) are excluded from participation in the study if they meet any one of the following conditions:

a. are currently pregnant or,
b. have a positive result at the urine pregnancy test (Screening/Baseline day 1) or,
c. intend to become pregnant during the study treatment period or,
d. are breast-feeding or,
e. are not willing to use highly effective birth control measures, such as: hormonal contraceptives - oral, implanted, transdermal, or injected - and/or mechanical barrier methods - spermicide in conjunction with a barrier such as a condom or diaphragm or IUD - during the entire course of and 30 days after the study treatment periods.

10. Any concurrent medical condition that, in the judgment of the PI, might interfere with the conduct of the study, confound the interpretation of the study results, or endanger the patient's well-being

11. Use of topical cyclosporine, topical corticosteroids or any other topical drug for the treatment of dry eye in either eye within 30 days prior to study enrolment

12. Contact lenses or punctum plug use during the study (previous use not an exclusion criteria but must be discontinued at the pre-screening visit)

13. History of drug addiction or alcohol abuse

14. Any prior ocular surgery (including refractive palpebral and cataract surgery) if within 90 days before the pre-screening visit

15. Participation in a clinical trial with a new active substance including medical devices during the past 60 days

16. Participation in another clinical trial study at the same time as the present study

4.3. ELIGIBLE EYE

Assuming that all the inclusion/exclusion criteria are met in both eyes, the worse eye (eligible eye) will be determined **at the baseline visit using** a stepladder approach, as follows:

1. Schirmer's Test (since this is the primary endpoint)-Worse eye determined as eye with lower Schirmer I score. If Schirmer I score is the same in both eyes, worse eye will be determined by NEI score (cornea+conjunctival staining).
2. NEI score (cornea+conjunctival staining).

If all of the above are identical, determination of the worse eye will be based on the Investigator's judgement, then **simply use the right eye** as the eligible eye.

4.4. ASSIGNMENT OF PATIENT NUMBER

Each patient who provides written consent to participate in this study will be assigned a unique 5-digit PID number (e.g. 01-001) consisting of a 2-digit study center number followed by the 3-digit screening number assigned sequentially by each study center, from 001 to 300.

4.5. RANDOMISATION

Eligible patients will be randomized in a 1:1:1 ratio to either rhNGF eye drops solution 20 µg/ml TID (~100 patients) or rhNGF eye drops solution 20 µg/ml BID plus vehicle eye drop solution SID (~100 patients) or vehicle eye drop solution TID (~100patients).

Randomization will be stratified according to absence/presence of a documented diagnosis of Primary Sjögren's Syndrome to ensure balanced assignment across treatment groups.

Each randomized patient will be allocated with randomization number, according to the stratified randomization list. Drop outs after randomization will not be replaced.

Randomization list as well as associated kit numbers will be be generated by a member of Syneos Health Biostatistics department, not involved in the conduct of the study.
Patients will be assigned to treatment in numerical order. A tear-off label from the kit box, with the kit number, will be attached to the investigational product dispensing log.

The enrollment of patients will be scheduled in order to assure an inclusion of **approximately 240 patients** without Primary Sjögren's Syndrome diagnosis **and at least 60 patients** with Primary Sjögren's Syndrome.

4.6. MASKING

The identity of the treatments will remain unknown to the patient, Investigator, site staff and Sponsor's clinical research personnel until the study is unmasked for the final statistical analysis (after data base lock) except in case of specific events that will require unmasking of the patient.

The vials containing rhNGF (20 µg/ml) or vehicle will be identical in appearance, and the contents of the vials will be indistinguishable. All staff directly involved in the analysis of study results will remain masked to treatment assignments while the study is in progress.

A list of sequential kit numbers will be generated by a member of the Syneos Health not involved in the conduct of the study. Each kit number will be randomly associated with a treatment group. Patients will be assigned to treatment in numerical order. A tear-off label from the kit box, with the kit number, will be attached to the investigational product dispensing log.

The investigator will be provided with an access, password protected, to the RAVE Randomization and Trial Supply Management system (RAVE RSTM) so only in case of a medical emergency the Investigator can open the treatment allocation for a specific patient.
Besides also Dompé Pharmacovigilance contact person will be provided with an access, password protected, to the RAVE Randomization and Trial Supply Management system (RAVE RSTM) so if required by the Pharmacovigilance activities the Pharmacovigilance contact person can open the treatment allocation for a specific Patient.

In the event of a medical emergency where the knowledge of patient treatment is required to provide the patient with appropriate care, Investigators will have the possibility to unmask the treatment assignment for a specific patient. The Investigators are encouraged to contact Syneos Health staff before becoming unmasked if there is sufficient time.

If the Investigator becomes unmasked for any reason, this information will be recorded on source data and in the eCRF of the study, specifying the date and the reason.

Unmasking events will be recorded and reported in the final study report.

5. STUDY MEDICATION

5.1. DESCRIPTION OF PRODUCT

5.1.1. Presentation of Non Investigational Medicinal Product (NIMP)

TEST PRODUCT NIMP	Blink® Tears
Pharmaceutical form	Eye Drops Solution
Administration	One drop of Blink® Tears will be instilled in both eyes during the 4 weeks of masked treatment, only if strictly needed by the patient. One drop of Blink® Tears will be instilled in both eye TID (morning, afternoon and evening) during the 12 weeks of follow up. The patient, only if strictly needed, can administer additional drops and must document in the patient's diary the n° of additional drops administered for each eye.
Administration route	Ocular

5.1.2. Presentation of Investigational Medicinal Product

TEST PRODUCT IMP	Recombinant human nerve growth factor (rhNGF), containing L-methionine as excipient (20 µg/mL) and/or Placebo vehicle, containing L-methionine as excipient (Vehicle vials).
Manufacturer active substance	Dompé Farmaceutici S.p.A., Italy

Manufacturer finished product	Bulk drug product is manufactured by Patheon, part of Thermo Fisher Scientific -Italy. Secondary packaging and labelling is performed by AndersonBrecon Inc.- PCI USA
Pharmaceutical form	Eye drops sterile buffered aqueous solution
Dose	Test and reference will be instilled in both eyes according to the following scheme: **Group 1**: one drop of rhNGF 20 µg/ml will be instilled in both eyes three times daily (every 6-8 hours, e.g. 7:00 am, 02:00 pm; 09:00 pm). **Group 2**: one drop of rhNGF 20 µg/ml will be instilled in both eyes two times daily plus one drop (40 µL) of vehicle will be instilled in both eyes once daily (every 6-8 hours, e.g. 7:00 am, 02:00 pm; 09:00 pm). NB: rhNGF will be instilled in the morning and in the evening while the vehicle will be instilled in the afternoon. **Group 3**: vehicle eye one drop will be instilled in both eyes three times daily (every 6-8 hours, e.g. 7:00 am, 02:00 pm; 09:00 pm).
Administration route	Ocular

5.2. FORMULATION AND PACKAGING

The Investigator will be provided with a subject monthly box, containing 4 weekly boxes, containing 7 daily boxes. Each daily box contains three marked vials (e.g. 1- Morning, 2- Afternoon and 3- Evening) of frozen IMP solutions (-20 ± 5°C) containing:

- rhNGF, at concentrations of 20 µg /mL, and/or
- vehicle (placebo).

Together with the IMP monthly box, the patients will be provided with a sufficient number of pipette and adaptors to be used for the administration of the IMP.
Pipette and adaptors will be provided separately in single sterile polyethylene packages and may be kept at room temperature.
The pipette is used with an adaptor consisting of a connecting device with dual connections: one end for the pipette and one end for the vial.
The patient will need to:

1. Put the adaptor on the top of the vial (after removing the plastic seal) by piercing the septum
2. Put the pipette on adaptor inlet
3. Draw the solution contained in the vial with the pipette until this reaches its predetermined capacity
4. Remove the pipette and use it as a dropper to administer one drop of IMP into each eye.

5.2.1. Labeling

5.2.1.1. NIMP Secondary packaging, single pane label for single vial (Blink® Tears)

Line No.	Text
1	NGF0118
2	Dompé farmaceutici s.p.a
3	Blink® Tears
4	Unique Patient N° □□-□□□
5	Eye drops solution
6	To be used ONLY during the masked treatment*
7	FOR OCULAR USE ONLY- LEAFLET: information for user
8	For clinical trial use only

* the patient can use the Blink ® Tears during the masked treatment only if strictly needed according the product leaflet

Line No.	Text
1	NGF0118
2	Dompé farmaceutici s.p.a
3	Blink® Tears
4	Unique Patient N° □□-□□□
5	Eye drops solution
6	To be used ONLY during the Follow up period*
7	Morning/afternoon/evening
8	FOR OCULAR USE ONLY- LEAFLET: information for user
9	For clinical trial use only

* the patient must use the Blink ® Tears during the Follow up period, three times daily (morning, afternoon and evening)

5.2.1.2. Primary packaging, single pane label for single vial (rh-NGF or Vehicle)

Line No.	Text	Comments
1	NGF0118	
2	Dompé farmaceutici s.p.a	
3	rhNGF 20 µg /ml and/or Vehicle	
4	Administration eye: RIGHT and LEFT	
6	Eye drops solution	
7	Batch: <vvvv>	Codified batch
8	Kit XXXX *	Format of kit no.: "XXXX"
10	Morning/afternoon/evening**	
13	**CAUTION: New Drug-Limited by Federal (or United States) law to investigational use**	

* The number of KIT will be reported according to the randomization list that will be generated
** Each vial will be a marked vial, one for each administration: morning, afternoon, evening. The vial will be a coloured vial one colour for each administration as follow: White-morning, yellow-afternoon and light blu-evening.

5.2.1.2. Secondary packaging, single pane label for daily box (3 marked vials of rh-NGF and/or Vehicle)

Line No.	Text	Comments
1	NGF0118	
2	Dompé farmaceutici s.p.a	
3	rhNGF 20 µg /ml and/or Vehicle	
4	Administration eye: RIGHT and LEFT	
6	Eye drops solution	
7	Batch: <vvvv>	Codified batch
8	Kit XXXX *	Format of kit no.: "XXXX"
9	Store in a refrigerator at 2-8 °C (36°F to 46°F) or at room temperature not exceeding 12 hours	
10	Do not shake	
11	Keep out of reach of children	
12	**CAUTION: New Drug-Limited by Federal (or United States) law to investigational use**	

* The number of KIT will be reported according to the randomization list that will be generated

5.2.1.3. Tertiary packaging, single panel label for weekly box (7 daily boxes)

Line No.	Text	Comments
1	NGF0118	
2	Dompé farmaceutici s.p.a	
3	rhNGF 20 µg /ml and/or Vehicle	
4	Administration eye: RIGHT and LEFT	
6	Eye drops solution	
7	Batch: <vvvv>	Codified batch
8	Kit XXXX *	Format of kit no.: "XXXX"
9	Store in a refrigerator at 2-8 °C (36°F to 46°F) for 7 days	
10	Do not shake	
11	Keep out of reach of children	
12	**CAUTION: New Drug-Limited by Federal (or United States) law to investigational use**	

* The number of KIT will be reported according to the randomization list that will be generated.

5.2.1.4. Quaternary packaging, tear- off label monthly box (4 weekly boxes, 28 days of treatment

Line No.	Text	Comments	Tear Off part of the label
1	Protocol no.: NGF0118		To be enclosed
2	Sponsor: Dompé farmaceutici s.p.a, Via Santa Lucia, 6 - 20122 Milano, Italy		To be enclosed
3	rhNGF 20 µg /ml and/or Vehicle		To be enclosed
4	Eye drops solution		
5	Contains 4 weekly boxes. One of each contains 7 daily boxes that contains 3 marked vials		
6	Directions for use: refer to dosing instructions		
4	Administration eye: RIGHT and LEFT	The administration will be according to the randomization list: Active for group 1; Active/Placebo for group 2 and Placebo for group 3.	To be enclosed
7	Batch: <vvvv>	Codified batch	To be enclosed
8	Kit XXXX	Format of kit no.: "XXXX"	To be enclosed
9	Unique Patient N° □□-□□□		To be enclosed
10	Store in a freezer at -20°C +/- 5° C		
11	Do not shake		
12	Keep out of reach of children		
13	For clinical trial use only		
14	**CAUTION: New Drug-Limited by Federal (or United States) law to investigational use**		

5.3. STORAGE AND HANDLING OF IMP

The Pharmacist and/or Investigator will be responsible for receipt, proper storage, and usage of study drug, as well as for the IMP distribution, collection of used and unused vials and final disposal of the remaining IMP.

The investigational product must be stored at -20 ± 5 °C at the investigational sites, in an appropriate locked room accessible only to the pharmacist, the Investigator, or a duly designated person.

A temperature probe and data logger will accompany the drug on shipment. It is essential that the investigational sites will verify the temperature excursion during shipment vs. the acceptable storage conditions, in order to identify potential stability concerns during shipment. These must be immediately communicated to the Sponsor that will decide upon appropriate actions to be taken. The IMP will be stored in a locked place, sheltered from light. The vials will be not shaken since agitation of vials may cause foaming and/or particle formation.

On Day 1 (baseline visit), the study personnel will give to the patient the monthly boxes containing the study medications

Patient should bring the study medication, one monthly box, at home as soon as possible and immediately store it in a freezer at -20 ± 5 °C.

The weekly box must be kept at 2-8°C for 7 days protected from light; the daily box can be kept at room temperature, before the patient will use the single vial for each instillation (both eyes) as long as 12 hours are not exceeded. Agitation of vials may cause foaming and/or particle formation. Drug preparation and administration instructions will be provided separately to the site and to the patients.

Together with the IMP monthly box, the patient will also receive a separate kit of vial adapters (one per vial), pipettes (1 per vial) and disinfectant wipes (1 per vial).

IMP eye drops solution instruction will be provided to patients.

Patients will use one vial to instill one drop in both eyes (**group 1**: rhNGF TID; **group 2**: rhNGF BID and vehicle SID; **group 3**: vehicle TID) between 7 AM and 9 PM (every 6-8 hours) for 4 weeks .

The IMP contains L-methionine as an excipient. The contents of each vial are for the daily administration to both eyes only. After the last administration the used vial should be returned to the original medication box and is not to be reused.

Any deviations from the recommended storage conditions should be immediately reported by the pharmacist to the Sponsor and Investigator, and the use of the drug should be suspended until they have given authorization for its continued use. The IMP supplies are to be used only in accordance with this protocol. The Investigator will not use any drug samples for other purposes (e.g., treating patients or deviating from the protocol with regard to dose regimen, duration of treatment, etc.). Under no circumstances will the Investigator give any drug samples to a third party.

5.4. DOSE, ROUTE AND SCHEDULE OF IMP ADMINISTRATION

5.4.1. Administration route

The Administration route is ophthalmic, the first administration is to be applied by investigator at site.

5.4.2. Dose regimen

In all patients both eyes will be treated for a period of 4 weeks.

The dosing scheme of the different study groups is summarized below:

Group 1: one drop of rhNGF 20 µg/ml will be instilled in both eyes three times daily (every 6-8 hours, e.g. 7:00 am, 02:00 pm; 09:00 pm).

Group 2: one drop of rhNGF 20 µg/ml will be instilled in both eyes two times daily plus one drop (40 µL) of vehicle will be instilled in both eyes once daily (every 6-8 hours, e.g. 7:00 am, 02:00 pm; 09:00 pm).

NB: rhNGF will be instilled in the morning and in the evening while the vehicle will be instilled in the afternoon.

Group 3: vehicle eye one drop will be instilled in both eyes three times daily (every 6-8 hours, e.g. 7:00 am, 02:00 pm; 09:00 pm).

During the 4 weeks of masked treatment only the administration of IMP is allowed. Nevertheless, if strictly needed, the patient can take a preservative free artificial tears (provided by the Sponsor). The use (n° drops/day) of preservative free artificial tears will be clearly documented in a patient's diary and in the eCRF.

Both the patients and the investigator will be masked to the study treatment.
Information about the study drug administration, and comments, will be recorded on the appropriate page of the eCRF.

5.5. ACCOUNTABILITY OF THE IMP

The Pharmacist and/or Investigator will confirm the receipt of the IMP supply in writing by signing and dating standard drug accountability forms.

At the week 4 (end of treatment visit) the patient will return the used or unused study boxes/vials to the Investigator.

The Pharmacist and/or Investigator will keep a cumulative inventory and dispensing records, and will maintain all supplies under adequate security.

An accurate drug disposition record will be kept, specifying the date and amount dispensed to each patient.

Adequate record of receipt and use or loss of drug will be retained. This inventory record must be available for inspection by the Sponsor and regulatory inspection at any time. Copies of this record will be provided to the Sponsor by Syneos Health throughout the duration of the study.

At the scheduled visit, the patient diary should be reviewed by the Investigator with the patient for completeness. Missing information should not be provided during the diary check but reported as missing.

At the conclusion of the study, and during the course of the study, the Investigator will complete the drug accountability forms. Partially used or unused study drug boxes will be verified by the Investigator and within one month after completion of the trial the partially used and unused study medication will be shipped to the Sponsor or will be destroyed after authorization by the Sponsor by an authorized company according to GCP regulations.

5.6. CONCOMITANT MEDICATION

As a general rule, no ophthalmic medication other than study drug will be given to the patient from the screening day until all of the final study evaluations have been completed, except for preservative free artificial tears.
The preservative free artificial tears will be provided by the Sponsor and can be used according to the following scheme:

1) During the 4 weeks of masked treatment, only if strictly needed, the patient will instill one drop in both eyes.
2) During the 12 weeks of Follow up period one drop will be instilled in both eyes TID (morning, afternoon and evening).

The use (n° drops/day) of preservative free artificial tears will be clearly documented in the patient's diary and eCRF.

All medications (including over-the-counter drugs, herbal products, vitamins, and antacids) taken within 4 weeks prior to the start of and throughout the study will be clearly documented on the Concomitant Medications eCRF page.
Medication entries should be specific to product name (if a combination drug product) and spelled correctly. The dose, unit, frequency, route of administration, start date, discontinuation date, and indication should also be recorded. For medications administered only one time, the frequency column may reflect "once."

6. STUDY PROCEDURE AND ASSESSMENTS

The first patient first visit (FPFV) is defined as the 1st visit performed at one of the clinical centers by the 1st screened patient. The last patient, last visit (LPLV) is defined as the last visit performed at one of the clinical centers by the last patient (i.e., the last visit foreseen by the study protocol), independently of whether the patient completed or withdrew from the study. The First Patient In (FPI) is defined as the first randomized patient at one of the clinical centers.

Patients will be evaluated according to the following scheme:

Interventional phase

- Screening visit (day -8),
- Baseline (day 1+2),
- Week 2 (day 14±2),
- Week 4 (day 28±2) or early exit

Follow up visits

- Week 8 (day 56±2),
- Week 12 (day 84±4)
- Week 16 (day 112±7)

The schedule of study procedures and assessments is tabulated by visit in the Schedule of Evaluations in § 2.0.

The descriptions of the procedures to be performed at each visit are provided below.

6.1. SCREENING AND RANDOMIZATION VISITS

During the screening visit (day -8) all procedures for inclusion will be performed. From the day of screening the patients will stop any kind of further ophthalmic treatment, until all of the final study evaluations have been completed, except preservative free artificial tears (wash out period from day -8 to day -1 +2). The wash out period should not be less than 7 days and more than 9 days.
At the end of the screening period, patients meeting the entry criteria for this study will be randomized 1:1:1 and treated for 4 weeks with either rhNGF eye drops 20 µg/mL TID, rhNGF eye drops 20 µg/mL BID and vehicle SID or vehicle TID.

	Day	**Procedures/Assessments**
Screening visit	*Day -8*	The following procedures will be performed (order below is mandatory): ➢ Explanation to the patient of study aims, procedures and possible risks ➢ Informed consent signature ➢ Screening number allocation ➢ Patient eligibility: Inclusion/exclusion criteria evaluation ➢ Pregnancy test for female patients of childbirth potential ➢ Demographic data ➢ Ocular and systemic medical history ➢ Previous ocular and systemic medications (prior to start the study) ➢ Ocular examination of both eyes: • Assessment by SANDE questionnaire • Assessment by IDEEL questionnaire • Assessment by EQ-5D-3L questionnaire • Assessment of best corrected distance visual acuity (BCDVA) • External Ocular Examination • Schirmer test I (without anesthesia) • Slit-lamp examination (SLE) to assess the eyelid (Meibomian glands), eyelid (erythema), eyelid (edema), lashes, conjunctiva erythema, lens, iris, anterior chamber, corneal horizontal diameter • TFBUT • Ocular surface staining (NEI score - corneal and conjunctival fluorescein staining) ➢ AE collection

	Day	Procedures/Assessments
Visit 1 Baseline	*Day 1 +2*	The following procedures will be performed (order below is mandatory): ➢ Pregnancy test for female patients of childbirth potential ➢ Previous ocular and systemic medications (prior to start the treatment) ➢ Ocular examination of both eyes: • Assessment by SANDE questionnaire • Assessment by IDEEL questionnaire • Assessment by EQ-5D-3L questionnaire • Assessment of best corrected distance visual acuity (BCDVA) • External Ocular Examination • Schirmer test I (without anesthesia) • Slit-lamp examination (SLE) to assess the eyelid (Meibomian glands), eyelid (erythema), eyelid (edema), lashes, conjunctiva erythema, lens, iris, anterior chamber, corneal horizontal diameter • TFBUT • Ocular surface staining (NEI score – corneal and conjunctival fluorescein staining) • Schirmer test II (with anesthesia) • Laser scanning confocal microscopy to assess goblet cells density (only selected sites) • Corneal endothelium and stroma evaluation (only the sites having a confocal microscope will do this type of evaluation) ➢ Patient eligibility: Inclusion/exclusion criteria evaluation ➢ Randomization ➢ Study drug dispensation ➢ Preservative free artificial tears dispensation ➢ AE collection The Investigator will dispense to the patients their monthly box containing the study drug for the following 4 weeks together with an adequate number of adapters and pipettes. The Investigator will dispense to the patients the preservative free artificial tears to be used only if strictly needed by the patient (the patient must follow the instruction in the product leaflet). After completing baseline evaluation patients will be administered, by PI, with the study treatment as per instructions, and will self-administer at home the subsequent doses. Patients will return to the clinical site on Day 14 (±2) (Week 2, visit 2). The patients will be instructed to enter information of self-administration (if the administration has been occur per eye), AE occurrence, concomitant medication intake and possible self-administration of preservative free artificial tears into the diary. The diary will be given from the PI or delegate during this visit.

6.2. STUDY VISITS AND FOLLOW-UP ASSESSMENTS

After the first two weeks of treatment the patient will undergo a medical assessment during the visit 2 (week 2). Following the completion of the double-blind treatment (visit 3, week 4), patients will be followed up for safety assessments for an additional 12 weeks post treatment and will be evaluated at the end of the safety follow-up period. During the safety follow-up period patients will not use further ophthalmic treatment except preservative free artificial tears, provided by Sponsor, one drop instilled in both eyes three times daily (morning, afternoon and evening). The patient, only if strictly needed, can administer additional drops and must document in the patient's diary the n° of additional drops administered for each eye.

	Day	Procedures/Assessments
At home	*Days 0-14 ±2*	➢ Self-administration at home of the IMP, three times daily every 6-8 h for both eyes (diary) ➢ Recording any new or changes in concomitant medications (diary) ➢ Recording any unusual medical conditions - AE monitoring (diary) ➢ Recording possible use of preservative free artificial tears (diary). Data will be recorded by the patient in the patient's diary.
Visiti 2 Week 2	*Day 14±2*	The following procedures will be performed (order below is mandatory): ➢ Ocular examination of both eyes: • Assessment by SANDE questionnaire • Assessment of best corrected distance visual acuity (BCDVA) • External Ocular Examination • Schirmer test I (without anesthesia) • Slit-lamp examination (SLE) to assess the Eyelid - Meibomian glands, Eyelid – Erythema, Eyelid - Edema Lashes, Conjunctiva Erythema, Lens, Iris, Anterior Chamber, Corneal Horizontal Diameter • Tear Film Break-up Time (TFBUT) • Ocular surface staining (NEI score - corneal and conjunctival fluorescein staining) ➢ Concomitant ocular and systemic medications ➢ Frequency of patient's artificial tear use during first 2 weeks of treatmen (to be reported in eCRF) ➢ AE monitoring During the visit 2, week 2, the patient must bring the diary assigned during the previous visit. The PI or a delegate must check if patient has correctly complete the diary. If not, the site staff must retrain the patient. At completion of the assessment the patient will be discharged and will be asked to return for the end of treatment visit on day 28±2 (Visit 3 week 4).

	Day	Procedures/Assessments
At home	*Days 14 ±2– 28 ± 2*	➢ Self-administration at home of the IMP, three times daily every 6-8 h for both eyes (diary) ➢ Recording any new or changes in concomitant medications (diary) ➢ Recording any unusual medical conditions - AE monitoring (diary) ➢ Recording possible use of preservative free artificial tears (diary). Data will be recorded by the patient on the patient's diary.
Visit 3 week 4	*Day 28*±2	The following procedures will be performed (the below order is mandatory): ➢ Ocular examination of both eyes: • Assessment by SANDE questionnaire • Assessment by IDEEL questionnaire • Assessment by EQ-5D-3L questionnaire • Assessment by PGIC questionnaire • Assessment of best corrected distance visual acuity (BCDVA) • External Ocular Examination • Schirmer test I (without anesthesia) • Slit-lamp examination (SLE) to assess the Eyelid - Meibomian glands, Eyelid – Erythema, Eyelid - Edema Lashes, Conjunctiva Erythema, Lens, Iris, Anterior Chamber, Corneal Horizontal Diameter • Tear Film Break-up Time (TFBUT) • Ocular surface staining (NEI score - corneal and conjunctival fluorescein staining) • Schirmer test II (with anesthesia) • Laser scanning confocal microscopy to assess goblet cells density(only selected sites) • Corneal endothelium and stroma evaluation (only the sites having a confocal microscope will do this type of evaluation) ➢ Assessment of compliance to treatment (from patient diary and IMP reconciliation from returned weekly boxes) ➢ Concomitant ocular and systemic medications ➢ Frequency of patient's artificial tear use during the last 2 weeks of treatment (to be reported in eCRF). ➢ AE monitoring During visit 3, week 4, PI or delegate must check and collect the first patient's diary concerning the treatment period. At completion of the assessment the patient will be discharged and will be asked to return for the follow up visit on day 56±2 (Visit 4 week 8). The Investigator will dispense to the patients the preservative free artificial tears (Blink ® Tears) to be self-administered three times daily, one drop in both eyes during the first 4 weeks of Follow up. The PI or delegate has to explain to the patients that, only if strictly needed, they can administer an additional numbers of drops of Blink ® Tears, by documenting all information in the patient's diary.

	Day	Procedures/Assessments
At home	*Days 28 ±2–56 ± 4*	➢ Recording any new or changes in concomitant medications (diary) ➢ Recording any unusual medical conditions - AE monitoring (diary) ➢ Artificial tears use during 4 weeks of FU (diary) Data will be recorded by the patient on the patient's diary.
Visit 4 Follow up week 8	*Day 56± 4*	The following procedures will be performed (the below order is mandatory): ➢ Ocular examination of both eyes: • Assessment by SANDE questionnaire • Assessment by IDEEL questionnaire • Assessment by EQ-5D-3L questionnaire • Assessment by PGIC questionnaire • Assessment of best corrected distance visual acuity (BCDVA) • External Ocular Examination • Schirmer test I (without anesthesia) • Slit-lamp examination (SLE) to assess the Eyelid - Meibomian glands, Eyelid – Erythema, Eyelid - Edema Lashes, Conjunctiva Erythema, Lens, Iris, Anterior Chamber, Corneal Horizontal Diameter • Tear Film Break-up Time (TFBUT) ➢ Ocular surface staining (NEI score - corneal and conjunctival fluorescein staining) ➢ Concomitant ocular and systemic medications ➢ Frequency of patient's artificial tear use during 4 weeks of FU (to be reported in eCRF). ➢ AE monitoring During visit 4, week 8, PI or delegate must check and collect the second patient's diary concerning the first follow up period. The Investigator will dispense to the patient the preservative free artificial tears (Blink ® Tears) to be self-administered three times daily, one drop in both eye during the second 4 weeks of Follow up. The PI or delegate has to explain to the patients that, only if strictly needed, they can administer an additional numbers of drops of Blink ® Tears, by documenting all information in the patient's diary.
At home	*Days 56 ±4–84 ± 4*	➢ Recording any new or changes in concomitant medications (diary) ➢ Recording any unusual medical conditions - AE monitoring (diary) ➢ Artificial tears use during 4 weeks of FU (diary) Data will be recorded by the patient on the patient's diary.

	Day	Procedures/Assessments
Visit 5 Follow up week 12	*Day 84 ± 4*	The following procedures will be performed (the below order is mandatory): ➢ Ocular examination of both eyes: • Assessment by SANDE questionnaire • Assessment by IDEEL questionnaire • Assessment by EQ-5D-3L questionnaire • Assessment by PGIC questionnaire • Assessment of best corrected distance visual acuity (BCDVA) • External Ocular Examination • Schirmer test I (without anesthesia) • Slit-lamp examination (SLE) to assess the Eyelid - Meibomian glands, Eyelid – Erythema, Eyelid - Edema Lashes, Conjunctiva Erythema, Lens, Iris, Anterior Chamber, Corneal Horizontal Diameter • Tear Film Break-up Time (TFBUT) ➢ Ocular surface staining (NEI score - corneal and conjunctival fluoresce instaining) ➢ Concomitant ocular and systemic medications ➢ Frequency of patient's artificial tear use during 4 weeks of FU (to be reported in eCRF). ➢ AE monitoring During visit 5, week 12, PI or delegate must check and collect the third patient's diary concerning the second follow up period. The Investigator will dispense to the patient the preservative free artificial tears (Blink ® Tears) to be self-administered three times daily, one drop in both eye during the last weeks of Follow up. The PI or delegate has to explain to the patients that, only if strictly needed, they can administer an additional numbers of drops of Blink ® Tears, by documenting all information in the patient's diary.
At home	*Days 84* ±4–*112* ± *7*	➢ Recording any new or changes in concomitant medications (diary) ➢ Recording any unusual medical conditions - AE monitoring (diary) ➢ Artificial tears use during 4 weeks of FU (diary) Data will be recorded by the patient on the patient's diary.

	Day	Procedures/Assessments
Visit 6 Follow up week 16 **Final visit or early termination visit (ETV)**	*Day 112* ± 7	The final visit is defined as the visit performed 84 ± 7 days after the last IMP administration (i.e., at day 112 ± 7). In case of premature study discontinuation, patients will undergo an early termination visit (ETV or end of study EOS as per eCRF). The following procedures will be performed (the below order is mandatory): ➢ Pregnancy test for female patients of childbirth potential ➢ Ocular examination of both eyes: • Assessment by SANDE questionnaire • Assessment by IDEEL questionnaire • Assessment by EQ-5D-3L questionnaire • Assessment by PGIC questionnaire • Assessment of best corrected distance visual acuity (BCDVA) • External Ocular Examination • Schirmer test I (without anesthesia) • Slit-lamp examination (SLE) to assess the Eyelid - Meibomian glands, Eyelid – Erythema, Eyelid - Edema Lashes, Conjunctiva Erythema, Lens, Iris, Anterior Chamber, Corneal Horizontal Diameter • Tear Film Break-up Time (TFBUT) • Ocular surface staining (NEI score - corneal and conjunctival fluorescein staining) • Schirmer test II (with anesthesia) • Laser scanning confocal microscopy to assess goblet cells density (only selected sites) • Corneal endothelium and stroma evaluation (only the sites having a confocal microscope will do this type of evaluation) ➢ Concomitant ocular and systemic medication ➢ Frequency of patient's artificial tear use during 4 weeks of FU (to be reported in eCRF) ➢ AE monitoring During visit 6, week 16, PI or delegate must check and collect the last patient's diary concerning the third follow up period.

6.3. EARLY WITHDRAWAL FROM THERAPY OR ASSESSMENT

6.3.1. Primary Reason For Discontinuation From The Study

A premature discontinuation will occur when a patient who signed the ICF ceases participation in the study, regardless of circumstances, before the completion of the study protocol procedures. Patients can be prematurely discontinued from the study for one of the following reasons:

- **Adverse event** (AE): Any significant AE that, in the opinion of the Investigator or concerned patient, is not compatible with study continuation.
- **Disease progression or worsening,** that according to the opinion of the Investigator is not compatible with study continuation..
- **Death**.
- **Lost to follow-up** (Every effort must be made to contact the patient; a registered letter must be sent).
- **Non-compliance with study drug**: an indication that a patient has not agreed with or followed the instructions related to the study medication.
- **Physician decision**: a position, opinion or judgment reached after consideration by a physician with reference to the patient.
- **Severe Protocol violation**: an event or decision that stands in contrast to the guidelines set out by the protocol.
- **Study terminated by the Sponsor**: an indication that a clinical study was stopped by Sponsor.
- **Withdrawal of consent**: study discontinuation requested by a patient for whatever reason.
- **Other reasons**, such as administrative reasons or pregnancy.

Before removal, each case should first be discussed with Dompé farmaceutici s.p.a.

The reasons for premature discontinuation from the study will be reflected on the Study Termination Record of the eCRF. Unless the patient has withdrawn consent, the follow up visit assessments should be performed as detailed in § 6.

The investigator should advise patients that prematurely discontinue on any therapies or treatments for their condition and refer them for further treatment as appropriate

6.3.2. Discontinuation procedures

For any patient discontinuing the study following randomization, the Investigator will:

- ask the patient to undergo, as far as possible, a final medical visit (ETV) to examine the patient's health conditions. This examination will verify that all values tested at screening have remained within a clinically acceptable range (i.e., not clinically significant changes compared to screening).
- arrange for alternative medical care of the withdrawn patient, if necessary.
- report in the eCRF date and time of the last dose administration, and date and primary reason of study discontinuation.
- record in the eCRF any follow-up if the patient is withdrawn for an AE. AE's should be followed until resolution.

6.3.3. Replacement procedure

Patients in this study who prematurely discontinue treatment will not be replaced.

It will be documented whether or not each patient completed the clinical study. If, for a patient, study treatment or observations are discontinued, the primary reason for discontinuation will be recorded.

6.4. END OF STUDY

Patients completing the double-blind treatment (Visits 1 Baseline to Visit 6 Follow up) will be considered completers.

For the purpose of this trial, the End of Study is defined as the date of the last visit of the last patient or upon completion of any follow-up procedure described in the protocol. The Investigator and the Sponsor have the right to discontinue the study at any time for reasonable medical and/or administrative reasons. As far as possible, this should occur after mutual consultation. Reasons for discontinuation have to be documented appropriately. In this event, no further patients will receive doses of the study drugs, and patients already having received a dose of study drug will not receive any further doses of the study IMP but will undergo all safety assessments scheduled after the last dose of study drug, up to an including the end of study examination.

7. ENDPOINTS

7.1. STUDY ENDPOINTS

The study objective is to assess the efficacy and safety of rhNGF when administered as eye drops to patients with moderate to severe dry eye.

Evaluation of the clinical efficacy and safety during and at the end of treatment with rhNG, will be performed on the basis of the following assessments at each time point.

Evaluations will be performed on day -8 (screening), day 1+2 (visit baseline), day 14±2 (week 2), day 28±2 (week 4 End of treatment), day 56±4 (week 8 Visit 4 FU), day 84±4 (week 12 Visit 5 FU), day 112±7 (week 16 Visit 6 FU), according to the schedule of evaluation (§ 2)

7.1.1. Primary endpoint

- Change from baseline in Schirmer test I (without anesthesia) Vs week 4.

7.1.2. Secondary endpoints

- Change from baseline in Symptoms questionnaire (SANDE) scores for severity and frequency assessed at 4 weeks of treatment;
- Change from baseline in Schirmer II test (with anesthesia) Vs week 4;
- Change from baseline in Corneal and conjunctiva vital staining with fluorescein (National Eye Institute [NEI] scales) Vs week 4;
- Change from baseline in Tear Film Break up time (TFBUT) Vs week 4;
- Number of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score >= 50% assessed at week 4;
- Quality of life (Impact of Dry Eye on Everyday Life (IDEEL) questionnaire;
- Patient global Impression of change (PGIC);
- EQ-5D-3L.

7.1.3. Exploratory endpoint

- Correlation between sign and symptoms scores;
- Proportion and frequency of preservative free artificial tears use (n° drops/day) during the treatment period;
- Frequency of preservative free artificial tears use (n° drops/day) during the follow up period.
- Change from baseline in Schirmer test I (without anesthesia) Vs week 2;
- Change from baseline in Symptoms questionnaire (SANDE) scores for severity and frequency assessed at 2 weeks of treatment ;

- Change from baseline in Corneal and conjunctiva vital staining with fluorescein (National Eye Institute [NEI] scales) Vs week 2;
- Change from baseline in Tear Film Break up time (TFBUT) Vs week 2;
- Number of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score >= 50% assessed at week 2;
- Change from baseline in goblet cells density Vs week 4

7.1.4. Safety endpoint

- Incidence and frequency of Treatment-emergent adverse events (TEAEs), assessed throughout the study.

7.1.5. Stratification according to absence /presence of Primary Sjögren's Syndrome

- The primary, secondary, explorative and safety endpoints (see 7.1.1, .7.1.2 7.1.3 & 7.1.4) will be also evaluated within each stratification subgroup (absence/presence of Primary Sjögren's Syndrome)..

8. EVALUATION OF ADVERSE EVENTS AND SAFETY INFORMATION

8.1. DEFINITIONS

Adverse Event

An **Adverse Event** (**AE**) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Adverse Drug Reaction

An **Adverse Drug Reaction (ADR)** is defined as any noxious and unintended response to a medicinal product related to any dose. Any responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. For the purposes of IND safety reporting, "reasonable possibility" means there are facts (evidence) or arguments to suggest a causal relationship between the drug and the adverse event.. Adverse events are to be considered unrelated if the relationship to the study drug, as described in the table in § 8.2.1, is none or unlikely; whereas any AE reported in the study having a possible, probable or highly probable relationship to study drug will be considered as an ADR. The determination of expectedness should be made by the Sponsor on the basis of the IB.

Serious Adverse Event

A **Serious Adverse Event** (**SAE**) is defined in line with (CFR - Code of Federal Regulations Title 21 Sec. 312.32) as any adverse experience that, in the view of either the Investigator or sponsor, meets any of the following criteria::

- results in death,
- is life-threatening (i.e. the patient was at immediate risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or prolongation of existing hospitalization.

NOTE: In general, hospitalization means that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.

- results in persistent or significant disability/incapacity.

NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

- is a congenital anomaly/birth defect,
- is an important medical event.

NOTE: An important medical event is an event that may not result in death, be life threatening, or require hospitalization but may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the patient's wellbeing and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization or the development of drug dependency or drug abuse

Pre-planned hospitalization or hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition are not considered to be SAEs (see Par. 8.3.2).
These events must be recorded in the AE page of the eCRF where a variable will be ticked to indicate that they are not SAEs.

Death shall always be reported as SAE and cause of death shall always be specified when known.

Unexpected Adverse Event/Reaction

An AE or ADR is considered unexpected if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed and listed in the Investigator Brochure. Events that are mentioned in the Investigator Brochure (section Reference Safety Information) as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation are considered unexpected (21 CFR312.32(a)).

Suspected serious unexpected adverse reaction

A **suspected serious unexpected adverse reaction** (**SUSAR**) is defined as an adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of a Serious Adverse Reaction.

As mentioned, the determination of expectedness should be made on the basis of the IB (section Reference Safety Information) .

Adverse Events (AEs) of special Interest (Sight-threatening Events)

The following adverse events are considered to be of special interest and by default shall be reported as SAEs (medically important criteria):

- AEs that caused a decrease in visual acuity of >30 ETDRS letters or > +0.6 LogMAR (compared with the last assessment of visual acuity at the last visit) lasting >1 hour
- AEs that caused a decrease in visual acuity to the level of Light Perception or worse lasting >1 hour
- AEs that required surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight
- AEs associated with severe intraocular inflammation (i.e., 4+ anterior chamber cell/flare or 4+ vitritis)
- AEs that, in the opinion of the Investigator, may require medical intervention to prevent permanent loss of sight.

8.2. ADVERSE EVENT (AE) MONITORING

At visit 3 (end of treatment), visit 4 (FU), vist 5 (FU) and visit 6 (FU), after the patient has had the opportunity to spontaneously mention any problems, the Investigator or appropriate designee should inquire about AEs by asking the standard questions:

- "Have you had any health problems since your last study visit?"
- "Have there been any changes in the medicines you take since your last study visit?"

AEs should be reported for any clinically relevant change in concomitant condition(s) that is the result of an untoward (unfavorable and unintended) change in patient's medical conditions. Changes in any protocol-specific ocular or systemic parameter evaluated during the study are to be reviewed by the Investigator. In addition, the patient's responses to any questionnaire utilized during the study are to be reviewed by the Investigator. Any untoward (unfavorable and unintended) change in a protocol-specific parameter or questionnaire response that is clinically relevant is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

All AEs should be followed-up to determine outcome of the reaction.

In order to collect as complete as possible information in the clinical study database, all ADRs and SAEs ongoing at the time the subject's study participation ends should be evaluated within 10 days after the final visit. After this period, all unresolved ADRs and SAEs will be reported as "ongoing" in the eCRF.

8.3. RECORDING

AE data should be obtained through observation of the patient, from any information volunteered by the patient, or through patient questioning.

Adverse Events:

All AEs (non-serious and serious) that occur during the course of the study will be recorded in the eCRF. Any pre-existing medical conditions or signs/symptoms present in a patient prior to the start of the study (i.e., before informed consent is signed) should be specified in the dedicated eCRF sections. Subsequent to signing an informed consent form, all untoward medical occurrences that occur during the course of the study must be documented on eCRF. AEs will be collected till last Follow Up visit (week 16).

When possible, signs and symptoms indicating a common underlying pathology should be documented as one comprehensive event. For each recorded event, the AE documentation must include the onset date, outcome, resolution date (if event is resolved), intensity (i.e., severity),any action with study treatment taken as a result of the event, and an assessment of the adverseevent relationship to the study treatment.

Serious Adverse Events:

The Investigator must record all SAEs, including sight-threatening events, occurring at any time during the study regardless of presumed causal relationship, on the Serious Adverse Event form in the eCRF of the EDC system within 24 hours of learning of the event; information on the SAE must also be recorded on a specific Non-Carbon Repeat SAE form (included in the Investigator's Site File).

8.3.1. Relationship of AEs to the Investigational Product

The Investigator will assess the possible relationship between the AE and the investigational medication, according to the criteria in **Table** below:

Relationship of the Adverse Event to the IMP

None (Intercurrent Event)	An event that is not and cannot be related to the Investigational Product, e.g. patient is a passenger in a road traffic accident or surgical intervention performed during the study, but planned before patient enrolment into the study
Unlikely (remote)	Relationship is not likely e.g. a clinical event including laboratory test abnormality with temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs, chemicals or underlying disease provide more plausible explanations
Possible	Relationship may exist, but could have been produced by the patient's condition or treatment or other cause
Probable	Relationship is likely, the AE abates upon discontinuation of Investigational Product and cannot be due to the patient's condition
Highly Probable	Strong relationship, the event abates upon discontinuation of Investigational Product and, if applicable, re-appears upon repeat exposure

An ADR is defined as an adverse experience which is reasonably likely to have been caused by the drug. Events considered "Possible", "Probable" and "Highly Probable" related to the IMP treatment and implying a reasonable possibility, if considered unexpected, will be reported to appropriate regulatory authorities.

8.3.2. Severity of AEs

The Investigator will grade the severity of any AE using the definitions in the Table below. For each episode, the highest severity grade attained should be reported.

Severity of the Adverse Event

Mild	Grade 1 - Does not interfere with patient's usual function (awareness of symptoms or signs, but easily tolerated [acceptable]).
Moderate	Grade 2 - Interferes to some extent with patient's usual function (enough discomfort to interfere with usual activity [disturbing]).
Severe	Grade 3 - Interferes significantly with patient's usual function (incapacity to work or to do usual activities [unacceptable])

8.4. SERIOUS ADVERSE EVENT REPORTING

8.4.1. Reporting Procedure for Investigators to Dompé and CRO

The Investigator must report all SAEs filling in and signing a SAE Report form, including sight threatening events, regardless of presumed causal relationship, to Dompé Drug Safety and Syneos Health Pharmacovigilance, by e-mail (preferred) or fax within 24 hours of learning of the event. Contact details for SAE reporting are provided below:

Syneos Safety reporting
safetyreporting@syneoshealth.com

Dompé Contact information
Dompé Drug Safety
Laura Boga, Senior Safety Manager
Email: farmacovigilanza@dompe.com
or Fax: +39.02.36026913

Dompé Medical Expert
Flavio Mantelli – Chief Medical Officer,
Email: flavio.mantelli@dompe.com
or Fax: +39.02.58383324

Pier Adelchi Ruffini – Global Head Clinical Development
Email: pieradelchi.ruffini@dompe.com
or Fax: +39.02.58383324

Dompé Clinical Development
Email: elisa.greco@dompe.com/ mauro.ferrari@dompe.com/ beth.butler@dompe.com
or Fax: +39.02.58383324

Respective IRB must also be informed of all SAEs according to local specific requirements.

If assistance is needed with the reporting of a SAE, Syneos Health/Sponsor may be contacted at the addressed provided above

Serious adverse events will be managed directly by the Dompé Drug Safety department, with Syneos Health support for follow-up requests.

The investigator should also report information on SAEs that continue after patient has completed his/her participation in the study (whether study completion or withdrawal), unless patient has withdrawn his/her consent.

Follow-up reports (as many as required) should be completed and faxed/e-mailed following the same procedure above, marking the SAE form as "follow up Number XX".

Whenever more than one SAE is observed, the Investigator should identify which is the primary adverse event, i.e. the most relevant one. If other events are listed in the same report, the Investigator, along with their relatedness to the Investigational Product, should identify which adverse events are serious and which are non-serious. In any case, the Investigator is requested to record his/her opinion about the relatedness of the observed event(s) with the investigational medication.

An assessment of expectedness and causality of each serious adverse event will be performed case by case by Dompé/Syneos Health. For SAE reported by the Investigator as not related that is subsequently assessed to be related by Dompé, the Investigator will receive a notification. Depending on the nature and seriousness of the AE, further information, including copies of appropriate medical records of the patient, as well as results of laboratory tests performed will need to be included in the patients chart. If the patient was hospitalized, a copy of the discharge summary should be available, if possible.

In line with CT3 Detailed Guidance and ICH E2A provisions, although the Investigator does not usually need to actively monitor patients for AEs once the trial has ended, if the Investigator becomes aware of a SAE occurring to a patient after that patient has ended his/her participation in the study (whether study completion or withdrawal), the SAE should be reported by the Investigator to the the Dompé/Syneos Health Pharmacovigilance. Such "post-study cases" should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

8.4.2. Conditions that should not be reported as serious adverse events

The conditions listed below, that may require hospitalization of a patient, are not considered to be SAE and shall not be reported as such, but only need to be recorded in the eCRF:

- Hospitalizations planned before entry into the clinical study which is part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition.
- Hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Hospitalization for treatments, which was elective or pre-planned, for a pre-existing condition that is unrelated to the indication under study and did not worsen.
- Hospitalization for general care not associated with any deterioration in condition.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of SAEs given above and not resulting in hospital admission.

In addition, the following situation shall not be considered SAE:

- Trial end points
- Abnormal test results that do not induce clinical signs and/or symptoms and require intervention/therapy, i.e. are not clinically significant.

8.4.3. Reporting Procedure to IRB and to Regulatory Authorities

In addition to reporting the SAE to Dompé, the Investigator must also comply with the requirements related to the reporting of SAEs to the IRB which approved the study. The requirements of IRBs vary from one IRB to another; however, as a minimum requirement, the Investigators must promptly report all suspected unexpected serious adverse reaction (SUSAR) to their IRB.

In line with provisions set forth in 21CFR312, Dompé shall notify all participating Investigators in an IND safety report of any suspected adverse reaction that is both serious and unexpected and of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than:

- seven calendar days after becoming aware of the information if the event is fatal or life threatening; to be followed by any relevant information within eight days.
- fifteen calendar days after becoming aware of the information if the event is serious but neither fatal nor life threatening.

The Investigators in turn shall notify their IRB.

If the results of an investigation show that an ADR not initially determined to be reportable is reclassified as reportable, the Sponsor shall report such reaction in a written safety report as soon as possible, but in no event later than 7/15 calendar days after the determination is made.

Treatment will be unblinded by Dompé Drug Safety Pharmacovigilance prior to submission of a SUSAR to Regulatory Authorities and only cases referred to active treatment will be considered expeditable for regulatory reporting, in line with law requirements.

Copies of all correspondence relating to reporting of any SAEs to the IRB should be maintained in the Investigator's Files.

Dompé shall also notify FDA in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible after Dompé determines that the information qualifies for reporting, in particular shall notify of:

- any suspected adverse reaction that is both serious and unexpected. Dompé must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event.

- findings from other studies that suggest a significant risk in humans exposed to the drug. Such a finding would result in a safety-related change in the overall conduct of the clinical investigation.
- findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- increased rate of occurrence of serious suspected adverse reactions.

8.4.4. Periodical Reporting to Regulatory Authorities

Dompé shall be responsible to prepare and submit annual safety reports (Development Safety Update Report – DSUR) to relevant Regulatory Authorities.

8.5. UNMASKING OF THE STUDY TREATMENT

Masked information on the identity of the assigned investigational product will be provided for each patient. If the treatment code needs to be broken in the interest of patient safety, Dompé must be informed in all cases in which the code was broken and of the circumstances involved.

Additionally, Dompé Drug Safety may be need to unmask the patient's treatment if the a reported SAE meets criteria of a Suspected Unexpected Serious Adverse Reaction (SUSAR) in order to fulfil expedited regulatory reporting requirements. Unmasked information shall not be disclosed to Investigators.

The identity of the treatments will remain unknown to the patient, Investigator, site staff and Dompé's clinical research personnel and Syneos Health staff (apart from pharmacovigilance).

8.6. FOLLOW-UP OF PATIENTS WITH ADVERSE EVENTS (AES)

The Investigator is responsible for adequate and safe medical care of patients during the trial and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial. All AEs should be followed-up to determine outcome of the reaction or until 10 days after the final visit. The Investigator should follow-up the event until resolution or stabilization of the condition. It is the Investigator's responsibility to assure that the patients experiencing AEs receive definite treatment for any AE, if required.

If patient was hospitalized due to a SAE, a copy of the discharge summary is to be forwarded to Syneos Health/Dompé as soon as it becomes available. In addition, a letter from the Investigator that summarizes the events related to the case as well as results of any relevant laboratory tests also may be requested. Further, depending upon the nature of the SAE, Dompé may request copies of applicable segments of the patient's medical records.

For pharmacovigilance purposes, all SAEs should be followed-up in order to elucidate as completely and practically as possible their nature and/or causality until resolution of all queries, clinical recovery is complete, laboratory results have returned to normal, stable condition is reached or the subject is lost to follow-up. Follow-up may therefore continue until after the subject has left the study up to 10 days after his/her discontinuation from the study for unrelated SAEs, and without timelines for related SAEs, unless the patient denies consent.

8.7. PREGNANCY IN THE CLINICAL TRIAL

Women of childbearing potential are not excluded from the study as long as adequate birth control methods are being utilized. Women of childbearing potential are defined as all women physiologically capable of becoming pregnant. Adequate birth control methods are summarized in the protocol's exclusion criteria.

Prior to enrollment in the clinical trial, female patients of childbearing potential and their partners must be advised of the importance of avoiding pregnancy during the entire course of the study treatment and for the 30 days after the study treatment period ends and of the potential risks associated with an unintentional pregnancy. During the trial (during the study treatment period and during the follow up), female patients are to be instructed to contact the Investigator immediately if they suspect they might be pregnant; in the same way, male patients who become aware that the partner might be pregnant, are to be instructed to contact the Investigator immediately.

The Investigator must report every pregnancy on a pregnancy report form as soon as possible (within 24 hours of learning of the pregnancy) to Syneos Health/Dompé Drug Safety contacts reported at Paragraph 8.4.1, even if no AE has occurred, and follow it to term.

The pregnancy form will be utilized to capture all pregnancy-related information until the birth of the child for both the patient and the partner.

If the pregnancy is associated with a SAE (eg, if the mother is hospitalized for dehydration), in addition to the pregnancy report form, a separate SAE report form must be filed as described in § 8.4 with the appropriate serious criterion (eg, hospitalization) indicated on the SAE report form. Miscarriage, stillbirth and any malformation/disease must be reported as a SAE. Any pregnancy leads to the immediate cessation of the study treatment.

8.8. ADVERSE EVENTS CAUSING TREATMENT DISCONTINUATION

If a patient is withdrawn from the study as a consequence of an AE, this must be recorded and reasoned in the eCRF, and the patient must be followed up until the resolution of the AE or as instructed by the medical monitor.

8.9. OVERDOSE

Cases of overdose (accidental or intentional) which may or may not result in serious adverse reactions are to be reported to Sponsor Drug Safety/Syneos Health by email or fax, following the same procedure for SAE, within 24 hours from the Investigator's knowledge of its occurrence. This includes reports related to drug intake with suicidal intentions and consequent drug overdose.
Since in the preclinical toxicology studies in animals and in the multiple ascending dose study performed in healthy volunteers none of the dose has caused an overdose as documented by adverse reaction, for the purpose of this study we define that the administration of more than 3 times the total daily dose on any given treatment day will be reported as an overdose, even if not associated with adverse reactions.

The Investigator shall provide in the SAE form information about symptoms, corrective treatment and outcome of overdose.

9. STATISTICS

The data documented in this study will be summarized using number of observations, mean, standard deviation (SD), median, minimum, and maximum values for quantitative variables, and frequencies for qualitative variables.

A statistical analysis plan (SAP) will be developed and finalized before database lock and de-masking. Final statistical analysis on the study variables will be presented in detail in the SAP.

9.1. SAMPLE SIZE

In order to evaluate the minimal effective daily dose of rhNGF eye drops, a Williams design has been chosen [15; 16]. For this study three treatment groups has been considered: rhNGF eye drops solution 20 µg/ml TID; rhNGF eye drops solution 20 µg/ml BID plus vehicle eye drop solution SID; vehicle eye drop solution TID.
To this purpose, the sample size has been determined applying the formula eported in the publication Chow et al., 2008 at page 301 [17].

The sample size calculation for the primary variable is based on the following assumptions:

- The probability level (α) for one-sided test is set at 0.025 (see table 12.1.2 at page 298 in Chow et al., 2008) and the power level at approximately 90%.

- DELTA, in change from baseline between treatments, of 5.3 and Standard Deviation for DELTA of 10.78. Both DELTA parameters are derived from results of co-variance analysis obtained from study NGF0216 in the subset of hyposecretive patients (i.e. excluding "evaporative-only" patients).

According to this calculation, 87 patients per treatment group (for a total of 261 patients) are adequate to observe the planned difference assumed for the minimum effective daily dose. Assuming a drop-out of ~15%, a total of 300 is the target number of patients proposed to be enrolled.

The inclusion of at least 60 subjects with documented diagnosis of Primary Sjögren's Syndrome within the planned 300 patients will have no impact on the initial study assumptions (Standard Deviation of 10.78 and DELTA of 5.3 mm) because the patients could have been enrolled based on the previous criteria on which sample size was based. Moreover, a similar prevalence of patients with Primary Sjögren's Syndrome has already been reported in the NGF0216 medical history (~25% of patient the FAS population).

9.2. POPULATION

Screened Population

The Screened Population will consist of all patients with the signature of the informed consent, the assignment of a PID number and regardless the completion of all the screening procedures.

Eligible Population

The Eligible Population will consist of all patients with all inclusion/exclusion criteria met. Otherwise the patient will be defined as screening failure.

Randomized Population

The Randomized Population will consist of all patients in the Screened Population who were assigned a randomization number.

9.3. COMPLIANCE WITH IMP ADMINISTRATION

The assessment of patients' compliance to the IMP will be made by determining the number of study medication vials dispensed to the patient at Day 1 Visit 1 baseline and the number of unused study medication vials returned at Week 4 Visit 3 End of treatment. The percentage Compliance will be evaluated according to the following formula:

$$\textbf{Overall compliance} = 100 * \frac{(\text{Number of vials dispensed} - \text{ Number of unused vials returned})}{3 * (\textbf{\textit{Numbers of days on treatment}})}$$

$$\textbf{Compliance for the eligible eye} = 100 * \frac{(\text{Number of drops administered to the eligible eye})}{3 * (\textbf{\textit{Numbers of days on treatment}})}$$

Gross non compliance will be defined as compliance lower than 80% or greater than 120% and in case of gross non compliance the patient will be excluded from the Per Protocol. Since this definition does not warrant that the study eye treatment is compliant, if indicated the SAP will contain further definitions based upon the diary card information.

9.4. STATISTICAL METHODOLOGY

9.4.1. Definitions

Enrolled Set

The Enrolled Set will consist of all patients who signed the ICF. This analysis set will be used for demographic, baseline and background characteristics.

Safety Population

The Safety Population (SAF) will consist of all randomized patients who took at least one dose of IP. This analysis set will be used for the safety analysis. Patients will be analyzed according to the treatment received.

Full Analysis Set

Full Analysis Set (FAS) will consist of all randomized patients who took at least one dose of IP and who have at least one post-baseline efficacy measurement for the primary endpoint. This analysis set will be used for the primary efficacy analysis. Patients will be analyzed according to the randomized treatment.

Per Protocol Set

Per Protocol Set (PP) will consist of all patients in the FAS who fulfil the study protocol requirements in terms of investigational medicinal product intake and collection of primary efficacy data and with no major deviations that may affect study results. This analysis set will be used for supportive efficacy analysis.Patients will be analyzed according to the treatment received.

Each patient will be coded by the Syneos Health statistician as valid or not valid for the Enrolled Set, SAF, FAS and PP.

9.4.2. Reasons for exclusion from the Full Analysis Set

Reasons for the exclusion from the Full Analysis Set are the following:

- failure to take at least one dose of the IMP at the study eye
- lack of any efficacy data post enrollment.

9.4.3. Reasons for exclusion from the Per Protocol set

Reasons for the exclusion from the Per Protocol set will be determined in the Blind Data Review Meeting and can be the following:

- lack of compliance with IMP administration
- missing primary efficacy data
- major deviation from inclusion/exclusion criteria (eligibility violations)
- intake of prohibited medications.

9.4.4. Demographic and baseline characteristics

Demographic and baseline characteristics will be descriptively summarized per treatment group according to their nature.

9.5. Analysis of ophthalmological evaluations

Primary endpoint will be analyzed using analysis of variance including only the treatment as main factor followed by pre-planned comparisons from Vehicle and rhNGF dosages according to Williams procedure. In addition, primary endpoint will be summarized using descriptive statistics for continuous variables by treatment and visit. The change from baseline value will also be summarized for all post-baseline visits.
An explorative sensitivity analysis of the primary endpoint will be conducted including in the analysis of variance the absence/presence of diagnosis of Primary Sjögren's Syndrome and its interaction with treatments as covariates. If the interaction term is statistically significant (at the 0.10 level given its explorative nature), the treatment effects within patients with and without Primary Sjögren's Syndrome will be provided.

Secondary endpoints will be presented by means of appropriate descriptive statistics.
Changes from baseline in global SANDE score, Schirmer test II, NEI scales, TFBUT, IDEEL, PGIC and EQ-5D-3L scores 4 will be analyzed in a similar manner as the Change from baseline in Schirmer test I (primary endpoint) in order to test treatment effect. Difference between treatment groups (Each active dose vs Placebo), in the percentage of patients who experienced a worsening in SANDE scores and/or NEI score will be tested using a chi-square test.

Explorative endpoints will be summarized by means of appropriate descriptive statistics. Any statistical testing will be descriptive in nature.

Additional details on the analyses will be provided in the statistical analysis plan.

9.5.1. Analysis of safety variables

- AEs

Adverse events (AEs) will be coded by System Organ Class (SOC) and Preferred Term (PT), using the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent AEs are all events occurring or worsening after the first dose of the IMP.

Treatment-emergent AEs will be summarized by treatment group. The number and percentage of patients with any AE and the number of TEAEs will be tabulated by SOC and PT, seriousness, relationship to treatment and severity. Individual AEs will be listed in patient data listings.

9.5.2. Analysis of Quality of Life variables

Data record in the questionnaires of quality of life will be presented with appropriate descriptive statistics and processed with appropriate inferential test.

9.5.3. Subgroup analysis

Sub-group analyses of primary, secondary, explorative endpoints and safety endpoints will be performed on patients with the Sjögren's syndrome for explorative purpose. Statistical details will be reported in the SAP.

9.5.4. Changes to the statistical plan

Any deviations from the original statistical plan will be escribed in the Clinical Study Report.

10. ETHICAL CONSIDERATIONS

10.1. INSTITUTIONAL REVIEW BOARD

Approval by the Institutional Review Board (IRB) before the start of the study will be the responsibility of the Principal Investigator (PI). A copy of the approval letter will be supplied to the sponsor, along with a roster of IRB members or the US Department of Health and Human Services (DHHS) general assurance number. During the course of the study, the PI will provide timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB of serious adverse events (SAEs) or other significant safety findings. The study protocol, informed consent form (ICF), information sheet advertisements, and amendments (if any) will be approved by the IRBs at the study centers in conformance with Code of Federal Regulations (CFR), Title 21, Part 56.

10.2. ETHICAL CONDUCT OF THE STUDY

The study will be conducted in full compliance with FDA and ICH guidelines for good clinical practice (GCP) and in accordance with the ethical principles that have their origins in the Declaration of Helsinki and 21 CFR § 312.120.

10.3. DATA MONITORING COMMITTEE

A Data Monitoring Committee is not required for this trial considering the following point:

- The drug under investigation is well characterized and known for not harming patients
- Tis clinical trial does not foresee an interim analysis
- The study design is not complex and already performed in other clinical trial in DED
- The study does not have a long duration.

10.4. PATIENT INFORMATION AND CONSENT

Patients, after being given an explanation of the study, will give voluntary and written informed consent before participating in any study-related procedures. A copy of the Experimental Subject's Bill of Rights (Footnote 1) will provided to a subject prior to performing the consent process. Each patient will read or be read (if he or she cannot read or write), assent understanding of, and sign or thumbprint an instrument of informed consent and after having had an opportunity to discuss them

1 The Protection of Human Subjects in Medical Experimentation Act (California Health and Safety Code 24170 – 24179.5) requires that a potential experimental subject (or subject's conservator, guardian, or other representative) be provided with a list of the rights of a subject in a medical experiment.

with the PI before signing; each patient will be made aware that he or she may withdraw from the study at any time.
The informed consent statement contains all the elements of informed consent and contains all the core elements and mandatory statements as defined in the CFR. Signed copies of the ICF and the form will be given to the patient, and both documents will be placed in the Investigator's site files. A unique patient identification (PID) number will be assigned according to § 4.3 of the protocol at the time the patient signs the ICF.

10.5. CONFIDENTIALITY

All information obtained during the conduct of the study will be regarded as confidential. An agreement for disclosure will be obtained in writing by the patient and will be included in the ICF. Patient's data collected during the study will be handled in accordance with applicable data protection laws and regulations.

On the CRFs patients will be identified ONLY by the assigned patient number. If patient names are included on copies of documents submitted to Dompé farmaceutici s.p.a. or Syenos Health, the names will be obliterated or masked and the assigned patient number added to the document.

The Investigator should keep a separate log (Patient Master List) of patient's codes, names and addresses.

10.6. COMPENSATION FOR MEDICINE-INDUCED INJURY AND INDEMNIFICATION

Before the trial formally starts, Dompé will take out a study-specific insurance contract according to national laws for patients/Investigators/Institutions participating in the clinical trial.
In case of questions about medical care, cost for medical care or insurance, patients can talk to their Investigator. Contact details will be given in the Patient Informed Consent Document.

11. DATA HANDLING AND RECORD KEEPING

11.1. CASE REPORT FORMS

All data relating to the study will be recorded on eCRFs to be provided by Syneos Health, through the EDC system. The PI is responsible for verifying that all data entries in the eCRFs are accurate and correct. The PI must sign the completed eCRF before its submission to the sponsor.

11.2. DATA MANAGEMENT

Data collection will involve the use of an EDC system , to which only authorized personnel will have access. In addition to periodic monitoring occurring within the system by Syneos Health Monitors, programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of this monitoring and these checks, queries may be electronically issued to the study centers and electronically closed by those study centers. The identifying information (assigned username, date, and time) for both the originator of the query (if created during the monitoring process) and the originator of the data change (if applicable), as well as the PI's approval of all changes performed on his or her patients' data, will be collected.

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidances for electronic records. Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (e.g., copies of eCRFs, regulatory documents) will be retained at the study center, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for audit by Dompé farmaceutici s.p.a.; its authorized representatives; and Regulatory Inspection by Regulatory Authority.

The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary via an audit trail.

11.3. DOCUMENTATION REQUIRED PRIOR TO INITIATION OF AND DURING THE STUDY

The following documents will be required from the Investigator prior to the initiation visit:

- Current, signed and dated Curriculum Vitae of Principal Investigator and any Sub-Investigators/co-workers. Updates should be provided at least every two years.
- A signed page of the final protocol and any amendments.

- A signed copy of the study Financial Agreement/Clinical Study Agreement with Syneos Health, including all study specific costs.
- List and any updates of delegated responsibility (Study Team Signature List / Delegation of Responsibilities form).
- A financial disclosure agreement completed and signed by the PI and all Sub-Investigators listed on Form FDA 1572. If applicable, the PI will provide an updated financial disclosure agreement to the Sponsor 1 year after the completion of the study.

11.4. ESSENTIAL DOCUMENT RETENTION

The Investigator will retain copies of all the essential documents (as defined by ICH-GCP E6 R2) until at least 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the Investigational Product. These documents should be retained for a longer period however if required by the applicable regulatory requirements. The Investigator should take measures to prevent accidental or premature destruction of these documents.

The essential documents include at least: the signed protocol, copies of the completed eCRFs, signed Patient Informed Consent Forms from all patients who consented, hospital records and other source documents, and all other documentation included in the Investigator Site File and Pharmacy/Dispensing File.

The Investigator will inform Dompé farmaceutici s.p.a. of the storage location of these essential documents and must contact Dompé farmaceutici s.p.a. before disposing of any. If the Investigator wishes to assign the files to someone else or to remove them to another location, he/she should consult with Dompé farmaceutici s.p.a. about this change.

Dompé farmaceutici s.p.a. will inform the Investigator in writing when these documents no longer need to be retained.

12. STUDY MANAGEMENT

The study will be performed in accordance with the protocol, the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and ICH Harmonised Tripartite Guideline for Good Clinical Practice (ICH-GCP E6-R2) and any local regulations.

12.1. MONITORING

Before any patient enters the study, a representative of Syneos Health, will meet with the PI and his or her staff to review the procedures to be followed during the study and to train them on recording the data in the eCRFs using the electronic data capture (EDC) system. After the first patient is enrolled, the Syneos Health representative, a monitor, will periodically monitor the progress of the study by conducting on-site visits. This CRA will also be able to review query statuses remotely, possibly warranting more frequent communication with the PI and his or her staff. The PI will make available to the CRA the eCRFs, source documents, signed consent forms, and all other study-related documents. The PI and his or her staff will be responsible for reviewing eCRFs, resolving data queries generated by the CRA via the system, providing missing or corrected data, approving all changes performed on his or her data, and endorsing the patient data within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned username and password that together will represent a traditional handwritten signature.

12.2. ACCESS TO RECORDS

The Investigator will allow designated Dompé farmaceutici s.p.a. representatives, including staff from Syneos Health, and regulatory/ethics bodies to have direct access to the source documents to verify the data reported in the eCRFs. Source documents are the originals of any documents used by the Investigator or hospital/institution that allow verification of the existence of the patient and substantiate the integrity of the data collected during the trial.

12.3. AUDIT AND INSPECTION

The study site may be audited by Syneos Health on behalf of the Dompé farmaceutici s.p.a. or inspected by a regulatory agency on one or more occasions. The Investigator may be informed in advance of such a visit.

12.4. PROTOCOL AMENDMENTS

Any amendment to this protocol will be provided to the PI in writing by Dompé farmaceutici s.p.a. No protocol amendment may be implemented (with the exceptions noted below) before it has been

approved by the IRB and the signature page, signed by the PI, has been received by Dompé farmaceutici s.p.a. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits. Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patients and must immediately be reported to Dompé farmaceutici s.p.a.

12.5. DISCONTINUATION OF THE STUDY

Dompé farmaceutici s.p.a. reserves the right to terminate the study in its entirety or at a specific study center at any timeon the basis of new information regarding safety or efficacy, or if study progress is unsatisfactory, or for other valid administrative reasons.

12.6. PUBLICATIONS

All data generated in this study will be the property of Dompé farmaceutici s.p.a. Publication of the results by the PI will be subject to mutual agreement between the PI and Dompé farmaceutici s.p.a. The Sponsor agrees that the study results (including negative and inconclusive as well as positive results) can be made publicly available by the Investigator publishing in peer reviewed journals; presenting results at scientific congresses; and posting information and results on internet-based public registers and databases.

In any case, study results will be communicated in full to the FDA by the submission of a complete Clinical Study Report.

As the Sponsor agrees that the study results can be published by the Investigator(s), the Investigator agrees to submit any manuscript (abstract, publication, paper etc.) to the Sponsor before any public disclosure.

This will be done in order to ensure that clinical trial results are reported in an objective, accurate and balanced manner. The Sponsor reviews proposed manuscripts prior to submission within a reasonable period of time (30-90 business days in relation with the complexity of the work).

The Investigator(s) will also be provided by the Sponsor with the clinical study report and the results of any additional analysis, tables, figures etc undertaken for the purposes of the article, in order to take responsibility for the content of the publication(s).

On an exceptional basis, the Sponsor may temporarily delay registration of certain data elements (e.g. compound, name, outcome, measures etc.) to seek necessary intellectual property protection. This is because early disclosure of such a data could, in some circumstances, prevent or negatively impact patentability.

13. REFERENCES

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Dompé

Study Protocol: NGF0118

14 APPENDICES

14.1 APPENDIX 1-SPONSOR APPROVAL PAGE

A 4 weeks, Phase II, multicenter, randomized, double-masked, vehicle-controlled, parallel group study with 12 weeks of follow-up to evaluate safety and efficacy of recombinant human Nerve Growth Factor (rhNGF) eye drops solution versus vehicle, in patients with moderate to severe dry eye (DE).

Sponsor Medical Expert: _____ Date: 08 /AUG/2019
ON BEHALF OF Flavio Mantelli, Chief Medical Officer

Sponsor Medical Expert: _____ Date: 08 /AUG/2019
Pier Adelchi Ruffini, Global Head Clinical Development

Sponsor Clinical Trial Manager: _____ Date: 08/AUG/2019
Mauro P. Ferrari, Clinical Development Senior Manager

Sponsor Clinical Trial Manager: _____ Date: 08 /AUG/2019
ON BEHALF OF Elisa Greco, Clinical Research Specialist

Sponsor Development Director _____ Date: 08 /AUG/2019
ON BEHALF OF Marcello Allegretti, Chief Scientific Officer

14.2 APPENDIX 2-INVESTIGATOR'S SIGNATURE PAGE

Investigator's Statement

I have read study protocol NGF0118 from the title *"A 4 week, Phase II, multicenter, randomized, double-masked, vehicle-controlled, parallel group study with 12 weeks of follow-up to evaluate safety and efficacy of recombinant human Nerve Growth Factor (rhNGF) eye drops solution versus vehicle, in patients with moderate to severe dry eye (DE)*" and agree to conduct the study as outlined in the protocol, and in accordance with the Declaration of Helsinki, ICH-GCP E6 (R2) and any local regulations, being responsible for personally supervise the study conduct and ensure study staff complies with protocol requirement.

Name of Principal Investigator (block letters):_____

Signature: _____ Date: _____

14.3 APPENDIX 3AMERICAN-EUROPEAN CONSENSUS CRITERIA FOR SJÖGREN'S SYNDROME

Reference: Vitali C, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002; 61:554-558.

In order to make a diagnosis of Sjögren's syndrome, the following criteria must be met:

I. Ocular Symptoms (at least one)

- Symptoms of dry eyes for at least 3 months
- A foreign body sensation in the eyes
- Use of artificial tears 3 or more times per day

II. Oral Symptoms (at least one)

- Symptoms of dry mouth for at least 3 months
- Recurrent or persistently swollen salivary glands
- Need for liquids to swallow dry foods

III. Ocular Signs (at least one)

- Abnormal Schirmer's test, (without anesthesia; ≤5 mm/5 minutes)
- Positive vital dye staining of the eye surface

IV. Histopathology

- Lip biopsy showing focal lymphocytic sialoadenitis (focus score ≥1 per 4 mm2)

V. Oral Signs (at least one)

- Unstimulated whole salivary flow (≤1.5 mL in 15 minutes)
- Abnormal parotid sialography
- Abnormal salivary scintigraphy

VI. Autoantibodies (at least one)

- Anti-SSA (Ro) or Anti-SSB (La), or both

For a primary Sjögren's syndrome diagnosis:

- Any 4 of the 6 criteria, must include either item IV (Histopathology) or VI (Autoantibodies)
- Any 3 of the 4 objective criteria (III, IV, V, VI)

For a secondary Sjögren's syndrome diagnosis:

- In patients with another well-defined major connective tissue disease, the presence of one symptom (I or II) plus 2 of the 3 objective criteria (III, IV and V) is indicative of secondary SS.

Exclusion Criteria

- Past head and neck radiation treatment
- Hepatitis C infection
- Acquired immunodeficiency syndrome (AIDS)
- Pre-existing lymphoma
- Sarcoidosis
- Graft versus host disease
- Current use of anticholinergic drugs