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

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,

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

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.

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.

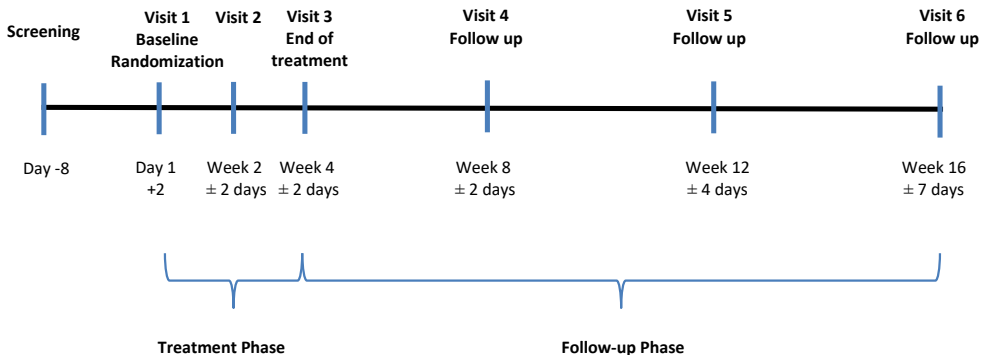

Figure 1:Study duration

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

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."

6.1. 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.

	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.

- 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) .

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).

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.

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.

- 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.

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	

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.

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

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.

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. 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. 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.

6.2. 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 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.

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.

8.3.1. 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])

- 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.

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).

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.