Statistical Analysis Plan for Interventional Studies

Sponsor Name: Dompé farmaceutici S.p.A

Protocol Number: NGF0118
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).

Protocol Version and Date: Version 2.0, Final 08-Aug-2019

Syneos Health Project Code: 7000843

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Revision History

Version #	**Date** (DD-Mmm-YYYY)	**Document Owner**	**Revision Summary**
1.1	29 May 2020		Update of SAP due to COVID-19 pandemic
1.2	17 Sep 2020		Sensitivy analysis on robustness of primary analysis and statistical tests (descriptive in nature) have been added.

I confirm that I have reviewed this document and agree with the content.

Approvals		
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1. Glossary of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BCDVA	Best Corrected Distance Visual Acuity
BID	Bis in die
CFR	Code of Federal Regulations
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRO	Contract Research Organization
DHHS	Department of Health and Human Services
DE	Dry Eye
EC	Ethics Committee
eCRF/CRF	Electronic/Case Report Form
EDC	Electronic Data Capture
EMA	European Medicine Agency
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HEOR	Health Economics and Outcomes Research
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDEEL	Impact of Dry Eye on Everyday Life
IP/IMP	Investigational Product/ Investigational Medicinal Product
IRB	Institutional Review Board
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
NEI	National Eye Institute
NIMP	Non Investigational Medicinal Product
NK	Neurotrophic Keratitis

PI	Principal Investigator
PGIC	Patient Global Impression of Change
PP	Per Protocol Set
PT	Preferred Term
rhNGF	Recombinant human nerve growth factor
RP	Retinitis pigmentosa
SAF	Safety Set
SANDE	Symptom Assessment in Dry Eye
SD	Standard Deviation
SID	Semel in die
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFBUT	Tear Film Break-Up Time
TID	Tris in die

2. Purpose

The purpose of this statistical analysis plan (SAP) is to ensure that the data listings, summary tables and figures which will be produced, and the statistical methodologies that will be used, are complete, in line with study protocol version 2.0 of 08 August 2019, and appropriate to allow valid conclusions regarding the study objectives.

Due to restrictions in the hospital clinical routines related to COVID-19 pandemic started in March 2020, Dompé has decided to stop prematurely enrollement in the study in order to comply with quarantine measures of each country and avoid risks of infection of COVID-19 illness itself for all involved subjects.

The study stopped to 261 patients instead of 300 originally planned; last subject enrolled was on March 25th, 2020. On March 9th, 2020 256 patients were randomized. Among them 185 had completed the study and 44 were early terminated subjects. So only 27 subjects are ongoing and 5 not randomized at the time of national emergency due to COVID-19.

Patients affected by COVID-19 will be identified using through Adverse form and Meddra coding (Peferred Term = 'Coronavirus infection').

2.1. Data collection and management of visits during COVID-19 pandemic

When possible, subject visits should occur in person, but in order to avoid any issues (e.g. unexpected site closure) that may affect subjects treatment, safety and data collection, Dompé allowed sites to perform remote subjects visits when an in-person visit(s) is not able to occur.

Remote subject visits is organized in advance as a preventive action plan should the sites close unexpectedly or a subject is unable/unwilling to come to the site for a visit(s).

If an in-person subject visit cannot occur as scheduled or be scheduled out of window because of site closure or of a subjects inability/unwillingness to come to the site, than a telephone (remote) visit should occur in place of the onsite visit(s).

When a site deems that a remote subject visit is required, SANDE questionnaire, IDEEL, EQ-5D-3L PGIC and diaries will be completed by the subject at home. Once the completed questionnaires and diaries are received by the site, the site should set up a telephone visit with the subject to review the completed questionnaire and diaries and evaluate the safety.

2.2. Responsibilities

Syneos Health will perform the statistical analyses and are responsible for the production and quality control of all tables, figures, and listings.

2.3. Timings of Analyses

The primary analysis of safety and efficacy data is planned after all patients complete the final study visit or terminate early from the study.

3. Study Objectives

3.1. Study Objective

The study objective is to assess the efficacy and safety of recombinant human nerve growth factor (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.

3.2. Brief Description

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), Week 2 (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.

3.3. Patient Selection

3.3.1. 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. Symptom Assessment in Dry Eye (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. (For patients already enrolled into the study under protocol 1) : Best corrected distance visual acuity (BCDVA) score of ≥ 0.1 decimal units in both eyes at the time of study enrolment.

5a. (Revised version in protocol version 2.0) : 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 with childbearing potential, have a negative pregnancy test.
7. (For patients already enrolled into the study under protocol 1) : 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 (ICF) signed by patients and/or legal representative must have been approved by the IRB/IEC for the current study.

7a. (Revised version in protocol version 2.0) : 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 (ICF) 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. (New criteria added in protocol version 2.0) 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 of the study protocol; 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.

3.3.2. 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. (For patients already enrolled into the study under protocol 1) : History of severe systemic allergy or ocular allergy (including seasonal conjunctivitis) or chronic conjunctivitis and/or keratitis other than dry eye.

4a. (Revised version in protocol version 2.0) : 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 (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 intrauterine device - 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 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. (For patients already enrolled into the study under protocol 1) : Participation in a clinical trial with a new active substance.

15a. (Revised version in protocol version 2.0) : 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.

3.4. Determination of Sample Size

In order to evaluate the minimal effective daily dose of rhNGF eye drops, a Williams design has been chosen [1] [2]. For this study three treatment groups have 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 reported in the publication Chow et al., 2008 at page 301 [3]

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[3]) 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 about 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).

Impact on the power of the study due to stopping enrollment in the study to 261 randomized subjects:

With 261 patients randomized, assuming a drop out rate of 15%, only 228 patients in total (76 patients by group) are considered adequate to observe the planned difference assumed for the minimum effective daily dose.

With 76 patients by group, with a DELTA, in change from baseline between treatments of 5.3 and Standard Deviation for DELTA of 10.78, the power to detect a difference will be at least 85%.

3.5. Treatment Assignment & Masking

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).

Following amendment n° 1 to the protocol, randomization will be stratified according to absence/presence of a documented diagnosis of Primary Sjögren's Syndrome.
The study was ongoing at the time of amendment and at the beginning of September 135 patients had already been randomized. The randomization list generated on March 22, 2019 will be stopped when the last randomization number used will be at the end of a block. Moving forward, the replacement list will be used. According to the amendment n° 1, the replacement randomization schedule will be stratified according to absence/presence of a documented diagnosis of Primary Sjögren's Syndrome.

Each randomized patient after amendment will be allocated with randomization number, according to the stratified randomization list using an Interactive Web Response System (IWRS).
Drop outs after randomization will not be replaced.

Randomization lists as well as associated kit numbers will 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.

For patients already enrolled in the study, the assignment to a strata will be based on Medical history form (see section 8.1).

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.

If the Investigator becomes unmasked for any reason, this information will be recorded on source data and in the electronic case report form (eCRF) of the study, specifying the date and the reason. Unmasking events will be recorded and reported in the final study report.

3.6. Administration of Study Medication

On Day 1 (baseline visit), the study personnel will give to the patient the monthly box, containing 4 weekly boxes, each containing 7 daily boxes. Each daily box contains three marked vials (e.g., 1 - Morning, 2 - Afternoon and 3 - Evening) of frozen investigational medicinal product (IMP) solutions (-20 ± 5°C) containing:

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

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.

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

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).

3.7. Study Procedures and Flowchart

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

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]**
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

*) 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.

4. Endpoints

4.1. Primary Efficacy Endpoint

- Change from baseline in Schirmer test I (without anesthesia) versus Week 4.

4.2. Secondary Efficacy Endpoints

- Change from baseline in Symptoms questionnaire (SANDE) scores for severity and frequency assessed at 4 weeks of treatment;
- Change from baseline in Schirmer test II (with anesthesia) versus Week 4;
- Change from baseline in corneal and conjunctiva vital staining with fluorescein (NEI scales) versus Week 4;
- Change from baseline in TFBUT versus Week 4;
- Number of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score ≥ 50% as 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.

4.3. Exploratory Endpoints

- 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) versus 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 (NEI score) versus Week 2;
- Change from baseline in TFBUT versus Week 2;
- Number of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score ≥ 50% as assessed at Week 2;
- Change from baseline in goblet cells density versus Week 4.

4.4. Safety Endpoints

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

5. Analysis Sets

5.1. Enrolled Set

The Enrolled Set will consist of all patients who signed the ICF.
This analysis set will be used for patients disposition and some listings.

5.2. Randomized Set

The Randomized Set will consist of all patients who signed the ICF and were subsequently randomized into the study, regardless of study treatment administration.

5.3. Safety Analysis Set

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

5.4. Full Analysis Set

Full Analysis Set (FAS) will consist of all patients randomized 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 analyzes according to the randomized treatment.

5.5. Per Protocol Set

Per Protocol Set (PP) will consist of all patients in the FAS who fulfil the study protocol requirements in terms of IMP 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 evaluated according to the treatment dose they will actually receive.

5.6. Protocol Deviations

Important protocol deviations will be collected in the eCRF and CTMS. Each instance of a protocol deviation will be determined to be either significant or not. Protocol deviations linked to COVID-19 will be identified with “COVID-19 XXXXXX”.

The major protocol deviations include, but are not limited to, the following (to be finalized before database lock):

- Non compliance with IP administration (less than 80% or more than 120%);
- missing primary efficacy data;
- Major deviation from inclusion/exclusion criteria (eligibility violations) (will be defined in blind conditions in the last blind data review meeting before database lock);
- intake of prohibited medications.

Protocol deviations will be reviewed during the course of the study and prior to database lock.

Patients with any major protocol deviations listed above will not be included in the PP set.

Number (%) of patients with at least one major protocol deviation leading to exclusion of subject from the Per-protocol will be included in a summary table, using the FAS Set.

All protocol deviations will be listed for all patients in the Randomized Set, including their assignment of minor, major, and the date the deviation occurred.

Protocol deviations linked to COVID-19 will be listed on a separate listing in the Randomized Set.

6. General Aspects for Statistical Analysis

6.1. General Methods

- SAS Version 9.4 or higher will be used for programming and production.
- Unless otherwise specified, summaries will be presented for each treatment and overall.
- Continuous variables will be summarized using the number of observations (n), n missing (when applicable), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using number of observations (n), n missing (when applicable), frequency and percentages of patients. 95% and 99% confidence limits for the mean will be calculated based on the t-distribution, where indicated.The denominator will be based on the total number of patients in the treatment group or overall, or on the total number of subjects with non-missing data, as appropriate.
- All relevant patient data will be included in listings including assessments of unscheduled visits. All patients entered into the database will be included in patient data listings.
- See Sections 15 and 17 for the definition of planned summary tables and listings. Templates for each unique table and patient listing are provided in a separate document.

6.2. Key Definitions

6.2.1. Baseline Value

Unless otherwise specified, the baseline value for any variable will be the last value taken prior to the start of medication. This includes screening assessment. Unscheduled measurements prior to first administration date will be considered in the calculation of baseline values.

6.2.2. Change from Baseline and Percent Change from Baseline at a Post-Treatment Time Point

Change from baseline is defined as the difference between the post-treatment value and the baseline value.

Percent change from baseline is defined as 100* (change from baseline)/ score at baseline.

6.2.3. Time Since Diagnosis of Dry Eye

Time since diagnosis of dry eye (in months) will be calculated as 12*(date of baseline - date of dry eye)/365.25.

If the date of dry eye is partially missing (month and/or day), then the following rules will be used to impute the start date:

- Missing day: replace the missing day by 01.
- Missing month : replace missing month by January

6.2.4. Number of Days on Treatment

Number of days on treatment is calculated as [(date of last instillation of treatment - date of first instillation of treatment) +1].

6.2.5. Compliance

Percentage Compliance (%) will be evaluated according to the following formula:

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

6.2.6. Number of Drops/Day

Drops/day during treatment period is defined as [sum of drops during treatment period / (date of Week 4 or date of last visit during treatment period – date of baseline +1)].

Drops/day during follow up period is defined as [sum of drops during follow up period / (date of Week 16 or date of last visit during follow up period – date of Week 4 + 1)].

6.3. Missing Data

6.3.1. Missing Data for Efficacy

For Schirmer test I, Schirmer test II, SANDE, fluorescein staining and TFBUT, the LOCF method will be used for imputing missing data in the FAS set at Week 4.

For missing data at Week 4, the data from the previous visit (Week 2 or early discontinuation visit if during treatment period) will be used to estimate the missing value. If a patient has missing data for all post baseline visits, baseline will be carried forward (this cannot happen for the primary end-point because of the FAS definition).

Several sensitivity analyses will be performed concerning the primary analysis in case of many missing values (decision to be made at the final blind Data Review Meeting, before data base lock).

The following strategies will be applied: (a) an analysis restricted to the complete cases (only subjects having a full data set for the primary outcome will be considered); (b) an analysis of repeated measures performed on all subjects having at least one post-baseline efficacy measurement and assuming that missing data are distributed as missing at random (see Appendix 1 for the SAS code); (c) an analysis considering the worst case method (the worst possible value of the scale is assigned to missing values).

For IDEEL and EQ-5D-3L questionnaires, missing data will be imputed according to the questionnaire manuals.

6.3.2. Missing Dates for Adverse Events

If the adverse event start date is partially or completely missing, then the following rules will be used to impute the start date for the purpose of determining treatment emergence status only:

- If the whole start date is missing, then the start date of first drug instillation will be used.
- Missing month: if the AE has occurred the same year as start date of drug instillation, replace the missing month of onset by the month of start date of drug instillation.

  If the AE has occurred the subsequent year after the year of start date of drug instillation, replace the missing month of onset by January.

  If the AE has occurred the previous year of the year of start date of drug instillation, replace the missing month of onset by December.
- Missing day: if the AE has occurred the same month and year as start date of drug instillation replace the missing day of onset by the day of start date of drug instillation.

- if according to month and year the AE has occurred after the start date of drug instillation replace the missing day of onset by 01.
- if according to month and year the AE has occurred before the start date of drug instillation replace the missing day by the last day of the month.

6.4. Visit Windows

CRF visits will be used without establishing acceptable visit windows, because the study is short.

6.5. Pooling of Centres

Not applicable.

6.6. Subgroups

The primary, secondary, explorative and safety endpoints will be also summarized within each stratification subgroup (absence/presence of Primary Sjögren's Syndrome).

In order to assess the impact of COVID-19 on primary efficacy endpoint and on safety, subgroup analyses will be performed (affected patients versus non affected patients) if 10% or more treated subjects are affected by COVID-19 during the study.

7. Demographic, Other Baseline Characteristics and Medication

Demographics and others baseline characteristics are presented in tables 14.1 to 14.1.3.1 (see section15)

7.1. Patient Disposition and Withdrawals

The following frequencies (number and percent) will be displayed in the patient disposition table, by treatment group and overall:

- Number of patients enrolled;
- Number of patients screen failure;
- Number of patients randomized (overall and by strata);
- Number (%) of patients in the FAS (Full Analysis Set) (overall and by strata);
- Number (%) of patients in the PP set (overall and by strata);
- Number (%) of patients in the Safety Set (overall and by strata);
- Number (%) of patients who completed the study (overall and by strata);
- Number (%) of patients who discontinued the study early and reasons for discontinuation (overall and by strata).

The disposition analyses will be based on the Enrolled Set.

The denominators for the percent calculations will be the number of patients in the randomized set or in the specific analysis set.

Patient completion status, date of completion/discontinuation and reason for discontinuation will be listed.

7.2. Demographic and Other Baseline Characteristics

The following baseline and demographic characteristics will be summarized per treatment group and overall:

- Age (years). Age is recorded directly in the database and is not calculated separately
- Gender (Male, Female)
- Race (American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White or Caucasian; Other)
- Ethnicity (Hispanic, Latino or Spanish; Not Hispanic, Latino or Spanish)
- Eligible eye (Right, Left)
- Time since diagnosis of dry eye

Demographic and background data will be summarized using summary statistics, as appropriate.

The Full Analysis Set will be used to present these data.

In case there is a relevant difference (≥ 10%) in sample size among the different datasets (Randomized, SAF, FAS and PP) , these data will be also presented using other sets.

7.3. Ocular and Systemic Medical History and Concomitant Diseases

Ocular and Systemic Medical History and Concomitant Diseases are presented in tables 14.1.3.2.1 to 14.1.3.2.2 (see section15).
Ocular and systemic medical history will be coded to system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) version 21.1.

Tables for ocular medical history and systemic medical history will be provided using the Safety Set.

Data will be summarized, by SOC and PT and sorted alphabetically. Conditions that are reported more than once for a given SOC and PT will be counted only once per patient on the PT level for each SOC.
The Safety Set will be used to present these data.

A corresponding data listing will be presented for all enrolled patients.

7.4. Medication

Medications are presented in tables 14.1.4.1.1 to 14.1.4.2.2 (see section15).
Prior and concomitant medications will be coded by the Anatomical Therapeutic Chemical (ATC) classification system according to the World Health Organization Drug Dictionary (WHODRUG), WHODrugDDEB2 - 201901.
A listing of prior and concomitant medications will be provided for all enrolled patients (prior medications) and randomized patients (concomitant medications).

7.4.1. Previous Ocular and Systemic Medication

Previous ocular and systemic medications are defined as those medications recorded on the Previous Ocular and Systemic Medications pages of the eCRF.

Tables for previous ocular medication and previous systemic medication will be provided using the Safety set.

For the summary tables, the count and percentage of patients under each ATC class level 2 and Preferred name will be summarized by treatment group.

If a patient has taken prior medications more than once, the patient will be counted only once under any given drug class.

7.4.2. Concomitant Ocular and Systemic Medication

Concomitant ocular and systemic medications are defined as those medications recorded on the Concomitant Ocular and Systemic Medications pages of the eCRF.

Tables for concomitant ocular medication and concomitant systemic medication will be provided using the Safety Set.

For the summary tables, the count and percentage of patients under each ATC class level 2 and Preferred name will be summarized by treatment group.

If a patient has taken concomitant medications more than once, the patient will be counted only once under any given drug class.

8. Efficacy

For the purpose of efficacy analysis in this trial, the statistical analysis (both descriptive and inferential) will be done on the eligible eye when applicable.

Results from both eyes will be presented in the listings.

Primary and secondary efficacy endpoints will be summarized using the FAS and Per Protocol set. Efficacy endpoints will be also summarized for patients with the Primary Sjögren's syndrome and for patients without the Primary Sjögren's syndrome .

Efficacy are presented in tables 14.2.1.1.1 to 14.2.2.15.2.3 (see section15)

8.1. Primary Efficacy Endpoint and Analysis

The primary efficacy endpoint is the change from baseline in Schirmer test I (without anesthesia) versus Week 4. The primary analysis is based on the FAS population. Missing data will be replaced by means of the Last Observation Carried Forward (LOCF) method.

The Schirmer test I 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. The same summary analysis will be provided after pooling the treated patients (20 µg/mL BID arm and 20 µg/mL TID) together. Comparison (descriptive in nature) of the change from baseline of each treatment versus placebo will be performed by means of a t-test at each timepoint.

The primary analysis will be performed by means of an analysis of variance including only treatment as main factor followed by pre-planned comparisons from Vehicle and rhNGF dosages according to Williams' procedure.
The first comparison will compare the rhNGF TID dose to the Placebo using Williams test.

In case of significant result then the rhNGF BID dose will be compared to the Placebo; if the result is not significant then the test will be stopped.

Description of the Williams' Test:

µ0 = Effect of Placebo
µ1 = Effect of rhNGF BID
µ2 = Effect of rhNGF TID

Hypotheses:
H0: µ0 = µ1 = µ2
H1: µ0< = µ1 ≤ µ2

The test develops into two phases:
* First step
Starting from the observed means X_i, determine the maximum likelihood estimates Mi (corrected mean of group i after amalgamation) under the alternative hypothesis.

If X_i satisfies the inequalities written in H1 then $M_i = X_i$
Otherwise pool any adjacent violators into the same value:
$M_i = (n_i * X_i + n_{i+1} * X_{i+1}) / (n_i + n_{i+1})$ where n_i = sample size of group i.

The process is repeated until the means are completely ordered.

* Second step
Calculate the test statistic given by
$T_k = (M_k – X_0)/ s*sqrt(1/ n_0 + 1/ n_k)$

where s = root mean square error and X_0 is the observed mean in the placebo group.

The fact that the kth dose level is the minimum effective dose is concluded if Tj > tj,α for all j≥k where the tj,α values are the critical values reported by Williams [2]).

The Schirmer test I values will be also listed.

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.

For patients already enrolled in the study, the assignment to a strata will be based on Medical history form.
If “Primary Sjogren” is recorded in the Medical condition of the Medical history form then the patient will be assigned to “Presence of Primary Sjogren”; if only “Sjogren” is recorded then the patient will be assigned to “Absence of Primary Sjogren”.In all other cases, the patient will be assigned to “Absence of Primary Sjogren”.

In order to assess the robustness of results of primary analysis, the Schirmer test I will be also evaluated by means of non parametric Fisher’s exact test after appling the following categorization at week 4:

- A patient is defined as “Responder” if the Schirmer test I value at week 4 is greater than 10 mm/5 minutes;
- A patient is defined as “Non responder” if the Schirmer test I value at week 4 is lower or equal than 10 mm/5 minutes.

8.2. Secondary Efficacy Endpoints and Analyses

The same exploratory sensitivity analysis will be also conducted for SANDE, Schirmer Test II, Corneal and Conjunctiva Vital Staining and TFBUT.

8.2.1. Change from baseline in Symptoms questionnaire (SANDE) scores for severity and frequency

The SANDE questionnaire is comprised of 2 questions at each visit:

(1) How often do your eyes feel dry and/or irritated?
(2) How severe do you feel your symptoms of dryness and/or irritation are?

One measure frequency of symptoms ranges from “0 mm = rarely” to “100 mm = all of the time,” and the other measure severity of symptoms ranges from “0 mm = very mild” to “100 mm = very severe”.

The global SANDE score will be calculated by multiplying the frequency score by the severity score and obtaining the square root [4].

Change from baseline at Week 4 will be analyzed using analysis of variance including treatment as factor followed by pre-planned comparisons from Vehicle and rhNGF dosages according to Williams’ procedure.

Descriptive statistics (actual and change from baseline) of SANDE scores will be presented by treatment and visit. Comparison (descriptive in nature) of the change from baseline of each treatment versus placebo will be performed by means of a t-test at each timepoint.

Symptoms questionnaire (SANDE) scores will be also listed.

8.2.2. Change from Baseline in Schirmer Test II (with Anesthesia)

The Schirmer test II (with anesthesia) 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. Comparison (descriptive in nature) of the change from baseline of each treatment versus placebo will be performed by means of a t-test at each timepoint.

The Change from baseline in Schirmer test II at Week 4 will be analyzed in a similar manner as the Change from baseline to Week 4 in Schirmer test I.

The Schirmer test II values will be also listed.

8.2.3. Change from Baseline in Corneal and Conjunctiva Vital Staining with Fluorescein (NEI Scales)

Corneal staining total score is defined as the sum of scores from 5 corneal areas: Central, Superior, Temporal, Nasal, and Inferior. The score for each area ranges from 0 to 3. Thus, the corneal staining total score can range from 0 to 15.

The conjunctiva is divided into a superior paralimbal area, an inferior paralimbal area and a peripheral area with a grading scale of 0–3 and with a maximal score of 9 for the nasal and temporal conjunctiva.

Thus, the conjunctival staining total score can range from 0 to 18.

Corneal and conjunctiva vital staining total score is the sum of corneal staining total score and conjunctiva total score.

Descriptive statistics (actual and change from baseline) for Corneal and conjunctiva vital staining total score, corneal score and conjunctiva score will be presented by treatment and visit. Comparison (descriptive in nature) of the change from baseline of each treatment versus placebo will be performed by means of a t-test at each timepoint.

The Change from baseline in Corneal and conjunctiva vital staining total score (NEI scales) at Week 4 will be analyzed in a similar manner as the Change from baseline to Week 4 in Schirmer test I.

The Corneal and conjunctiva vital staining score with fluorescein will be listed.

8.2.4. Change from Baseline in Tear film break-up time (TFBUT)

Descriptive statistics (actual and change from baseline) for TFBUT will be presented by treatment and visit. Comparison (descriptive in nature) of the change from baseline of each treatment versus placebo will be performed by means of a t-test at each timepoint.

Change from baseline in TFBUT at Week 4 will be analyzed in a similar manner as the Change from baseline to Week 4 in Schirmer test I.

TFBUT values will be listed.

8.2.5. Number of Patients who Experienced a Worsening in Symptom Scores (SANDE) and/or NEI Score ≥ 50% Assessed at Week 4

Number and percentage of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score ≥ 50% assessed at Week 4 will be summarized by treatment group.

Difference, between treatment group (Each active dose – Placebo), in the percentage of patients who experienced a worsening will be tested using a chi-square test.

8.2.6. Quality of Life/Impact of Dry Eye on Everyday Life (IDEEL)

The IDEEL questionnaire will be filled in at screening, baseline-Day1, Week 4, Week 8, Week 12 and Week16.

IDEEL is a 3-module questionnaire with 57 questions, and it assesses dry eye symptoms, the effect of dry eye disease on quality of life, and treatment satisfaction over the last 2 weeks. The 3 modules consist of:

- Dry eye Quality of Life (27 questions) comprising three sections: “Daily activities”, “Feelings” and “Work”.
- Dry eye Treatment satisfaction & Bother (10 questions) comprising two sections: “Treatment – In general” and “Treatment- Eye drop”.
- Dry eye Symptom bother (20 questions).

Module 1:

Dry eye impact on daily life (27 questions) comprising 3 QoL domains: 1.a “Daily activities limitations”, 1.b “Emotional well being” and 1.c “Work limitations”.

26 questions will be considered as part of one of these 3 domains. Question 22 will not be considered part of a domain.

1.a: Daily Activities

Daily activities section	QOL content domain	Variable Name	Used in calculation of domain score?
1. Doing close work in the **morning or afternoon** (such as crossword puzzles, reading, looking at a computer, and/or sewing)	Daily Activity Limitations	IDLACT1	Yes
2. Doing close work in the **evening or at night**	Daily Activity Limitations	IDLACT2	Yes
3. Driving	Daily Activity Limitations	IDLACT3	Yes
4. Being around and/or using scented products (such as cologne or hairspray)	Daily Activity Limitations	IDLACT4	Yes
5. Working on a computer	Daily Activity Limitations	IDLACT5	Yes
6. Going somewhere where there is tobacco smoke or being around someone who smokes	Daily Activity Limitations	IDLACT6	Yes
7. Wearing contact lenses	Daily Activity Limitations	IDLACT7	No
8. Wearing make-up near or on my eyes	Daily Activity Limitations	IDLACT8	No

Daily activities section	QOL content domain	Variable Name	Used in calculation of domain score?
9. Flying on an airplane	Daily Activity Limitations	IDLACT9	No

Response for questions 1 to 9 (IDLACT1-IDLACT9)	Original response code	Item score
I did not do this activity for reasons other than my dry eyes	6	5
None of the time	5	5
A little of the time	4	4
Some of the time	3	3
Most of the time	2	2
All of the time	1	1
I can **no longer** do this activity **due to my dry eyes**	0	0

The response option “I did not do this activity for reasons other than my dry eyes” has a response coded 6 but a scored item value of 5.

The original response code is the value to be used for data-entry. The item score is used during the computation of the Daily Activity Limitations Scale Score. Higher item scores are intended to reflect better quality of life (i.e. less limitations on daily activities).

Only 6 questions (9 (IDLACT1-IDLACT6) are included in the Daily activity Limitations scale score. Questions 7, 8 and 9 are excluded.

If 50% (3) or fewer of the 6 questions used in calculating Daily Activity Limitations score have missing item score, then the scale score is calculated by multiplying the mean of the non missing item score by 20. If 4 or more of the 6 item scores are missing then the scale score is not calculated and should be set at missing.

Multiplying by 20 transforms the scale score to a 0 to 100 scale, with 0 reflecting the greatest degree of limitations on daily activities measurable by the scale and 100 reflecting the greatest freedom from limitations on daily activities.

1.b Feelings

Feelings	QOL content domain	Variable Name	Used in calculation of domain score?
10. Irritability	Emotional Well-Being	IDLEMO1	Yes
11. Impatience	Emotional Well-Being	IDLEMO2	Yes
12. Feeling sad	Emotional Well-Being	IDLEMO3	Yes
13. Worry that my dry eyes will get worse	Emotional Well-Being	IDLEMO4	Yes

Feelings	QOL content domain	Variable Name	Used in calculation of domain score?
14. Feeling annoyed	Emotional Well-Being	IDLEMO5	Yes
15. Feeling like my eyes do not look nice	Emotional Well-Being	IDLEMO6	Yes
16. Feeling like I have to make adjustments to my life	Emotional Well-Being	IDLEMO7	Yes
17. Feeling different from other people because of my dry eyes	Emotional Well-Being	IDLEMO8	Yes
18. Feeling like I am always aware of my eyes	Emotional Well-Being	IDLEMO9	Yes
19. Feeling older than I really am	Emotional Well-Being	IDLEMO10	Yes
20. Feeling like people look at me and think I am fine when I'm not	Emotional Well-Being	IDLEMO11	Yes
21. Feeling like there is nothing I can do for my dry eyes	Emotional Well-Being	IDLEMO12	No

Response for questions 10 to 21	Original response code	Item score
None of the time	4	4
A little of the time	3	3
Some of the time	2	2
Most of the time	1	1
All of the time	0	0

11 questions (IDLEMO1- IDLEMO11) are included in the Emotional Well-Being score. Question 21 (IDLEMO12) is excluded from calculation.

If 50% (5) or fewer of the 11 questions used in the calculation of Emotional Well-Being score have missing item score, then the scale score is calculated by multiplying the mean of the non missing item scores by 25. If 6 or more of the 11 item scores are missing then the scale score is not calculated and should be set at missing.

Multiplying by 25 transforms the scale score to a 0 to 100 scale, with 0 reflecting the worst level of emotional well-being measurable by the scale and 100 reflecting the best.

1.c Work

Work	QOL content domain	Variable Name	Used in calculation of domain score?
22. Are you currently working?	Work limitations	IDLWRKYN	-

Work	QOL content domain	Variable Name	Used in calculation of domain score?
23. Feeling distracted	Work limitations	IDLWRK1	Yes
24. Feeling like I couldn't concentrate	Work limitations	IDLWRK2	Yes
25. Having to take a break from work	Work limitations	IDLWRK3	Yes
26. Having to change the way I work (such as the way I read, look at a computer, or work outside)	Work limitations	IDLWRK4	Yes
27. Having to change my work environment (such as how close I am to an air conditioning or heating vent)	Work limitations	IDLWRK5	Yes

Response for question 22 (IDLWRKYN)	Original response code	Item score
Yes	1	1
No	0	0

Response for questions 23 to 27 (IDLWRK1-IDLWRK5)	Original response code	Item score If IDLWRKYN=0	Item score If IDLWRKYN=1
None of the time	4	Missing	4
A little of the time	3	Missing	3
Some of the time	2	Missing	2
Most of the time	1	Missing	1
All of the time	0	Missing	0

5 questions (IDLWRK1-IDLWRK5) are included in the Work Limitations domain..

If 50% (2) or fewer of the 5 questions used in the calculation of the Work Limitations score have missing item scores, then the scale score is calculated by multiplying the mean of the non missing item scores by 25. If 3 or more of the 5 item scores are missing then the scale score is not calculated and should be set to missing.

Multiplying by 25 transforms the scale score to a 0 to 100 scale, with 0 reflecting the greatest degree of limitation at work measurable by the scale and 100 reflecting the least limitation at work.

Module 2:

Dry eye Treatment satisfaction & Bother module (10 questions) comprising 2 QoL domains: 2.a “Treatment satisfaction / Happiness” and “Treatment-related bother”.

2.a Treatment - In general

Treatment in General	QOL content domain	Variable Name	Used in calculation of domain score?
1. OVER THE LAST TWO WEEKS, how often did you use treatment for your dry eyes?	-	IDLTREAT	-
2. I was happy with how quickly my treatments worked	Treatment Satisfaction/ Happiness	IDLTSA1	Yes
3. I was happy with how long the effects of my treatments lasted	Treatment Satisfaction/ Happiness	IDLTSA2	Yes
4. The treatments I used **completely eliminated** my dry eye symptoms	Treatment Satisfaction/ Happiness	IDLTSA3	Yes
5. The treatments I used **relieved most** of my dry eye symptoms	Treatment Satisfaction/ Happiness	IDLTSA4	Yes
6. I was bothered by how often I had to use dry eye treatments	Treatment- Related Bother	IDLTBO1	Yes

Response for question 1 (IDLTREAT)	Original response code	Item score
None of the time	0	0
A little of the time	1	1
Some of the time	2	2
Most of the time	3	3
All of the time	4	4

Response for questions 2 to 5 (IDLTSA1- IDLTSA4)	Original response code	Item score If IDLTREAT=0	Item score If IDLTREAT NE 0 or missing
None of the time	0	Missing	0
A little of the time	1	Missing	1
Some of the time	2	Missing	2
Most of the time	3	Missing	3
All of the time	4	Missing	4
Response for question 6 (IDLTBO1)			
None of the time	4	Missing	4
A little of the time	3	Missing	3
Some of the time	2	Missing	2
Most of the time	1	Missing	1
All of the time	0	Missing	0

4 questions (IDLTSA1 - IDLTSA4) are included in the Treatment Satisfaction/Happiness scale score.

If 50% (2) or fewer of the 4 questions used in the calculation of Treatment Satisfaction/Happiness score have missing item score, then the scale score is calculated by multiplying the mean of the non missing item score by 25. If 3 or more of the 4 item scores are missing then the scale score is not calculated and should be missing.

Multiplying by 25 transform the scale score to a 0 to 100 scale, with 0 reflecting the lowest level of satisfaction/happiness with treatment measurable by the scale and 100 reflecting the highest level of satisfaction/happiness with treatment..

2.b Treatment- Eye Drops

Treatment- Eye Drops	QOL content domain	Variable Name	Used in calculation of domain score?
7. Do you ever use eye drops to treat your dry eyes?	-	IDLDRPYN	-
8. I was bothered by blurriness shortly after using my eye drops	Treatment- Related Bother	IDLTBO2	Yes
9. I was embarrassed when I had to use my eye drops	Treatment- Related Bother	IDLTBO3	Yes
10. I felt like I could not go anywhere without my eye drops	Treatment- Related Bother	IDLTBO4	Yes

Response for question 1 (IDLDRPYN)	Original response code	Item score
Yes	1	1
No	0	0

Response for question 8 to 10 (IDLTBO2- IDLTBO4)	Original response code	Item score If IDLDRPYN=0	Item score If IDLDRPYN NE 0
None of the time	4	Missing	4
A little of the time	3	Missing	3
Some of the time	2	Missing	2
Most of the time	1	Missing	1
All of the time	0	Missing	0

4 questions (IDLTBO1 - IDLTBO4) are included in the Treatment-Related Bother scale score.

If 50% (2) or fewer of the 4 questions used in the calculation of Treatment-Related Bother scale score have missing item scores, then the scale score is calculated by multiplying the mean of the non missing item score by 25. If 3 or more of the 4 item scores are missing then the scale score is not calculated and should be set at missing.

Multiplying by 25 transforms the scale score to a 0 to 100 scale, with 0 reflecting the greatest degree of treatment related bother measurable by the scale and 100 reflecting the lowest degree of treatment-related bother.

Module 3:

Dry eye Symptom bother (20 questions) comprising a unique domain.

Symptom Bother	QOL content domain	Variable Name	Used in calculation of domain score?
1.OVER THE LAST TWO WEEKS, how often did you experience dry eye symptoms?	Symptom Bother	IDLSYM1	Yes
2. Eyes that felt gritty or sandy	Symptom Bother	IDLSYM2	Yes
3. Felt like I needed to close my eyes even though I was not tired	Symptom Bother	IDLSYM3	Yes
4. Burning or stinging eyes	Symptom Bother	IDLSYM4	Yes
5. Tired eyes	Symptom Bother	IDLSYM5	Yes
6. Blurry vision	Symptom Bother	IDLSYM6	Yes
7. Itchy eyes	Symptom Bother	IDLSYM7	Yes
8. Irritated eyes	Symptom Bother	IDLSYM8	Yes
9. Eyes that felt like they had been scratched by something	Symptom Bother	IDLSYM9	Yes
10. Eye dryness	Symptom Bother	IDLSYM10	Yes
11. Mucus in, around, or coming out of my eyes	Symptom Bother	IDLSYM11	Yes
12. Puffy or swollen eyes	Symptom Bother	IDLSYM12	Yes
13. Eye redness	Symptom Bother	IDLSYM13	Yes
14. Aching or sore eyes	Symptom Bother	IDLSYM14	Yes
15. Felt like something was in my eye	Symptom Bother	IDLSYM15	Yes
16. Frequent and/or rapid blinking	Symptom Bother	IDLSYM16	Yes
17. Difficulty blinking because of little or no moisture in my eyes	Symptom Bother	IDLSYM17	Yes
18. Sensitivity to light, glare, and/or wind	Symptom Bother	IDLSYM18	Yes
19. Sensitivity to recirculated air (such as air conditioning and heat)	Symptom Bother	IDLSYM19	Yes
20. Headaches associated with dry eye symptoms	Symptom Bother	IDLSYM20	Yes

Response for question 1 (IDLSYM1)	Original response code	Item score
None of the time	0	0
A little of the time	1	1
Some of the time	2	2
Most of the time	3	3
All of the time	4	4

Response for questions 2 to 20 (IDLSYM2 - IDLSYM20)	Original response code	Item score
I did not have this symptom / Not applicable	0	0
Not at all	1	1
Slightly	2	2
Moderatly	3	3
Very much	4	4

All questions (IDLSYM1 – IDLSYM20) are included in the Symptom Bother scale score (IDLSYM).

If 50% (10) or fewer of the 20 questions used in the calculation of Symptom Bother scale score have missing item scores, then the scale score is calculated by multiplying the mean of the non missing item score by 25. If 11 or more of the 20 item scores are missing then the scale score is not calculated and should be set at missing.

Multiplying by 25 transforms the scale score to a 0 to 100 scale, with 0 reflecting the greatest degree of treatment related bother measurable by the scale and 100 reflecting the lowest degree of treatment-related bother.

Changes from baseline in each scale score will be analyzed using an mixed model for repeated measures (MMRM). The analyses will include the fixed, categorical effects of treatment (3 levels: rhNGF 20 µg/mlTID, rhNGF 20 µg/ml BID and vehicle TID), visit (4 levels: Weeks 4, 8, 12, 16) and treatment by visit interaction. Subject will be considered as a random effect.The covariance matrix used will be "unstructured". Comparisons versus vehicle TID will be provided using least square means at each visit and overall.

IDEEL data will be also listed.

8.2.7. Patient Global Impression of Change (PGIC)

Patient Global Impression of Change (PGIC) will be collected at Week 4, Week 8, Week 12 and Week 16.

A 7-point scale is used, representing the degree to which the general state of health have changed relative to start of the study. On the PGIC, 1 = very much improved and 7 = very much worse.

A frequency table will summarize the responses for each treatment by visit. To take into account the ordinal nature of the response, p-values based on the Wilcoxon rank sum test comparing each rhNGF to Placebo will be computed.

PGIC data will be also listed.

8.2.8. EQ-5D-3L

EQ-5D-3L will be collected at screening, baseline, Week 4, Week 8, Week 12 and Week 16.

The Questionnaire EQ-5D-3L is a 5-dimension instrument assessing quality of life.
The 5 dimensions are Mobility, Self-Care, Usual Activity, Pain/Discomfort, and Anxiety/Depression.
Each dimension is scored as 1 = no problem, 2 = some problem, and 3 = extreme Problem.

No imputation will be done on missing values.

Descriptive summary statistics for the single dimension scores ("Mobility", "Self-Care", "Usual Activities", "Pain/Discomfort" and "Anxiety/Depression") will be presented by visit and treatment group.

Shift tables comparing results from Baseline to each visit will be presented with percentages based on subjects with a non-missing value at Baseline and post-baseline visit.

The patients provide an assessment of their best health state by means of a score between 0 and 100 (EQ visual analogue scale – VAS).

The change in VAS score from the baseline visit to the post-baseline visit will be analyzed using an mixed
model for repeated measures (MMRM). The analyses will include the fixed, categorical effects of treatment (3 levels: rhNGF 20 µg/mlTID, rhNGF 20 µg/ml BID and vehicle TID), visit (4 levels: Weeks 4, 8, 12, 16) and treatment by visit interaction. Subject will be considered as a random effect.The covariance matrix used will be "unstructured". Comparisons versus vehicle TID will be provided using least square means at each visit and overall.

EQ-5D-3L data will be listed.

8.3. Exploratory Endpoint

All exploratory endpoints will be summarized using Full Analysis Set. Statistical testing has only a descriptive value.

8.3.1. Proportion and frequency of preservative-free artificial tears use (n° drops/day) during the treatment period

The proportions and n° drops/day (see definition in 6.2.6) will be summarized during the treatment period, by treatment group.

8.3.2. Proportion and Frequency of Preservative-Free Artificial Tears Use (n° drops/day) During the Follow-Up Period

The proportions and n° drops/day (see definition in 6.2.6) will be summarized during the follow up period, by treatment group.

8.3.3. Change from Baseline in Schirmer Test I (Without Anesthesia) Versus Week 2

Change from baseline in Schirmer test I (without anesthesia) at Week 2 will be analyzed using the same analysis used for the primary efficacy end-point.

8.3.4. Change from Baseline in Symptoms Questionnaire (SANDE) Scores for Severity and Frequency Assessed at 2 Weeks

Change from baseline in symptoms questionnaire (SANDE) scores for severity and frequency assessed at 2 weeks will be analyzed using the same analysis used for the primary efficacy end-point.

8.3.5. Change from Baseline in Corneal and Conjunctiva Vital Staining with Fluorescein (NEI Scales) Versus Week 2

Change from baseline in corneal and conjunctiva vital staining with fluorescein (NEI scales) versus Week 2 will be analyzed using the same analysis used for the primary efficacy end-point.

8.3.6. Change from Baseline in Tear Film Break-Up Time (TFBUT) Versus Week 2

Change from baseline in TFBUT versus Week 2 will be analyzed using the same analysis used for the primary efficacy end-point.

8.3.7. Number of Patients who Experienced a Worsening in Symptom Scores (SANDE) and/or NEI Score ≥ 50% Assessed at Week 2

Number of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score ≥ 50% assessed at Week 2 will be summarized by treatment group.

8.3.8. Change from Baseline in Goblet Cells Density at week 4

Goblet cells density is measured at baseline, Week 4 and Week 16.

Change from baseline in goblet cells density at Week 4 will be analyzed using the same analysis used for the primary efficacy end-point.

The goblet cells density 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.

Goblet cells density will be also listed

8.4. Post Hoc Endpoint

Some correlation between sign and symptom scores could be computed for exploratory purpose.

9. Safety

The population used for safety analyses will be the Safety Set (SS). Safety will be assessed on the basis of adverse events (AEs).

Safety tables are presented in tables 14.1.5.1 and 14.1.5.2 and 14.3.1.1 to 14.3.2.4 ((see section15)

9.1. Extent of Exposure

The study drug administration (Day 1 to Week 4) will be captured in the patient diary including the administration of preservative-free artificial tears (Day 1 to Week 12).

The extent of exposure, otherwise referred to as the time from first instillation of study medication to last instillation of study medication is defined as:

Number of days on treatment = date of last instillation of treatment – date of first instillation of treatment +1

The data will be summarized by treatment group and presence/absence of primary Sjogren. A listing will be also provided.

9.2. Treatment Compliance

The assessment of patients' compliance to the IMP will be made by determining the number of drops administered to the eligible eye (see section 6.2.5).

Gross noncompliance will be defined as compliance for the eligible eye lower than 80% or greater than 120% and in case of gross noncompliance the patient will be excluded from the Per Protocol set.

9.3. Adverse Events / Adverse Drug Reactions

Adverse events (AEs) will be coded by SOC and PT, using the Medical Dictionary for Regulatory Activities (MedDRA 21.1).

Treatment-emergent adverse events (TEAEs) are all events occurring or worsening after the first dose of the IMP.

TEAEs will be summarized by SOC ,PT, treatment arm and phase (Treatment phase or Follow up). Both the number and percentage of patients who experience the event and the number of events will be summarised per treatment arm. Percentages will be based on the number of patients in the Safety Set.

All tables for TEAEs will be also summarized separately for each strata.

An overall summary of the number and percentage of patients and number of the events with any TEAEs, potentially Related TEAEs, Serious TEAEs, Serious Potentially Related TEAEs, TEAEs leading to study discontinuation, TEAEs leading to death and TEAE of special interest (AESI)will be generated, and presented by treatment arm and phase (Treatment phase or Follow up)

TEAEs will be sorted alphabetically by SOC, and then sorted alphabetically by PTs within SOC.

Separate tables will be presented by severity, and for SAEs, ocular TEAEs, related ocular TEAEs, related TEAEs, and TEAEs leading to study discontinuation.

"Possible", "probable", "highly probable" or missing relationships are to be considered as related to study drug for the summary tables. "None" and "unlikely" relationships are to be considered not related to study drug.

Individual AEs will be listed in patient data listings. A listing of patients died due to COVID-19 will be also provided on randomized set.

9.4. Laboratory Evaluations

Not applicable

9.5. Vital Signs

Not applicable

9.6. ECG

Not applicable

9.7. Physical Examination

Not applicable

10. Interim Analyses

No interim analysis was planned

11. Changes from Analysis Planned in Protocol

IDEEL and EQ-5D will be analysed using a mixed model for repeated measures (MMRM) instead of analysis of variance as the method seems more appropriate due to the repeated measures.

Exploratory sensitivity analysis will be also conducted for SANDE, Schirmer Test II, Corneal and Conjunctiva Vital Staining and TFBUT instead of only primary efficacy endpoint.

Overall compliance will not be calculated, as we don't have in the database the number of unused vials. We only have the number of vials not returned to the site whatever the reasons

Additional analyses have been planned to investigate the impact of COVID-19 pandemic on primary endpoint and on patient safety profiles (in case of 10% randomized patients affected).

Summary statistics on primary endpoint reporting the two treatment doses (20 µg/mL BID arm and 20 µg/mL TID) pooled versus placebo has been added to see the overall effect of the rhNGF treatment.

A sensitivity analysis on primary endpoint based on classification of patients in "Responders" and "Non Responders" based on the Schirmer Test I at the end of treatment has been added. This analysis will assess the robustness of results by considering an exact statistical method (not depending on assumption of normality of the data) and based on the status of the patients at the end of treatment.

12. Reference List

1. Williams DA. The comparison of several dose levels with a zero dose control. 1972. Biometrics 28, 519-531.

2. Williams DA. A test for differences between treatment means when several dose levels are compared with a zero dose control. 1971. Biometrics 27, 103-117.

3. Shein-Chung Chow, Jun Shao, Hansheng Wang; Samples Size Calculations in Clinical Research - Marcel Dekker, Inc. 2003I, SBN: 0-8247-0970-5, p. 186-189.

4. F Amparo, DA Schaumberg, R Dana; Comparison of two questionnaires for dry eye symptom assessment: the ocular surface disease index and the symptom assessment in dry eye Ophthalmology 2015 July; 122 (7), 1498 - 1503

13. Programming Considerations

All tables, figures, listings (TFLs), and statistical analyses will be generated using SAS for Windows, Release 9.4. (SAS Institute Inc., Cary, NC, USA). Computer-generated table, listing and figure output will adhere to the following specifications.

13.1. General Considerations

- One SAS program can create several outputs, or a separate SAS program will be created for each output.
- One output file can contain several outputs.
- Output files will be delivered in Rich Text Format (RTF) that can be manipulated in MSWord.
- Numbering of TFLs will follow ICH E3 guidance.

13.2. Table, Listing, and Figure Format

13.2.1. General

- All TFLs will be produced in landscape format on A4 paper size, unless otherwise specified.
- All TFLs will be produced using the Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- The data displays for all TFLs will have a minimum blank 1-inch margin on all 4 sides.
- Headers and footers for figures will be in Courier New font, size 8 which is the smallest acceptable point size for the Regulatory Authorities.
- Legends will be used for all figures with more than 1 variable, group, or item displayed.
- TFLs will be in black and white (no color), unless otherwise specified.
- Specialized text styles, such as bolding, italics, borders, shading, and superscripted and subscripted text, will not be used in the TFLs, unless otherwise specified. On some occasions, superscripts 1, 2, or 3 may be used (see below).
- Only standard keyboard characters will be used in the TFLs. Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used. Hexadecimal-derived characters will be used, where possible, if they are appropriate to help display math symbols (e.g., µ). Certain subscripts and superscripts (e.g., cm2, Cmax) will be employed on a case-by-case basis.
- Mixed case will be used for all titles, footnotes, column headers, and programmer-supplied formats, as appropriate.

13.2.2. Headers

- All output should have the following header at the top left of each page:
- Dompé farmaceutici S.p.A

  Protocol NGF0118

  Draft/Final Run *<date>*

- All outputs should have Page n of N at bottom right corner of each page. TFLs are internally paginated in relation to the total length (i.e., the page number should appear sequentially as page n of N, where N is the total number of pages in the table).

- The date in which output was generated should appear along with the program name as a footer on each page.

13.2.3. Display Titles

- Each TFL is identified by the designation and a numeral. (i.e., Table 14.1.1). ICH E3 numbering will be used. A decimal system (x.y and x.y.z) is used to identify TFLs with related contents: for example, the set of tables 14.2.1.1.x (i.e. tables 14.2.1.1.1, 14.2.1.1.2, 14.2.1.1.3, …) will be for the primary end-point. The title is centered. The analysis sets are identified on the line immediately following the title. The title and table designation are single spaced. A solid line spanning the margins will separate the display titles from the column header.

- There will be 1 blank line between the last title and the solid line in the column headers.

Table x.y.z
First Line of Title
Second Line of Title if Needed
ITT Analysis Set

13.2.4. Column Headers

- Column headings are displayed immediately below the solid line described above in initial upper-case characters.

- In the case of efficacy tables, the variable (or characteristic) column will be on the far left followed by the treatment group columns and total column (if applicable). P-values may be presented under the total column or in separate p-value column (if applicable). Within-treatment comparisons may have p-values presented in a row beneath the summary 14.2.statistics for that treatment.

- For numeric variables, “unit” will be included in column or row heading, when appropriate.

- Analysis set sizes will be presented for each treatment group in the column heading as (N = xx) (or in the row headings, if applicable). This is distinct from the ‘n’ used for the descriptive statistics representing the number of patients in the analysis set.

- The order of treatments in the tables will be active treatment first and vehicle, followed by a total column (if applicable).

13.2.5. Body of the Data Display

13.2.5.1. *General Conventions*

Data in columns of a table or listing are formatted as follows:

- Alphanumeric values are left-justified.

- Whole numbers (e.g., counts) are right-justified.

- Numbers containing fractional portions are decimal aligned.

13.2.5.2. *Table Conventions*

- Units will be included where available.
- If the categories of a parameter are ordered, then all categories between the maximum and minimum category are presented in the table, even if n = 0 for all treatment groups in a given category that is between the minimum and maximum level for that parameter. For example, the frequency distribution for symptom severity would appear as:

Severity Rating	N
severe	0
moderate	8
Mild	3

Where percentages are presented in these tables, zero percentages will not be presented and so counts of 0 will be presented as 0 and not as 0 (0%).

- If the categories are not ordered (e.g., Medical History), then only those categories for which there is at least 1 patient represented in 1 or more groups are included, except for reasons for discontinuations where all categories will be shown.
- Unknown or Missing categories are added to each parameter for which information is not available for 1 or more patients.
- Unless otherwise specified, the estimated mean and median for a set of values are printed out to 1 more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum should report the same significant digits as the original values. For example, for systolic blood pressure:

N	XX
Mean	XXX.X
Std Dev	X.XX
Median	XXX.X
Minimum	XXX
Maximum	XXX

- P-values are reported in the format: “0.xxx”, where xxx is the value rounded to 3 decimal places.
- Percentage values are printed to one decimal place, in parentheses with no spaces, one space after the count (e.g., 7 (12.8%), 13 (5.4%)). Unless otherwise noted, for all percentages, the number of patients in the analysis set for the treatment group who have an observation will be the denominator. Percentages after zero counts should not be displayed and percentages equating to 100% are presented as 100%, without decimal places.
- As general rule, the percentage of patients is calculated as a proportion of the number of patients assessed in the relevant treatment group (or overall) for the analysis set presented.
- Where a category with a subheading (such as system organ class) has to be split over more than one page, the subheading will be followed by “(cont)” at the top of each subsequent page.

The overall summary statistics for the subheading should only be output on the first relevant page.

13.2.5.3. *Listing Conventions*

- Listings will be sorted for presentation in order of: patient number, treatment groups, visit/collection day and visit/collection time.
- Dates are printed in SAS DATE9.format (“ddMMMyyyy”: 01JUL2000). Missing portions of dates are represented on patient listings as dashes (--JUL2000).
- All observed time values are to be presented using a 24-hour clock HH:MM or HH:MM:SS format (e.g., 11:26:45, or 11:26). Time will only be reported if it was measured as part of the study.
- Units will be included where available.

14. Quality Control

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses.

Programs for the production of SDTM domains, ADaM/analysis datasets and TFLs will be double-programmed. For datasets, tables and listings, the production programming results and validation programming results will be compared electronically.

A more complete overview of the development of programs is detailed in Syneos Health SOP Developing Statistical Programs (3907).

Syneos Health SOPs Developing Statistical Programming Specifications (3906), Developing Statistical Programs (3907) and Conducting the Transfer of Biostatistical Deliverables (3908) describe the quality control procedures that are performed for all SAS programs and outputs. Quality control is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by reviewingf the produced output.

15. Index of Tables

Table Number	Name	Analysis Set	Topline
14.1.1.	Patient disposition	Enrolled Set	Yes
14.1.2.1	Major Protocol Deviations	Full Analysis Set	
14.1.2.2	Reasons for Exclusion from Analysis Populations	Randomized Set	
14.1.3.1	Demographic and Baseline Characteristics	Full Analysis Set	Yes
14.1.3.2.1	Ocular Medical History by MedDRA System Organ Class and Preferred Term	Safety Set	
14.1.3.2.2	Systemic Medical History by MedDRA System Organ Class and Preferred Term	Safety Set	
14.1.4.1.1	Summary of Previous Ocular medications	Safety Set	
14.1.4.1.2	Summary of Previous Systemic Medications	Safety Set	
14.1.4.2.1	Summary of Concomitant Ocular Medications	Safety Set	
14.1.4.2.2	Summary of Concomitant systemic medications	Safety Set	
14.1.5.1	Compliance to study treatment	Safety Set	
14.1.5.2	Exposure to Study Treatment	Safety Set	
14.2.1.1.	Analysis of Change from Baseline in Schirmer test I at Week 4 - Eligible eye	Full Analysis Set	Yes
14.2.1.2	Analysis of Change from Baseline in Schirmer test I tat Week 4 - Eligible eye	Per Protocol Set	Yes
14.2.1.3	Exploratory Sensitivity Analysis of Change from Baseline in Schirmer test I at Week 4 - Eligible eye	Full Analysis Set	
14.2.1.4	Exploratory Sensitivity Analysis of Change from Baseline in Schirmer test I at Week 4 - Eligible eye	Per protocol Set	
14.2.1.5.1	Summary of Schirmer test I by treatment and visit (mm) - Eligible eye	Full Analysis Set	Yes
14.2.1.5.2	Summary of Schirmer test I by treatment (pooled) and visit (mm) - Eligible eye	Full Analysis Set	
14.2.1.6	Summary of Schirmer test I by treatent and visit (mm) – Presence of Primary Sjogren -Eligible eye	Full Analysis Set	
14.2.1.7	Summary of Schirmer test I by treatment and visit (mm) – Absence of Primary Sjogren- Eligible eye	Full Analysis Set	
14.2.1.8	Summary of Responders (based on Schirmer test I) by treatment and visit (mm) - Eligible eye	Full Analysis Set	
14.2.1.9.1	Summary of Schirmer test I by treatment and visit - Eligible eye	Per Protocol Set	Yes

Table Number	Name	Analysis Set	Topline
14.2.1.9.2	Summary of Schirmer test I by treatment (pooled) and visit - Eligible eye	Per Protocol Set	
14.2.1.10	Summary of Schirmer test I by treatment and visit - Presence of Primary Sjogren - Eligible eye	Per Protocol Set	
14.2.1.11	Summary of Schirmer test I by treatment and visit - Absence of Primary Sjogren - Eligible eye	Per Protocol Set	
14.2.1.12	Summary of Responders (based on Schirmer test I) by treatment and visit (mm) - Eligible eye	Per Protocol Set	
14.2.2.1.1	Analysis of Change from Baseline in symptoms questionnaire (SANDE) at Week 4	Full Analysis Set	Yes
14.2.2.1.2	Analysis of Change from Baseline in symptoms questionnaire (SANDE) at Week 4	Per Protocol Set	Yes
14.2.2.1.3	Exploratory Sensitivity Analysis of Change from baseline in symptoms questionnaire (SANDE) at week 4	Full Analysis Set	
14.2.2.1.4	Exploratory Sensitivity Analysis of Change from baseline in symptoms questionnaire (SANDE) at week 4	Per Protocol Set	
14.2.2.1.5	Summary of Symptoms Questionnaire (SANDE) by treatment and visit	Full Analysis Set	Yes
14.2.2.1.6	Summary of Symptoms Questionnaire (SANDE) by treatment and visit - Presence of Primary Sjogren	Full Analysis Set	
14.2.2.1.7	Summary of Symptoms Questionnaire (SANDE) by treatment and visit - Absence of Primary Sjogren	Full Analysis Set	
14.2.2.1.8	Summary of Symptoms Questionnaire (SANDE) by treatment and visit-	Per Protocol Set	Yes
14.2.2.1.9	Summary of Symptoms Questionnaire (SANDE) by treatment and visit- Presence of Primary Sjogren	Per Protocol Set	
14.2.2.1.10	Summary of Symptoms Questionnaire (SANDE) by treatment and visit- Absence of Primary Sjogren	Per Protocol Set	
14.2.2.2.1	Analysis of Change in Schirmer test II from Baseline to Week 4 - Eligible eye	Full Analysis Set	
14.2.2.2.2	Analysis of Change in Schirmer test II from Baseline to Week 4 - Eligible eye	Per Protocol Set	
14.2.2.2.3	Exploratory Sensitivity Analysis of Change from Baseline in Schirmer test II at Week 4 - Eligible eye	Full Analysis Set	

Table Number	Name	Analysis Set	Topline
14.2.2.2.4	Exploratory Sensitivity Analysis of Change from Baseline in Schirmer test II at Week 4 - Eligible eye	Per Protocol Set	
14.2.2.2.5	Summary of Schirmer test II by treatment and visit - Eligible eye	Full Analysis Set	
14.2.2.2.6	Summary of Schirmer test II by treatment and visit - Presence of Primary Sjogren - Eligible eye	Full Analysis Set	
14.2.2.2.7	Summary of Schirmer test II by treatment and visit - Absence of Primary Sjogren - Eligible eye	Full Analysis Set	
14.2.2.2.8	Summary of Schirmer test II by treatment and visit - Eligible eye	Per Protocol Set	
14.2.2.2.9	Summary of Schirmer test II by treatment and visit - Presence of Primary Sjogren - Eligible eye	Per Protocol Set	
14.2.2.2.10	Summary of Schirmer test II by treatment and visit - Absence of Primary Sjogren - Eligible eye	Per Protocol Set	
14.2.2.3.1	Analysis of Change from baseline in Corneal and conjunctiva vital staining with fluorescein (National Eye Institute [NEI] scales) to Week 4	Full Analysis Set	
14.2.2.3.2	Analysis of Change from baseline in Corneal and conjunctiva vital staining with fluorescein (National Eye Institute [NEI] scales) to Week 4	Per Protocol Set	
14.2.2.3.3	Exploratory Sensitivity Analysis of Change from baseline in Corneal and conjunctiva vital staining with fluorescein (National Eye Institute [NEI] scales) to Week 4- Eligible eye	Full Analysis Set	
14.2.2.3.4	Exploratory Sensitivity Analysis of Change from baseline in Corneal and conjunctiva vital staining with fluorescein (National Eye Institute [NEI] scales) to Week 4 - Eligible eye	Per Protocol Set	
14.2.2.3.5	Summary of Corneal and conjunctiva vital staining with fluorescein (National Eye Institute [NEI] scales)	Full Analysis Set	
14.2.2.3.6	Summary of Corneal and conjunctiva vital staining with fluorescein (National Eye Institute [NEI] scales) - Presence of Primary Sjogren	Full Analysis Set	
14.2.2.3.7	Summary of Corneal and conjunctiva vital staining with fluorescein (National Eye Institute [NEI] scales) - Absence of Primary Sjogren	Full Analysis Set	
14.2.2.3.8	Summary of Corneal and conjunctiva vital staining with fluorescein (National Eye Institute [NEI] scales)	Per Protocol Set	
14.2.2.3.9	Summary of Corneal and conjunctiva vital staining with fluorescein (National Eye Institute [NEI] scales) - - Presence of Primary Sjogren	Per Protocol Set	

Table Number	Name	Analysis Set	Topline
14.2.2.3.10	Summary of Corneal and conjunctiva vital staining with fluorescein (National Eye Institute [NEI] scales) - Absence of Primary Sjogren	Per Protocol Set	
14.2.2.4.1	Analysis of Change from baseline in Tear Film Break up time at week 4 - Eligible eye	Full Analysis Set	
14.2.2.4.2	Analysis of Change from baseline in Tear Film Break up time at week 4 - Eligible eye	Per Protocol Set	
14.2.2.4.3	Exploratory Sensitivity Analysis of Change from Baseline in Tear Film Break up time at Week 4 - Eligible eye	Full Analysis Set	
14.2.2.4.4	Exploratory Sensitivity Analysis of Change from Baseline in Tear Film Break up time at Week 4 - Eligible eye	Per Protocol Set	
14.2.2.4.5	Summary of Tear Film Break up time (TFBUT) by treatment and visit (seconds) - Eligible eye	Full Analysis Set	
14.2.2.4.6	Summary of Tear Film Break up time (TFBUT) by treatment and visit (seconds) - Presence of Primary Sjogren - Eligible eye	Full Analysis Set	
14.2.2.4.7	Summary of Tear Film Break up time (TFBUT) by treatment and visit (seconds) - Absence of Primary Sjogren - Eligible eye	Full Analysis Set	
14.2.2.4.8	Summary of Tear Film Break up time (TFBUT) by treatment and visit (seconds) - Eligible eye	Per Protocol Set	
14.2.2.4.9	Summary of Tear Film Break up time (TFBUT) by treatment and visit (seconds) - Presence of Primary Sjogren - Eligible eye	Per Protocol Set	
14.2.2.4.10	Summary of Tear Film Break up time (TFBUT) by treatment and visit (seconds) - Absence of Primary Sjogren -Eligible eye	Per Protocol Set	
14.2.2.5.1	Number of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score >= 50% assessed at week 4	Full Analysis Set	
14.2.2.5.2	Number of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score >= 50% assessed at week 4 - Presence of Primary Sjogren	Full Analysis Set	
14.2.2.5.3	Number of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score >= 50% assessed at week 4 - Absence of Primary Sjogren -	Full Analysis Set	

Table Number	Name	Analysis Set	Topline
14.2.2.5.4	Number of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score >= 50% assessed at week 4	Per Protocol Set	
14.2.2.5.5	Number of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score >= 50% assessed at week 4 - Presence of Primary Sjogren	Per Protocol Set	
14.2.2.5.6	Number of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score >= 50% assessed at week 4 - Absence of Primary Sjogren	Per Protocol Set	
14.2.2.6.1	Quality of life Impact of Dry Eye on Everyday Life (IDEEL) questionnaire	Full Analysis Set	
14.2.2.6.2	Quality of life Impact of Dry Eye on Everyday Life (IDEEL) questionnaire- Presence of Primary Sjogren	Full Analysis Set	
14.2.2.6.3	Quality of life Impact of Dry Eye on Everyday Life (IDEEL) questionnaire- Absence of Primary Sjogren	Full Analysis Set	
14.2.2.6.4	Quality of life Impact of Dry Eye on Everyday Life (IDEEL) questionnaire	Per Protocol Set	
14.2.2.6.5	Quality of life Impact of Dry Eye on Everyday Life (IDEEL) questionnaire - Presence of Primary Sjogren	Per Protocol Set	
14.2.2.6.6	Quality of life Impact of Dry Eye on Everyday Life (IDEEL) questionnaire -Absence of Primary Sjogren	Per Protocol Set	
14.2.2.7.1	Patient global Impression of change (PGIC)	Full Analysis Set	
14.2.2.7.2	Patient global Impression of change (PGIC) - Presence of Primary Sjogren	Full Analysis Set	
14.2.2.7.3	Patient global Impression of change (PGIC) - Absence of Primary Sjogren	Full Analysis Set	
14.2.2.7.4	Patient global Impression of change (PGIC)	Per Protocol Set	
14.2.2.7.5	Patient global Impression of change (PGIC) - Presence of Primary Sjogren	Per Protocol Set	
14.2.2.7.6	Patient global Impression of change (PGIC)- Absence of Primary Sjogren	Per Protocol Set	
14.2.2.8.1	EQ-5D-3L – Health score	Full Analysis Set	
14.2.2.8.2	EQ-5D-3L – Health score - Presence of Primary Sjogren	Full Analysis Set	
14.2.2.8.3	EQ-5D-3L – Health score - Absence of Primary Sjogren	Full Analysis Set	

Table Number	Name	Analysis Set	Topline
14.2.2.8.4	EQ-5D-3L – Health score	Per Protocol Set	
14.2.2.8.5	EQ-5D-3L – Health score - Presence of Primary Sjogren	Per Protocol Set	
14.2.2.8.6	EQ-5D-3L – Health score - Absence of Primary Sjogren	Per Protocol Set	
14.2.2.8.7	Summary statistics of EQ-5D-3L by dimension and level	Full Analysis Set	
14.2.2.8.8	Summary statistics of EQ-5D-3L by dimension and level - Presence of Primary Sjogren	Full Analysis Set	
14.2.2.8.9	Summary statistics of EQ-5D-3L by dimension and level- Absence of Primary Sjogren	Full Analysis Set	
14.2.2.8.10	Summary statistics of EQ-5D-3L by dimension and level	Per Protocol Set	
14.2.2.8.11	Summary statistics of EQ-5D-3L by dimension and level - Presence of Primary Sjogren	Per Protocol Set	
14.2.2.8.12	Summary statistics of EQ-5D-3L by dimension and level - Absence of Primary Sjogren	Per Protocol Set	
14.2.2.8.13	Shift from baseline of EQ-5D-3L by dimension and level	Full Analysis Set	
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14.2.2.10.	Analysis of Change in Schirmer test I from Baseline to Week 2 – Eligible eye	Full Analysis Set	
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14.2.2.13.	Analysis of Change from baseline in Tear Film Break up time at week 2 – Eligible eye	Full Analysis Set	
14.2.2.14.1	Number of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score >= 50% assessed at week 2	Full Analysis Set	
14.2.2.14.2	Number of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score >= 50% assessed at week 2- Presence of Primary Sjogren	Full Analysis Set	
14.2.2.14.3	Number of patients who experienced a worsening in symptom scores (SANDE) and/or NEI score >= 50% assessed at week 2 - Absence of Primary Sjogren	Full Analysis Set	

Table Number	Name	Analysis Set	Topline
14.2.2.15.1	Analysis of Change from baseline in goblet cells density – Eligible eye	Full Analysis Set	
14.2.2.15.2.	Summary of goblet cells density (cells/mm²) - Eligible eye	Full Analysis Set	
14.2.2.15.3	Summary of goblet cells density (cells/mm²) - Presence of Primary Sjogren – Eligible eye	Full Analysis Set	
14.2.2.15.4	Summary of goblet cells density (cells/mm²) - Absence of Primary Sjogren – Eligible eye	Full Analysis Set	
14.3.1.1.1	Treatment-Emergent Adverse Events – Overall Summary	Safety Set	Yes
14.3.1.1.2	Treatment-Emergent Adverse Events – Overall Summary - Presence of Primary Sjogren	Safety Set	
14.3.1.1.3	Treatment-Emergent Adverse Events – Overall Summary - Absence of Primary Sjogren	Safety Set	
14.3.1.2.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set	
14.3.1.2.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Presence of Primary Sjogren	Safety Set	
14.3.1.2.3	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Absence of Primary Sjogren	Safety Set	
14.3.1.3.1	Treatment-Emergent Ocular Adverse Events Study Treatment by MedDRA System Organ Class and Preferred Term	Safety Set	
14.3.1.3.2	Treatment-Emergent Ocular Adverse Events Study Treatment by MedDRA System Organ Class and Preferred Term - Presence of Primary Sjogren	Safety Set	
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14.3.1.4.1	Treatment-Emergent Ocular Adverse Events Related to Study Treatment by MedDRA System Organ Class and Preferred Term	Safety Set	
14.3.1.4.2	Treatment-Emergent Ocular Adverse Events Related to Study Treatment by MedDRA System Organ Class and Preferred Term - Presence of Primary Sjogren	Safety Set	
14.3.1.4.3	Treatment-Emergent Ocular Adverse Events Related to Study Treatment by MedDRA System Organ Class and Preferred Term - Absence of Primary Sjogren	Safety Set	

Table Number	Name	Analysis Set	Topline
14.3.1.5.1	Treatment-Emergent Adverse Events related to study treatment by System Organ Class and Preferred Term	Safety Set	
14.3.1.5.2	Treatment-Emergent Adverse Events related to study treatment by System Organ Class and Preferred Term - Presence of Primary Sjogren	Safety Set	
14.3.1.5.3	Treatment-Emergent Adverse Events related to study treatment by System Organ Class and Preferred Term - Absence of Primary Sjogren	Safety Set	
14.3.1.6.1	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	Safety Set	Yes
14.3.1.6.2	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Presence of Primary Sjogren	Safety Set	
14.3.1.6.3	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term - Absence of Primary Sjogren	Safety Set	
14.3.1.7.1	Treatment-Emergent Adverse Events Leading to study discontinuation by System Organ Class and Preferred Term	Safety Set	
14.3.1.7.2	Treatment-Emergent Adverse Events Leading to study discontinuation by System Organ Class and Preferred Term - Presence of Primary Sjogren	Safety Set	
14.3.1.7.3	Treatment-Emergent Adverse Events Leading to study discontinuation by System Organ Class and Preferred Term - Absence of Primary Sjogren	Safety Set	
14.3.1.8.1	Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term	Safety Set	
14.3.1.8.2	Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term - Presence of Primary Sjogren	Safety Set	
14.3.1.8.3	Treatment-Emergent Adverse Events of Special Interest by System Organ Class and Preferred Term - Absence of Primary Sjogren	Safety Set	
14.3.1.9.1	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity	Safety Set	

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14.3.1.9.3	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity - Absence of Primary Sjogren	Safety Set	
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14.3.2.2	Serious Treatment-Emergent Adverse Events, Listing	Randomized Set	
14.3.2.3	Treatment-Emergent Adverse Events Leading to study discontinuation, Listing	Randomized Set	
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14.2.1.12	Schirmer test I at each visit by dose group - Presence of Primary Sjogren	Full Analysis Set
14.2.1.13	Schirmer test I at each visit by dose group - Absence of Primary Sjogren	Full Analysis Set
14.2.1.14	Change from baseline of Schirmer test I (95% C.I.) by dose group	Full Analysis Set
14.2.1.15	Change from baseline of Schirmer test I (95% C.I.) by dose group - Presence of Primary Sjogren	Full Analysis Set
14.2.1.16	Change from baseline of Schirmer test I (95% C.I.) by dose group - Absence of Primary Sjogren	Full Analysis Set
14.2.2.1.11	SANDE score at each visit by dose group	Full Analysis Set
14.2.2.1.12	SANDE score at each visit by dose group - Presence of Primary Sjogren	Full Analysis Set
14.2.2.1.13	SANDE score at each visit by dose group - Absence of Primary Sjogren	Full Analysis Set
14.2.2.1.14	Change from baseline of SANDE score (95% CI) by dose group	Full Analysis Set
14.2.2.1.15	Change from baseline of SANDE score (95% CI) by dose group - Presence of Primary Sjogren	Full Analysis Set
14.2.2.1.16	Change from baseline of SANDE score (95% CI) by dose group - Absence of Primary Sjogren	Full Analysis Set
14.2.2.2.11	Schirmer test II at each visit by dose group	Full Analysis Set
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14.2.2.2.13	Schirmer test II at each visit by dose group - Absence of Primary Sjogren	Full Analysis Set
14.2.2.2.14	Change from baseline of Schirmer test II (95% CI) by dose group	Full Analysis Set
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14.2.2.2.16	Change from baseline of Schirmer test II (95% CI) by dose group- Absence of Primary Sjogren	Full Analysis Set
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14.2.2.3.14	Change from baseline of Corneal and conjunctiva vital staining total score (95% CI) by dose group	Full Analysis Set

Figure Number	Name	Analysis Set
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14.2.2.3.16	Change from baseline of Corneal and conjunctiva vital staining total score (95% CI) by dose group- Absence of Primary Sjogren	Full Analysis Set
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14.2.2.4.14	Change from baseline of Tear film break-up time (TFBUT) (95% CI) by dose group	Full Analysis Set
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14.2.2.5.9	Barplot of Number of Patients who Experienced a Worsening in Symptom Scores (SANDE) and/or NEI Score ≥ 50% Assessed at Week 4 by dose group - Absence of Primary Sjogren	Full Analysis Set

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16.2.1.2	Patient Disposition – Randomized patients	Randomized Set
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16.2.2.2	Protocol Deviations due to COVID-19	Randomized Set
16.2.3.1	Patients Excluded from Analysis Set	Randomized Set
16.2.4.1	Demographics and Baseline Characteristics	Enrolled Set
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16.2.4.3	Previous Ocular and Systemic Medications	Enrolled Set
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16.2.6.2.5.2	Quality of Life Impact of Dry Eye on Everyday Life (IDEEL) Questionnaire – Feelings	Randomized Set
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Listing Number	Name	Analysis Set
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18. Appendices

APPENDIX I SAMPLE SAS CODE IN STATISTICAL ANALYSIS

1) Sample Code for Efficacy Analysis : Schirmer test I

An Analysis of variance will be used for Schirmer test I, followed by Williams test. An example of the SAS code to perform this analysis is below.

```
**************************************************************************
* SAS Code: GLM (Analysis ofvariance) followed by William test
* Variables in the model:
*&var=CHG = Change from baseline in Schirmer test I at week 4
*&trt=trt01p = treatment planned
**************************************************************************;

%macro WILLIAMS(dat = , trt = , var = );

/*######################### WILLIAMS TEST ################################*/

/*For Williams Test, We Assume a Monotonic Dose Relationship (i.e. x0 <= x1 <= x2 <=... x7 etc.). If this does not occur, then a dose that does not conform (when sorted by dose level) should be combined with next closest dose and averaged.Keep doing this until we get conformance. Note that this relies on comparing vs x0, so x0 should always be lowest result*/

%global lsm1 maxdose contmean;

/*Assign a New Dose Number (Consecutive) for Processing*/

proc sort data = &dat. out = DOSEN (keep = &trt.) nodupkey;
        by &trt.;
run;
data DOSEN;
        set DOSEN;
        DOSEN = _N_;
run;
data &dat.2;
        merge &dat. DOSEN;
        by &trt.;
run;
```

```
proc glm data = &dat.2 noprint outstat=STAT_(keep = _TYPE_ DF SS where=(_TYPE_="ERROR"));
        class DOSEN;
        model &var. = DOSEN;
        lsmeans DOSEN / pdiff cl;
        output out = STAT p=LSMEAN r=resid LCL=LCI UCL=UCI STDP=STDERR;
run;

proc sort data = STAT out = STAT2 (keep = &trt. DOSEN LSMEAN LCI UCI STDERR) nodupkey;
        by DOSEN;
run;

/*Get Max Dose Level for Processing*/
proc sql noprint;
        select compress(put(max(DOSEN),best.)) into :MAXDOSE
        from STAT2;
quit;
%put &maxdose.;

/*Get LSMEAN for Placebo/Control for Processing*/
proc sql noprint;
        select compress(put(LSMEAN,best.)) into :CONTMEAN
        from STAT2(where=(DOSEN=1));
quit;
%put &contmean.;

/*Get Number of Observations and Merge Back on to GLM Output*/
proc univariate data = STAT noprint;
        by DOSEN;
        var RESID;
        output out = N N=N;
run;

data STAT_2 (drop = _TYPE_ SS);
        set STAT_;
        if nmiss(DF,SS) = 0 then MSE = SS/DF;
        do DOSEN = 1 to &maxdose.;
        output;
        end;
run;

data STAT2;
        merge STAT2(in=a) N STAT_2;
        by DOSEN;
        if a;
run;


/*Get Dose Level 1 LSMean for Checking Whether Each Dose >= Dose1*/
proc sql noprint;
        select compress(put(LSMEAN,best.)) into :LSM1
```

```
        from STAT2(where=(DOSEN=1));
quit;
%put &lsm1.;

/*Output All LSMEANS and N for All Dose Levels Present*/
%macro VAR(var = );
proc sort data = STAT2;
        by MSE DF;
run;
proc transpose data = STAT2 out = STAT2_&var.(drop = _NAME_) prefix=&var.;
        by MSE DF;
        id DOSEN;
        var &var.;
run;
%mend VAR;
%VAR(var = LSMEAN); %VAR(var = N);

data STAT3(drop = _LABEL_);
        merge STAT2_LSMEAN STAT2_N;
run;

data STAT4;
        set STAT3;
        array LSMEAN(&maxdose.); array N(&maxdose.); array DIFF(&maxdose.); array
DENOM(&maxdose.);
        array T(&maxdose.);
        CONTROL = LSMEAN(1);
        do j = 1 to &maxdose.-1;
                if LSMEAN(j) > LSMEAN(j+1) then do;
                        EN = N(j+1);
                        EMEAN = LSMEAN(j+1);
                        NMEAN = N(j+1)*LSMEAN(j+1);
                        do k = j to 1 by -1;
                                if EMEAN < LSMEAN(k) then do;
                                        EN = EN + N(k);
                                        NMEAN = NMEAN + N(k)*LSMEAN(k);
                                        *EMEAN = (EMEAN*N(k)/(EN)) + ((N(k)*LSMEAN(k))/(EN));
                                        EMEAN = NMEAN/EN;
                                        do r = k to j+1;
                                                LSMEAN(r) = EMEAN;
                                        end;
                                end;
                        end;
                end;
        end;
        do j = 2 to &maxdose.;
                DIFF(j) = (LSMEAN(j)-CONTROL);
                DENOM(j) = ((MSE*((1/N(j))+(1/N(1))))**0.5);
                T(j) = DIFF(j)/DENOM(j);
        end;
run;
```

```
data STAT5 (drop = EMEAN EN MSE DF j k r DIFF: DENOM:);
        set STAT4;
        array LSMEAN(&maxdose.); array T(&maxdose.); array p(&maxdose.);
        do i = 2 to &maxdose.;
                p(i) = 1 - probmc("Williams",T(i),.,DF,i-1);
        end;
run;

%macro OUT(var2=, dat = , out = );
data &out.(keep = DOSE:);
        set &dat.;
        %do i = 1 %to &maxdose.;
                rename &var2.&i.=DOSE&i.;
        %end;
run;
%mend OUT;

%OUT(var2 = LSMEAN, dat = STAT3, out = LSMEAN1);
%OUT(var2 = LSMEAN, dat = STAT5, out = LSMEAN2);
%OUT(var2 = N, dat = STAT5, out = N);
%OUT(var2 = T, dat = STAT5, out = T);
%OUT(var2 = P, dat = STAT5, out = P);

data WILLIAMS (keep = TYPE DOSE1-DOSE&maxdose.);
        retain TYPE DOSE1-DOSE&maxdose.;
        length TYPE $50.;
        set LSMEAN1(in=a) LSMEAN2(in=b) N(in=c) T(in=d) P(in=e);
        if a then TYPE = "LSMeans (Original)";
        if b then TYPE = "MLE";
        if c then TYPE = "No. Obs";
        if d then TYPE = "Williams T Statistic";
        if e then TYPE = "P-Value";
run;
%mend WILLIAMS;
```

2) Sample Code for Efficacy Analysis : Schirmer test I in case of presence of many missing data

For RMM, if SAS mixed model is used, the sample SAS codes will be like the following:

```
PROC MIXED DATA=SCHIRMERI;
CLASS usubjid TRT01P visit;
MODEL chg = TRT01P TRT01P * visit /ddfm=kr;
repeated visit / sub = usubjid type = un;
lsmeans TRT01P / cl diff at time = Week4;
```

3) Sample Code for Exploratory sensitivity Efficacy Analysis : Schirmer test I

```
PROC MIXED DATA=SCHIRMERI;
CLASS STRATA TRT01P ;
MODEL chg = TRT01P STRATA STRATA*TRT01P /solution;
lsmeans STRATA*TRT01P / pdiff cl  at time=Week4;
```

4) Sample Code for Efficacy Analysis : IDEEL and EQ-5D-3L

```
PROC MIXED DATA=IDEEL;
CLASS usubjid TRT01P visit;
MODEL chg = TRT01P  visit TRT01P * visit /ddfm=kr;
repeated visit / sub = usubjid type = un;
lsmeans TRT01P*visit / cl pdiff;
lsmeans TRT01P / cl pdiff;
```

5) Sample Code for Efficacy Analysis: PGIC

A Wilcoxon rank sum test will be used for PGIC. An example of the SAS code to perform this analysis is reported below.

```
**************************************************************************
* SAS Code: Wilcoxon
* Variables in the model:
* aval = value of PGIC
*trt01pn = treatment planned
**************************************************************************;

    PROC NPAR1WAY  DATA=PGIC WILCOXON;
    WHERE TRT01P  in ( “Placebo” “Dose 1”);
    CLASS TRT01P;
    VAR AVAL;
    RUN;
```

6) Sample Code for Efficacy Analysis: Proportion of subjects with worsening in SANDE and/or NEI score>=50%

```
**************************************************************************
```

* SAS Code: Wilcoxon

* Variables in the model:

* aval = worsening in symptom scores (SANDE) and/or NEI score >= 50% : yes or No

*trt01pn = treatment planned

**********;

```
PROC FREQ DATA=Prop;
WHERE TRT01P  in ( “Placebo” “Dose 1”);
TABLES trt01p*aval / chisq;
RUN;
```