Dompé Farmaceutici S.p.a.

A 8 weeks, Phase II, single-centre, randomized, double-masked, vehicle-controlled, parallel group study with 4 weeks of follow-up to evaluate preliminary efficacy and safety of recombinant human Nerve Growth Factor (rhNGF) eye drops solution versus vehicle in patients after cataract and refractive surgery

Protocol/CIP No: NGF0116

Clinical Trials No: NCT03035864

Statistical Analysis Plan

Version 1.0

Final

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CROMSOURCE

Signature Page

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1 SOPs to be followed

The statistical analysis will be carried out according to the following CROMSOURCE SOPs:

SOP number	SOP title
SOP-ST-03	Statistical Analysis Plan
SOP-ST-04	SAS Programming and Validation
SOP-ST-05	Data Review Meeting
SOP-ST-06	Study Unblinding for Analysis
SOP-ST-08	Trial Statistics File

2 Abbreviations

AE	Adverse Event
AESI	Adverse Event Of Special Interest
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical Classification
BCDVA	Best Corrected Distance Visual Acuity
BDRM	Blind Data Review Meeting
CDISC	Clinical Data Interchange Standards Consortium
CFB	Change from Baseline
CIP	Clinical Investigational Plan
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
IMP	Investigational Medicinal Product
LASIK	Laser-assisted in situ keratomileusis
LOCF	Last Observation Carried Forward
MMP	Matrix Metallopeptidase 9
NEI	National Eye Institute
PPS	Per Protocol Analysis Set
PT	Preferred Term
QC	Quality Control
SAE	Serious Adverse Effect
SAF	Safety Set
SANDE	Symptom Assessment In Dry Eye
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SDTM	Study Data Tabulation Model
SLE	Slit Lamp Examination
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TFBUT	Tear Film Break-Up Time
TLF	Tables, Listings And Figures
VAS	Visual Analog Scale
WHO	World Health Organisation

3 Protocol / Clinical Investigation Plan

This NGF0116 study is conducted under the sponsorship of Dompé farmaceutici S.p.A.. The clinical monitoring, data management, statistical analysis and medical writing are performed by CROMSOURCE under contract and in collaboration with Dompé farmaceutici S.p.A..

This Statistical Analysis Plan (SAP) provides a complete, expanded and detailed description of the planned statistical methods outlined in the study protocol Final Version 3.0 (dated 12Apr2017).

It lists all Tables, Listings and Figures (TLFs) of the final analysis, which are intended to be included in the Clinical Study Report. All TLFs will be produced by CROMSOURCE.

Analysis of changes in nerve count and morphology at scanning laser in vivo corneal confocal microscopy is not covered by this SAP. Confocal microscopy assessment will be reported in a separate part of the CSR.

3.1 Study Objectives

The primary objective of this study is to assess efficacy and safety of rhNGF when administered as eye drops to patients after cataract and refractive surgery.

The objectives are reflected by the endpoints as stated in section 3.4.

3.2 Study Design

This is a Phase II, single-centre, randomized, double-masked, parallel-arm, vehicle-controlled trial, designed to evaluate the preliminary efficacy and safety of rhNGF eye drops at 20 µg/ml concentration administered six times daily for 8 weeks in patients who underwent cataract and corneal refractive surgery, both known to damage the corneal sensory nerve plexus.

Eligible patients will be randomized 2:1 to either rhNGF eye drops 20 µg/ml (120 patients) *or vehicle* (60 patients) *six times daily and treated for 8 weeks:*

Group 1: *rhNGF 20 µg/mL: One drop (40 µL) corresponding to 0.80 µg of rhNGF will be instilled into each eligible eye six times a day (every 2h), for a total daily dose of 9.6 µg (both eyes, if applicable), for 56 consecutive days..*

Group 2: *Vehicle: One drop (40 µL) will be instilled into each eligible eye six times a day (every 2h).*

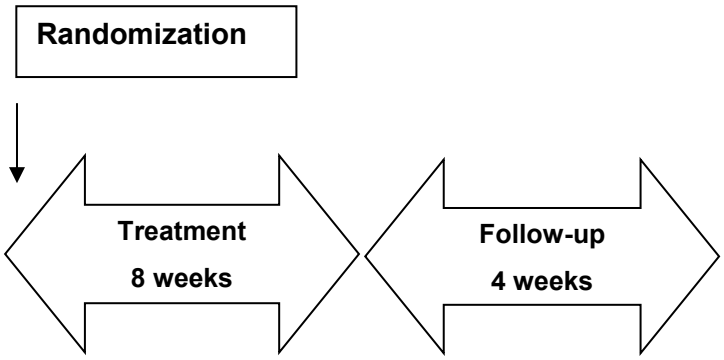
In all patients, both eyes will be treated, if meet the eligibility criteria. If only one eye is eligible, then only that eye will be treated.

In the 4 week follow up no further treatment is planned except artificial tears, per Investigator decision. Administration of such medications will be recorded in eCRF (number of drops per day).

Drop-Outs after randomization will not be replaced.

The study flow chart is given below:

Figure 3.2.1 Study flow chart



3.3 Study Schedule

Table 1: Study procedures (from study protocol)

Study procedures	Baseline Visit (Day 0)	Week 4 (Day 28±2)	Week 8** (ETV) (Day 56±2)	Week 12 (Follow-up Visit) (Day 84±2)
Informed Consent	X			
Inclusion/Exclusion Criteria	X			
Urine Pregnancy Test	X	X	X	
Randomization	X			
Demographics	X			
Ocular and General Medical History	X			
Previous and Concomitant Ocular And Systemic Medications	X	X	X	X
Frequency of artificial tear use	X	X	X	X
Record Adverse Events (AEs)	X	X	X	X
Verify patient study medication dosing compliance		X	X	
SANDE questionnaire	X	X	X	X
Best Corrected Distance Visual Acuity (BCDVA)	X		X	X
Cochet-Bonnet aesthesiometry	X		X	
External Ocular Examination	X	X	X	X
Slit Lamp Examination (SLE)	X	X	X	X
Fluorescein staining (NEI scale)	X	X	X	X
Tear Film Break-up Time (TFBUT)	X	X	X	X
Corneal confocal microscopy*	X		X	
Study drug dispensation	X	X		

* Only for patients who underwent laser-assisted in situ keratomileusis (LASIK) surgery

** ETV – Early Termination Visit to be performed according to Visit Week 8 procedures, if premature treatment discontinuation occurs.

Note: Patient diary will be reviewed for potential AEs, and details as applicable

Abbreviations: SANDE - Symptom Assessment In Dry Eye

3.4 Efficacy and Safety Endpoints

In the study protocol the following study endpoints are specified.

Clinical efficacy and safety parameters will be evaluated at each time point (days 0, 28±2, 56±2 and 28±2 days after discontinuation of treatment) with the following endpoints:

Primary Efficacy Endpoint

- *Change from baseline in Symptom Assessment in Dry Eye (SANDE) scores for severity and frequency assessed at 8 weeks of treatment*

Co-primary Efficacy Endpoint

- *Changes in Cornea vital staining with fluorescein (National Eye Institute (NEI) scales) assessed at week 8*

Secondary Endpoints

- *Changes in SANDE scores (face values) for severity and frequency*
- *Changes in Conjunctival vital staining with fluorescein (NEI scales)*
- *Changes in Tear film break-up time (TFBUT)*
- Changes in Cochet-Bonnet *corneal aesthesiometry*
- *Changes in Nerve count and morphology at scanning laser in vivo corneal confocal microscopy (only patients who had LASIK surgery)* – not covered by this SAP.

Safety Endpoint

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

3.5 Interim Analyses

No interim analyses are planned.

3.6 Sample Size estimation

Sample size was calculated by assuming at single eye level a mean difference from baseline mean SANDE scores of -30±20 in the rhNGF groups versus -20±20 in vehicle group (80% power, alpha =0.05; 2-sided test), considering that the active comparator has already proven safe and effective in dry eye patients. The sample size has been calculated based on a 2:1 randomization by the following formula:

$n1 = (0.5) \times n \times (1 + k)$

$n2 = (0.5) \times n \times (1 + (1/k))$

with n1= active treatment and n2= vehicle and n= 63 and k= n1 /n2 = 2/1=2. Therefore n1= 94,5 and n2=47.25. Assuming a 5% drop out rate, a total of 100 patients in the active arm and 50 in the vehicle arm are required.

However, in order to provide the mean of detecting a significant difference also on a clinical sign of the effect of the rhNGF therapy (namely Co-primary Efficacy Endpoint cornea vital staining with fluorescein (National Eye Institute [NEI] scales)), sample size calculation was also performed by assuming, at single eye level, a mean difference from baseline in Cornea NEI scale scores of -3.9±2.2 in the rhNGF groups versus -2.9±2.2 in vehicle group (80% power, alpha =0.05; 2-sided test), considering that the active comparator has already proven safe and effective in dry eye patients. The sample size has been calculated based on a 2:1 randomization by the following formula:

$n1 = (0.5) \times n \times (1 + k)$

$n2 = (0.5) \times n \times (1 + (1/k))$

with n1= active treatment and n2= vehicle and n= 76 and k= n1 /n2 = 2/1=2. Therefore n1= 114 and n2=57. Assuming a 5% drop out rate, a total of 120 patients in active arm and 60 in the vehicle arm are required. This calculation is based on one study eye per patient. (Whereas also two study eyes per patient may occur, that will increase power to above 80%).

Considering the two calculations performed to determine the sample size, in this study will be enrolled 180 patients (120 patients enrolled in active arm and 60 in the vehicle arm) in order to detect both changes at the same time in the variables.

3.7 Changes in the Conduct of Study or Planned Analysis compared to protocol/CIP

This SAP implements the subsequent deviations and clarifications from the analysis specification of the study protocol:

- For the SAP, study endpoints are presented as provided in the protocol synopsis and protocol section 2 (study objectives).
- Definition of Screen Failures. In the study protocol (section 10.1.1) a screen failure is defined as patient who is not eligible, i.e. is not respecting all the inclusion/exclusion criteria. According to the study protocol, such patients should not be randomized and enrolled.
  To streamline presentation of patient flow for reporting and to extend definition also for protocol deviations, screen failure will be defined as screened patients, who are not randomized. By this, patients, who were randomized although they did not comply with eligibility criteria will not be considered as screen failure. On the contrary, patients, who comply with all eligibility criteria but dropped out from the study before randomization (e.g. due to consent withdrawal) will be considered as screen failure.
- Definition of compliance: in section 10.3, the study protocol demands further compliance definitions based on diary card information to investigate compliance with study eye treatment. However, as no eye-specific assessments were recorded on diary card, no such definitions were established.
- In the study protocol, no inferential analyses are specified. However, purely exploratory 95% confidence intervals and hypothesis testing for the difference between treatment groups will be implemented in the SAP on sponsor's request. These inferential procedures will be purely exploratory without adjusting for type I error rate.

4 General Definitions

4.1 Report Language

All TLFs will be prepared in English.

4.2 Analysis Software

The statistical analysis will be performed using the SAS® statistical software package (Statistical Analysis System, Version 9.3 or later).

5 Data Preparation

5.1 Data Handling and Medical Coding

For data quality control and medical coding please refer to the Data Management Plan including the Data Validation Plan in its most recent version.

5.2 CDISC

All output as defined in the SAP will be generated based on CDISC ADaM datasets following ADaM implementation Guide 1.0, as per contract with Dompé farmaceutici S.p.A.. SDTM programming will follow SDTM version 1.3 together with SDTM implementation guide 3.1.3.

Specifications for the ADaM datasets (as well as SDTM datasets) are described in a separate document.

5.3 SAS-Programming Quality Level

The following quality level of programming deliverables will be applied, as per contract with Dompé Farmaceutici S.p.A.. All statistical output will receive a tailored Quality Control (QC) approach by:

- Full independently double programmed reproduction (QC) of CDISC:
  - SDTM datasets
  - ADaM datasets
- Full independently double programmed reproduction (QC) of results of all tables and inferential analyses
- Listings will not be double programmed. However, complex listings for BDRM requiring a complex selection will undergo a fully independent double programmed QC.
- All tables and listings will undergo comparison with specification (i.e. SAP and templates), cross checking with other tables and listings, a sensibility review and SAS-log review by a senior statistician.

6 Analysis Sets and Subgroups

6.1 Analysis Sets

A patient will be defined as screened after the signature of the informed consent, regardless of the completion of all the screening procedures. A patient will be defined as screen failure, if he was screened but not enrolled in the study.

Enrolled Set:

A patient will be defined as enrolled in the study if he/she is randomized. This analysis set will be used for presentation of study disposition.

If not stated otherwise, analyses based on the Enrolled Set will be summarized by the treatment randomized.

Safety Set (SAF):

The Safety Set will be defined as all enrolled patients who receive at least one dose of the investigational medicinal product (IMP) at the study eye(s). *This analysis set will be used for the demographic, baseline and background characteristics and safety analysis.* All analyses based on the SAF will be summarized by the treatment received.

Full Analysis Set (FAS):

The Full Analysis Set will be defined as all patients in the SAF, who have at least one post-baseline efficacy measurement in a study eye. This analysis set will be used for the primary and co-primary efficacy analysis and all other efficacy analyses. All efficacy analyses based on the FAS will be summarized by the treatment randomized.

Per Protocol Set (PPS):

The Per Protocol Set will be defined as *all patients in the FAS who fulfill the study protocol requirements in terms of investigational medicinal product intake and collection of primary and co-primary efficacy data and with no major deviations that may affect study results. This analysis set will be used for supportive efficacy analysis.* All efficacy analysis based on the PPS will be summarized by the treatment randomized.

Each patient could either have 1 or 2 study eyes eligible for the analysis. For each patient a main (study) eye will be identified to enable a patient based presentation of analysis.

For patients with only 1 study eye (i.e. treated eye), this eye will be defined as ‘Main Eye’.

For patients with 2 study eyes, the study eye with the higher corneal staining score at baseline will be considered as ‘Main Eye’ unless corneal staining score is not available at Week 8 Visit for this eye.

In this case, the other eye will be considered as ‘Main Eye’. If both eyes are equally worse, the right eye will be the ‘Main Eye’.

The eye not selected as ‘Main Eye’, will be called ‘Secondary Eye’.

After all patients have completed study and prior to database lock, a blinded data review meeting (BDRM) will be performed to assign patients to analysis sets and to define 'Main Eyes'. Details of BDRM will be specified in a separate BDRM-plan.

The BDRM plan may consider the following criteria for exclusion of a patient from the PPS:

- *lack of compliance with investigational medical product administration*

  A compliance below 80% or greater than 120% will lead to exclusion from the PPS (compliance definition please refer to section 7.2.5).
- *exposure to an IMP dose different from the one assigned to the patient*
- *missing primary or co-primary efficacy data*
- *failure to satisfy any inclusion/exclusion criteria (eligibility violations)*
- *intake of prohibited medications*

Moreover, a review of protocol deviations and potential consequences for the analysis will be evaluated during the BDRM. The results of the BDRM will be summarized in BDRM Minutes, which will be finalized before unmasking.

6.2 Subgroup Definitions

For supportive efficacy analysis, subgroup of patients with '1 study eye only' vs. '2 study eyes' will be utilized.

7 Definition of Time Points and Analysis Variables

7.1 Definition of Time Points

Analyses of endpoints will be performed based on evaluations obtained on days 0, 28±2, 56±2 and 28±2 days after discontinuation of study treatment.

Baseline will be defined as the value collected at the Baseline Visit. Study day 1 is, subsequently defined as the day after the Baseline Visit.

The Treatment Day of an event/assessment will be calculated relative to the First Study Treatment Administration as specified on the eCRF page 'Study Drug Dosing Dates',

The Treatment day of events/assessments occurring before the First Study Treatment Administration was calculated as:

- Treatment Day = (Date of assessment/event - Date of First Study Treatment Administration).

For events/assessments occurring on or after First Study Treatment Administration, Treatment Day will be calculated as:

- Treatment Day = (Date of assessment/event - Date of First Study Treatment Administration) + 1.

Visits will be analysed as they were collected. Unscheduled visits during study treatment will be considered for imputation purposes only (Last-observation carried forward).

For dropout patients, the last study visit is documented on the eCRF in the Week 8 Visit section. In this case, the visit needs to be shifted to Week 4 or Week 12 visits or Unscheduled Visit depending on the visit window specified below.

Conformance with the visit schedule will be evaluated during the BDRM. In case of substantial deviations from visit schedule, a supportive analysis will be considered to investigate influence of these deviations on primary as well as secondary endpoints and documented in BDRM minutes.

Study completers will be defined as patients, who answered the question "Did the patient complete the study" on the eCRF page 'End of Study' as YES.

Table 2: Study Visits

Scheduled Visit	Scheduled Visit Label	Scheduled Study Day	Visit Window
Baseline Visit Day 0	Baseline	0	Study day = 0
Week 4	Week 4	28	Study day in [26 – 30]
Week 8	Week 8	56	Study day in [54 – 58]
Follow-up Visit Week 12	Week 12	84	Difference Date Week 12 – Date of Last Study intake in [26 – 30]
Documented unscheduled Visits will be labeled as "Unscheduled Visit 1", "Unscheduled Visit 2"…..			
For Visit Window Week 12, Date of Last Study Intake as specified on eCRF Page "Study Drug Dosing Dates"			

7.2 Analysis Variables

This chapter describes all endpoints which will be summarized as described in section 9.

7.2.1 Disposition parameters

Disposition parameters are recorded on the eCRF Page 'End of Study'.

Study discontinuations will be defined only for patients in the Enrolled Set. A patient discontinued the study prematurely, if the question 'Did the patient complete the study' was answered as 'No'.

Primary Reason for Study Discontinuation is documented on the eCRF Page 'End of Study' in categories 'Adverse Event', 'Lost to Follow-Up', 'Decision unrelated to an Adverse Event', 'Non-Compliance', 'Study terminated by the sponsor', 'Study terminated by the investigator', 'Other'.

If the study day of discontinuation as documented on the eCRF page is below 54 days, discontinuation will be considered as 'During Treatment Period', otherwise it will be considered as 'During Follow-Up Period'.

If the eCRF question 'Was the emergency envelope opened during the study?' was answered 'Yes', the patient will be considered as unmasked.

7.2.2 Demographic Characteristics

Demographic characteristics are recorded on the eCRF page "Demography".

Gender (Male, Female), Ethnicity ('Hispanic, Latino, Spanish', 'Not Hispanic, Latino, Spanish'), and Race ('White', 'Black or African American', 'Asian', 'Native Hawaiian or Other Pacific Islander', 'American Indian or Alaska Native', 'Other') will be analyzed as recorded on the eCRF.

Age (years) will be calculated at Baseline as:

- the integer part of (Date of Baseline Visit - date of birth)/365.25.

  In case of incomplete dates, missing days will be set to 1st and missing months will be set to July.

7.2.3 History of Corneal Surgery and other Medical History

The details of Corneal Surgery are recorded on the eCRF page "Medical history".

The following parameters will be analysed:

- Patients with previous cataract surgery (Yes/No)
- Eyes involved in previous cataract surgery per patient (Right Eye only, Left Eye only, Both Eyes)
- Patients with previous refractive surgery (Yes/No)
- Eyes involved in previous refractive surgery per patient (Right Eye only, Left Eye only, Both Eyes)
- Patients with previous LASIK surgery (Yes/No)

- Eyes involved in previous LASIK surgery per patient (Right Eye only, Left Eye only, Both Eyes)

Identification of study eye(s) ('Right eye', 'Left eye') is recorded on the "Study Eye" eCRF page and will be analyzed as derived categories 'Both Eyes', 'Left Eye only', 'Right Eye only'.

All other medical history is recorded on the "Medical history" eCRF page.

Medical history contains information about conditions that a patient might have suffered prior to Baseline visit, or conditions that are ongoing at the time of the Baseline visit.

The medical history terms as specified by the investigator will be coded to a Preferred Term (PT) and a System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) thesaurus.

In the event that coding information will not be available for a specific medical history record, the record will be presented as 'Uncodable Record'). However, for final TLFs it is anticipated that all medical history records are coded.

7.2.4 Prior and Concomitant Medication

Prior and Concomitant medication data will be collected throughout the study on the 'Prior and Concomitant Medications' eCRF page. *All medications (including over-the-counter drugs, herbal products, vitamins, and antacids) taken within 4 weeks prior to the start of and throughout the study must be recorded*.

Prior medications are defined as medications that were stopped before the date of first study treatment administration, i.e. stopped on treatment day 1 or before.

Concomitant medications comprise all medications that a patient used at any stage during the treatment or Follow-up period, i.e. medications, which are ongoing at treatment day 1 or medications which started on or after treatment day 1.

Relative start and stop day of a medication will be defined as the corresponding treatment day as specified in section 7.1. If for a medication 'Ongoing' duration is specified, no stop day will be calculated.

From the above follows that a medication can either be prior or concomitant.

The Investigator Terms (Generic Medication Name, and Indication) will be coded using the Enhanced WHO-Drug Dictionary, B-Files, Version MARCH/2016.

Prior and concomitant medication data will be summarized by WHO-ATC class 2 (Therapeutic Main Class) and WHO drug name (Preferred Term).

<u>Missing Codes or Medication Dates Imputation:</u>

In the event that coding information will not be available for a specific concomitant medication, the concomitant medications will be presented as 'Uncodable Medication'. However, for final TLFs it is anticipated that all medication records are coded.

Missing and/or incomplete dates for prior and concomitant medications will be imputed for calculating relative start and stop days only. Dates will be listed as missing/incomplete [with "-" replacing missing information] but the Start/Stop Day listed between square brackets to denote it was calculated based on missing data (i.e. [-28], [1], [Ongoing]).

Missing and/or incomplete dates will be imputed in a manner that assumes the worst case scenario.

Technically, incomplete stop dates will be imputed as follows:

- For a missing day (but month and year is available), it will be assumed that medication have been stopped on the last day of the respective month.
- For a missing month (but year is available), it will be assumed that medication have stopped on 31st December of the respective year.
- For a completely missing stop date, the medication will be assumed as being ongoing.

Similarly, incomplete start dates will be imputed as follows:

- For a missing start day (but month and year is available), onset is assumed on the first day of the respective month.
- For a missing start month (but year is available), onset is assumed on 1st January of the respective year.
- For a completely missing start date, no imputation is performed. However, the medication will be considered as concomitant, unless indicated different by stop date.

7.2.5 Measurements of Exposure and Treatment Compliance

Exposure

Exposure will be summarized by the parameters Treated Eyes and Treatment Duration.

Information about the type of eyes treated are recorded on the eCRF page 'Study Eye' at the Baseline Visit. Generally, all eligible eyes should be treated. The parameter Treated Eyes will be presented in the following categories:

- Both eyes: answer to eCRF question 'Which eye(s) will be treated' is Right Eye and Left Eye.
- Left eye only: answer to eCRF question 'Which eye(s) will be treated' is only Left Eye.
- Right eye only: answer to eCRF question 'Which eye(s) will be treated' is only Right Eye.

Treatment duration will be derived based on dates of first and last study treatment administration recorded on the 'Study Drug Dosing Dates' eCRF page. It will be calculated as

- Date of Last Study Treatment Administration – Date of First Study Treatment Administration +1. If a patient has not received any study treatment in any eye, treatment duration will be set to 0.

Compliance

The assessment of patients' compliance to the IMP will be made by determining the number of study medication vials dispensed to the patient at Day 0 baseline Visit, Week 4 Visit and the number of unused study medication vials returned at Week 4 Visit and Week 8 Visit,

respectively. This information is collected on eCRF page 'Study Drug Dosing and Accountability'.

Compliance will be evaluated according to the following formula:

$$\textit{Compliance}\ (\%) = 100 * \frac{\textit{Number of vials dispensed} - \textit{Number of unused vials returned}}{\textit{Number of expected days on treatment}}$$

The number of expected days on treatment will be set to 56. For each patient, the number of vials dispensed will be derived as the sum of provided numbers in the column "# Vials Dispensed" on the eCRF Page 'Study Drug Dosing and Accountability; the number of unused vials returned will be derived as the sum of provided numbers in the column "# Vials Unused" on the eCRF Page 'Study Drug Dosing and Accountability'.

Compliance will be presented categorical as <80%, 80-120%, >120%.

No further analyses will be planned on compliance. All other collected data including diary information on treatment compliance will be evaluated during the BDRM for relevant protocol deviations and will be listed.

7.2.6 Study Medication

Table 3: Study Treatments' shows the Study Treatments and how they will be labelled in all TLF outputs.

Table 3: Study Treatments

Study Treatment	Study Treatment Label
rhNGF 20µg/mL	rhNGF
Vehicle	Vehicle

7.2.7 Efficacy Variables

Primary Endpoints: SANDE Score

The Symptom Assessment in Dry Eye (SANDE) questionnaire is a short questionnaire to evaluate both dry eye intensity and frequency by using a 100 mm visual analogue scale (VAS). The patient symptoms of ocular dryness and/or irritation will be quantified on the scale based on two questions that assess both severity and frequency of symptoms.

For the assessment, the patients mark on the 100 mm VAS line the point that they feel represents their perception of their current state. The VAS score is determined by measuring in millimeters from the left hand end of the line to the point that the patient marks. The SANDE scores will be then evaluated for the 2 questions severity (0-100) and frequency (0-100).

The SANDE score will be assessed at Baseline, Week 4, Week 8 and Week 12 visit and is recorded on the eCRF page 'Symptoms Assessment in Dry Eye'. At each visit, only one assessment is performed aggregating the situation for both eyes (i.e. no separate assessment per study eye).

Primary endpoints will be defined as:

- Change from Baseline in SANDE frequency score at Week 8
- Change from Baseline in SANDE severity score at Week 8

If at least one SANDE assessment is missing at Week 8, the values of the last post-baseline assessment (including those from unscheduled visits) with non-missing values for frequency and severity will be imputed (LOCF). No imputation is performed in case of a missing baseline value (as defined in section 7.1).

Additionally, SANDE frequency and severity scores as well as respective changes from Baseline will be evaluated without any imputation for Week 4, Week 8 and Week 12, respectively.

Co-Primary Efficacy Endpoint: Corneal Staining (NEI Scale)

As grading scale of the corneal and conjunctiva damage, the NEI/Industry Workshop guidelines will be used [2]. The cornea is divided into five sectors (central, superior, inferior, nasal and temporal), each of which is scored on a scale of 0–3, with a maximal score of 15.

Briefly, on the grading scale used grade 0 reflects normal/healthy situation, whereas grade 3 reflects a severe damage in each considered sector.

Ocular Surface Staining is assessed separately for each eye at Baseline, Week 4, Week 8 and Week 12 visit and is recorded on the eCRF page 'Ocular Surface Staining (NEI score)'.

Corneal Staining will be derived as sum of scores of the five corneal sectors (central, superior, inferior nasal and temporal) ranging from 0 to 15. Corneal Staining will only be calculated, if all 5 sector scores are available. If at least one corneal staining assessment is missing at Week 8, the values of the last post-baseline assessment (including those from unscheduled visits) with non-missing values for frequency and severity will be imputed (LOCF).

Co-Primary endpoint will be defined as:

- Change from Baseline (CFB) in Corneal Staining at Week 8 for Main Eye.

In addition, the endpoint Change from Baseline in Corneal Staining at Week 8 for Secondary Eye will be considered as descriptive supportive analysis (only for patients in Subgroup 2 eyes treated).

To estimate the between patient variability, the Individual Mean Change will be derived for the subgroup of patients in the FAS with 2 eyes treated, as:

- Mean of CFB Main eye and CFB Secondary Eye, per patient at Week 8

To estimate the within patient variability, the Individual Difference in CFB for Corneal Staining between Study Eyes will be derived for the subgroup of patients in the FAS with 2 eyes treated, as:

- CFB Main eye - CFB Secondary Eye, per patient at Week 8

Additionally, Corneal Staining scores as well as respective Changes from Baseline will be evaluated for Week 4, Week 8 and Week 12, respectively. No imputation will be envisaged for these endpoints.

Secondary Endpoints: Conjunctival Staining (NEI Scale)

As grading scale of the corneal and conjunctiva damage, the NEI/Industry Workshop guidelines will be used [2].

Both nasally and temporally, 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, respectively.

Briefly, on the grading scale used grade 0 reflects normal/healthy situation, whereas grade 3 reflects a severe damage in each considered sector.

Ocular Surface Staining is assessed separately for each eye at Baseline, Week 4, Week 8 and Week 12 visit and is recorded on the eCRF page 'Ocular Surface Staining (NEI score)'.

Conjunctival Staining will be derived as sum of scores of the conjunctival area (nasal-superior paralimbal, nasal-inferior paralimbal, nasal-peripheral, temporal-superior paralimbal, temporal-inferior paralimbal, temporal-peripheral) ranging from 0 to 18. Conjunctival Staining will only be calculated, if all 6 area scores are available. Both scores will be derived for each eye separately.

Secondary endpoint will then be defined as:

- Change from Baseline in Conjunctival Staining at Week 8 for the Main Eye as well as for the Secondary Eye for Week 4, Week 8 and Week 12, respectively.

No imputation will be envisaged for these parameters.

Secondary Endpoint: Tear Film Break-Up Time (TFBUT)

TFBUT will be measured by determining the time to tear break-up. The TFBUT will be measured twice during the first minute after the instillation of the fluorescein. If the 2 readings differ by more than 2 seconds a third reading is taken. The TFBUT value recorded on the eCRF Page 'Tear Film Break Up Time' *will be the average of the 2 or 3 measurements.*

A TFBUT > 10 seconds will represent normal values, whereas values ≤ 10 seconds are likely for Dry Eyes.

TFBUT is assessed separately for each eye at Baseline, Week 4, Week 8 and Week 12 visit.

TFBUT value as well as respective Changes from Baseline will be evaluated for Week 4, Week 8 and Week 12, respectively. No imputation will be envisaged for this parameter.

Secondary Endpoint: Corneal sensitivity

Corneal sensitivity is measured continuously in cm by the Cochet-Bonnet aesthesiometer at Day 0 and Week 8 visits in each of the four quadrants of the cornea: Superior nasal, inferior nasal, superior temporal, inferior temporal. It is assessed separately for each study eye.

Corneal sensitivity values as well as respective Changes from Baseline will be evaluated for Day 0 and Week 8 visits, respectively. No imputation will be envisaged for this parameter.

7.2.8 Safety Variables

Adverse Events (AE)

AE data are collected on the 'Adverse Events' eCRF page. Corrective medications or procedures due to an AE are documented on the eCRF pages 'Prior and Concomitant Medications' and 'Concomitant Procedures' respectively.

The AE Description (Investigator term) will be analyzed on Preferred Term (PT) and System Organ Class (SOC) level using MedDRA.

Based on the information provided on the 'Adverse Events' eCRF page, the following definitions will be utilized:

- An ocular event will be identified, if the question 'Is this an ocular event?' is answered 'Yes'.
- An AE with missing severity will be counted as severe.
- A Serious Adverse Event (SAE) is any adverse event where the question 'Is the event serious?' has been answered as 'Yes'. If this question is not answered the event will be considered as 'Serious' for analysis purposes.
- *The following adverse events are considered to be of special interest (AESI) and by default shall be reported as SAEs (medically important criteria):*
    - *AEs that caused a decrease in visual acuity of >30 ETDRS letters or > +0.6 LogMAR (compared with the last assessment of visual acuity at the last visit) lasting >1 hour*
    - *AEs that caused a decrease in visual acuity to the level of Light Perception or worse lasting >1 hour*
    - *AEs that required surgical intervention (e.g., conventional surgery, vitreous tap or biopsy with intravitreal injection of anti-infectives, or laser or retinal cryopexy with gas) to prevent permanent loss of sight*
    - *AEs associated with severe intraocular inflammation (i.e., 4+ anterior chamber cell/flare or 4+ vitritis)*
    - *AEs that, in the opinion of the Investigator, may require medical intervention to prevent permanent loss of sight.*

  For analysis purposes, AESI will be identified by ticked box 'Medically significant or important medical condition' in the eCRF section 'SAE criteria'. This means in particular, that all AESIs will be considered as SAEs.
- An AE leading to premature withdrawal of the study treatment is defined as an AE where in the eCRF section 'Action taken with study treatment' the boxes 'Withdrawn' and 'Definitely' are ticked.
- An AE leading to study treatment interruption is defined as an AE where in the eCRF section 'Action taken with study treatment' the boxes 'Withdrawn' and 'Temporarily' are ticked.
- An AE leading to study discontinuation is defined as an AE where in the eCRF section 'Action regarding Patient' the box 'Patient Withdrawn' is ticked (this should match with the primary reason for early withdrawal of 'Adverse Event' on the End of Study eCRF page).
- An AE is classified as 'Related' to Study Treatment if the relationship to study medication recorded as 'Possible' or 'Probable' or 'Highly Probably'. An AE will be classified as unrelated to study medication if the relationship to study medication was recorded as 'None' or 'Unlikely'. AEs with missing relationship to study treatment will be counted as 'Related' to Study Treatment.
- A Fatal AE is defined as an AE where the outcome is recorded as 'Fatal'.

These definitions will apply accordingly also for the subsequent sub-classes of AEs.

Non Treatment-emergent adverse events (Non-TEAEs)

A Non-TEAE is defined as any AE, which started before the first administration of study treatment. They are identified by the ticked box 'Before Treatment Period' in the eCRF Section 'Did the event occurred:'.

Treatment-emergent adverse events (TEAEs)

A treatment-emergent adverse event is defined as an AE that started on or after the date of the First Study Treatment Administration. A TEAE will be identified, if The eCRF question 'Did the event occurred:' was answered either with 'During Treatment period' or 'During Follow-Up Period'.

The incidence and frequency of TEAEs will serve as safety endpoint of the study.

TEAEs in the Treatment Period

This will be defined as a TEAE (as defined above) with a start date on or after the date of first study treatment administration and before the Week 8 Visit. It will be identified, if eCRF question 'Did the event occurred:' was answered with 'During Treatment period'.

TEAEs in the Follow-up Period

This is defined as a TEAE (as defined above) with a start date on or after the Week 8 Visit. It will be identified, if eCRF question 'Did the event occurred:' was answered with 'During Follow-Up period'.

For listing purposes, treatment day of onset of AE will be presented according to the definition given in section 7.1.

<u>Missing Codes or Incomplete AE start dates:</u>

In the event that coding information will not be available for a specific AE, the event will be presented as 'Uncodable Event'). However, for final TLFs it is anticipated that all events are coded.

If the eCRF question 'Did the event occur:' was not answered, AEs will be classified to sub-class Non-TEAEs, TEAE in the Treatment Period or TEAE in the Follow-up Period based on the AE onset date utilizing the definitions given above. If this is not possible, the event will be classified as TEAE in the Treatment Period.

Missing and/or incomplete AE onset dates will be imputed for calculating relative start and stop days only. Dates will be listed as missing/incomplete [with "-" replacing missing information] but the onset Day listed between square brackets to denote it was calculated based on missing data (i.e. [1]).

Missing and/or incomplete dates will be imputed in a manner that assumes the worst case scenario:

- For a missing start day (but month and year is available), onset is assumed on the first day of the respective month.

- For a missing start month (but year is available), onset is assumed on 1st January of the respective year.
- For a completely missing start date, no imputation will be performed.

If for Non-TEAEs this procedure results in an onset date before date of informed consent, informed consent date will be used.

If for TEAEs 'During treatment period' this procedure results in an onset date before date of first study treatment, date of first study treatment will be used.

If for TEAEs 'During Follow-Up period' this procedure results in an onset date before date of Week 8 visit, date of Week 8 visit will be used.

Best Corrected Visual Acuity (BCDVA)

Best-corrected visual acuity is measured at Day 0 Baseline, Week 8 and Week 12 visit using standard charts, lighting, and procedures. All eyes must be tested at 4 meters first. When a patient cannot read at least 20 letters on the chart at 4 meters, the patient is tested at 1 meter.

In addition, the Snellen Equivalent is collected, which is based on smallest line read correctly (i.e. no or max. 1 error). The Scale is categorical and does not easily lend itself to statistical analysis or easy comparison but the logarithm of the minimal angle of resolution (logMAR) scale allows visual acuity to be assessed as a continuous measurement.

Visual acuity is recorded on the eCRF page 'Best Corrected Distance Visual Acuity'.

For the analysis, the BCDVA score and the logMAR as well as respective changes from baseline will be evaluated at Week 8 and Week 12. No imputation will be envisaged for these endpoints.

The BCDVA score will be derived as the total numbers of letters, which were read correctly at 4 meter plus the total number of letters read at 1 meter as collected on the eCRF page.

When 20 or more letters are read at 4 meters the visual acuity score (i.e. BCDVA score) *for that eye is recorded as the number of letters correct at 4 meters plus 30. The patient gets credit for the 30 letters at 1 meter even though they did not have to read them. If no letters are read correctly at either 4.0 meters or 1 meter, then the visual acuity score is recorded as "0."*

The logMAR will be derived as – log (Snellen Equivalent result). For this derivation the Snellen equivalent result is presented as fraction as documented in the eCRF field 'Snellen Equivalent Result'. LogMAR values derived from Snellen equivalent results range from -0.3 (20/10) to 1.6 (20/800) and will by rounded by 2 decimals. An increase in logMAR reflects a worsening of visual acuity.

If for a patient only ability for counting fingers is reported, logMAR will be set to 2; if for a patient only recognition of hand motion is reported, logMAR will be set to 3 *[1]*.

Slit lamp examination

Slit lamp examination is performed separately for each eye at Baseline, Week 4, Week 8 and Week 12 visit and is recorded on the eCRF page 'Slit Lamp Examination (Biomicroscopy)'.

Grading of the eyelids, lashes, conjunctiva, cornea, lens, iris and anterior chamber will be done according to the following scales:

Eyelid - Meibomian glands

0 = None (none are plugged).

1 = Mild (1 to 2 glands are plugged).

2 = Moderate (3 to 4 glands are plugged).

3 = Severe (All glands are plugged).

Eyelid - Erythema

0 = None (normal).

1 = Mild (redness localized to a small region of the lid(s) margin OR skin).

2 = Moderate (redness of most or all lid margin OR skin).

3 = Severe (redness of most or all lid margin AND skin).

4 = Very severe (marked diffuse redness of both lid margin AND skin).

Eyelid - Edema

0 = None (normal).

1 = Mild (localized to a small region of the lid).

2 = Moderate (diffuse, most or all lid but not prominent/protruding).

3 = Severe (diffuse, most or all lid AND prominent/protruding).

4 = Very severe (diffuse AND prominent/protruding AND reversion of the lid).

Lashes

0 = Normal

1 = Abnormal

Conjunctiva – Erythema

0 = None (normal).

1 = Mild (a flush reddish color predominantly confined to the palpebral or bulbar conjunctiva).

2 = Moderate (more prominent red color of the palpebral or bulbar conjunctiva).

3 = Severe (definite redness of palpebral or bulbar conjunctiva).

Lens

0 = No opacification (normal lens).

1 = Mild lens opacification.

2 = Moderate lens opacification.

3 = Severe lens opacification.

Iris

0 = Normal

1 = Abnormal.

Anterior Chamber Inflammation

0 = None (no Tyndall effect).

1 = Mild (Tyndall effect barely discernible).

2 = Moderate (Tyndall beam in the anterior chamber is moderately intense).

3 = Severe (Tyndall beam in the anterior chamber is severely intense).

All grading assessments of different eye structures will be evaluated as collected on the eCRF at Baseline Visit, Week 4, Week 8 and Week 12. No imputation will be envisaged for these parameters.

No aggregated presentation is planned for other assessments done during Slit lamp evaluation.

External ocular examination

External Ocular Examination assesses the motility of the extraocular muscles and the appearance and function of the eyelids before the instillation of any dilating or anesthetic eye drops.

Motility of extraocular muscle and appearance/function of eye lids is assessed separately for each eye at Baseline, Week 4, Week 8 and Week 12 visit and is recorded on the eCRF pages 'External Ocular Examination' and 'Appearance and Function of Eyelids'.

For the analysis, the Motility of the Extraocular Muscle will be evaluated by the field of movements Right and up ('Normal', 'Abnormal'), Right ('Normal', 'Abnormal'), Right and Down ('Normal', 'Abnormal'), Left and Up ('Normal', 'Abnormal'), Left ('Normal', 'Abnormal'), Left and Down ('Normal', 'Abnormal') as documented at the eCRF at Baseline Visit, Week 4, Week 8 and Week 12. No imputation will be envisaged for these parameters.

Appearance and Function of Eyelids will be summarized by the following parameters:

- Incidence of proven eyelid deformity/abnormality, which will be considered as present, if the question 'Evidence of eyelid deformity or abnormality' on the eCRF page 'Appearance and Function of Eyelids' is answered 'Yes'.

- Incidence of abnormal motor function of eyelids (i.e. upper lid elevation and forceful lid closure), which will be considered as present, if the question 'Motor function of eyelids' on the eCRF page 'Appearance and Function of Eyelids' is answered 'ABNORMAL'.

- Incidence of corneal exposure in case of closed eyelids, which will be considered as present, if the question 'Is there corneal exposure when the eyelids are closed?' on the eCRF page 'Appearance and Function of Eyelids' is answered 'Yes'.

- Incidence of proven punctual occlusion, which will be considered as present, if the question 'Is there evidence of punctual occlusion?' on the eCRF page 'Appearance and Function of Eyelids' is answered 'Yes'.

- Incidence of punctual plugs, which will be considered as present, if the box 'Punctual plugs' is ticked on the eCRF page 'Appearance and Function of Eyelids'.

- Incidence of thermal or surgical occlusion, which will be considered as present, if the box ‘Thermal or surgical occlusion’ is ticked on the eCRF page ‘Appearance and Function of Eyelids’.

- Incidence of Other punctual occlusion, which will be considered as present, if the respective ‘Other’ box is ticked on the eCRF page ‘Appearance and Function of Eyelids’.

8 Analysis Methods

8.1 General Methods

All analyses for this exploratory study will be done by using appropriate descriptive statistics by study group. All results will be summarized in tables. Patient individual data will be provided in Listings. No graphs are envisaged for this study.

For **continuous variables**, the mean, standard deviation, coefficient of variation (in %), minimum, median and maximum will be presented, together with the total number of observations and the number of missing and non-missing values. Unless otherwise specified minimum and maximum values will be reported to the same number of decimal places as the recorded measurements, mean and median are reported to one more decimal place and standard deviation one additional decimal place more than the mean.

For **categorical variables**, absolute and relative frequencies will be reported. Relative frequencies will be based on all observations and reported as a percentages to one decimal place. Unless otherwise specified, percentages will be based on the number of patients in considered analysis set including also percentages for missing categories. Only categories with non-null values will be presented in summary tables.

Incidences like adverse events, medical history and concomitant medications will be reported on a subject basis. The percentages will be calculated using the number of patients in the considered analysis data set.

8.2 Specific Methods for Efficacy Analyses

As a general principle, all efficacy analyses will be performed on a patient-level, considering the Main Eye for the analysis of Co-Primary and Secondary efficacy endpoint. Efficacy data in Secondary eye will be present as descriptive summaries and listed.

For the primary and co-primary efficacy endpoints, mean change from baseline will be compared between treatment groups. The null hypothesis will be tested that there is no difference between rhNGF and vehicle in the mean overall CFB between both treatments:

H_0: $\mu_{rhNGF} = \mu_{Vehicle}$

H_1: $\mu_{rhNGF} \neq \mu_{Vehicle}$

Where μ is the mean change from baseline at considered visit within the given treatment.

This hypothesis will be tested exploratory at a 5% level of significance with an Analysis of the Covariance (ANCOVA) with treatment, respective baseline value and eye subgroup (1 vs 2 study eyes treated) in the model.

The Least-squares means estimate of the treatment effect and the treatment group difference (both with 95% confidence intervals) will be reported. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as “<0.001”. Due to the high numbers of observations, the assumption of normality is assumed.

The ANCOVA analysis will be performed for the following endpoints:

- Change from Baseline in SANDE Frequency and Severity Score at Week 8 (LOCF) for the FAS as exploratory primary efficacy analyses
- Change from Baseline in SANDE Frequency and Severity Score at Week 8 (LOCF) for the PPS as supportive to primary efficacy analyses

- Change from Baseline in SANDE Frequency and Severity Score (without imputation) at Week 8 for the FAS as supportive to primary efficacy analyses
- Change from Baseline in Corneal Staining at Week 8 (LOCF) for the FAS as exploratory to co-primary efficacy analyses
- Change from Baseline in Corneal Staining at Week 8 (LOCF) for the PPS as supportive to co-primary efficacy analyses
- Change from Baseline in Corneal Staining (without imputation) at Week 8 for the FAS as supportive to co-primary efficacy analyses

8.2.1 Statistical/Analytical Issues

8.2.1.1 Adjustments for Covariates

Not alpha adjustment is envisaged, as all statistical hypotheses testing will be performed in an exploratory manner.

8.2.1.2 Handling of Dropouts or Missing Data

In the derivation of endpoints there will be no replacement of missing data except for primary endpoint CFB in SANDE Frequency and Severity Score and co-primary efficacy endpoint CFB in Corneal Staining, age, adverse event dates as well as concomitant medication dates. Details of applied imputations are described in the respective sections of chapter 7.2.

8.2.1.3 Multiple Comparisons/Multiplicity

Due to this being an exploratory study, no adjustment of any p-values will be made to account for inflation of the Type 1 error rate arising from multiple comparisons or multiple endpoint testing.

8.3 Specific Methods for Safety Analyses

As a generally principle, adverse event data will be analyzed separately by study period (Non-TEAE, TEAE).

All other safety assessments will be summarized by Visit and Eye (Main Eye/Secondary Eye).

According to the study protocol, both eyes of a patient should be treated, if eligible. However, there might be the situation, that one eye will not be treated. If a visit-based safety assessment was performed in an eye, which has not been treated with study medication, it will not be included in descriptive summaries but displayed in listings. Such assessments will be flagged in the listings accordingly.

9 Overview of Tables, Listings and Figures

This section describes the TLFs per topic with variables and populations used. For the content, titles and layout of tables see the table shells, which will be added as appendix to this document.

9.1 Disposition of Patients

A disposition summary of patients includes the number (n) and percentage (%) of patients screened, screen failures, included in the Enrolled Set, included in the SAF, FAS as well as in the PPS as defined in section 6.1. Presentation will be provided by study treatment and overall. Percentages, if applicable, will be based on the total number of patients (of considered treatment group) included in the Enrolled Set. A listing will also be provided for this information on individual patient level for the Enrolled Set.

A summary of study discontinuation will be provided for the Enrolled Set including number and percentage of discontinuations study during treatment period, primary reason for study discontinuation during treatment period, discontinuations during the Follow-Up period, primary reason for study discontinuation during the Follow-Up Period as well as study completers. Moreover, number and percentages of patients who were unmasked during study will be provided. Presentation will be provided by study treatment and overall. Percentages will be based on the total number of patients (of considered treatment group) included in the Enrolled Set.

A listing will also be provided for this information added by the date of first and last study medication intake as documented on the eCRF page ‘Study Drug Dosing Dates’.

For Screen failure a listing will be provided including the primary reason for discontinuation.

9.2 Protocol Deviations and Patient Eligibility

Protocol Deviations that might affect the efficacy of treatment will be reviewed during BDRM. A major protocol deviation will lead to an exclusion from the PPS.

The number of patients in the FAS who had at least one Major Protocol Deviation as well as a specific type of protocol deviation (as defined during the BDRM) will be summarized by absolute counts (n) and percentages (%) and displayed by treatment group and overall. Percentages will be based on the number of patients in the FAS.

A listing will be provided presenting all protocol deviation data for the Enrolled Set.

The eligibility of all patients for entry into the study will be assessed at the Baseline visit by the inclusion and exclusion criteria (‘Inclusion Criteria’ and ‘Exclusion Criteria’ eCRF pages). Two listing will be presented including all patients of the Enrolled Set, who fail/meet at least one Inclusion or Exclusion criteria, along with all their deviating Inclusion and Exclusion responses, respectively.

9.3 Demographic and Other Baseline Characteristics

9.3.1 Demographic Characteristics

Demographic data age, gender, ethnicity as well as race will be summarized by treatment group and overall for the SAF by treatment group and overall. Demographic Data will also be listed.

9.3.2 History of Corneal surgery and other Medical History

Summary statistics will be provided for patients with previous cataract surgery and involved eyes per patient, patients with previous refractive surgery and involved eyes per patient and patients with previous LASIK surgery and involved eyes per patient as well as identified Study Eyes per patient ('Left Eye only', 'Right Eye only', 'Both Eyes') and Identified Main Eye ('Left Eye', 'Right Eye' as defined in section 6.1) by treatment group and overall for patients in the SAF. A listing will also be provided.

Other Medical History will be summarized for the SAF by treatment group and overall on a per-patient basis (i.e. if a patient reported the same event repeatedly the event will be counted only once at the specific level of display). Absolute counts (n) and percentages (%) will be presented for the number of patients with at least one Medical History event, and per SOC and per PT within SOC.

A listing presents all medical history data for the SAF.

9.3.3 Prior and Concomitant Medications

Prior and Concomitant Medications will be summarized for the SAF on a per-patient basis (i.e. if a patient reported the same medication repeatedly the medication will be counted only once at the specific level of display). Absolute counts (n) and percentages (%) will be presented for the number of patients with at least one medication, and per WHO-ATC Drug Class 2 (ATC therapeutic main class) and per WHO-DD Drug Name (Preferred Term) within WHO-ATC Drug Class 2.

A Listing will be presented for Prior and Concomitant medications of patients in the SAF providing all collected details on the eCRF.

9.4 Measurements of Exposure and Treatment Compliance

Exposure will be evaluated by summary statistics for the parameters Treated Eyes and Treatment Duration by treatment group. This analysis will be performed for the SAF. This information will be listed.

Compliance will be summarized categorical (<80%, 80-120%, >120%) for the FAS by treatment group. This information as documented on the eCRF Page 'Study Drug Dosing and Accountability' will be listed for the SAF accordingly.

Further information on compliance as recorded on the eCRF Page 'Diary Information' and 'Exposure' at Week 4 and Week 8 will be listed for the SAF.

Further information on compliance as recorded on the eCRF Page 'Patient Diary' at Week 4 and Week 8 will be listed for the SAF.

9.5 Efficacy Results

9.5.1 Primary Efficacy Analysis

Results of the SANDE Frequency and SANDE Severity Score at Week 8 (absolute values as well as changes from baseline) will be summarized descriptively by treatment group. For the primary analysis LOCF is applied as described in section 7.2.7. The exploratory p-value and estimates for treatment effect as well as treatment group difference resulting from the ANCOVA analysis specified in section 8.2 will be reported in addition for Week 8 Visits. Primary analysis will be performed on the FAS.

For supportive purposes, this analysis of Week 8 results will be repeated for the PPS to investigate the effect of protocol deviations on the results.

If the covariate 'Number of Study Eyes' would result in a significant effect, the ANCOVA analysis will be repeated for each subgroup separately.

A similar analysis will be performed for the SANDE Frequency and SANDE Severity Score (without imputation) at Week 8. This analysis will be performed for the FAS only.

A descriptive analysis will be performed for the SANDE Frequency and SANDE Severity Score (without imputation) at Baseline, Week 4 and Week 12 as well as respective CFB without performing statistical inference. This analysis will be performed for the FAS only. All data on SANDE Scores will be listed on the FAS, indicating clearly imputed values.

9.5.2 Co-Primary Efficacy Analysis

Results of the co-primary endpoint Change from Baseline in Corneal Staining at Week 8 will be summarized descriptively by treatment group for Main Eye and Secondary Eye for the FAS.

For the co-primary analysis LOCF is applied as described in section 7.2.7. The exploratory p-value and estimates for treatment effect as well as treatment group difference resulting from the ANCOVA analysis specified in section 8.2 will be reported in addition for the Main-Eye results at Week 8.

For supportive purposes, this analysis of Main Eye results at Week 8 will be repeated for the PPS to investigate the effect of protocol deviations on the results.

If the covariate 'Number of Study Eyes' would result in a significant effect, the ANCOVA analysis will be repeated for each subgroup separately.

To investigate the influence of within and between patient variability, a descriptive analysis will be presented based on subgroup of patients in the FAS with 2 study eyes including CFB in Corneal Staining in Main Eye, Secondary Eye as well as the Individual Mean Change (i.e. mean of change in Main and Secondary Eye in each patient) and Individual Difference between Study Eyes at Week 8.

A similar analysis will be performed for the absolute values as well as for CFB in Corneal Staining (without imputation) at Week 4, Week 8 and Week 12. ANCOVA analysis will be performed for CFB at Week 8 in the Main Eye. This analysis will be performed for the FAS and all data will be listed for the FAS.

9.5.3 Secondary Efficacy Analysis

The secondary endpoints Conjunctival Staining, TFBUT as well as Corneal Sensitivity endpoints (absolute values as well as CFB) will be summarized descriptively for patients in the FAS by treatment group and study visit for Main Eye and Secondary Eye. No inference will be performed for these parameters.

Listing on secondary efficacy endpoints including assessments for Main Eye and Secondary Eye will be provided for FAS, in addition.

9.6 Safety Results

9.6.1 Adverse Events

9.6.1.1 Brief Summary of Adverse Events

Reporting of AEs is focused to treatment emergent AEs.

An overview of AEs, TEAEs, TEAEs during Treatment Period, TEAEs during Follow-up Period, TEAEs leading to premature withdrawal of the study treatment. TEAEs leading to study discontinuation, serious TEAEs, Fatal TEAEs, treatment related TEAEs, treatment related serious TEAEs, TEAEs of special interest and Mild, Moderate and Severe TEAEs will be given by study treatment and overall for patients in the SAF. For each events, the number and percentages of patients with at least one event as well as the total number of events will be provided.

9.6.1.2 Display of Adverse Events

Adverse event descriptive tables will be summarized separately for each study treatment and overall.

They will be summarized on a per-patient basis (i.e. if a patient reported the same event repeatedly the event will be counted only once at the specific level of display). Absolute counts (n) and percentages (%) will be presented for the number of patients with at least one Adverse event, and per SOC and per PT within SOC, for the SAF. Percentages will be based on the number of patients in the population. In addition number of events will be provided.

Descriptive tables will be ordered by descending frequency of the overall number of patients within each SOC regardless of treatment group, and then ordered within each SOC by the overall number of patients within each PT regardless of treatment group. In the event of equal frequencies tables will be ordered by active treatment frequency and then alphabetically.

The following tables will be provided:

- Non-TEAE
- TEAEs
- TEAEs by severity.
- Treatment related TEAEs.
- Serious TEAEs.
- Treatment related serious TEAEs
- TEAEs that occur with a relative frequency in the active treatment of at least twice the relative frequency in the vehicle group.
- TEAEs leading to premature withdrawal of the Study Treatment.
- TEAEs leading to study discontinuation.
- TEAEs during Treatment Period
- TEAEs during Follow-up Period.

9.6.1.3 Listings of Adverse Events

Listings will present all Adverse Event data for the SAF by patient.

In addition specific listings will be created for:

- TEAEs leading to premature withdrawal of study treatment
- TEAEs leading to study treatment interruption
- TEAEs related to study treatment
- Serious AEs
- Serious TEAEs related to study treatment
- Fatal TEAEs

Corrective procedures as documented on the eCRF page 'Concomitant Procedures' will be listed for all patients in the SAF.

9.6.2 Clinical Laboratory Evaluation

A Listing will be provided for patients in the SAF displaying the results of pregnancy tests at Baseline, Week 4 and Week 8 as documented on the eCRF Page 'Urine Pregnancy Test'.

9.6.3 Best Corrected Visual Acuity

BCDVA score and logMAR (absolute values as well as changes from baseline) will be summarized descriptively by treatment group and study visit for the Main Eye as well as the Secondary Eye. This analysis will be performed on the SAF. All BCDVA data will be listed.

9.6.4 Slit Lamp Examination

All grading assessments of different eye structure (excluding assessment for Other structures) will by will be summarized descriptively by treatment group and study visit for the Main Eye as well as the Secondary eye. This analysis will be performed on the SAF.

All data recorded on the eCRF page 'Slit Lamp Examination (Biomicroscopy)' will be listed.

9.6.5 External Ocular Examinations

All evaluations of the motility of extraocular muscle Right and Up, Right, Right and Down, Left and Up, Left, Left and Down will by will be summarized descriptively by treatment group and study visit for the Main Eye as well as the Secondary Eye. This analysis will be performed on the SAF. These data will also be listed.

Incidences of proven eyelid deformity/abnormality, abnormal motor function of eyelids, corneal exposure in case of closed eyelid, proven punctual occlusion, punctual plugs, thermal or surgical occlusion or other punctual occlusion will be presented by treatment group and study visit for the Main Eye as well as for the Secondary Eye.

Incidences will be calculated as number and percentages of affected patients. The analysis will be performed on the SAF. Moreover, these date will be listed.

10 References

1. Holladay, JT (1997) Proper Method for Calculating Average Visual Acuity. Journal of Refractive Surgery, 13, pp. 388-391.
2. Lemp MA. Report of the National Eye Institute/Industry Workshop on clinical trials in dry eye. CLAO J1995, 21(4):221–32.

11 Tables, Listings and Figures

Details on Tables and Listings (TLFs) will be provided in a separate document and are attached as appendix to this SAP.

TLF Number	Title
List of Tables	
Table 14.1-1.1	Summary of Patient Disposition
Table 14.1-1.2	Summary of Study Discontinuation (Enrolled Set)
Table 14.1-2.1	Summary of Protocol Deviations (FAS)
Table 14.1-3.1	Summary of Demographic Data (Enrolled Set)
Table 14.1-4.1	Summary of History of Corneal Surgery (SAF)
Table 14.1-5.1	Summary of Medical History (SAF)
Table 14.1-6.1	Summary of Prior Medications (SAF)
Table 14.1-6.2	Summary of Concomitant Medications (SAF)
Table 14.1-7-1	Summary of Treatment Compliance (FAS)
Table 14.2-1.1	Summary of SANDE Scores at Week 8 (LOCF) (FAS)
Table 14.2-1.2	Summary of Change from Baseline of SANDE Scores at Week 8 (LOCF) (FAS)
Table 14.2-1.2.1	Summary of Change from Baseline of SANDE Scores at Week 8 in Subgroups (LOCF) (FAS)
Table 14.2-1.3	Summary of SANDE Scores at Week 8 (LOCF) (PPS)
Table 14.2-1.4	Summary of Change from Baseline of SANDE Scores at Week 8 (LOCF) (PPS)
Table 14.2-2.1	Summary of SANDE Scores by Visit (Observed) (FAS)
Table 14.2-2.2	Summary of Change from Baseline of SANDE Scores by Visit (Observed) (FAS)
Table 14.2-3.1	Summary of Corneal Staining at Week 8 (LOCF) (FAS)
Table 14.2-3.2	Summary of Change from Baseline of Corneal Staining at Week 8 (LOCF) (FAS)
Table 14.2-3.2.1	Summary of Change from Baseline of Corneal Staining at Week 8 in Subgroups (LOCF) (FAS)
Table 14.2-3.3	Summary of Corneal Staining at Week 8 (LOCF) (PPS)
Table 14.2-3.4	Summary of Change from Baseline of Corneal Staining at Week 8 (LOCF) (PPS)
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12 Appendices

Statistical Analysis Plan: Tables, Listings and Figures Mock Shells Attachment (Separate Document)