NOVARTIS

Clinical Development

SAF312

CSAF312B12201 / NCT04630158

A 12-week parallel group, randomized, placebo-controlled, double-blinded, multi-center study to evaluate efficacy and safety of 2 concentrations of SAF312 eye drops (5 mg/ml and 15 mg/ml) used twice-daily in the treatment of post-operative corneal induced chronic pain (CICP) following Photorefractive Keratectomy (PRK) or Laser-assisted in Situ Keratomileusis (LASIK) surgeries

Statistical Analysis Plan (SAP)

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Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Classification
b.i.d.	bis in diem/Twice a day
CICP	Corneal Induced Chronic Pain
COVID-19	Coronavirus Disease 2019
CRC	Central Reading Center
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
EOS	End of Study
EOT	End of Treatment
FAS	Full Analysis Set
IE	Intercurrent Events
IOP	Intraocular Pressure
LASEK	Laser Assisted Sub-Epithelial Keratectomy
LASIK	Laser-assisted in Situ Keratomileusis
LSM	Least Square Mean
MAR	Missing at Random
MedDRA	Medical Dictionary for Drug Regulatory Affairs
mg	milligram(s)
mL	milliliter(s)
ml	milliliter(s)
MMRM	Mixed Model Repeated Measure
NGF	Nerve Growth Factor
OPAS	Ocular Pain Assessment Scale
PK	Pharmacokinetics
PRK	Photorefractive Keratectomy
PRO	Patient-reported Outcomes
REML	Residual/Restricted Maximum Likelihood
RK	Radial Keratotomy
QoL	Quality of Life
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMILE	Small Incision Lenticule Extraction
SMQ	Standardized MedDRA Query
SOC	System Organ Class
TRPV1	Transient Receptor Potential Vanilloid 1
VA	Visual Acuity
VAS	Visual Analogue Scale
WHO	World Health Organization

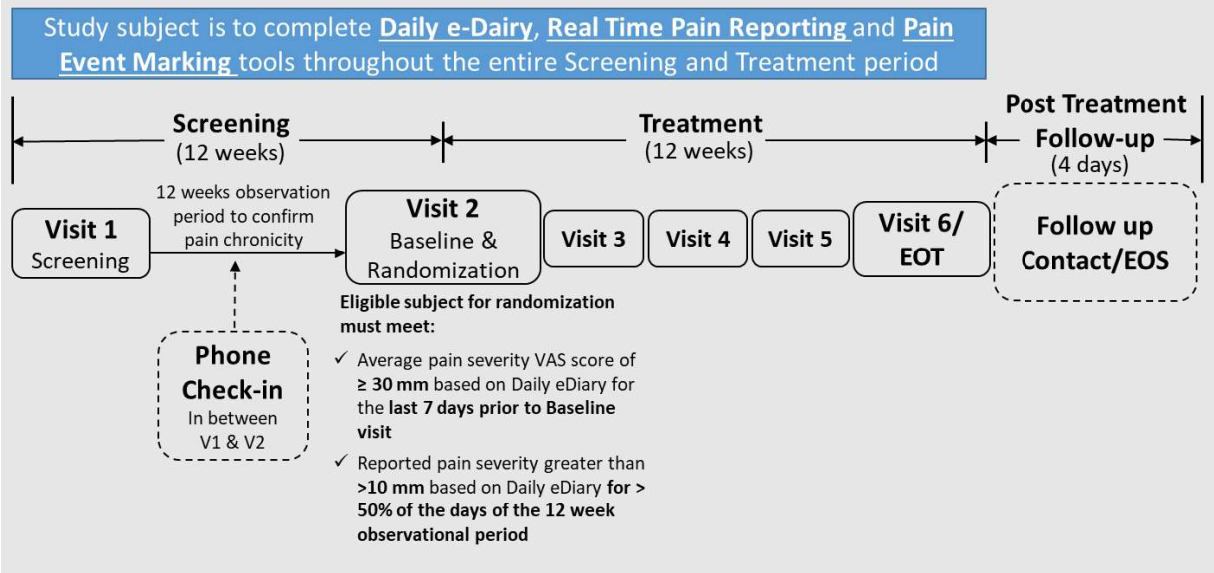
1 Introduction

The purpose of the Statistical Analysis Plan (SAP) is to describe the implementation of statistical analysis planned in the study protocol, and to provide detailed statistical methods that will be used for the Clinical Study Report (CSR) of study CSAF312B12201.

Data will be analyzed according to the data analysis plan described in this document that will be incorporated into the [CSAF312B12201 CSR-Section 9.7] and [CSAF312B12201 CSR-Appendix 16.1.9].

1.1 Study design

Figure 1-1 Study Design



This study is a Phase 2 randomized, double-blinded, multi-center, parallel group, placebo-controlled evaluation of the safety and efficacy of SAF312, 5 mg/ml and 15 mg/ml eye drops versus placebo used twice-daily in both eyes for 12 weeks. Eligible subjects will have undergone refractive surgery (i.e., PRK, LASIK, LASEK, RK, or SMILE) or cataract surgery in both eyes, with or without refractive enhancement in one or both eyes at least 4 months prior to Screening, and have been suffering from chronic ocular pain as a result of the surgery. Both eyes do not necessarily need to have undergone surgery on the same day. If the second eye underwent surgery on a different day than the first eligibility for time since surgery would be based on the date of the second surgery. In cases where more than one procedure was performed on an eye (e.g. refractive surgery with CICP followed some time later by cataract surgery, or cataract surgery followed some time later by refractive enhancement), the Screening visit must be ≥ 4 months after the most recent procedure. Eligible patients must also demonstrate chronicity of the pain as described in the inclusion criteria.

The study will consist of a 12-week observation period starting from Screening Visit (Visit 1) until the Baseline/Randomization Visit (Visit 2). Subjects who qualify for randomization will then be asked to attend visits every 2 weeks for the first 4 weeks, and then monthly for the

remainder of the 12-Week treatment period. End of Treatment (EOT) will occur at Visit 6 when the subject receives the last study treatment. End of Study (EOS) will occur 4 days after EOT. Visit 6/EOT is the time point for primary analysis.

Potential participants will be required to provide written informed consent prior to any study-specific Screening procedures being performed. Once informed consent is obtained subjects will be evaluated for eligibility based on the inclusion and exclusion criteria. Final eligibility will be based on an assessment of the subject's pain severity VAS prior to randomization, as well as their response to a single drop of topical ocular anesthetic (e.g. tetracaine, proparacaine eye drops per clinical practice). Response to anesthetic is defined as a ≥ 60% reduction in ocular pain within 5 minutes after instillation of the anesthetic drop. The use of the anesthetic test is necessary for the selection of subjects with a primarily peripheral neuropathic type pain (i.e. primarily resulting from stimulation of the peripheral nerves) versus a purely central neuropathic pain. Subjects with a primarily central neuropathic pain are unlikely to experience significant improvement with a topical ocular treatment targeting the peripheral nerves.

Overall, approximately 150 subjects will be enrolled in the study. Subjects who meet eligibility criteria at Visit 2 will be randomized to one of the 3 treatment groups (SAF312 5 mg/mL, SAF312 15 mg/mL, or placebo) in a 1:1:1 ratio. Randomization will be stratified according to baseline mean pain severity over the 7 days prior to Baseline Visit (≥ 75 mm or <75mm).

No interim analysis planned.

1.2 Study objectives and endpoints

Table 1-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To demonstrate the efficacy of at least 1 of 2 concentrations of SAF312 (5 mg/ml or 15 mg/ml) with superiority to placebo in reducing ocular pain severity	• Change from baseline to Week 12 in weekly mean pain severity Visual Analog Scale (VAS)
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate additional efficacy of 2 concentrations of SAF312 vs placebo	• Change from baseline to Day 7 and Day 14 using the pain severity VAS • Change from baseline to Week 12 in pain frequency VAS • Change from Baseline to Week 12 in Ocular Pain Assessment Scale (OPAS) sub-scale Quality of Life
• To demonstrate SAF312 does not induce negative effects to the ocular surface after prolonged TRPV1 inhibition	• Change from baseline to Week 12 in ocular surface parameters (e.g. corneal and conjunctival staining score, Schirmer score, conjunctival redness score)

Objective(s)	Endpoint(s)
• To evaluate the safety of 2 concentrations of SAF312 (0.5 and 1.5%)	• Comparison of adverse events rates between active and placebo
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**
[redacted]	[redacted]
• To monitor a subject's behavior regarding artificial tear/gel/lubricant use	• Frequency of artificial tear/gel/lubricant use over the 12-week treatment period
• To monitor a subject's behavior regarding rescue medication use	• Frequency of rescue medication use over the 12-week treatment period
• To evaluate corneal nerve density and morphology	• Change from Baseline to Week-12 in total corneal nerve fiber length • Presence of microneuromas • Density of corneal dendritiform cells

2 Statistical methods

2.1 Data analysis general information

The analysis will be performed by the Biostatistics and statistical programming groups of Novartis, using SAS 9.4 or above.

For categorical variables, frequencies and percentages will be computed. For continuous variables, descriptive statistics, including number of non-missing observations, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented. Where appropriate, point estimates and two-sided 95% confidence intervals of treatment group differences will be provided.

These summary statistics will be presented by treatment group unless otherwise specified.

2.1.1 General definitions

2.1.1.1 Study Treatment

Any drug administered to the study participants as part of the required study procedures; includes investigational drug (s), and control(s), which includes:

- SAF312 15 mg/mL (1.5%) eye drops, suspension, b.i.d.
- SAF312 5 mg/mL (0.5%) eye drops, suspension, b.i.d.
- SAF312 Placebo eye drops, suspension, b.i.d.

All dosage strengths of SAF312 and placebo will be identical in appearance (in Drop-tainers for b.i.d. dosing of both eyes each day). The following abbreviated treatment groups will be used as the headers in the tables:

- SAF312 15 mg/ml
- SAF312 5 mg/ml
- SAF312 Placebo

2.1.1.2 Baseline and post-Baseline

Baseline (Day 1) is the date of first dose of study treatment. The baseline value for efficacy and safety variables is the last available value collected prior to or at the first date of study treatment. Missing baseline data will not be imputed.

All data collected after the first date of treatment are defined as *post-baseline*. The *study day* for a baseline or post-baseline scheduled or unscheduled visit is defined as:

Study day = (Date of visit) – (Date of first dose of study treatment) + 1;

The *study day* for a scheduled or unscheduled visit before baseline is defined as

Study day = (Date of visit) – (Date of first dose of study treatment).

2.1.1.3 End of study/end of treatment/unscheduled visit day mapping:

The end of treatment date (date of last exposure from 'Study Treatment' CRF form) is the date of the last study treatment prior to/on the end of study date. The end of study date (from 'Study disposition' CRF) is the date when a subject completes or discontinues the study. For reporting data by visit in outputs, visit window (Section 2.1.1.5) rules will be applied based on study day to allocate assessments to the actual (reported) visit number.

2.1.1.4 Unscheduled visits

Unscheduled visit measurements will be included in the following:

1. derivations of measurements at scheduled visits per specified visit windowing rules below.
2. derivations of baseline/last on-treatment measurements.
3. derivations of the maximum/minimum on-treatment values and maximum/minimum changes from baseline values for safety analyses.
4. subject data listings where appropriate.

2.1.1.5 Visit Windows

Visit windows will be applied for all measurements except data from e-diary daily. Weekly mean will be calculated every 7 days starting from study day 1.

Table 2-1 Allocation of assessments to analysis visit window

Scheduled main visit name/label	Target study day	Analysis visit window in study days	Visit Label
Visit 1 Screening	-84	≤ -1	Screening
Visit 2 Baseline	1	1	Baseline
Visit 3	14	2 - 21	Visit 3 (week 2)
Visit 4	28	22 - 42	Visit 4 (week 4)
Visit 5	56	43 - 70	Visit 5 (week 8)
Visit 6 EOT	84	≥ 71	Visit 6 / EOT (week 12)

To allocate assessments to each scheduled visit

- If no measurement is available within a visit window, the assessment will be considered missing for the visit.
- If there is more than one measurement available within the same visit window, use the following rules:
  1. The record closest to the target day will be used.
  2. If there are multiple records with the same distance to the target day, the latest record will be used.
  3. If there are multiple records with the same distance on the same day, the average will be used.

2.1.1.6 7-day average of assessments

The Pain Severity Visual Analog Scale (VAS) score is captured in the e-diary daily by the patient for the entire 6 months of the study (observational period and treatment period), and weekly mean of the scores is calculated by averaging the available Pain Severity VAS scores during the 7 days of that week. Pain frequency will be analyzed in the same manner.

To calculate the frequency of artificial tear/gel/lubricant use, the information is captured daily as mentioned above, and the daily frequency collected by the patient in e-diary during the 7 days of that week will be averaged.

2.1.1.7 Change from baseline for continuous parameters

Change from baseline will be calculated as:

change from baseline = post-baseline value – baseline value

For summary statistics the raw values (and not imputed values) will be used.

2.2 Analysis sets

The Full Analysis Set (FAS) comprises all subjects to whom study treatment has been assigned by randomization. According to the intent to treat principle, subjects will be analyzed according

to the treatment and strata they have been assigned to during the randomization procedure. Mis-randomized subjects who do not take study medication will be excluded from FAS.

The Safety Set (SAF) includes all subjects who received at least one dose of study treatment. Subjects will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the subject took at least one dose of that treatment or the first treatment received if the randomized treatment was never received.

The number and percentage of subjects within each of the above analysis sets will be summarized.

Rules of exclusion criteria of analysis sets with protocol deviations and subject classification are specified in Appendix.

2.2.1 Subgroup of interest

The subgroups of interest are specified below:

- Baseline age group: < 65 years, and >= 65 years
- Sex: male, female
- Race: Caucasian, Asian and Others
- Eye color:
    1. If the two irises of a subject are the same color as Black, Brown, Hazel, Green, Blue or Gray, the subject will be classified as one of the categories: “Black/Brown”, “Hazel/Green”, or “Blue/Gray”.
    2. If the two irises of a subject are of the same color but different from the colors listed above, or if the two irises have a different color, the subject will be classified as “Other”.
- Baseline pain severity: 7-day average pain severity VAS >= 75, 7-day average pain severity VAS < 75
- Region: Japan, Non-Japan

2.3 Subject disposition, demographics and other baseline characteristics

Subject characteristics and study conduct summaries include tables and listings such as subject disposition table, demographics and baseline characteristics tables, summary of screen failures by reason and listing of subjects excluded from analysis sets.

2.3.1 Subject disposition

Subject disposition will be summarized separately by treatment group and total for the FAS. Specifically, the number and proportion of subjects who discontinued the study will be summarized by treatment and total. The primary reason for premature study discontinuation will be summarized in the table.

2.3.2 Demographics and baseline characteristics

Demographics table will include age, sex, race, ethnicity, ancestry, and eye color.

Baseline characteristics table will include: type of prior surgery(PRK,LASIK, LASEK, RK, SMILE or Cataract), time (days) since last surgery, corneal fluorescein staining(sum score), conjunctival lissamine staining(sum score), conjunctival redness score (Temporal and Nasal), schirmer score, Pain Characterization Questionnaire (question 2 only), 7-day average of pain severity VAS score, 7-day average of pain frequency VAS score, 7-day average of artificial tear/gel/lubricant use frequency and 7-day frequency of rescue medication use .

Demographic and baseline characteristics will be summarized for FAS populations by treatment group using frequencies and percentages (for categorical variables) and descriptive statistics of mean, standard deviation, minimum, median and maximum (for continuous variables).

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class, preferred term and treatment group, for ocular and non-ocular histories/conditions, respectively.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

The SAF will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

2.4.1 Study treatment / compliance

The duration of exposure in days to study treatment will be summarized by means of descriptive statistics by treatment group. The duration of exposure is defined as: date of the last administration of study treatment (date of last exposure in CRF ‘Study Treatment’ form) – date of first administration of study treatment (date of first exposure in CRF ‘Study Treatment’ form) + 4 + 1.

Compliance will be presented by summarizing the total number of days without missing a dose or dose interrupted within the treatment period by treatment group. Reason for premature discontinuation from the study treatment will also be summarized.

2.4.2 Prior, concomitant and post therapies

Prior medications are defined as drugs taken and stopped prior to the first administration of study treatment. Any medication given at least once between the day of the first dose of the study treatment and the end of study visit will be a concomitant medication. Prior or concomitant medication will be identified based on recorded or imputed start and end dates of taking the medication.

Prior and concomitant medication will be summarized by treatment group (separately for ocular and non-ocular medications/therapies), presented in alphabetical order by ATC classification codes and preferred term. The tables will be presented with overall number and percentage of subjects receiving at least one drug of a particular ATC code and at least one drug in a particular

preferred term. Medications will be coded according to the WHO Drug Reference List dictionary.

In addition, all information will be listed including the reported name, laterality, and treatment start/end date, etc.

2.4.3 Rescue medication

There is no rescue medication that will be proactively provided to study sites or subjects. However, at the discretion of the investigator, medication (local or systemic, over the counter or prescription) used for pain relief will be allowed and will be specified if used for ocular or non-ocular pain. Rescue medication will be the newly assigned medication for pain (ocular or non-ocular) during treatment period. Pain medication used as background therapy will not be counted as rescue medication.

The number and percentage of subjects who received any rescue medication will be summarized by treatment group. The 7-day frequency of rescue medication use will be summarized by week and treatment group.

2.4.4 Prohibited medication

Moreover, concomitant medications that are prohibited as per protocol (Table 2-2) and given during the conduct of the study will be provided. The number and percentage of subjects taking concomitant medications will be summarized by treatment group.

Table 2-2 Prohibited medication

Medication	Prohibition period	Action taken
Artificial tears/gels/lubricant eye drops other than those started before enrollment	Study duration	No action
Use of topical ocular medications (prescription or over the counter) within 4 hours prior to a study visit	Study duration	Reschedule study visit outside of the 4 hour window
Use of ocular or oral pain medication within 4 hours of a study visit	Study duration	Reschedule the study visit outside of the 4 hour window
Ocular, nasal, inhaled, or systemic corticosteroids	Study duration	No action
Use of oral or topical ocular antihistamines, mast cell stabilizers (e.g. Ketotifen)	Study duration	No action
Neuromodulators and NGF for any reason	Study duration	Discontinue study treatment

2.5 Analysis of the primary objective

The primary objective of the study is to demonstrate the efficacy of at least 1 of 2 concentrations of SAF312 (5 mg/ml or 15 mg/ml) with superiority to placebo in reducing ocular pain severity.

For the purpose of the statistical analyses presented in this document, the following terminology is used:

- Intercurrent events (IE) - Events that occur after treatment initiation and either preclude observation of the variable or affect its interpretation (e.g. rescue medications, discontinuation of treatment, switching treatment, terminal events such as death, etc.)
- Missing at Random (MAR) – the multiple imputation model will be built based on similar patients (i.e. with the same covariates and observed measurement history) in the same treatment arm.
- Jump to Reference (J2R) – the multiple imputation model will be built based on the available placebo data (including partial information from patients that discontinued prematurely). The imputation model will include important background characteristics and observed data.

2.5.1 Primary endpoint

The primary clinical question of interest is: What is the effect of SAF312 versus placebo on change from baseline in pain severity after treatment in subjects with CICP, had they not taken rescue or prohibited medications, and had they not discontinued treatment?

The justification for the primary estimands is that they will capture the effect of the study drug for the full duration when administered without confounding effects from prohibited medications or rescue medications. They also account for discontinuation from treatment due to AEs, lack of efficacy, and use of prohibited medications. The hypothetical strategy assumes the subjects with Intercurrent events (IEs) will behave like other subjects who did not take rescue/prohibited medications and stayed on study treatment.

The analysis of the primary endpoints will be based on FAS.

The primary estimand is defined as follows for signs and symptoms:

- The target **population** is subjects with CICP persisting at least 4 months after refractive surgery or cataract surgery, and chronicity of pain confirmed during the 3-month observation period who meet the inclusion and exclusion criteria.
- The primary **endpoint** is the change from baseline in ocular pain severity VAS at Week 12. The score is derived by averaging the seven daily measurements of each week.
- The treatment of interest is SAF312 arms versus placebo, had they not needed rescue or prohibited medications and behaved like other patients who did not take them, had they not discontinued treatment and behaved like other patients who did not discontinue treatment.

Table 2-3 The handling of intercurrent events strategy for primary estimands

Intercurrent Events	Strategy

Rescue medications for pain relief due to any reason	• The data on the days will be excluded and treated as missing. • Missing weekly mean pain score values will be handled under MAR assumption in MMRM
Prohibited medications that could confound the primary endpoint (See Table 2-2) • Ocular, nasal, inhaled, or systemic corticosteroids • Use of oral or topical ocular antihistamines, mast cell stabilizers	• The data on the day(s) + 3 days following the last day of these prohibited medications will be excluded and treated as missing. • Missing weekly mean pain score values will be handled under MAR assumption in MMRM
• Any new use or change in dosing of neuromodulators for any reason, or any use of topical ocular NGF	• The data starting from the day will be excluded and treated as missing • Missing weekly mean pain score values will be handled based on the MAR assumption in MMRM
Discontinuation of study treatment due to any reasons (e.g. AEs, pandemic)	• The data after study treatment discontinuation will be treated as missing. • Weekly mean pain score values at or after the week of study treatment discontinuation will be handled under MAR assumption in MMRM

- The **summary measure** is the treatment difference of the variable means between SAF312 arms and placebo respectively.
  - SAF312 15 mg/ml vs SAF312 placebo
  - SAF312 5 mg/ml vs SAF312 placebo

2.5.2 Statistical hypothesis, model, and method of analysis

The primary objective of the study is to show that at least one SAF312 arm will improve weekly mean pain severity VAS score in comparison with its placebo by rejecting the null hypothesis below at a significance level α=0.05 (2-sided).

$$H_1: \mu_T = \mu_V \text{ vs. } H_2: \mu_T \neq \mu_V$$

where μ_T and μ_V are mean change from baseline of weekly mean pain severity VAS score in SAF312 arm and the placebo arm.

Dunnett procedure will be used to adjust overall type I error (0.05) among the comparisons between each SAF312 arm and the placebo arm.

Mixed model repeated measure (MMRM) analysis will be used with change from baseline at each week on treatment as response variable, and treatment, week and baseline score as covariates. Two interaction term (treatment*week and baseline*week) will also be included in the model.

An unstructured within subject correlation structure will be used for covariance matrix. If the unstructured covariance matrix results in a lack of convergence, then other covariance structures will be investigated. Toeplitz, First Order Autoregressive AR(1) and Compound Symmetry will be applied, in the specified order, until the model converges.

The Kenward-Roger approximation will be used to estimate denominator degree of freedom. REML (residual/restricted maximum likelihood) method will be used to estimate parameters.

The two-sided p value for the least square mean (LSM) difference between the SAF312 and the placebo group at each week will be reported for the difference. The primary inference will be based on LSM difference at Week 12 (Visit 6).

Line plots (LSM ± 1 SE) will be presented by treatment groups and post-baseline day/visit. The x-axis will be study visit and the y-axis will be the change from baseline value.

2.5.3 Handling of missing values not related to intercurrent event

The primary MMRM model implicitly imputes missing data under MAR assumption.

2.5.3.1 Handling of missing daily pain severity values within a week

The weekly mean of the seven 24-hour average pain severity assessments will be calculated based on the available assessments. If only one measurement is available, the mean will be based on that value. If no measurement is available, the weekly mean VAS score will be missing. The data collected beyond 12 weeks will not be analyzed.

2.5.3.2 Handling of missing weekly mean pain score values

For all analyses, imputation of intermittent missing value of pain severity VAS score before treatment discontinuation will be carried out following a MAR mechanism for all treatment arms.

2.5.4 Supportive analyses

The subgroup analyses will be conducted to assess the consistency of treatment effect across various subgroups described in Section 2.2.1. Subgroup analyses will be conducted using the same model and analysis strategies described in the primary analyses but fitted by category of each of the subgroups. Subgroup variables that are used as fixed effects in the model will be removed from the model statement in the subgroup analysis if applicable. Subgroups will be presented graphically using forest plots. If a subgroup has limited number of subjects, the analyses on this subgroup may fail to converge and not be implemented. Instead, summary statistics for subgroup will be provided.

2.5.4.1 Supplementary estimand

The target population, the primary variable and the summary measure of this estimand are the same as for the primary estimand. The supplementary estimand is defined to estimate the treatment effect of SAF312 versus placebo, regardless of occasional rescue medication, prohibited medications and treatment discontinuations due to any reason.

The justification for the supplementary estimand is that they will capture the effect of the study drug when administered in the real world with intercurrent events considered as inherent in the treatment regimen.

Table 2-4 The handling of intercurrent events strategy for supplementary estimands

Intercurrent Events	Strategy
Rescue medications for pain relief due to any reason	• All observed data will be used for analysis • Missing weekly mean pain score values will be multiple imputed under MAR assumption
Prohibited medications that could confound the primary endpoint (See Table 2-2) • Ocular, nasal, inhaled, or systemic corticosteroids • Use of oral or topical ocular antihistamines, mast cell stabilizers	• All observed data will be used for analysis • Missing weekly mean pain score values will be multiple imputed under MAR assumption
• Any new use or change in dosing of neuromodulators for any reason, or any use of topical ocular NGF	• All observed data will be used for analysis • Missing weekly mean pain score values will be multiple imputed under MAR assumption
Discontinuation of study treatment due to any reason	• Weekly mean pain score values at or after the week of study treatment discontinuation will be multiple imputed based on J2R assumption for the SAF312 arms and under MAR assumption for the placebo arm

Mixed model covariance matrix will be handled in the same manner as primary estimand.

2.6 Analysis of the key secondary objective

There is no key secondary objective in the study.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

For secondary endpoints:

- Change from baseline in pain severity Visual Analog Scale (VAS) at Day 7 and Day 14
- Change from baseline to Week 12 in pain frequency VAS
- Change from baseline in OPAS subscale Quality of Life at Week 12
- Change from baseline to Week 12 in ocular surface parameters (corneal staining score, conjunctival staining score, Schirmer score, conjunctival redness score)

2.7.2 Statistical hypothesis, model, and method of analysis

No statistical hypothesis test will be performed on the secondary endpoints. Summary statistics (mean, median, 25th percentile, 75th percentile, standard deviation, minimum and maximum, the number of non-missing observations, and 95% confidence interval) by treatment arm will be provided.95% confidence interval will be provided for the difference between the SAF312 arm vs. placebo for pain severity VAS, pain frequency VAS, OPAS subscale Quality of Life and ocular surface parameters.

Where laterality applies, each eye will be summarized separately.

2.7.3 Handling of missing values/censoring/discontinuations

All observed data will be used for analysis and missing data will not be imputed.

2.8 Safety analyses

For all safety analyses, the SAF will be used. All listings and tables will be presented by treatment group.

Adverse Events will be reported at subject level and other safety endpoints will be reported at eye level (Left and Right) where appropriate.

2.8.1 Adverse events (AEs)

Summary tables for AEs will summarize for pre-treatment AEs and treatment emergent AEs (TEAEs) separately:

- Pre-treatment AEs are adverse events started between ICF signature and prior to the first administration of study treatment.
- TEAEs are adverse events started after the first administration of study treatment or events present prior to start of the treatment but increased in severity based on preferred term.

The number and percentage of subjects with AEs will be summarized for ocular and non-ocular respectively, by treatment, in the following ways:

- Primary system organ class and preferred term.
- Primary system organ class, preferred term and maximum severity.
- Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries for TEAEs will be provided for study medication related AEs, death, serious adverse events (SAE), other significant AEs leading to discontinuation.

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class. All of these analyses will be based on the most updated MedDRA version available prior to the database lock.

All adverse events reporting will be included in the subject listings respectively.

2.8.1.1 Adverse events of special interest / grouping of AEs

Not applicable.

2.8.1.2 Adverse event reporting for clinical trial safety disclosure

For the legal requirements of ClinicalTrials.gov, two required tables on TEAEs which are not serious adverse events with an incidence greater than 5% and on TEAEs and SAEs suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for the same subject, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is >1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE (respectively non-SAE) has to be checked in a block e.g., among AEs in a ≤1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment, and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.2 Deaths

Deaths will be listed separately.

2.8.3 Laboratory data

Not applicable.

2.8.4 Other safety data

Where laterality applies, each eye will be summarized separately.

Corrected Visual Acuity

Snellen visual acuity (VA) testing in each eye will be conducted. The Snellen numerator and denominator will be entered in the eCRF. ETDRS will be derived from the Snellen visual acuity for summary (Table 2-5).

Table 2-5 Converting Snellen Fraction to Approximate ETDRS Letters Score

Snellen Fraction/ decimal	Approximate ETDRS Letters Score
≤ 0.005	0
> 0.005 to 0.015	1
> 0.015 to 0.020	3
> 0.020 to 0.025	5
> 0.025	85 + (50*log10[Snellen fraction]) rounded to the nearest integer

If numerator Snellen = 0 and denominator Snellen = 0, then ETDRS letters score is taken as missing.

Descriptive summaries (mean, median, 25th percentile, 75th percentile, standard deviation, minimum and maximum, the number of non-missing observations, and 95% confidence interval) of change from baseline VA values will be presented at each study visit by treatment group.

Intraocular Pressure

Intraocular pressure (IOP) measurements will be recorded in mmHg and rounded to the nearest whole number for summary.

Descriptive summaries (mean, median, 25th percentile, 75th percentile, standard deviation, minimum and maximum, the number of non-missing observations, and 95% confidence interval) of change from baseline IOP values will be presented at each study visit by treatment group.

Slit Lamp Exam and Fundus Exam/Ophthalmoscopy

Slit lamp and Fundus exams will be performed, and results will be captured in the source document at each visit. The eCRF will record only if those assessments were indeed performed or not for compliance perspective.

Subject listing will be provided.

Corneal Endothelial Cell Microscopy

At the Baseline and End of Treatment Visits, Specular microscopy of the corneal endothelial cell images will be obtained by the Investigator and submitted to the Central Reading Center (CRC) to determine the changes in endothelial cell count, density, and shape from the initial baseline to the end of treatment.

Listing of the parameters will be provided by subject by visit.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

Not applicable.

2.11 Patient-reported outcomes

In addition to the VAS, patient-reported outcomes include the following:

- OPAS questionnaire subscales

[redacted]

No test will be performed on the PRO endpoints that are not pertaining to the primary endpoint. Please refer to Section 2.7 and Section 2.13 for detail.

2.12 Biomarkers

Not applicable.

2.13 Other Exploratory analyses

Exploratory endpoints include:

- Frequency of artificial tears/gel/lubricant use over the 12-week treatment period
- Frequency of rescue medication use over the 12-week treatment period
- Change from Baseline to Week 12 in total corneal nerve fiber length
- Presence of microneuromas
- Density of corneal dendritiform cells

The analysis will be based on FAS. Descriptive summaries (mean, median, 25th percentile, 75th percentile, standard deviation, minimum and maximum, the number of non-missing observations, and 95% confidence interval) of frequency of artificial tears/gel/lubricant use and frequency of rescue medication use will be presented by week and treatment group.

The details of the rest exploratory analysis will be documented in Data Exploration Strategy separately. If any of the exploratory analysis is considered of clinical or regulatory relevance, it will be included in an SAP/CSR via amendment or addendum process as appropriate.

2.14 Interim analysis

Not applicable.

3 Sample size calculation

Assuming a true treatment difference in change from baseline in weekly mean pain severity VAS of 15 mm and a SD of 23 mm, a sample size of 50 subjects per arm provides approximately 83% power that the primary analysis will be statistically significant at the two-sided 5% significance level adjusted by 2 comparisons.

See Table 3-1 for power to detect a significant difference from placebo under various assumed treatment-effect of weekly mean pain severity VAS and SD.

Query Advisor 7.0 is used for the estimate.

Table 3-1 Power to detect a significant difference from placebo under different assumed treatment effects and SD with N = 50 pts/arm

	Treatment effect: difference from placebo in change from baseline in weekly mean pain severity VAS	
SD of change from baseline in weekly mean I pain severity VAS	15	20
17	98%	>99%
20	92%	>99%
23	83%	97%

The sample size may increase by up to 20% (i.e. 60 pts/arm) in order to maintain power in case dropout increases during the pandemic.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 AE date imputation

5.1.1.1 Adverse event end date imputation

1. If the AE end date month is missing, the imputed end date should be set to the earliest of the (treatment follow-up period date, 31DECYYYY, and/or date of death).

2. If the AE end date day is missing, the imputed end date should be set to the earliest of the (treatment follow-up period date, last day of the month, and/or date of death).

3. If AE year is missing or AE is ongoing, the end date will not be imputed.

5.1.1.2 Adverse event start date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.c) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < treatment start date then AE start reference date = min (informed consent date, earliest visit date).
2. Else AE start reference date = treatment start date

Impute AE start date

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the treatment start date year value, the AE started before treatment. Therefore:
    a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JulYYYY).
    b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the treatment start date year value, the AE started after treatment. Therefore:
    a. If the AE month is missing, the imputed AE start date is set to the year start point (01JanYYYY).
    b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).
4. If the AE start date year value is equal to the treatment start date year value:
    a. And the AE month is missing the imputed AE start date is set to the AE reference start date + 1 day.
    b. Else if the AE month is less than the treatment start month, the imputed AE start date is set to the mid-month point (15MONYYYY).

c. Else if the AE month is equal to the treatment start date month or greater than the treatment start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

5.1.2 Concomitant medication date imputation

5.1.2.1 Concomitant treatment end date imputation

1. If CM end day is missing and CM month/year are non-missing, then impute CM day as the minimum of treatment follow-up period date, date of death and the last day of the month.
2. If CM end month are missing and CM year is non-missing, then impute CM day as the minimum of treatment follow- up period date, date of death and the end of the year (31DECYYYY).
3. If CM end year value is missing, the date uncertainty is too high to impute a reliable date. Therefore, if the CM end year value is missing or ongoing, the imputed CM end date is set to NULL.
4. If imputed CM end date is less than the CM start date, use the CM start date as the imputed CM end date.

5.1.2.2 Concomitant treatment start date imputation

The following table explains the notation used in the logic matrix. Please note that **missing start dates** will not be imputed.

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) Uncertain	(1) Uncertain	(1) Uncertain	(1) Uncertain
YYYY < TRTY	(2.a) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start	(2.b) Before Treatment Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Treatment Start	(4.a) Uncertain	(4.c) After Treatment Start
YYYY > TRTY	(3.a) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start	(3.b) After Treatment Start

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to treatment start date.

2. If the CM start date year value is less than the treatment start date year value, the CM started before treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the mid-year point (01JulYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).
3. If the CM start date year value is greater than the treatment start date year value, the CM started after treatment. Therefore:
    a. If the CM month is missing, the imputed CM start date is set to the year start point (01JanYYYY).
    b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).
4. If the CM start date year value is equal to the treatment start date year value:
    a. And the CM month is missing, or the CM month is equal to the treatment start date month, then the imputed CM start date is set to one day prior treatment start date.
    b. Else if the CM month is less than the treatment start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
    c. Else if the CM month is greater than the treatment start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

5.2 Statistical models

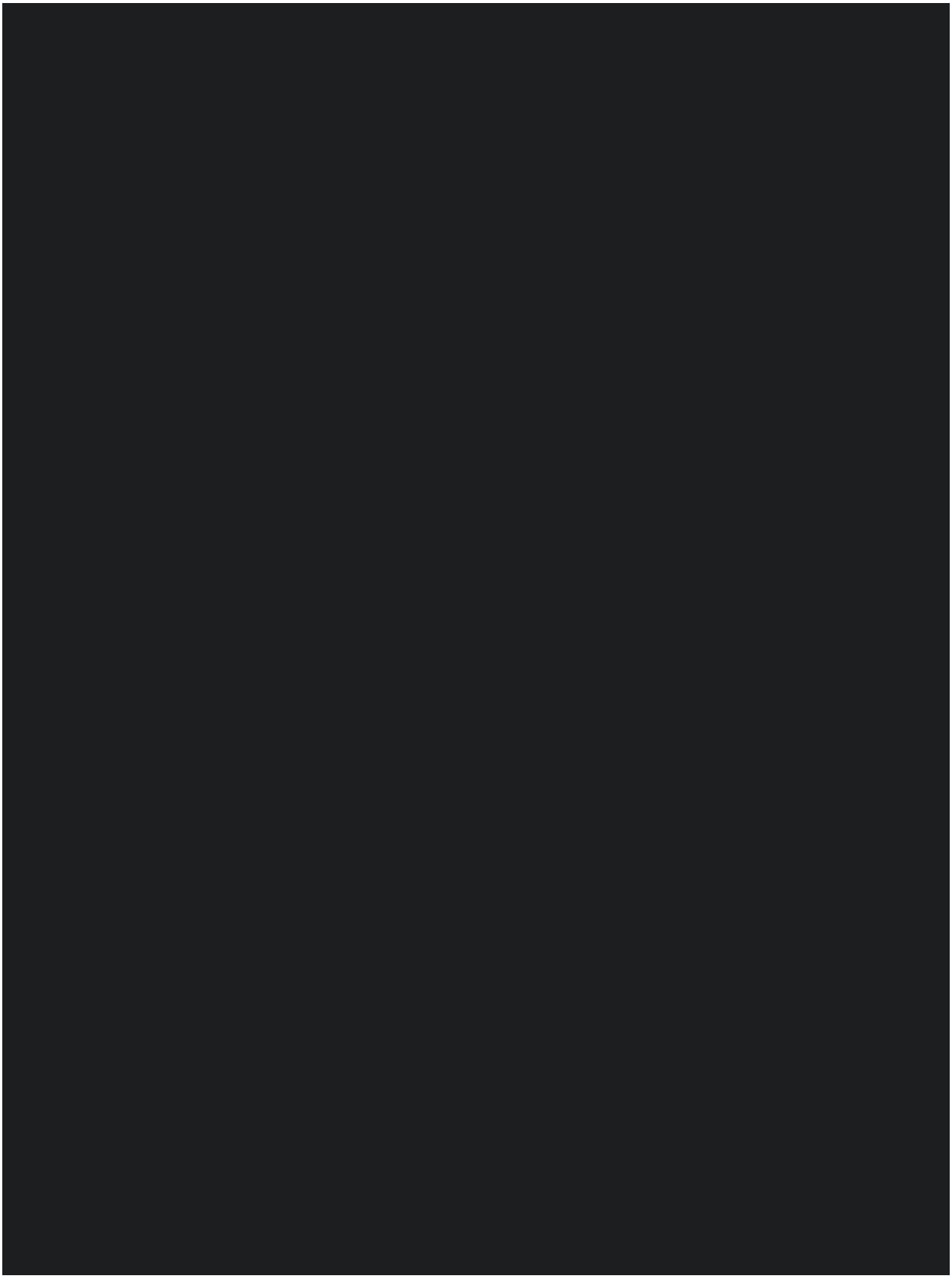
5.2.1 Primary Analysis

The following MMRM model will be used for the primary estimand and supplementary estimand:

change from baseline in weekly mean pain severity VAS score = intercept + baseline weekly mean pain severity VAS score + treatment + week + treatment*week + baseline weekly mean pain severity VAS score * week + error

[redacted]

5.2.2 Supplementary Analysis



5.3 Rule of exclusion criteria of analysis sets

Table 5-1 Protocol deviations

PD ID	Deviation Text	Data exclusion
INCL01	written informed consent not obtained	Exclude from all analysis sets
INCL02a	refractive or cataract surgery <4 months in either eye prior to screening, and/or ocular pain is not persistent since surgery, and/or not seen for ocular pain since surgery by an ophthalmologist	Include in all analysis sets
INCL03a	pain severity VAS <30 mm at screening visit	Include in all analysis sets
INCL04	<60% reduction in ocular pain within 5 min after instillation of single topical ocular anesthetic drop at screening visit	Include in all analysis sets
INCL05a	average pain severity VAS <30 mm based on daily eDiary for last 7 days prior to baseline visit	Include in all analysis sets
INCL06	pain severity >10 mm based on daily eDiary for ≤ 50% of days during the 12-week observational period	
INCL07	subject <18 years of age at screening	Include in all analysis sets
EXCL01a	corrective contact lenses within 14 days of screening visit, and any use of contact lenses for the duration of the study	Include in all analysis sets
EXCL02	use of artificial tears, gels, lubricants, or pain medication within 4 hrs of conducting assessments at screening visit	Include in all analysis sets

PD ID	Deviation Text	Data exclusion
EXCL03	use of nerve growth factor eye drops within 14 days of the screening visit	Include in all analysis sets
EXCL04	seasonal allergic conjunctivitis, or other acute or seasonal ocular diagnosis that is active at the time of screening or baseline visits or would be active during the study	Include in all analysis sets
EXCL05	any history ocular HSV or HZV infection, or other severe ocular conditions such as GvHD, Stephen's Johnson Syndrome, sarcoidosis	Include in all analysis sets
EXCL06	presence of any ocular infection (bacterial, viral, or fungal) within 30 days prior to screening visit	Include in all analysis sets
EXCL07	chronic topical ocular medications (i.e. cyclosporine, lifitegast) initiated <6 months prior to screening visit, or any anticipated changes during the study	Include in all analysis sets
EXCL08	amniotic membrane transplantation on ocular surface within 30 days prior to screening visit	Include in all analysis sets
EXCL09	use of ocular or nasal corticosteroids within 30 days of screening visit	Include in all analysis sets
EXCL10	use of neuromodulatory medications (e.g. gabapentin, pregabalin) or opioid use for non-ocular pain within 30 days of screening visit	Include in all analysis sets
EXCL11	chronic medications (both over the counter and prescription) that have not been stable for at least 30 days prior to screening visit, or any anticipated change in the chronic medication regimen	Include in all analysis sets
EXCL12	history of hypersensitivity to any of the study drugs or its inactive ingredients or to active ingredients of similar chemical classes	Include in all analysis sets

PD ID	Deviation Text	Data exclusion
EXCL13	severe psychiatric disorders or major psychiatric illness requiring hospitalization in the last 6 months or requiring treatment with more than one psychiatric medication	Include in all analysis sets
EXCL14	past history of a chronic or recurring ocular or systemic condition that could interfere with efficacy assessments, or preclude safe administration of study medication per investigator's judgement	Include in all analysis sets
EXCL15	uncontrolled systemic or ocular diseases which could affect trial parameters	Include in all analysis sets
EXCL16	subjects with spinal cord injuries who are at risk of autonomic dysfunction	Include in all analysis sets
EXCL17	participation in a clinical trial within 3 months prior to screening visit	Include in all analysis sets
EXCL18	pregnant or breastfeeding females, or those with a positive pregnancy test	Include in all analysis sets
EXCL19	women of childbearing potential unless using basic methods of contraception during dosing of study treatment	Include in all analysis sets
EXCL20a	Subjects who for any reasons are unable or unwilling to comply with the specific requirements of the protocol	Include in all analysis sets
WITH01	Subject withdrew consent but continued to receive study treatment	Include in all analysis sets
WITH02	subject received prohibited medication requiring treatment discontinuation (i.e. neuromodulators or nerve growth factors) but continued to receive study treatment	Include in all analysis sets

PD ID	Deviation Text	Data exclusion
WITH03	subject unable to tolerate the protocol-specified dosing schedule despite use of rescue medication; treatment discontinuation required but continued to receive study treatment	Include in all analysis sets
TRT01	randomized subject administered incorrect treatment and/or dose	Include in all analysis sets
TRT02	study treatment dose adjustments and/or interruptions made	Include in all analysis sets
TRT03	compliance with study treatment <80% or >120% per eDiary entries	Include in all analysis sets
TRT04	Treatment not given due to COVID-19	Include in all analysis sets
TRT05	Drug supply method changed due to COVID-19	Include in all analysis sets
COMD01	Prohibited concomitant medication (e.g. corticosteroids, antihistamines) and/or procedure as per protocol	Include in all analysis sets
COMD02	Prohibited changes in concomitant medication regimen as per protocol	Include in all analysis sets
OTH01	Any other protocol deviation with impact on patient rights or safety	Include in all analysis sets
OTH02	Any other protocol deviation with impact on trial's scientific value/data integrity	Include in all analysis sets
OTH03	Any other PD without impact on patient safety/rights or trials's scientific value/data integrity	Include in all analysis sets
OTH04	Subject missed a visit or assessment not allowed in the study	Include in all analysis sets
OTH05	Missed visit due to COVID-19	Include in all analysis sets
OTH06	Visit not done at study site due to COVID-19	Include in all analysis sets
OTH07	Assessment / procedure changed due to COVID-19	Include in all analysis sets
OTH08	Discontinuation due to COVID-19	Include in all analysis sets

PD ID	Deviation Text	Data exclusion
OTH09	Unblinding for non-emergent situation, or masking process not followed with impact on data integrity (e.g. treatment identity revealed based on description of appearance)	Include in all analysis sets
OTH10	staining strips moistened with anesthetic	Include in all analysis sets
OTH11	electronic diary compliance <50%	Include in all analysis sets

5.4 Data issue of conjunctival lissamine staining & conjunctival redness from Site [redacted]

Site [redacted] used a different grading scale to evaluate conjunctival lissamine staining and conjunctival redness from what were specified in the protocol.

All data for conjunctival lissamine staining and conjunctival redness for Site [redacted] will be flagged in listings and excluded in the summary for these assessments.

6 Reference

1. Carpenter JR, Roger JH, Kenward MG (2013) Analysis of longitudinal trials with protocol deviation: a framework for relevant, accessible assumptions, and inference via multiple imputation. J Biopharm Stat; 23(6):1352-71.
2. DIA missing data: https://www.lshtm.ac.uk/research/centres-projects-groups/missing-data

[redacted]