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Novartis Research and Development

SAF312

Clinical Trial Protocol 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

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
B-hCG	Beta-human chorionic gonadotropin
b.i.d.	twice a day
CFR	Code of Federal Regulation
CICP	Corneal Induced Chronic Pain
Cmax	Maximum of serum concentration
CMO&PS	Chief Medical Office and Patient Safety
CO	Clinical Operation
COVID-19	Coronavirus disease 2019
CRA	Clinical Research Associate
CRC	Central Reading Center
CRF	Case Report/Record Form (paper or electronic)
CTT	Clinical Trial Team
D	Death
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	First in human
GCP	Good Clinical Practice
GCS	Global Clinical Supply
ICH	International Council for Harmonization
IE	Intercurrent Events
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IN	Investigator Notification
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
IVCM	In Vivo Confocal Microscopy

LASEK	Laser Assisted Sub-Epithelial Keratectomy
LASIK	Laser-assisted in Situ Keratomileusis
LSM	Least square mean
MAR	Missing at Random
MedDRA	Medical dictionary for regulatory activities
MFD	Maximum feasible dose
mg	milligram(s)
mL	milliliter(s)
ml	milliliter(s)
MMRM	Mixed model repeated measure
NGF	Nerve growth factor
OPAS	Ocular Pain Assessment Scale
PK	pharmacokinetic(s)
PRK	Photorefractive Keratectomy
RDO	Retrieved Dropped Out
RK	Radial Keratotomy
QMS	Quality Management System
REML	Residual/restricted maximum likelihood
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMILE	Small Incision Lenticule Extraction
SMQ	Standardized MedDRA Query
SUSAR	Suspected Unexpected Serious Adverse Reactions
TRPV1	Transient Receptor Potential Vanilloid 1
UTE	Unsatisfactory therapeutic effect
VA	Visual acuity
VAS	Visual Analogue Scale
WoC	Withdrawal of consent
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product”.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.
Discontinuation from study	Point/time when the participant permanently stops receiving the study treatment and further protocol required assessments or follow-up, for any reason. No specific request is made to stop the use of their samples or data.
Discontinuation from study treatment	Point/time when the participant permanently stops receiving the study treatment for any reason (prior to the planned completion of study drug

	administration, if any). Participant agrees to the other protocol required assessments including follow-up. No specific request is made to stop the use of their samples or data.
Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Vehicle	A vehicle refers to the inactive version of the investigational medicinal product (IMP) i.e., it contains all the components of the IMP with the exception of the drug (active ingredient). In this protocol, the term placebo may be used interchangeably with vehicle as the placebo also does not contain any drug (active ingredient).
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a subject does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Amendment rationale (Version No.3, 06-Oct-2021)

The main purpose of this amendment is to modify the types of refractive surgery to be included, as well as revise some of the inclusion criteria so that the patients recruited for the study will be more representative of the true population of patients experiencing post-operative corneal induced chronic pain. This amendment also makes specific allowance for optometrists to serve as a primary care provider for the purposes of the study.

- Section 5 "Population" and throughout the document : To modify the types of refractive surgery in the study population so that it is inclusive of subjects with various types of corneal refractive surgery or cataract surgery in both eyes (including LASEK, RK, SMILE and Cataract surgeries) with resulting CICP.
- Section 5.1 Revised Inclusion Criteria #2 to #2a: Revision of the criterion to include optometrist since in some US states, optometrists may be the primary eye care professional managing patients with post-surgical CICP.
- Section 5.1 Revised Inclusion Criteria #3 to #3a: Revision of Visit 1 pain severity question to "worst pain over the last 7 days". Since chronic pain fluctuates, this single screening question may be more representative of their overall experience with CICP. The ocular pain severity VAS cutoff is revised from ≥ 50 mm to ≥ 30 mm.
- Section 5.1 Revised Inclusion Criteria #5 to #5a: The last 7 days average pain severity VAS prior to the Baseline visit (Visit 2) is revised from ≥ 50 mm to ≥ 30 mm to align with threshold value outlined in Inclusion Criteria #3a at screening visit.
- Section 5.2 Revised Exclusion Criteria #1 to #1a: Since many CICP are using bandage and scleral lenses as non-pharmacological treatment for CICP, this patient group is now included.
- Section 5.2 Revised Exclusion Criteria #20 to #20a: Remove the duplicative text similar to Exclusion Criteria #14. The criteria is also updated to exclude the subject who is unable or willing to comply with the protocol requirements.
- Section 8.1 "Screening": Addition of clarification under what circumstance re-screening is permitted under the current protocol version.
- Tablet 8-1 and Table 8-2: To include "Contact IRT" as a mandatory task in the assessment schedule and the proposed sequence to perform the task
- Section 8.5.1.8 "Post-Anesthetic Severity of Eye Pain: Anesthetic procedure is updated to align with other modifications in this amendment
- Section 12.4.6 Revised the supplementary estimand based on treatment policy strategy.

Amendment rationale (Version No.2, 25-Mar-2021)

The main purpose of this amendment is to provide clarifications and updates on various aspects of the protocol, as well as update required elements as per the new OneCTP Protocol template Version 4.0.

- Revision per the updated protocol template of "Treatment discontinuation" to "Discontinuation of study treatment" in the protocol where applicable
- Section 2 "Primary Estimands": Update to primary estimand
- Addition of Section 4.6 "Rationale for Public Health Emergency mitigation procedures" per the updated protocol template
- Section 5.1 "Inclusion Criteria": Revision and clarification for select criteria
- Section 5.2 "Exclusion Criteria": Revision and clarification for select criteria
- Section 6.1.1 "Investigational and control drugs": Revised "unblinded study personnel" to "unblinded site personnel" for clarification
- [redacted]
- Table 6-2 "Prohibited medication": Clarification to prohibited medication table
- Section 6.4 "Treatment blinding": Removal of unblinded study role since the updated study medication packaging design does not reveal the appearance of the study medication while performing the study medication accountability check.
- Section 6.7 "Preparation and dispensation": Revised "unblinded study personnel" to "unblinded site personnel" for clarification
- Section 7 "Informed consent procedures": Revision with the text in alignment with addition of Section 4.6 "Rationale for Public Health Emergency mitigation procedures" per the updated protocol template
- Section 8 "Visit schedule and assessments": Revision and clarification for the schedule of assessment
- Section 8.2 "Subject demographics/other baseline characteristics" Addition of baseline characteristics to align wit with the information to be captured in the CRF
- Section 8.3 "Efficacy" Revision and clarification for selected parameters in efficacy section
- Section 8.4 "Safety" Revision and clarification for selected parameters in safety section
- Section 8.5 "Additional assessments" Clarification and addition of description for assessments under this section
- Section 9 "Discontinuation and completion": Addition, revision and re-numbering of the section according to the new protocol template

- Section 10 "Safety monitoring and reporting": Minor revision of the wording according to new protocol template
- Section 12 "Data analysis and statistical methods" Statistical analysis and methods were revised with the following:
    - 12.4.2: Randomization strata removed from the MMRM model
    - 12.4.3: Update to primary estimand
    - 12.4.6: update to supplementary estimand

Amendment rationale (Version No.1, 22-Sep-2020)

The main purpose of this amendment is the change of the indication term and study design based on FDA recommendations.

In addition, this amendment includes modifications to account for the COVID-19 pandemic, or any similar scenario that may occur during the course of the study.

Major changes to the protocol

- Protocol summary: Updated based on the changes within the protocol.
- Section 1.1 Background: The indication term chronic ocular surface pain (COSP) was updated to corneal induced chronic pain (CICP)
- Section 3 "Study design": 12-week observation period was added to confirm chronicity of eye pain. During the observation period subjects will be contacted by the site via phone call for confirmation of pain reporting compliance and safety check-in
- Section 5 "Population": Adjustments to inclusion/exclusion criteria to be aligned with FDA and clinical site feedback
    - Inclusion criteria 2 – Subjects who have undergone PRK or LASIK surgery in both eyes ≥ 4 months prior to screening
    - Inclusion criteria 4 - Subjects who demonstrate a ≥60% reduction in ocular pain
    - New inclusion criteria 5 and 6 were added at Baseline visit
    - Exclusion criteria 1 – Clarification of contact lenses use during the study
    - Exclusion criteria 3 – Use of nerve growth factor eye drops within 14 days of the Screening Visit was added as a new exclusion criteria
    - Exclusion criteria 8 – Subjects with amniotic membrane transplantation on ocular surface within 30 days prior to the Screening Visit was added as a new exclusion criteria
- Section 8 "Visit Schedule and Assessments" in Table 8-1 "Assessment schedule" additional assessments of the cornea [redacted] were added or updated as follows: Corneal Endothelial Cell Microscopy new examination, [redacted] updated and removed ActiGraph.

The following new sections to evaluate efficacy and safety were added:

- Section 8.3.1 Pain Severity and Frequency will be collected separately using VAS
- Section 8.4.6 Dilated Fundus Exam
- Section 8.4.7 Corneal Endothelial Cell Microscopy

The following new assessments were added under Section 8.5:

- Section 8.5.1.1 In Vivo Confocal Microscopy only at selected sites for exploratory analysis
- Section 8.5.1.3 Corneal Fluorescein Staining the degree of staining is based on Modified NEI Scale. Figure 8-2 was added.
- Section 8.5.1.4 Conjunctival Lissamine Staining will be assessed based on the proportion of the staining area. Oxford grading scale was removed. Table 8-3 was added

[redacted]

Modifications were made to include revised Estimands per ICH E9 (R1) guidance in the following:

- Section 2 "Objectives and endpoints" in Table 2-1 multiple updates to reflect study design changes
  - Primary endpoint was changed from mean global pain Visual Analog Scale (VAS) to mean pain severity VAS
  - Updates to the secondary [redacted] objectives and endpoints
  - Section 2.1 - Addition of Primary Estimands

Modifications were made to the statistical analysis and methods in the following sections:

- Section 12 "Data analysis and statistical methods" Statistical analysis and methods were revised with the following
  - Section 12.4 Updated strategy in primary endpoint(s)/estimand(s)
  - Section 12.5 Addition of secondary endpoints

[redacted]

  - Section 12.8 Possible sample size increase due to the pandemic

Changes were incorporated to address the COVID-19 pandemic in the following sections:

- Section 7 Informed Consent Procedures
- Section 8 Visit Schedule and Assessments
- Section 8.4 Safety

Other changes incorporated in this amendment are:

- List of Abbreviations: Updated with new relevant abbreviations
- Glossary of terms: Updated with new relevant terms

Other minor clarifications were made where applicable, including Section 6 "Treatment", Section 8.1 "Screening", and Section 8.2 Subject demographics"

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

Protocol summary

Protocol number	CSAF312B12201
Full Title	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-dailyin the treatment of post-operative corneal induced chronic pain (CICP) following Photorefractive Keratectomy (PRK) or Laser-assisted in Situ Keratomileusis (LASIK) surgeries.
Brief title	Study of efficacy and safety of SAF312 eye drops in subjects with post-operative corneal induced chronic pain (CICP)
Sponsor and Clinical Phase	Novartis Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The study is designed to demonstrate the safety and efficacy of two dose concentrations of SAF312 eye drops (5 mg/ml and 15 mg/ml) in subjects with CICP persisting at least for 4 months after refractive or cataract surgery and chronicity confirmed during the observational period. The study will also determine the optimal dose to carry forward for further development.
Primary Objective	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.
Secondary Objectives	1. To evaluate additional efficacy of 2 concentrations of SAF312 vs placebo (e.g., time to pain improvement, quality of life) 2. To demonstrate SAF312 does not induce negative effects to the ocular surface after prolonged TRPV1 inhibition 3. To evaluate the safety of 2 concentrations of SAF312 (5 mg/ml and 15 mg/ml)
Exploratory objectives	[redacted] 2. To monitor a subject's behavior regarding use of artificial tear/gel/lubricant and rescue medication 3. To evaluate corneal nerve density and morphology
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 their surgery. Eligible patients must also demonstrate chronicity of the pain at Baseline Visit as described in inclusion criteria. Overall approximately 150 subjects will be enrolled in the study and randomized to one of 3 study arms in 1:1:1 ratio
Population	The study population will consist of subjects (≥ 18 years old) with persistent ocular surface pain for at least 4 months after refractive or cataract surgery

	(including clear lensectomy). The goal is to randomize a total of approximately 150 subjects.
Key Inclusion criteria	• Subjects who 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, ≥4 months prior to Screening Visit and experiencing persistent ocular surface pain since the surgery, and have been seen by an ophthalmologist or optometrist at least once with complaint of continued ocular pain since surgery. NOTE: The 4 month requirement must be based on the date of the last surgery. • Subjects who demonstrate a ≥ 60% reduction in ocular pain within 5 minutes after instillation of a single topical ocular anesthetic drop at Screening Visit. At Baseline • Subjects with an average pain severity VAS score of ≥ 30 mm based on Daily eDiary for the last 7 days prior to Baseline Visit (Visit 2). • Subjects who have reported pain severity >10 mm based on Daily eDiary for > 50% of the days of the observational period (Screening).
Key Exclusion criteria	• Use of nerve growth factor eye drops within 14 days of the Screening Visit • Seasonal allergic conjunctivitis, or other acute or seasonal ocular diagnosis that are active at the time of Screening or would be active during the course of the study. • Any history of ocular herpes simplex virus or herpes zoster virus infection, or other severe ocular conditions such as graft versus host disease, Stevens-Johnson syndrome or sarcoidosis. • Presence of any ocular infection (bacterial, viral, or fungal) within 30 days prior to Screening. • Chronic topical ocular medications (i.e., cyclosporine, lifitegrast) initiated <6 months prior to Screening Visit, or any anticipated change during the study. • Use of ocular or nasal corticosteroids within 30 days of Screening Visit. • Use of neuromodulatory medications (e.g., gabapentin, pregabalin) or opioid use for non-ocular pain within 30 days of Screening Visit. • 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. • Subjects requiring hospitalization within 6 months prior to screening for severe psychiatric disorders or major psychiatric illness (e.g., psychosis, schizophrenia, mania, depression).
Study treatment	Subjects will be assigned one of the following 3 treatments - SAF312 5 mg/ml (0.5%), SAF312 15 mg/ml (1.5%) or SAF312 placebo eye drops, administered as one drop in each eye twice-daily for three months
Efficacy assessments	• Pain Severity Visual Analog Scale (VAS) • Pain Frequency VAS • OPAS questionnaire [redacted]
Key safety assessments	• Visual Acuity • Slit Lamp Examination • Intraocular Pressure • Dilated Fundus Exam

	• Corneal Endothelial Cell Microscopy
Other assessments	• In Vivo Confocal Microscopy • Conjunctival Redness • Corneal Fluorescein Staining • Conjunctival Lissamine Staining • Schirmer's Test • Pain Characterization Questionnaire [redacted]
Data 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). 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. 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.
Key words	Eye pain, corneal induced chronic pain (CICP), photorefractive keratectomy (PRK), laser-assisted in situ keratomileusis (LASIK), Laser Assisted Sub-Epithelial Keratectomy (LASEK), Radial Keratotomy (RK), Small Incision Lenticule Extraction (SMILE), Cataract, adults, randomized study, placebo

1 Introduction

1.1 Background

Transient Receptor Potential Vanilloid 1 (TRPV1) receptors belong to the superfamily of TRP Ca^{2+}-permeable non-selective cation channels (Clapham et al 2001). These channels are expressed primarily on a subset of somatic and visceral primary afferent sensory neurons (Holzer 2004; Gunthorpe et al 2002; Hayes et al 2000). TRPV1 can be activated by capsaicin, noxious heat, acidic solutions, mechanical distortion, hyperosmolarity and inflammatory mediators such as bradykinin, prostaglandins and nerve growth factor (NGF), which are likely to be released or upregulated by tissue damage or in specific disease conditions (Caterina and Julius 2001; Geppetti and Trevisani 2004). The activation of TRPV1 results in nociceptive stimuli interpreted by the brain as pain. Importantly, chronic peripheral nociceptor activity can further increase the release of the inflammatory mediators which regulate TRPV1 activity, and results in a sensitization of the channel and a lowering of its thresholds for activation causing hyperalgesia and allodynia. Taken together, these findings indicate that TRPV1 is a key integrator of nociceptive and inflammatory response information.

Accumulating data indicates a primary role for TRPV1 receptors in ocular pain (Zhang et al 2007; Yang et al 2013; Mergler et al 2010). Furthermore, the chronic stimulation of corneal and conjunctival nerves in many ocular conditions, creates a cycle of stimulus amplifications due to damage on the ocular surface, inflammation, and constant exposure of inflammatory cytokines in the tears. This is of particular importance in regards to the highly innervated cornea.

SAF312 is a highly selective and potent antagonist of TRPV1. Topical ocular administration of SAF312 in nonclinical studies has resulted in high ocular exposure with relatively low systemic exposure, which could enable ocular pain management while avoiding known systemic side effects associated with TRPV1 antagonism (eg, heat insensitivity, transient hyperthermia, autonomic dysreflexia in patients with spinal cord injury). Plasma exposure of SAF312 after 4-times daily ocular administration of 15 mg/ml (1.5%) eye drops (the highest dose to be used in this study) was very low (Day 8 Cmax (maximum of serum concentration), 0.941 ng/mL and AUC0-24h, 15.1 ng*h/ml) and at least 100-fold and 37-fold lower than corresponding exposure values (Cmax, 93.9 ng/ml and AUCtau, 554 ng*h/ml) after repeated oral dosing of 12.5 mg b.i.d. where tolerability risks were not observed, yet noted at higher oral doses.

Two clinical studies with topical ocular SAF312 eye drops, suspension (eye drops) have been conducted to date. One study was the first in human (FIH) study assessing the safety of SAF312 eye drops, followed by a proof of concept study for acute pain relief after PRK surgery compared to vehicle. The safety of topical ocular SAF312 eye drops has been demonstrated in both studies for all tested dose concentrations of 1.5 mg/ml to 25 mg/ml (0.15% up to 2.5%), no indication of delayed wound healing, and esthesiometry measurements demonstrated no anesthetic effect when compared to tetracaine 0.5% (marketed topical ocular anesthetic as positive control) or vehicle (as negative control). These findings are of importance to provide reassurance that the drug is not simply anesthetizing the ocular surface and leaving the patient at risk due to inhibition of the natural ocular defensive mechanisms or inhibition of corneal epithelial cell migration (e.g., response to injury). Proof of concept for the efficacy of SAF312 eye drops was demonstrated with the study meeting both primary endpoints of a statistically

significant difference in Visual Analogue Scale (VAS) pain severity score at 6 hours post-operatively, and the average of 0-12 hour VAS between SAF312-treated eyes and Vehicle-treated eyes. For detailed information, please refer to the IB.

Although many patients suffer from acute ocular pain due to various causes, the treatment of corneal induced chronic pain remains an unmet need since there are currently no topical ocular treatments available that are safe to be used chronically. CICP may be considered as neuropathic in nature, but is perpetuated by continuous nociceptive stimuli from the peripheral neurons. It is also known that many patients with chronic pain do not necessarily describe their symptom as “pain”, and that the description can change from day to day or even within a day. Therefore, the term “pain” is used as an umbrella term which can include other symptoms the patient may describe as painful like burning, stinging, foreign body sensation, stabbing, pressure, grittiness or sandiness.

Due to the fact that CICP is driven by malfunctioning peripheral nerve impulses, treatment with a topical ocular drop could provide significant relief for patients who have a need for chronic treatment.

SAF312 is currently under development as a topical ocular eye drop suspension for the treatment of corneal induced chronic pain (CICP). Chronic ocular pain has been reported with the most common types of elective ocular refractive vision correction surgical procedures, Photorefractive Keratectomy (PRK) and Laser-assisted in situ Keratomileusis (LASIK). It has been reported that approximately 95% of patients experience pain immediately following LASIK or PRK surgery. Many patients have resolution of their pain within 1 month after surgery. However, up to 60% of patients continue to have chronic pain beyond 1 month, and up to 44% after 6 months; in some cases the pain will continue for many years or even permanently (Shtein 2011; Levitt et al 2015; Benatti and Afshari 2016). Therefore, the pain experienced by these patients can be considered as a form of peripheral neuropathy. Similarly chronic pain may occur following other surgeries such as laser-assisted sub epithelial keratectomy (LASEK), radial keratectomy (RK), and small incision lenticule extraction (SMILE) and following cataract surgery.

Patients who experience CICP regardless of the cause, may have concurrent (i.e., coexisting or underlying) ocular conditions which require the use of other ocular medications to treat the concurrent condition(s) as deemed appropriate by the patient’s physician. Because SAF312 is intended to perform as an analgesic, current treatments the patient may be using for concurrent ocular conditions will be allowed to continue, and SAF312 eye drops will be administered in addition to those current treatments.

1.2 Purpose

The study is designed to demonstrate the safety and efficacy of two dose concentrations of SAF312 eye drops (5 mg/ml and 15 mg/ml) in subjects with CICP persisting at least for 4 months after refractive or cataract surgery, and chronicity of pain confirmed during the 3 month observation period. The study will also determine the optimal dose to carry forward for further development.

2 Objectives and endpoints

Table 2-1 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 (eg, corneal and conjunctival staining score, Schirmer score, conjunctival redness score)
• 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]	
• 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

Objective(s)	Endpoint(s)
	• Density of corneal dendritiform cells

2.1 Primary Estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g premature discontinuation of treatment).

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. Further details can be found in Section 12.

The primary estimands are described by the following attributes:

1. Population: subjects with CICP persisting at least 4 months after refractive surgery, and chronicity of pain confirmed during the 3-month observation period. Further details about the population are provided in Section 5.
2. Endpoint: change from baseline in ocular pain severity VAS. The score is derived by averaging the seven daily measurements of each week.
3. Treatment of interest: the randomized treatment (SAF312 or placebo) with or without treatment for any underlying ocular conditions. Further details about the investigational treatment and control treatment are provided in Section 6.

Handling of remaining intercurrent events (IE):

1. Rescue medications: had subjects not taken rescue medication and behaved like other subjects who did not take them (hypothetical strategy)
2. Prohibited medications: had subjects not taken prohibited medication and behaved like other subjects who did not take them (hypothetical strategy)
3. Treatment discontinuation for any reasons: had patients taken the assigned treatment for the entire study duration and behaved like other subjects who did not discontinue treatment (hypothetical strategy)

The summary measure: difference in variable means between SAF312 and placebo.

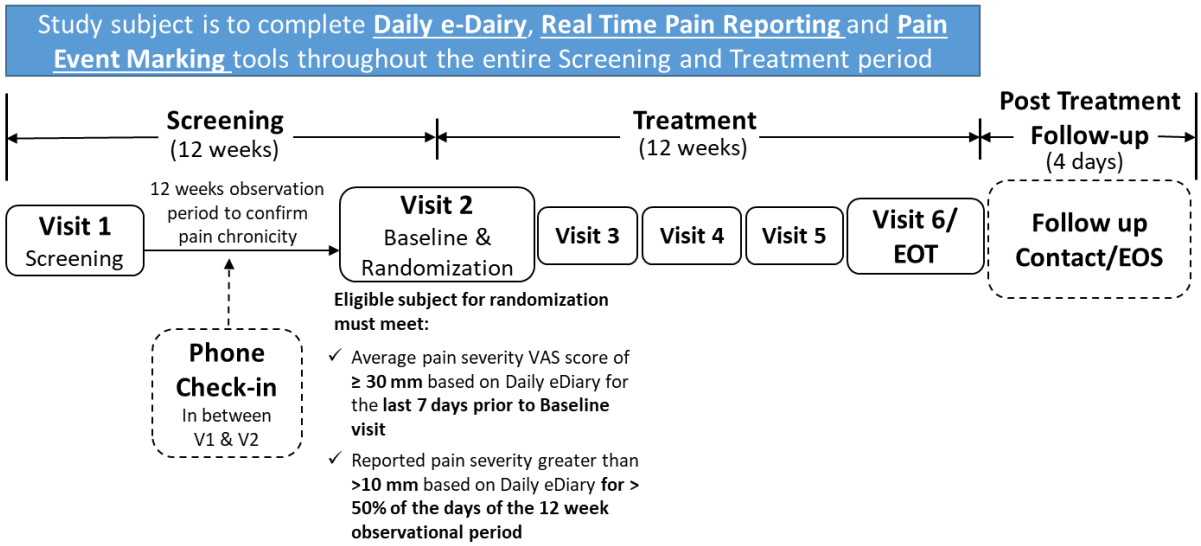
Supplementary estimands to the primary estimand are defined in Section 12.

2.2 Secondary Estimands

Not applicable.

3 Study design

Figure 3-1 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) in both eyes 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 their 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 most recent surgery. In cases where more than one procedure was performed on an eye (eg, 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 inclusion criteria. Overall approximately 150 subjects will be enrolled in the study (i.e. approximately 50 subjects will be enrolled in each treatment arm in 1:1:1 ratio).

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 two 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.

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 (Section 5). 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 (eg, 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. Subjects who meet eligibility criteria at Visit 2, will be randomized to one of the three treatment groups (SAF312 5 mg/ml, SAF312 15 mg/ml, placebo) in a 1:1:1 ratio. Subjects will visit the study site for assessments as outlined in the visit assessment schedule (see Table 8-1).

All subjects will be allowed to continue their current treatment regimen for any underlying or unrelated ocular condition if applicable (eg, treatment for glaucoma, dry eye) as long as eligibility criteria are met. No new treatments can be initiated once the subject has begun participation in the study unless additional treatments are needed for proper management of an adverse event. Whenever topical ocular eye drops other than the investigational medicinal product (IMP) are administered, the subject should first dose with their concomitant medication(s) and wait approximately 10 minutes prior to instillation of the assigned IMP.

4 Rationale

4.1 Rationale for study design

This study will evaluate the safety and efficacy of two concentrations of SAF312 twice daily for 12 weeks in the treatment of CICP following refractive or cataract surgery. The aim is to evaluate the treatment effect of SAF312 compared to placebo, and to determine the appropriate concentration to carry forward for further development.

The active and placebo IMPs will be presented in identical packaging to ensure no bias to the study results due to knowledge of the treatment assignment. Due to the difference in appearance of SAF312 eye drops vs placebo eye drops (milky white vs clear, respectively), sites will be required to have an unblinded staff member to manage drug dispensation, drug accountability, as well as collection of adverse events or subject reports of product comments/complaints. All other site staff and Sponsor staff will be blinded to treatment assignments. To ensure masking of subjects to their treatment assignment, no subject will receive both placebo and active treatment so no change in appearance of the test article will be noticeable by a particular subject. Subjects may be informed that their study treatment may appear cloudy or white, but must not be informed about the specific identity of the treatments based on differences in appearance.

A 12-week observation period prior to randomization is included as a method to confirm the chronicity of their ocular pain, observe trends in the subject's pain occurrences ([redacted]), and to observe behaviors with artificial tears and rescue medications prior to receiving randomized treatment. This observation period confirms the selection of

appropriate subjects with chronic pain, as well as provides meaningful data [redacted] regarding changes induced by study treatment. During this observational period, subjects will be observed in their real-world setting with no changes to their medications or actions. The only requirement will be completion of eDiary data, and pain assessments.

4.2 Rationale for dose/regimen and duration of treatment

Topical ocular administration of SAF312 eye drops in non-clinical studies has resulted in high ocular exposure with minimal systemic exposure, which is expected to enable ocular pain management while avoiding systemic side effects. In the FIH study CSAF312X2101, dose concentrations of 5 mg/ml, 15 mg/ml and 25 mg/ml (0.5%, 1.5% and 2.5%, respectively) were administered as a single drop 4 times daily in one eye of a subject for 7 days. A supra-therapeutic dose concentration of SAF312 eye drops was tested using the maximum feasible dose (MFD) of 25 mg/ml (2.5%) and administered 8 times daily for 7 days. In each evaluation, SAF312 was safe and well tolerated at single and multiple ocular doses, even up to supra-therapeutic dose concentration levels. Esthesiometry assessments also demonstrated the lack of any anesthetic effect of SAF312 eye drops when compared to Tetracaine topical ocular anesthetic drops.

In the proof-of-concept study for the treatment of acute ocular pain after PRK (photorefractive keratectomy) surgery, SAF312 at 25 mg/ml (2.5%) was administered 4 times daily (every 6 hours) for 72 hours. SAF312 was safe and well tolerated with no notable systemic or ocular adverse events, and no delay in wound healing. Systemic exposure of SAF312 was confirmed to be minimal (Cmax 2.40 ng/mL on Day 4) which is consistent with the lack of observed systemic adverse events.

An ocular PK study in rabbits was conducted to determine the tissue concentrations of SAF312 eye drop in selected ocular tissues and plasma following a single topical ocular administration in both eyes, at four different dose concentrations of SAF312 at 5 mg/ml, 10 mg/ml, 15 mg/ml and 25 mg/ml (0.5%, 1.0%, 1.5% and 2.5%, respectively). Concentrations of SAF312 in the cornea and conjunctiva were greater than ten times the IC_{50} (estimate of the IC_{90}) for up to 12 hours post-instillation (12 hours was the end of the evaluation period). There was an approximate dose-proportionality for increase in SAF312 area under the curve (AUC) and Cmax in the cornea and conjunctiva, and Cmax between 5 mg/ml and 10 mg/ml, but less than dose-proportional above 10 mg/ml. There was also differentiation in exposure observed between 5 mg/ml and 10 mg/ml but no clear differentiation between 10 mg/ml and 15 mg/ml or 25 mg/ml.

In toxicology studies completed to date, no notable adverse events were identified after 2 weeks of topical ocular dosing. Likewise, no notable adverse in-life events were observed when SAF312 was administered up to a dose concentration of 25 mg/ml (2.5%) four times daily for 13 weeks.

Based on these data, the Phase 2 study includes dosing of SAF312 at concentrations of 5 mg/ml (0.5%, lowest feasible dose) and 15 mg/ml (1.5%, highest feasible dose) to ensure evaluation of the full range of possible concentrations, and evaluation of concentrations that have potential to reveal a dose response based on differentiated tissue exposure. With target tissue exposure concentrations remaining well above the estimated IC_{90} for at least 12 hours, b.i.d. dosing has been selected as the dosing frequency.

Twelve weeks of exposure will allow for proper assessment of: 1) the efficacy of treatment response, 2) the safety of prolonged TRPV1 inhibition in the eye, and 3) the sustainability of the effect of the treatment (eg, no loss of effect over time). Both eyes will be treated with the IMP. Because it is difficult for subjects to clearly delineate pain from one eye or the other, treating both eyes will avoid confounding the data with pain that may not be addressed in the eye that does not receive treatment. There have been no safety concerns identified with the use of SAF312 eye drops, and the systemic exposure via topical ocular administration is very low, therefore dosing both eyes is not expected to pose additional safety risks to the subject.

Because PK has already been evaluated in both the FIH and the Phase 2a PRK (PoC) studies, PK is not planned as part of this Phase 2 study in patients with CICP. Plasma samples may, however, be collected ad hoc in cases of SAEs.

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Currently, there is no standard of care for CICP. If pharmacological treatments are needed, treatments may include short-term off-label use of topical ocular steroids, or non-steroidal anti-inflammatory medications, or oral pain medications.

Subjects will be allowed to continue using medications needed to treat concurrent ocular conditions. The use of placebo (vehicle) as a comparator is therefore not considered to be an undue risk to the subjects enrolled in the trial. Moreover, since there is no standard of care for the treatment of CICP, the use of placebo as a comparator will allow for the establishment of the magnitude of change in the clinical endpoints that may be seen spontaneously during treatment, and therefore provide a better estimate of the true treatment effect of SAF312.

4.4 Purpose and timing of interim analyses/design adaptations

Not applicable.

4.5 Risks and benefits

As of yet there is no known benefit to receiving topical ocular SAF312 treatment for the Corneal Induced Chronic Pain (CICP) indication. The safety, tolerability and pharmacokinetics of SAF312 eye drops has been evaluated in two studies. A FIH Phase 1 study established the safety and tolerability of SAF312 eye drops when used at concentrations as high as 25 mg/mL (2.5%) up to 8 times per day, for 7 days, established the lack of an anesthetic effect, and revealed low systemic exposure of the drug. The PoC study in acute pain after PRK surgery confirmed the low systemic exposure and demonstrated efficacy of SAF312 eye drops in reducing post-operative pain compared to placebo when dosed 4 times per day for 3 days. In both studies, the adverse effects observed with oral dosing of SAF312 (eg, heat insensitivity, transient hyperthermia, autonomic dysreflexia in patients with spinal cord injury) were not observed. Together, these data support the anticipated safety and efficacy of SAF312 eye drops for the treatment of CICP. Because there is no standard of care for CICP, and treatment options for chronic pain are limited, SAF312 may provide a novel approach to address the current unmet need for patients in need of a chronic treatment for CICP.

Any risks to subjects in this current study may be minimized by compliance with the eligibility criteria and study procedures, as well as close monitoring by the study staff.

When dosed orally, SAF312 resulted in autonomic dysreflexia in one subject with spinal cord injury. Even though systemic exposure with SAF312 is very low with topical ocular administration, due to the severity of this potential event, patients with spinal cord injury will be excluded from the study.

Patients will undergo certain ophthalmological procedures which are standard in clinical practice and ophthalmic clinical studies. The assessment of the ocular surface requires the use of fluorescein and lissamine vital dyes. As with any application of a substance to the ocular surface, the patient may have unknown hypersensitivities to the dyes. Any subject demonstrating a potential hypersensitivity reaction will receive appropriate medical care. To minimize any risks, the study and associated procedures will be carried out by experienced study staff under the supervision of the Principal Investigator.

Subjects enrolled in the study will be allowed to continue any current medications they may be prescribed to treat a concurrent or underlying ocular condition which avoids any risk of worsening of those conditions due to study requirements. Although subjects may receive placebo instead of active drug, the use of placebo is not considered a risk since it is the same formulation as the IMP but without the active ingredient. If patients receive inadequate treatment of CICP due to the use of placebo, patients will be allowed to use rescue medication to avoid any undue risk or suffering as a result of study requirements.

Given the minimal systemic exposure after topical ocular administration, and the lack of safety findings in non-clinical or clinical studies conducted to date, the foreseeable risks associated with SAF312 eye drops are considered low compared to the anticipated benefit for patients with CICP. There may be risks associated with the use of SAF312 which are unknown at this time.

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, mitigation procedures to ensure subject safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures, and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Population

The study population will consist of subjects (≥ 18 years old) with chronic ocular pain persisting for at least 4 months after refractive (i.e. PRK, LASIK, LASEK, RK, or SMILE) or cataract surgery (including clear lensectomy). The goal is to randomize a total of approximately 150 subjects in approximately 30 centers. Assuming a screening failure rate of approximately 50%, approximately 300 subjects are planned to be screened.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Subjects ≥ 18 years old who have given written informed consent.

2a. Subjects who have undergone refractive surgery (PRK, LASIK, LASEK, RK, or SMILE) or cataract surgery in both eyes, with or without refractive enhancement in one or both eyes, ≥4 months prior to Screening Visit and experiencing persistent ocular surface pain since the surgery, and have been seen by an ophthalmologist or optometrist at least once with complaint of continued ocular pain since surgery.

NOTE: The 4 month requirement must be based on the date of the last surgery.

3a. Subjects with worst ocular pain severity (VAS) of ≥ 30 mm) over the last 7 days prior to screening .

4. Subjects who demonstrate a ≥ 60% reduction in ocular pain within 5 minutes after instillation of a single topical ocular anesthetic drop at Screening Visit (as calculated by the electronic Patient Reported Outcome (ePRO) device).

At Baseline Visit

5a. Subjects with an average pain severity VAS score of ≥ 30 mm based on Daily eDiary for the last 7 days prior to Baseline Visit (Visit 2).

6. Subject who have reported pain severity VAS score >10 mm based on Daily eDiary for >50% of the days of the 12-week observational period (as calculated in the ePRO portal).

5.2 Exclusion criteria

Subjects meeting **any** of the following criteria are not eligible for inclusion in this study.

1a. Use of corrective contact lenses within 14 days of the Screening Visit and any use of corrective contact lenses for the duration of the study (bandage or scleral lenses are permitted).

2. Use of artificial tears, gels, lubricants or pain medication within 4 hours of conducting assessments at the Screening Visit.

3. Use of nerve growth factor eye drops within 14 days of the Screening Visit.

4. Seasonal allergic conjunctivitis, or other acute or seasonal ocular diagnosis that are active at the time of Screening or Baseline visits or would be active during the course of the study.

5. Any history of ocular herpes simplex virus or herpes zoster virus infection, or other severe ocular conditions such as graft versus host disease, Stevens-Johnson syndrome, sarcoidosis.

6. Presence of any ocular infection (bacterial, viral, or fungal) within 30 days prior to Screening Visit.

7. Chronic topical ocular medications (ie, cyclosporine, lifitegrast) initiated <6 months prior to Screening Visit, or any anticipated change during the study.

8. Subjects with amniotic membrane transplantation on ocular surface within 30 days prior to Screening Visit.

9. Use of ocular or nasal corticosteroids within 30 days of Screening Visit

10. Use of neuromodulatory medications (eg, gabapentin, pregabalin) or opioid use for non-ocular pain within 30 days of Screening Visit.

11. 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.

    NOTE: chronic refers to medications taken on a specific regimen which includes medications that may not be taken daily (e.g., bisphosphonates given once per month, sliding scale medications such as insulin or coumadin).
12. History of hypersensitivity to any of the study drugs or its inactive ingredients or to active ingredients of similar chemical classes.
13. Subjects requiring hospitalization within 6 months prior to screening for severe psychiatric disorders (e.g. psychosis, schizophrenia, mania, depression) or major psychiatric illness.
14. Past history of a chronic or recurring ocular or systemic condition that could interfere with efficacy assessments, or preclude safe administration of study medication, according to the investigator's judgement.
15. Have uncontrolled systemic (e.g. hypertension, cardiac failure, severe kidney or liver disease) or ocular diseases (e.g. proliferative retinal diseases) which could affect trial parameters.
16. Subjects with spinal cord injuries who are at risk of autonomic dysfunction.
17. Participation in an interventional clinical trial within 3 months prior to Screening Visit
18. Pregnant or breastfeeding females or those with a positive pregnancy test at Baseline.
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using effective methods of contraception during dosing of study treatment. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or bilateral tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps)
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example, hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS).

    In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

20a. Subjects who for any reasons are unable or unwilling to comply with the specific requirements of the protocol.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

SAF312 will be supplied to the subject as ocular eye drops to be administered into the conjunctival sac. Subjects will self-administer their first dose at the clinical study site in the presence of an *unblinded* site personnel prior to completion of Visit 2. Subsequent drops will be administered at home by subjects.

Sponsor-qualified medical personnel will be readily available to advise on trial related medical questions or problems. Any questions related to the identity of the IMP must be addressed by an *unblinded* site personnel.

Table 6-1 Investigational and control drug

Investigational/ Control Drug	Pharmaceutical Dosage Form	Route of Administration	Presentation	Sponsor (global or local)
SAF312 15 mg/ml	eye drops, suspension	topical ocular	double blind opaque droptainer	Novartis Global
SAF312 5 mg/ml	eye drops, suspension	topical ocular	double blind opaque droptainer	Novartis Global
SAF312 Placebo	eye drops, suspension	topical ocular	double blind opaque droptainer	Novartis Global

6.1.2 Additional study treatments

There are no additional study treatments included in this study. Subjects will be allowed to continue any current treatment regimen for concurrent or underlying ocular conditions. No new treatments can be initiated once the subject has begun participation in the study Screening Visit (Visit 1) unless additional treatments are needed for proper management of an adverse event. If used, any new medication must be recorded on the Concomitant medications therapies page of the CRF.

6.1.3 Treatment arms/group

At Baseline (Visit 2), all eligible subjects will be randomized (ratio 1:1:1) via Interactive Response Technology (IRT) to one of the treatment arms in the double-blinded treatment.

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

6.1.4 Treatment duration

Subjects will dose both eyes with their assigned treatment for 12 weeks (84 days).

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications (systemic or ocular), procedures, and significant non-drug therapies administered after the subject is enrolled into the study must be recorded on the appropriate Case Report Forms (CRF).

Artificial tears and rescue medications should only be used when needed, and should NOT be used prophylactically.

If a subject is using other topical ocular medications for the treatment of concurrent ocular conditions, the subject should first dose with their concomitant medication(s) and wait approximately 10 minutes prior to instillation of the study medication.

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed starting from Screening Visit (Visit 1).

Table 6-2 Prohibited medication

Medication	Prohibition period	Action taken
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
New use or change in dosing of neuromodulators for any reason, and any use of topical ocular NGF	Study duration	Discontinue study treatment

All medications administered after the subject enrolls in the study must be listed on the Concomitant medications/Significant non-drug eCRF page.

6.2.3 Rescue medication

There is no rescue medication that will be proactively provided to study sites or subjects. However, on 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. The data will be entered by the subject in the electronic daily diary (eDiary).

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the informed consent form, the subject is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

At visit 2 after completion of the observation period, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for each package of study treatment to be dispensed to the subject.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment. The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

Randomization will be stratified according to baseline mean pain severity over the 7 days prior to Baseline Visit (≥75mm or <75mm).

6.4 Treatment blinding

Subjects, investigator staff, persons performing the assessments, study monitors and Clinical Trial Team (CTT) will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the following exceptions: unblinded site personnel will be required for initial dose administration, and discussions with subjects that may contain unblinding information (2) the identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, and schedule of administration.

Unblinding of the investigator may occur in the case of subject emergencies and at the conclusion of the study.

6.5 Dose escalation and dose modification

Investigational study treatment dose adjustments and/or interruptions are not permitted.

6.5.1 Dose modifications

Dose modification, adjustment and/or interruptions are not allowed in this study. For subjects who do not tolerate the protocol-specified dosing schedule, rescue medication should be used. If the subject is still unable to tolerate the protocol-specified dosing schedule, the subject should be discontinued from the study treatment.

6.5.2 Follow-up for toxicities

Not applicable

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator should promote compliance by instructing the subject to take the study treatment exactly as described in the protocol by stating that compliance is necessary for the subject's safety and the validity of the study. The subject should inform the investigator if he/she was unable for any reason to use the study treatment as required. This information should be captured in the source document at each visit.

Study treatment will be packaged in droptainers for b.i.d. dosing of both eyes each day. A new droptainer will be opened daily for use during a single day. In addition to subject reported compliance, site staff will record used versus unused bottles as support for assessment of treatment compliance. All study treatment dispensed and returned must be recorded in the Drug Accountability Log and returned to the Sponsor.

6.6.2 Recommended treatment of adverse events

There are no adverse events of special interest (AESI) that require specific treatment instructions. Investigators must treat adverse events as needed and according to investigator judgement. Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required in order to treat the subject safely. Most often, discontinuation from study treatment and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment

for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis study monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time in case of emergency. The investigator will ensure appropriate site personnel are available as his/her backup if needed. Investigators will also ensure subjects are provided the appropriate contact information in case of emergency.

Once the treatment code has been broken for a particular subject, that subject must be discontinued from study treatment, while adverse event (AE) treatment and follow-up continue as appropriate.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs (Section 6.1.1).

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

An *unblinded* site personnel will instruct the subject on proper drug storage and use, and will dispense the assigned medication to the subject, prior to instillation of the first dose of study medication at the site.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a subject's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the subject is no longer appropriate or possible, and that it is in the interest of the subject's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the subject's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of 1 month supply. In this case, regular phone calls or virtual contacts (e.g., every 2 weeks or more frequently if needed) will occur between the site and the subject for instructional purposes, safety monitoring, investigation of any adverse events, ensuring subjects continue to benefit from treatment, and discussion of the subject's health status until the subjects can resume visits at the study site.

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated

site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by study monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all used and unused study treatment and packaging at each returning visit and at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate, during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis study monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

Not applicable

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification (IN)

or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e., pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g., telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect, prevail and must be implemented and appropriately documented (e.g., the presence of an impartial witness, sign/dating separate ICFs by trial subject and person obtaining informed consent, etc.).

8 Visit schedule and assessments

Assessment schedule (Table 8-1) lists all the assessments and when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible, and follow the proposed in-office assessment sequence as outline in (Table 8-2) . Missed or rescheduled visits should not lead to automatic discontinuation. Visits that occur after the rescheduling of a previous visit should be done based on the initial protocol visit timing, and not based on the previous visit.

If the EOS follow-up contact cannot be done on time (EOT+4 days), the contact should be made later, but should not be made earlier (i.e., at least 4 days should elapse prior to the follow-up contact).

Subjects who prematurely discontinue the study, for any reason, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the AE and concomitant medications recorded on the CRF.

Subjects should avoid dosing with any topical ocular medications or any pain medications within 4 hours of a scheduled visit.

If the COVID-19 pandemic limits or prevents on-site study visits, in which IMP could not be dispensed and other study assessments may not be performed, alternative methods of IMP dispensing and safety monitoring may be implemented. Depending on local regulations, site capabilities and patient's visit status in the study, phone calls or virtual contacts (e.g. teleconsult) can be performed for safety follow-up for the duration of the pandemic, until it is safe for the subject to visit the site again.

Table 8-1 Assessment Schedule

Period	Screening			Treatment					Post Treatment Follow-up
Visit Name	Visit 1 Screening	Phone Check-in	Visit 2 Baseline	Visit 2 Randomization	Visit 3	Visit 4	Visit 5	Visit 6 / EOT	Follow-up Contact / EOS
Days	-84	-42 ± 7	1	1	14 ± 2	28 ± 2	56 ± 2	84 ± 2	EOT + 4
Informed consent	X								
Demography	X								
Medical history / current medical conditions	X								
Previous /Con Meds	X	X	X		X	X	X	X	X
Inclusion / Exclusion criteria	X		X						
Pregnancy test (dipstick/strip)			S					S	
Adverse Events	X	X	X		X	X	X	X	X
Anesthetic test	X								
Placebo response mitigation training video and knowledge check	S			S[1]					
Dispense electronic diary	S								
[redacted]									
Pain Severity VAS	X[2]	R	R[3]	R[4]	R[4]	R[4]	R[4]		
Pain Frequency VAS	X[2]	R		R[4]	R[4]	R[4]	R[4]		
[redacted]									
Artificial tears use	X[2]	R		R[4]	R[4]	R[4]	R[4]		
Rescue medications	X[2]	R		R[4]	R[4]	R[4]	R[4]		
OPAS Questionnaire	X		X[6]		X[6]	X[6]	X[6]	X[6]	
[redacted]									
Pain Characterization Questionnaire	X								

Period	Screening			Treatment					Post Treatment Follow-up
Visit Name	Visit 1 Screening	Phone Check-in	Visit 2 Baseline	Visit 2 Randomization	Visit 3	Visit 4	Visit 5	Visit 6 / EOT	Follow-up Contact / EOS
Days	-84	-42 ± 7	1	1	14 ± 2	28 ± 2	56 ± 2	84 ± 2	EOT + 4
Visual Acuity	X		X					X	
Slit lamp examination	X		X		X	X	X	X	
Signs evaluation: (Corneal fluorescein staining; Conjunctival lissamine staining. Conjunctival redness; Schirmer score)	X		X		X	X	X	X	
Contact IRT	X			X	X	X	X	X	
Intraocular Pressure (IOP)			X					X	
Ophthalmoscopy dilated fundus exam			X					X	
Corneal endothelial cell microscopy			X					X	
In vivo confocal microscopy[7]			X					X	
Dispense study medication				S[8]	S	S	S		
Collect electronic diary [redacted]								S	
Collect study medication					S	S	S	S	
Electronic diary compliance check[9]			S		S	S	S	S	

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only

R Reminder for the tasks to be completed by the subject outside of the clinical site

[1] The Pain Assessment Knowledge Check can be optional for any subject who had completed the Knowledge Check already during Screening Visit (Visit 1).
[2] Two entries to be completed on the same day of screening. The first entry is to be made at the time of the on-site screening visit, the second entry and all subsequent entries are to be completed at home before their evening dose of study medication.

[3] Confirm eligibility based on the eDiary data.

[4] Remind the subject to complete the once daily eDiary recording prior to the evening dose of study medication every day until the evening prior to the EOT visit.

[redacted]

[6] Enter the PIN code and select the scheduled visit on the Visit Selection menu to allow the study subject to complete the questionnaire on the tablet device

[7] To be conducted at selected sites only

[8] Study medication is only dispensed after the subject is randomized

[9] Review subject daily eDiary entry compliance and subject reported outcome of Pain Severity VAS, Pain Frequency, Frequency of Artificial Tear use and rescue medication use. If pain rescue medication were reported in eDiary, request further detailed medication information and make entry into eCRF concomitant medication page.

Table 8-2 Proposed in-office Assessment Sequence

Visit 1 (Screening)	Visit 2 (Baseline/ Randomization)	Visits 3 / 4 / 5	Visit 6 (EOT)
ICF / Demographics / MH / Incl + Excl	Con meds / AE / MH / Incl + Excl	Con meds / AE	Con meds / AE
Concomitant medications / adverse events	Pregnancy test	OPAS questionnaire	Pregnancy test
Placebo response mitigation training video[1]	Confirm eligibility on pain severity VAS	[redacted]	eDiary compliance check
Dispense eDiary	eDiary compliance check	Slit-lamp exam	OPAS questionnaire
Pain severity and frequency VAS	OPAS questionnaire	Conjunctival redness	[redacted]
Use of artificial tears / rescue medications	[redacted]	Corneal fluorescein staining	Visual acuity
Pain Characterization questionnaire	Visual acuity	Lissamine conjunctival staining	Slit-lamp exam
OPAS questionnaire	Slit-lamp exam	Schirmer test	Conjunctival redness
[redacted]	Conjunctival redness	eDiary compliance check	Corneal fluorescein staining
Visual acuity	Corneal fluorescein staining	Contact IRT	Lissamine conjunctival staining
Slit-lamp exam	Lissamine conjunctival staining	Collect/dispense IMP	Schirmer test
Conjunctival redness	Schirmer test	eDiary [redacted] reminders	IOP
Corneal fluorescein staining	IOP		Dilated fundus exam
Lissamine conjunctival staining	Dilated fundus exam		Specular Microscopy / *Confocal microscopy
Schirmer test	Specular Microscopy / Confocal microscopy[2]		Collect meds / devices
Anesthetic test	Contact IRT		Contact IRT
Contact IRT	Randomize/dispense IMP		
[redacted]	Dose in clinic (*unblinded site personnel only*)		
eDiary [redacted] reminders	eDiary [redacted] reminders		
	Placebo response mitigation training video[3]		

NOTE:

[1] Includes Pain Assessment Knowledge Check

[2] Confocal microscopy is performed only at select sites after specular microscopy

[3] Pain Assessment Knowledge Check can be performed optionally at Visit 2, but should be performed if not completed previously

8.1 Screening

Subjects will be screened at the Screening Visit (Visit 1), and eligible subjects will be enrolled into the observational period of the study.

Re-screening of subjects who fail entry criteria for any reason is permitted only under select circumstances as outlined below.

- Screen failure due to stabilization timeframes: If it is determined prior to the completion of Screening Visit that the subject did not meet eligibility pertaining to any of the following:
  - < 4 months since the surgical procedure (Inclusion #2a),
  - Timeframe required for stabilization of chronic medications or medical history (Exclusion #1a, 2, 3, 4, 6, 7, 8, 9, 10, 11, 17, 20a), or
  - Time window required for ocular medication or pain medication use prior to the screening visit (Exclusion #2),

  the subject will be screen failed and may be brought back at a later date after the proper timeframes have been achieved to re-attempt the screening process.
- Screen failure under protocol version 02 due to ocular pain severity eligibility criteria that would have been met under protocol version 03: If a subject was screen failed under protocol version 02 due to the following pain severity inclusion criteria:
  - Ocular pain severity VAS < 50 mm at Screening Visit (per Inclusion #3)

  the subject may be brought back at a later date to re-attempt the screening process.
- Screen failure due to insufficient reduction in ocular pain during the anesthetic test caused by technologic or procedural issues: If a subject was screen failed due to an insufficient ocular pain reduction during the anesthetic test, the subject may be allowed to re-screen in specific circumstances (including device malfunction, procedural errors). In all cases, the site must receive Sponsor approval prior to re-screening.

In the case of re-screening, the subject will receive a new subject number and all screening assessments required at Screening Visit must be completed, regardless whether the assessments were conducted at the previous screening visit.

Re-screening is only allowed one time for each subject, with the exception of subjects who screen failed due to pain severity eligibility criteria under protocol version 02. A subject who screen failed under this criterion potentially could be re-screened a second time based on the additional re-screening criteria stated above. Re-screening must not be used as a method to force subject eligibility into the study.

8.1.1 Information to be collected on screening failures

Subjects who sign an informed consent form and are subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF. The informed consent, demographic information, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data

will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a serious adverse event (SAE) during the screening phase (see 10.1.2 SAE section for reporting details). If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail that the subject was not randomized.

Subjects who are randomized and fail to start treatment, e.g. subjects randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate eCRF.

8.2 Subject demographics/other baseline characteristics

The following information will be collected/documented at Screening/Baseline Visits for each randomized subject:

- Age
- Sex
- Race/Ethnicity
- Ancestry (applicable for Japanese and Chinese only)
- Iris color

Ocular baseline characteristic will include:

- Time since date of the last surgery
- Surgery type (PRK,LASIK, LASEK, RK, SMILE or Cataract)
- Pain Characterization Questionnaire
- Frequency of artificial tear use
- Frequency of rescue medication use
- Corneal fluorescein staining
- Conjunctival lissamine staining
- Conjunctival redness score
- Schirmer score

Baseline values of efficacy parameters:

- Pain Severity VAS
- Pain frequency VAS
- OPAS
- [redacted]

8.3 Efficacy

8.3.1 Pain Severity and Frequency Visual Analog Scales

The pain severity Visual Analogue Scale (VAS) is to be completed through an electronic diary by the subject at the Screening Visit, and thereafter every evening (before bed during the observational period, and before their evening dose of study medication during the study treatment period). The subject will provide a score for severity of their ocular pain over the past

24 hours by putting a vertical mark on the horizontal scoring line. The severity scoring line utilizes the anchors of 'No Pain' to 'Very Severe' pain.

The Pain Frequency Visual Analogue Scale (VAS) is to be completed through an electronic diary by the subject at the Screening Visit, and thereafter every evening (before bed during the observational period, and before their evening dose of study medication during the study treatment period). The subject will provide a score for frequency of their ocular pain over the past 24 hours by putting a vertical mark on the horizontal scoring line. The frequency scoring line utilizes the anchors of 'Rarely' to 'All the Time'.

8.3.2 OPAS questionnaire

The Ocular Pain Assessment Survey (OPAS) questionnaire is completed electronically by the subject at each office visit as indicated in the Schedule of Assessments. The OPAS will be used to assess the subject's ocular pain, aggravating factors, quality of life, and perception of overall improvement of ocular and non-ocular pain. The OPAS is a multidimensional tool specifically designed to assess ocular pain in subjects with eye pain of any origin.

8.3.4 Appropriateness of efficacy assessments

The efficacy assessments included in this study for the evaluation of ocular pain are commonly used in clinical research.

8.4 Safety

Safety assessments are specified below and the assessment schedule details when each assessment is to be performed. If the COVID-19 pandemic limits or prevents on-site study visits, phone calls or virtual contacts should be conducted for safety monitoring and discussion of the subject´s health status, until the subject can again visit the site.

Clinically significant abnormalities, per the opinion of the Investigator, for any of the safety parameters will be recorded on the ocular medical history page of the eCRF if present at the time of informed consent, and on the AE page if occurring on or after the time of consent.

For details on AE collection and reporting, refer to Section 10.1 - Definition of adverse events and reporting requirements

8.4.1 Laboratory evaluations

Not Applicable

8.4.2 Pregnancy

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and must agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria.

All women of childbearing potential who are not surgically sterile will have a urine pregnancy test. These assessment results must be captured in the source documentation. Additional urine pregnancy tests may be performed at the discretion of the investigator and/or according to local requirements and the test results will be recorded in the source document. A positive urine pregnancy test requires immediate interruption of study drug until serum beta-human chorionic gonadotropin (B-hCG) is performed and found to be negative. If positive, the subject must be discontinued from the trial.

8.4.3 Visual Acuity

Visual acuity (VA) will be performed using a Snellen chart. VA testing should precede IOP measurement, the administration of eye drops to dilate or anesthetize the eye, or any examination requiring contact with the eye.

8.4.4 Slit Lamp Examination

At every scheduled visit, the anterior segment's structures of the study eye will be carefully examined according to clinical practice. The slit lamp results will be recorded in the source documents.

8.4.5 Intraocular Pressure

Intraocular pressure (IOP) will be measured according to the standard clinical practice and expressed in mmHg. Every effort should be made to use the same method/instrument throughout the study.

If using Goldmann applination tonometry, the IOP measurement should be performed after the corneal fluorescein staining and lissamine conjunctival staining at Visit 2 and Visit 6, to avoid the staining outcomes are confounded by the anesthetic.

8.4.6 Dilated Fundus Exam

For the fundus exam pupil must be dilated. Fundus results will be recorded in the source documents

8.4.7 Corneal Endothelial Cell Microscopy

Each site must use the specified brand of equipment for use on all subjects at the site. Certification of the equipment and examiners at each investigative site will occur prior to evaluation of study subjects. 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. A standardized procedure for the collection of the Specular microscopy images will be provided by the CRC in a separate manual.

8.4.8 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/subject population.

8.5 Additional assessments

8.5.1 Other Assessments

In vivo confocal microscopy is included as an exploratory assessment at select sites to evaluate corneal nerve morphology in patients with CICP.

The following ocular surface assessments (corneal and conjunctival staining, conjunctival redness, Schirmer's test) are included to evaluate whether long term inhibition of TRPV1 receptors with SAF312 eye drops has an adverse effect on ocular surface parameters.

[redacted]

Finally, the Pain Characterization questionnaire will be used to gain greater detail regarding the subject's ocular pain.

Frequency of artificial tear/gel/lubricant use and rescue medication use will be captured in the eDiary on a daily basis to gain insights to subject behavior with these products.

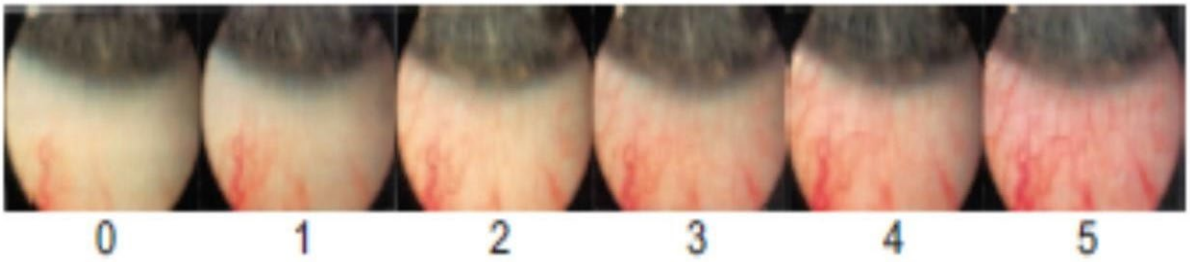
8.5.1.1 In Vivo Confocal Microscopy

In Vivo Confocal Microscopy (IVCM) will be performed by the Investigators only at selected sites for exploratory analysis. The images will be sent to an independent reader for objective and subjective evaluation to quantify and evaluate the distribution and morphology of corneal nerves. A standardized procedure for the collection of the images will be provided in a separate manual.

8.5.1.2 Conjunctival Redness

Redness of the interpalpebral conjunctiva will be evaluated by the investigator using the McMonnies scale (Figure 8-1). The inter-palpebral region of the temporal and nasal regions will each be graded using the 0-5 scale.

Figure 8-1 McMonnies Redness Photographic Scale



8.5.1.3 Corneal Fluorescein Staining

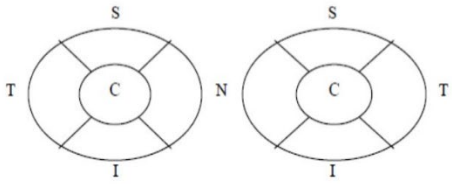
Corneal fluorescein staining will be conducted by the Investigator. For individual subjects, corneal fluorescein staining should be assessed by the same examiner at all visits using the same slit lamp and the same settings.

Fluorescein impregnated strips (to be provided by Novartis) will be used to deliver dye to the ocular surface. To wet the strip, a single drop of sterile saline solution (or similar) is placed on the tip of the strip. Anesthetic drops must NOT be used as a wetting agent.

Immediately after application of the wetting drop, the strip should be gently flicked to remove excess fluid. Immediately after flicking the strip, the wet tip of the strip is allowed to gently touch the inner edge of the inferior cul-de-sac of the eye to draw the fluorescein onto the ocular surface. The subject should be instructed to not rub their eyes and gently blink several times to distribute the dye across the ocular surface.

The degree of staining is based on the Corneal Fluorescein Modified NEI Scale. Each of the five regions (as depicted in the diagram, and defined as central (C), superior (S), inferior (I), temporal (T), and nasal (N)) will be graded based on a scale of 0 to 4, with higher scores suggestive of higher degrees of corneal staining (Figure 8-2). The examiner will indicate the appropriate score for each region. If the assessment falls between grades, round up to the higher score. After entry of the scores per region, the total or composite (sum) score for each eye will be automatically calculated (maximum score = 20/eye).

Figure 8-2 Corneal Fluorescein Modified NEI Scale



Grade 0	No staining
Grade 1	Superficial micropunctate staining covering < 25% of the corneal surface
Grade 2	Macropunctate staining AND/OR superficial micropunctate staining covering 25-50% of the corneal surface
Grade 3	Some coalesced macropunctate staining AND/OR superficial micropunctate staining covering 51-75% of the corneal surface
Grade 4	Numerous coalesced macropunctate areas and/or patches AND/OR superficial micropunctate staining covering > 75% of the corneal surface

8.5.1.4 Conjunctival Lissamine Staining

Conjunctival lissamine staining will be conducted by the Investigator and after corneal fluorescein staining. For individual subjects, conjunctival lissamine staining should be assessed by the same examiner at all visits using the same slit lamp and the same settings.

Lissamine impregnated strips (to be provided by Novartis) will be used to deliver the dye to the ocular surface. To wet the strip, a single drop of sterile saline solution (or similar) is placed on the tip of the strip. Anesthetic drops must NOT be used as a wetting agent.

Immediately after application of the wetting drop, the strip should be gently flicked to remove excess fluid. Immediately after flicking the strip, the wet tip of the strip is allowed to gently touch the inner edge of the inferior cul-de-sac of the eye to draw the lissamine onto the ocular surface. The subject should be instructed to not rub their eyes and gently blink several times to distribute the dye across the ocular surface.

The degree of lissamine staining in the temporal and nasal inter-palpebral conjunctiva will be assessed based on the proportion of the area that is covered by staining. The proportion of staining area will be assessed based on the table provided in Table 8-3:

Table 8-3 Grading of Conjunctival Staining

Grading scale	Percentage of the staining area
0	0%
1	1%–15%
2	16%–30%
3	31%–45%
4	>45%

The score for nasal and temporal regions will be captured separately and the total conjunctival lissamine staining will be the sum of the nasal and temporal scores (total score of 0-8).

8.5.1.5 Schirmer's Test (without anesthesia)

The Schirmer’s test will be performed without anesthetic in both eyes simultaneously, and after completion of ocular surface stainings.

The subject should be seated in the examining chair with the room lights dimmed and their head against a headrest for comfort. Prepare the sterile strips (Tear Flo™ or similar) while they are still in the package by folding the rounded end at the indentation (approximately 5 mm from the tip). The strip will be bent and inserted between the bulbar and palpebral conjunctiva over the inferior lid margin in the lateral third of the eyelid towards the lateral canthus, and left in place for 5 minutes with the eyes closed. Tear secretion is measured in millimeters of the length of strip wetted by tears. The measurement (score) will be made to the nearest whole number.

8.5.1.6 Mitigation of Placebo Response Training Video and Pain Assessment Knowledge Check

At Screening Visit (Visit 1): Upon completion of ICF but before starting the use of ePRO device, the subject will use the study tablet device, personal mobile device, laptop, or tablet to watch a video regarding placebo response mitigation.

After completing the video, a printed copy of the Pain Assessment Knowledge Check will be given to the subject to have him/her complete the questions in order to check their level of

understanding of the video content. Site staff should review the responses with the subject and answer any questions they may have regarding incorrect responses or the information as a whole.

At Baseline/Randomization Visit (Visit 2): if the subject meets criteria for randomization, the study subject is expected to watch the Video once more BEFORE they leave the clinic. The Pain Assessment Knowledge Check can be optional for any subject who had completed the Knowledge Check already during Visit 1 (Screening).

8.5.1.7 Pain Characterization Questionnaire

The Pain Characterization questionnaire is a series of questions asking about the specific details of the subject's ocular pain (e.g., pain descriptors, timing throughout the day) that is not already captured in the other questionnaires included in the efficacy assessments. The pain characterization questionnaire will be collected electronically at Screening Visit only and therefore not intended for any safety or efficacy assessments.

8.5.1.8 Post-Anesthetic Severity of Eye Pain

The anesthetic test will be administered to identify subjects with primarily peripheral neuropathic pain.

The subject will be asked to complete the pre-anesthetic pain severity VAS question in the ePRO. After the subject records the pain severity score, one drop of topical ocular anesthetic will be administered in each eye per the study site standard practice (e.g., Tetracaine, proparacaine). Once the anesthetic has taken effect, within 5 min of drop instillation, the subject will complete the post-anesthetic severity eye pain VAS question in the ePRO. For both the pre- and post-anesthetic pain severity, the subject will complete the pain severity VAS considering the pain at the time when each question is completed. The question is the same pain severity question as described in Section 8.3.1., with the severity scoring line anchors of 'No Pain' to 'Very Severe' pain.

The ePRO will calculate the difference between the pre-anesthetic pain severity score and the post-anesthetic score (must be ≥ 60% for subject to qualify for the study).

[redacted]

[redacted]

9 Discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is permanently stopped for any reason (prior to the planned completion of study drug administration, if any) and can be initiated by either the subject or the investigator.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Discontinuation from study treatment is required under the following circumstances:

- Subject decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment (Section 6.2.2)
- Any situation in which continued study participation might result in a safety risk to the subject
- Following emergency unblinding
- Adverse events
- Unsatisfactory therapeutic effect

If discontinuation from study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's discontinuation from study treatment and record this information.

Subjects who discontinue from study treatment agree to return for the end of treatment and follow-up visits indicated in the Assessment Schedule (refer to Section 8).

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After discontinuation from study treatment, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- AE / SAE

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code in Section 6.6.3.

9.1.2 Discontinuation from study

Discontinuation from study is when the subject permanently stops receiving the study treatment, and further protocol-required assessments or follow-up, for any reason.

If the subject agrees, a final evaluation at the time of the subject's study discontinuation should be made as detailed in the assessment table (refer to Section 8).

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.2 Withdrawal of informed consent/Opposition to use data/biological samples

Withdrawal of consent/opposition to use data/biological samples occurs when a subject:

- Explicitly requests to stop use of their biological samples and/or data (opposition to use subject's data and biological samples)

and

- No longer wishes to receive study treatment

and

- Does not want any further visits or assessments (including further study-related contacts)

This request should be in writing (depending on local regulations) and recorded in the source documentation.

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw their consent/opposition to use data/biological samples and record this information.

Where consent to the use of Personal and Coded Data is not required in a certain country's legal framework, the subject therefore cannot withdraw consent. However, they still retain the right to object to the further collection or use of their Personal Data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

If the subject agrees, a final evaluation at the time of the subject's withdrawal of consent/opposition to use data/biological samples should be made as detailed in the assessment table (refer to Section 8).

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation, including processing of biological samples that has already started at time of consent withdrawal/opposition. No new Personal Data (including biological samples) will be collected following withdrawal of consent/opposition.

9.3 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision.

Sites will contact the subjects by telephone 4 days after EOT visit (Visit 6) to inquire about any adverse events that began after the last treatment with IMP. The investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls.

9.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development

In taking the decision to terminate, Novartis will always consider subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a subject who discontinued from study treatment: The investigator should contact such information to the subject, when the subject should stop taking drug, when the subject should come in for a final visit(s) that the safety follow up period must be completed if applicable and which visits to be performed. . The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An AE is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade

mild: usually transient in nature and generally not interfering with normal activities

moderate: sufficiently discomforting to interfere with normal activities

severe: prevents normal activities

2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single subject
3. Its duration (start and end dates or ongoing) and the outcome must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken with study treatment

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased

- Drug interrupted/permanently discontinued

6. its outcome

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued until the end of study visit.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

10.1.2 Serious adverse events

An SAE is defined as any AE [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the subject’s general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might

require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety immediately, without undue delay, under no circumstances later than within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site. Information about all SAEs is collected and recorded on the eSAE with paper back. Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with European Union (EU) Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial subject becomes pregnant, the study treatment should be stopped, and the pregnancy consent form should be presented to the trial subject. The subject must be given adequate time to read, review and sign the pregnancy consent form. This consent form is

necessary to allow the investigator to collect and report information regarding the pregnancy. To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship between the use of SAF312 eye drops and any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

If a female partner of a male trial subject who took study treatment in this study becomes pregnant, pregnancy outcomes should be collected. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

After consent is provided, the pregnancy reporting will occur up to one year after the estimated date of delivery.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (European Medicines Agency (EMA) definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE (see Table 10-1). Misuse or abuse will be collected and reported in the safety database within 24 hours of Investigator's awareness only if it is associated with an SAE.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document as a protocol deviation (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Only if associated with an AE	Only if associated with an SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

Not applicable

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic CRF (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 Code of Federal Regulation (CFR) Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Randomization codes and data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and study monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made

available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The study monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice (GCP), the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the study monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the study monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 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.

The Safety Set 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.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the FAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation (SD), median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, SD, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in days to SAF312 and placebo will be summarized by means of descriptive statistics using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

12.4 Analysis of supporting primary objectives

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

12.4.1 Definition of primary endpoint(s)

The primary endpoint is the change from baseline in weekly mean pain severity VAS at Week 12. The weekly mean pain severity VAS will be calculated as the mean of the daily pain severity VAS from the 7 days of the week. Baseline value will be calculated as the mean of the daily pain severity VAS from the 7 days prior to the first dose.

12.4.2 Statistical model, hypothesis, 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 in comparison with its placebo by rejecting the null hypothesis below at a significance level α=0.05 (2-sided).

$$H1: u_T = u_v \text{ vs. } H2: u_T \neq u_v$$

where u_T and u_v are mean change from baseline of weekly mean pain severity VAS at Week 12 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. 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.

12.4.3 Handling of intercurrent events of primary estimand

In the primary analysis, the estimand will be the treatment effect of SAF312 against placebo, had subjects not taken prohibited or rescue medications as described below, and had they stayed on the study treatment for the whole study duration. 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.

For subjects who use rescue medications for pain relief due to any reason, the data on the day(s) will be excluded and treated as missing.

For subjects who take the following prohibited medications:

- 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.

For subjects with new use or changes in dosing of neuromodulators for any reason or topical ocular NGF, the data starting from the day will be excluded and treated as missing.

For subjects who discontinue study treatment for any reason, the data collected following the treatment discontinuation will be excluded and treated as missing. Missing data after study treatment discontinuation will be based on the Missing at Random (MAR) assumption.

The multiple imputations will be carried out on the weekly mean pain severity VAS.

12.4.4 Handling of missing values not related to intercurrent event

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

Handling of missing daily pain severity values within a week (within-week imputation)

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.

Handling of missing weekly mean pain score values (weekly mean imputation)

For all analyses, imputation of intermittent missing observations before treatment discontinuation will be carried out following a MAR mechanism for all treatment arms.

12.4.5 Sensitivity analyses for primary endpoint/estimand

Not applicable.

12.4.6 Supplementary analysis

A supplementary clinical question of interest is: What is the effect of SAF312 versus placebo on change from baseline in weekly mean pain severity VAS score, regardless of discontinuation from study treatment discontinuations for any reason, and regardless of occasional use of rescue medication or prohibited medications?

The supplementary analyses to the primary analysis will be performed on the FAS population. The supplementary analysis will be performed using all observed data regardless of intercurrent events (a treatment policy strategy). The target population, the primary variable and the summary measure of the supplementary estimand for the supplementary estimand are the same as for the primary estimand. Differently from the primary estimand, this analysis considers all intercurrent events are inherent in the treatment regimen and will not exclude any observed data even when subjects take rescue/prohibited medications or discontinue treatment.

For subjects who use rescue medications for pain relief due to any reason, all observed data will be used for analysis. If not available, missing data will be under the MAR assumption for both SAF312 and placebo arms.

For subjects who take the following prohibited medications:

- Ocular, nasal, inhaled, or systemic corticosteroids
- Use of oral or topical ocular antihistamines, mast cell stabilizers

All observed data will be used for analysis. If not available, missing data on the day(s) +3 days of the IEs will be under the MAR assumption for both SAF312 arms and placebo arm.

For subjects with new use or change in dosing of neuromodulators for any reason or topical ocular NGF, all observed data will be used for analysis. If not available, missing data on the days of IEs will be under the MAR assumption for both SAF312 and placebo arms.

For subjects who discontinue from study treatment due to any reason, retrieved drop-out (RDO) data collected after study treatment discontinuation will be used for analysis. If not available, missing data after treatment discontinuation will be multiply imputed based on Jump to Reference assumption for SAF312 arms and under the MAR assumption for placebo arm.

The supplementary analysis will be performed using MMRM but includes all the observed data and imputed data if appropriate.

Subgroup analysis

Subgroup analyses of the primary endpoints will be outlined in the statistical analysis plan (SAP).

12.5 Analysis supporting secondary objectives

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)

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, and OPAS subscale Quality of Life.

12.5.1 Safety endpoints

For all safety analyses, the safety set will be used. The safety assessments are adverse events (ocular and non-ocular), slit lamp biomicroscopy, IOP, visual acuity, ophthalmoscopy, and corneal endothelial cells evaluations. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period starts from the date of the first administration of study treatment to 4 days after the date of the last administration of study treatment.

The safety analysis will consist of descriptive summaries. Continuous variables will be presented with n, mean, SD, median, minimum and maximum. Categorical data will be displayed with frequency and percentage.

Adverse events

All information obtained on adverse events will be displayed by treatment group and subject.

The number (and percentage) of subjects with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

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

Ocular and non-ocular adverse events will be summarized separately. Separate summaries will be provided for study treatment related adverse events, death, SAE, other significant adverse events leading to discontinuation.

Subject listings of all adverse events will be provided. Deaths and other serious or clinically significant non-fatal adverse events will be listed separately. 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.

12.5.2 Patient reported outcomes

Patient-reported outcomes include the following:

- OPAS questionnaire subscales
- [redacted]

Summary of change from baseline will be provided by treatment group. No test will be performed on the PRO endpoints.

12.6 Analysis of exploratory endpoints

Exploratory endpoints include:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- 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.

[redacted]

For continuous endpoints, summary statistics (mean, median, 25th percentile, 75th percentile, SD, minimum and maximum, the number of non-missing observations, and 95% confidence interval) will be provided by treatment arm at each time point. Differences of change from baseline endpoints between each SAF312 arm vs. placebo will be summarized at each post-baseline visit with 95% confidence interval.

For frequency of pain events, artificial tears/gel/lubricant, rescue medications, and microneuromas, percentage of subjects by treatment group over time will be presented. The difference in percentage between each SAF312 and placebo will be summarized with 95% confidence interval.

12.7 Interim analyses

No interim analysis is planned for this trial. A final analysis will be performed after all subjects have completed Week 12 or discontinued prior to Week 12.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

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 12-1 for power to detect a significant difference from placebo under various assumed treatment effect of weekly mean pain severity VAS and SD.

nQuery Advisor 7.0 is used for the estimate.

Table 12-1 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 l 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.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis study monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site

is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study subjects. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study subjects.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

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16 Appendices

Not applicable