Excelencia en oftálmicos

Statistical Analysis Plan (PAE)

Version 1.0

Phase I clinical study to evaluate the safety and tolerability of PRO-185 ophthalmic solution

applied in clinically healthy subjects

Protocol Code: SOPH185-0521/I

Version Date: May 1, 2021

Sponsor: Laboratorios Sophia, S.A. de C.V.

This document was prepared in accordance with FDA, ICH, and GCP guidelines.

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Content

1. Abbreviations

AO	Both eyes
AVMC	Best corrected visual acuity
OF	Standard deviation
EA	Adverse event
eCRF	Electronic Case Report Form
FC	Heart rate
FCI	Informed Consent Form
FR	Respiratory rate
ICH	International Council for Harmonization *of Technical Requirements of Pharmaceuticals for Human Use)*
ITT	Intention-to-treat population
KS	Kolmogorov-Smirnov
bpm	Beats per minute
PAD	Diastolic blood pressure
PAE	Statistical analysis plan
PAS	Systolic blood pressure
PI	Investigational Product
PIO	Intraocular pressure
PP	Population by protocol
PRO-185	Naphazoline Hydrochloride 0.03%
rpm	Breaths per minute
SDV	*Source document verification*
SEC	*Self-evident correction*
SW	Shapiro-Wilk
TF	Fluorescein staining
TVL	Lissamine green staining
X^2	Chi square

2. Introduction

This document describes the statistical analysis plan (SAP) designed for the SOPH185 protocol. 0521/I (Phase I clinical study to evaluate the safety and tolerability of PRO-185 ophthalmic solution applied to clinically healthy subjects). This PAE is intended to complement the study protocol. Any deviation from this document will be described in the Final Clinical Study Report [1].

3. Study Design

This is a Phase I, controlled, non-comparative, open-label, single-center clinical study, see Figure 1.

3.1 Objectives

3.1.1 Main objective

To evaluate the safety and tolerability of PRO-185 ophthalmic solution in ophthalmologically healthy subjects.

3.1.2 Specific objectives

- To evaluate the safety of PRO-185 ophthalmic solution by the incidence of subjects who present an increase >5 mmHg in intraocular pressure (IOP) after 20 minutes of its application compared to the initial value.
- To evaluate the safety of PRO-185 ophthalmic solution by the incidence of subjects presenting a heart rate change >15 beats per minute (bpm) 20 minutes after application.
- To evaluate the safety of PRO-185 ophthalmic solution by the incidence of subjects presenting an increase in systolic blood pressure (SBP) >15 mmHg or >10 mmHg in diastolic blood pressure (DBP) after 20 minutes of its application.
- Evaluate tolerability by the incidence of grade 3 and 4 conjunctival hyperemia.
- Evaluate tolerability by the incidence of pharmacological mydriasis.
- Evaluate tolerability by the incidence of expected and unexpected adverse events (AEs). expected.

3.2 Study Hypothesis

3.2.1 Null hypothesis (H0)

PRO-185 ophthalmic solution is not safe and tolerable for ophthalmic use because more than 10% of subjects experienced any of the following AEs: increased IOP (>5 mmHg), changes in HR (>15 bpm), increased systemic blood pressure (>15 mmHg SBP or >10 mmHg DBP), pharmacological mydriasis, or grade 3 and 4 conjunctival hyperemia.

$$H_0 = p - p_0 \leq \delta$$

3.2.2 Alternative hypothesis (H1)

PRO-185 ophthalmic solution is safe and tolerable for ophthalmic use, as it did not present any of the following AEs in more than 10% of subjects: increased IOP (>5 mmHg), changes in HR (>15 bpm), increased systemic blood pressure (>15 mmHg in SBP or >10 mmHg in DBP), pharmacological mydriasis, or grade 3 and 4 conjunctival hyperemia.

$$H_1 = p - p_0 > \delta$$

3.3 Study Variables

3.3.1 Primary outcome variables

- Intraocular pressure
- Heart rate
- Systemic blood pressure
- Pupillary size
- Conjunctival hyperemia

3.3.2 Secondary outcome variables

- Best corrected visual acuity (BCVA)
- Corneal and conjunctival staining changes with lissamine green (LG)
- Corneal and conjunctival staining changes with fluorescein (TF)
- Incidence of chemosis
- Incidence of adverse events
- Incidence of unexpected adverse events

3.3.3 Exploratory Variables

- Respiratory rate
- Body temperature

3.4 Subject's duration in the study/treatment

Up to 11 days, 1 drop 4 times a day in both eyes (OE) for 8 days, see Table 1.

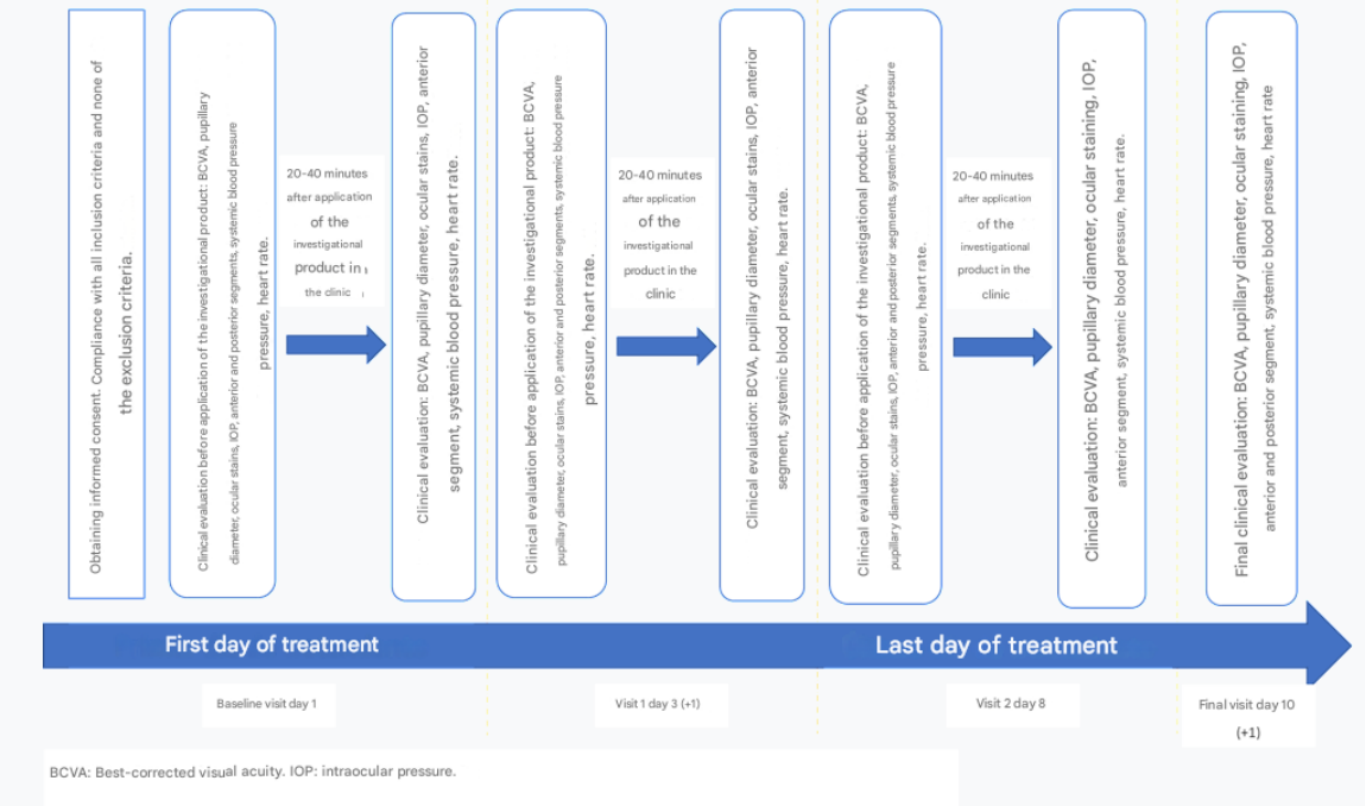

Figure 1. Study diagram

Table 1. Study schedule

Procedures	*Baseline visit* *Day 1*		*Visit 1* *Day 3 (+1)*		*Visit 2* *Day 8*		*Final visit* *Day 10 (+1)*
	Pre-Tx	Post-Tx	Pre-Tx	Post-Tx	Pre-Tx	Post-Tx	Without treatment
FCI Signature	X						
Medical record	X						
Eligibility criteria	X						
Subject code assignment	X						
Adverse events	X	X	X	X	X	X	X
Heart rate	X	X	X	X	X	X	X
Frequency respiratory	X		X		X		X
Blood pressure	X	X	X	X	X	X	X
Temperature (°C)	X		X		X		X
Pregnancy test in urine	X						X
AVMC	X		X		X		X
Evaluation of the anterior segment		X		X		X	
Pupillary diameter measurement	X	X	X	X	X	X	X
Eye stains	X	X	X	X	X	X	X
Intraocular pressure	X	X	X	X	X	X	X
Evaluation of the posterior segment	X		X		X		X
Application of the medicine in visit	X		X		X		
Delivery of material for the subject		X					
Delivery of the medication study		X					
Evaluation of medications concomitants	X		X		X		X
Evaluation of the adherence			X		X		
Return of the medicine of the study						X	
Withdrawal from the diary of subject						X	

Pre-Tx: pretreatment, indicates the assessments to be performed before administration of the investigational drug. Post-Tx: post-treatment, indicates the evaluations to be performed within 20–40 minutes after administration of the investigational drug. ICF: informed consent form. BCVA: best-corrected visual acuity.

3.5 Randomization

As this is an open, non-comparative study, randomization of subjects entering the study is not necessary.

3.6 Subject code assignment

After verifying the inclusion/exclusion criteria, eligible subjects will be identified by a number and their initials.

The initials of the subject of study will be obtained starting with the first letter of the name, followed by the first letter of the first surname and the first letter of the second surname, obtaining a maximum of three letters. In case the person has two names or a compound surname, the first letter will always be used.

Example:

TO. Arieh Daniel Mercado Carrizalez	B. Juan De la Torre Orozco
to. Initials: AMC	b. Initials: JDO

Once the subject has been selected, they will be assigned a number that will identify them throughout the study. This code will consist of eight numbers in the following order from left to right:

- three digits of the molecule under study according to the sponsor's name.
- two digits corresponding to the research center number.
- three digits of the consecutive number assigned to its inclusion in the research center.

Example:

185-01-001

4. Sample Size Calculation

The sample size calculation was based on the study's primary objective: to evaluate the safety and tolerability of PRO-185 ophthalmic solution (naphazoline hydrochloride 0.03%) in ophthalmologically healthy subjects. To meet the study's primary objective, 22 subjects are estimated to contribute OA to the study.

4.1 Calculation methodology

A search was carried out in the open access search engines PubMed (pubmed.ncbi.nlm.nih.gov) and Web of Science (webofscience.com), finding until May 2021, 102 results in PubMed and 24 in Web of Science that matched the keywords of

Search: *"Naphazoline Ophthalmic".* The extract was generated from this search, and the integrated database was reviewed to eliminate duplicate matches and filter out those articles that were consistent with the study objective. After reviewing the *abstracts* (available only in 89 articles), 7 articles were selected for full-text review. Of these, 5 articles were selected to make the sample size proposal.
[2, 3, 4, 5], one of them is a review article [6], this was used only as a reference (see Annex 9.1).

The mean ± standard deviation (SD) sample size used in the selected studies was 24.4 ± 21.24 subjects (range 6–60). Considering a 10% proportion in the incidence of AEs, these values were entered into an online tool [7] to estimate the sample size and power, following the specific equations for the calculation [8].
Finally, the calculated value was increased by 20% to account for possible losses.

4.2 Proposal

PRO-185 ophthalmic solution is expected to present in less than 10% of subjects any of the following AEs: increased IOP (>5 mmHg), heart rate changes (>15 bpm), increased systemic blood pressure (>15 mmHg in SBP or >10 mmHg in DBP), pharmacological mydriasis or grade 3 and 4 conjunctival hyperemia, 20 minutes after its application with respect to its initial value.

The sample size was calculated using the equation for a non-superiority proportion [8].
This equation is useful for non-inferiority/superiority testing, if we want to test whether a proportion (p) is not superior to a reference value, p0. The idea is that statistically significant differences between the proportion and the reference value cannot be of interest unless the difference is greater than a threshold ÿ (10% in this case). This type of calculation is useful in clinical studies where the value of ÿ is chosen based on clinical judgment and subject matter expertise (see Appendix 9.1).

The hypothesis test is:

$$H_0: p - p_0 \leq \delta$$
$$H_1: p - p_0 > \delta$$

Equations

The calculation to estimate the sample size and power was performed using an online tool and following the equations [8]:

$$n = p(1-p)\left(\frac{z_{1-\alpha} + z_{1-\beta}}{p - p_0 - \delta}\right)^2$$

$$1 - \beta = \Phi(z - z_{1-\alpha}) + \Phi(-z - z_{1-\alpha}), z = \frac{p - p_0 - \delta}{\sqrt{\frac{1-p}{n}}}$$

Where:

n is the sample size,

p0 is the reference value,

Φ is the function of the standard normal distribution,

Φ^{-1} is the function of the standard normal distribution,

α is the Type I error,

β is the Type II error, which means that, 1-ÿ is the power, and

δ is the test margin.

According to the previous calculation, 18 subjects are estimated per treatment arm. Considering potential losses, the estimate increases by 20%. This estimate is consistent with the average number of subjects used in the clinical studies reviewed in the PubMed and Web of Science searches (24 subjects).

5. Clinical Data Management

Clinical data management (CDM) enables the generation of high-quality, reliable, and statistically valuable data. CDM is the process of collecting, cleaning, and managing subject information in a study in compliance with regulatory standards (21 CFR Part 11, ICH, and GCP guidelines). It encompasses eCRF design, eCRF commenting, database design, *data entry , source document verification (SDV),* discrepancy management (queries), medical *coding, soft lock,* and hard lock *[9].*

In accordance with roles and responsibilities, multiple users can be created, whose access types to the eCRF can be limited to data entry (principal investigator, PI), medical coding, database design, or quality control *(QC)* [9, 10]. Discrepancy handling
will be performed based on the flow in Figure 2.

The CDM team will include the following roles:

- Data Manager,
- Database designer/programmer,
- Clinical coder *(Medical coder),*
- Clinical data coordinator,
- Quality control, and
- Capturist *(data entry associate).*

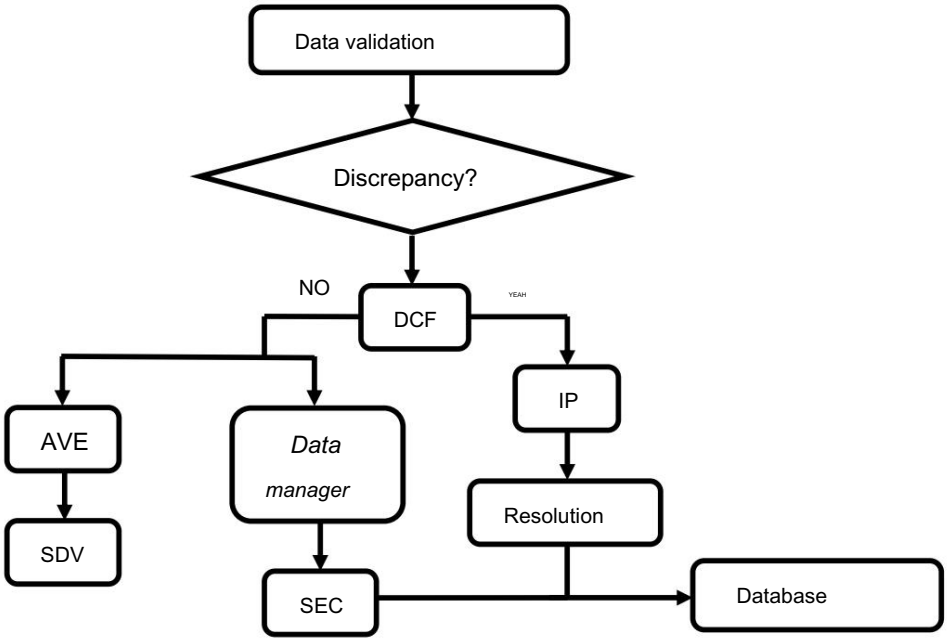

Figure 2. Discrepancy management (DCF, medical note; CRA, clinical monitor; SEC, self-evident correction) [9]

6. Statistical Methodology

The PAE was developed considering the evaluation criteria described in the study protocol.

Statistical analysis will be performed by personnel from Laboratorios Sophia, SA de CV. The SPSS statistical package version 19.0 for Windows (IBM Corporation, Armonk, NY, USA) will be used. Coding will be performed using consecutive numbers. Data will be collected and organized in an Excel spreadsheet (Microsoft® Office). The data will then be exported to the SPSS package platform. Variables will be categorized according to their nature (see Table 2). The statistical tests used will follow the corresponding assumptions for nonparametric statistics.

Table 2. Operational Definition of the Variables

Variable	Conceptual Definition	Operational Definition	Type of measurement	Value of reference	Proof statistics
Pressure Intraocular	Tonometry is the objective measurement of IOP, based on the force required to flatten the cornea or the degree of corneal indentation produced by a fixed force.	By means of tonometry Goldmann based on the Imberk-Fick principle.	Quantitative discreet	10 – 21 mmHg	Kolmogorov-Smirnov or U Mann's Whitney*
Heart rate	The pulse is a measurement of the FC, that is, the amount of	For each heartbeat, the left ventricle contracts and expels blood into the heart.	Discrete quantitative	60 – 100 bpm	Kolmogorov-Smirnov or U

Variable	Conceptual Definition	Operational Definition	Type of measurement	Reference value	Statistical test
	times the heart beats per minute.	of the aorta. This forceful expulsion of blood creates a wave that is transmitted to the periphery of the body through the arteries. Measured with a electronic or manual blood pressure monitor.			Mann's Whitney*
Pressure systemic arterial	It is the force exerted by blood against the walls of the arteries. SBP is the pressure inside the artery when the heart contracts and pumps blood through the body; while DBP is the pressure inside the artery when the heart is in resting and filling with blood.	Measure with a blood pressure monitor and a stethoscope.	Discrete quantitative	PAS: 120 – 139 mmHg PAD: 80 – 89 mmHg	Kolmogorov-Smirnov or Mann U Whitney*
Diameter pupillary	The natural pupil of the human eye is usually approximately circular, for a given subject, the pattern of aberrations, diffraction, depth of field and retinal illumination depend on the pupil diameter, which in turn varies depending on the ambient lighting.	The pupillary diameter results from the balance between the sphincter muscle of the pupil and the radial fibers of the iris that have only innervation autonomous [11].	Quantitative continues	2 – 6 mm	Kolmogorov-Smirnov or U Mann's Whitney*
Conjunctival hyperemia	It is defined as the simplest reaction of the conjunctiva to a stimulus, a red appearance secondary to the vasodilation of the vessels is observed. the conjunctiva of variable intensity.	Direct observation. Classification by Efron scale (see Annex 9.2).	Qualitative ordinal	Degrees: 0= Normal 1= Very mild 2= Mild 3= Moderate 4= Severe	Pearson's X^2 or Exact of Fisher*
Changes in the AVMC	Spatial visual acuity is the ability to distinguish separate elements of an object and identify them as a whole. It is quantified as the minimum angle of separation (located at the nodal point of the eye) between two objects that allows them to be perceived as separate objects.	Snellen chart	Continuous quantitative	0.6 to 2.0	Kolmogorov-Smirnov or U Mann's Whitney*
Changes in Corneal and conjunctival TVL	Detection of epithelial defects in the cornea and conjunctiva.	Direct observation with slit lamp, it will be graded according to the SICCA (see Annex 9.3) [12].	Discrete quantitative	0 to 6	Kolmogorov-Smirnov or U Mann's Whitney*
Changes in Corneal and conjunctival TF	Detection of epithelial defects in the cornea and conjunctiva.	Direct observation with slit lamp, will be graded according to the SICCA (see Annex 9.3) [12].	Quantitative discreet	0 to 6	Kolmogorov-Smirnov or U

Variable	Conceptual Definition	Operational Definition	Type of measurement	Reference value	Statistical test
					Mann's Whitney*
Incidence of Chemosis	It is conjunctival edema, the result of an inflammatory reaction. It is classified as present or absent.	The evaluator will use a narrow beam of light at 60° and measure whether the conjunctiva separates by ÿ1/3 of the entire eyelid opening or if it extends beyond the gray line.	Nominal qualitative	Present / Absent	McNemar
Incidence of EA	Any adverse medical event that occurs in a patient or clinical research subject who has been administered a pharmaceutical product and that does not necessarily have a causal relationship with it. treatment [13].	All AEs will be reported (according to the protocol) and not only those where the PI suspects a causal relationship with the treatments	• Quantitative discreet • Nominal qualitative	• Incidence • Seriousness (gravity) • Causality	• Mann University Whitney • *X* 2 of Pearson or Exact of Fisher*
Frequency respiratory	The process involves inspiration and expiration, diffusion of oxygen from the pulmonary alveoli to the blood and carbon dioxide from the blood to the alveoli, and the transport of oxygen to body tissues and organs.	The FR is the amount of breaths a person takes per minute at rest.	Quantitative discreet	12 – 16 rpm	Kolmogorov-Smirnov or U Mann's Whitney*
Body temperature	clinical parameter that reflects the physiological state of the organism. It is the balance between heat produced and heat lost.	Degree of heat or cold, expressed in terms of a specific scale, using a thermometer.	Quantitative continues	36.7 – 37.4°C	Kolmogorov-Smirnov or U Mann's Whitney*

Abbreviations: BCVA, best-corrected visual acuity; AE, adverse event; HR, heart rate; RR, respiratory rate; PI, principal investigator; bpm, beats per minute; DBP, diastolic blood pressure; SBP, systolic blood pressure; IOP, intraocular pressure; rpm, breaths per minute; TF, fluorescein staining; TVL, lissamine green staining; X 2 , Chi-square.
*When applicable.

6.1 Population analysis

Statistical analysis will be presented to give an overall summary of the subjects entered into the study and an overview of the safety and tolerability of its results. The data provided by the research site will be summarized for this purpose, according to their nature. The Shapiro-Wilk test will be performed to determine whether the quantitative data are normally distributed.

The results of the quantitative variables will be presented in measures of central tendency: mean, standard deviation, maximum and minimum. The changes in pupil diameter, BCVA, and in the Body temperature will be expressed as continuous variables. Changes in IOP, HR, systemic blood pressure, TVL, and TF will be expressed as discrete variables.

The results of nominal and ordinal qualitative variables will be presented as frequencies, proportions, and/or percentages. For these, 2 x 2 frequency tables will be constructed. All percentages will be presented with one decimal place.

The level of difference considered significant will be an alpha (ÿ) of 0.05 or less. The triangulation between the type of variable and the measurements is shown in Table 3.

Table 3. Triangulation of concepts [1]

Variable type	Variable	A1 A2 B1	B2 C1	C2 C3 C4 D1 D2 D3 D4	E1	E2
Selection						
A1	Demographics	DT				
A2	Medical history/Selection criteria	DT				
Basal						
B1	Vital signs	B B	B	B B T	TM	
B2	Assessment comprehensive ophthalmological	DTB	TB B			
Security						
C1	PIO		B B		TM	
C2	HR, SBP, DBP	B		B	TM	
C3	Pupillary diameter		B	B	TM	
C4	Conjunctival hyperemia		T	T	T	
Secondary Safety Outcome						
D1	AVMC		B	B	TM	
D2	Corneal and conjunctival stains		B	B	TM	
D3	Chemosis		T	T	T	
D4	Incidence of AE	TM TM TM TM TM T TM TM T TM TM TM				
Exploratory						
E1	FR	B			TM B	
E2	Body temperature	B			TM	B

Abbreviations: BCVA, best-corrected visual acuity; B, bivariate analysis; D, descriptive statistics; AE, adverse event; HR, heart rate; RR, respiratory rate; M, multivariate analysis; DBP, diastolic blood pressure; SBP, systolic blood pressure; IOP, intraocular pressure; T, 2x2 contingency table.

6.2 Safety & Tolerability Analysis

6.2.1 Analysis for primary variables

The analysis of safety and tolerability outcomes will be conducted in the safety population, defined as all subjects who received at least one dose of the investigational product (PRO-185), regardless of their adherence to the protocol (intention-to-treat, ITT, population).

Statistical analysis for quantitative primary variables will be estimated using the Kolmogorov-Smirnov statistic for the difference in measurements, once the values have been adjusted for baseline within each individual. Where applicable, the nonparametric Mann-Whitney U test will be used.

conjunctival hyperemia, the X test will be used 2 Pearson or Fisher exact values For expected under 5.

6.2.2 Analysis for secondary variables

For the analysis of these variables, the same primary analysis will be performed as long as the necessary measurements are available.

6.3 Exploratory analysis

The analysis of exploratory variables, FR and body temperature, will be performed on those subjects who complete their participation without deviations from the study protocol (per-protocol population, PP).

6.4 Other analyses

The final results report will be displayed in tables or graphs, as appropriate.

6.4.2 Procedure for handling missing data

An imputation procedure for missing data is not contemplated.

7. Change control

Newly created document, no changes apply.

Author of the document

8. Bibliography

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[3] Abelson MB, Allansmith MR, Friedlaender MH. Effects of topically applied ocular decongestant and antihistamine. Am J Ophthalmol, 1980;90(2): 254-7.

[4] Abelson MB, Butrus SI, Weston JH, Rosner B. Tolerance and absence of rebound vasodilation following topical ocular decongestant usage. Ophthalmology, 1984; 91(11): 1364-7.

[5] Nayak BK, Kishore K, Gupta SK. Evaluation of oxymetazoline and naphazoline in benign red eyes: a double blind comparative clinical trial. Indian J Ophthalmol, 1987; 35(4): 190-3.

[6] Hosten LO, Snyder C. Over-the-Counter Ocular Decongestants in the United States - Mechanisms of Action and Clinical Utility for Management of Ocular Redness. Clin Optom (Auckl), 2020; 12: 95-105.

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[11] Leon-Sarmiento F, Prada DG, Gutiérrez C. Pupil, pupillometry and pupilography. *Beurol Colomb Act,* 2008; 24: 188-97.

[12] Whitcher JP, Shiboski CH, Shiboski SC, Heidenreich AM, Kitagawa K, Zhang S, Hamann S, Larkin G, McNamara NA, Greenspan JS, Daniels TE; Sjögren's International Collaborative Clinical Alliance Research Groups. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's Syndrome International Registry. Am J Ophthalmol, 2010; 149(3): 405-15.

[13] Mexican Official Standard, *NOM-220-SSA1-2016, Pharmacovigilance Facilities and Operations,* CDMX: Official Gazette of the Federation, 2017.

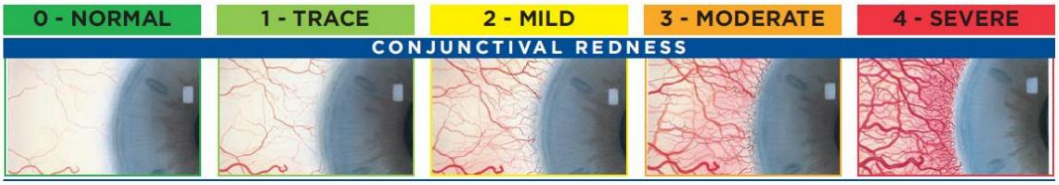
9. Annexes

9.1 Review of Articles for sample size calculation, PRO-185 (Naphazoline Hydrochloride 0.03%)

Reference	Summary	Subjects	Treatment
Hurwitz P, Thompson JM. Uses of naphazoline (privine®) in ophthalmology. Arch Ophthal. 1950; 43(4): 712-7. doi: 10.1001/archopht.1950.00910010723008.	Naphazoline hydrochloride has been widely used as a nasal decongestant. Considering its potential uses as an ocular decongestant, it was decided to evaluate its properties in certain clinical conditions. A series of experiments were conducted to evaluate the effects of naphazoline on intraocular pressure, pupillary size, and the accommodation and condition of ocular blood vessels in 60 patients (both eyes). The 0.1% naphazoline solution was well tolerated by the eye. A mild to moderate burning sensation was experienced after instillation. Occasionally, itching occurred, and some patients with lightly pigmented irides reported blurred vision. transitory.	60	Naphazoline 0.1%
Abelson MB, Allansmith MR, Friedlaender MH. Effects of topically applied ocular decongestant and antihistamine. Am J Ophthalmol. 1980; 90(2): 254-7.	In two independent studies involving 25 subjects each, 0.05% naphazoline produced significant whitening of histamine-induced red eyes and ocular itching (but did not prevent itching). Antazoline significantly inhibited itching (but not red eyes). The combination of naphazoline and antazoline produced significant whitening and inhibition of itching in all histamine-challenged eyes. The combination of both drugs was more effective than either component individually in preventing redness. The antihistamine/vasoconstrictor combination was equally effective for itching.	25	Naphazoline 0.05%
Abelson MB, Butrus SI, Weston JH, Rosner B. Tolerance and absence of rebound vasodilation following topical ocular decongestant usage. Ophthalmology. 1984; 91(11): 1364-7. doi: 10.1016/s0161-6420(84)34140-9.	Two commercial preparations of topical ophthalmic vasoconstrictors were evaluated for their bleaching ability, duration of action, tolerability, and rebound vasodilation in 11 healthy volunteers. Both treatments, naphazoline hydrochloride 0.02% and tetrahydrozoline hydrochloride 0.05%, significantly decreased initial redness after a single application (Part I); however, naphazoline produced significantly more bleaching than tetrahydrozoline. Only naphazoline maintained bleaching after 10 days (Part II). The level of redness remained significant after baseline for 8 hours after a single instillation for both vasoconstrictors and for 6 hours after multiple administrations of naphazoline. The decrease in tetrahydrozoline's effectiveness after the 10-day study period may encourage its overuse. No vasoconstrictor produced rebound vasodilation after discontinuation.	11	Naphazoline 0.02%
Nayak BK, Kishore K, Gupta SK. Evaluation of oxymetazoline and naphazoline in benign red eyes: a double blind comparative clinical trial. Indian J Ophthalmol. 1987; 35(4): 190-3.	The efficacy of oxymetazoline and naphazoline (0.01%) was evaluated in 20 patients with red eye. The decongestive action of oxymetazoline 0.01% on days 3 and 7 was 66.66% and 80.55% compared to 22.22% and 50% for naphazoline 0.01%.	20	Naphazoline 0.01%

	0.01%. A significant improvement in conjunctival symptoms such as itching, foreign body sensation, tearing, and burning was observed with oxymetazoline compared with naphazoline. No ocular toxicity or AEs were observed during the study.		
Hosten LO, Snyder C. Over-the-Counter Ocular Decongestants in the United States - Mechanisms of Action and Clinical Utility for Management of Ocular Redness. Clinical Optometry, 2020; 12: 95 – 105.	This review provides a current, clinically relevant summary of the mechanism of action, efficacy, and safety of available OCT decongestants for the reduction of ocular redness caused by minor irritations. Currently, the OCT products marketed in the US include tetrahydrozoline 0.05%, naphazoline 0.012% to 0.03%, and brimonidine 0.025%. All 3 agents are adrenergic receptor agonists but vary in their receptor-binding properties: tetrahydrozoline is a selective ÿ1-adrenergic receptor agonist, naphazoline is a combination ÿ1/ÿ2 receptor agonist, and brimonidine is a selective ÿ2 receptor agonist. These OCT decongestants produce vasoconstriction of conjunctival blood vessels, resulting in a rapid reduction of ocular redness. In general, reported ocular AEs are minimal, mild, and transient, with no significant systemic AEs. However, ocular decongestants with ÿ1-adrenergic receptor agonist activity have been associated with loss of effectiveness after continued use (tachyphylaxis) and rebound redness upon discontinuation. In clinical studies, brimonidine has not been associated with tachyphylaxis, and rebound redness has been rarely reported.	146	Naphazoline 0.012 to 0.03%

9.2 Efron scale for conjunctival hyperemia



9.3 SICCA Ocular Staining Score (modified from Whitcher et al, 2010) [12].

Score by staining pattern:

	Lissamine green (conjunctiva only) Grade Points	Fluorescein (cornea only) Grade Points
0	0-9	0
1	10-32	1-5
2	33-100	6-30
3	>100	>30

Additional points for fluorescein staining only:

+1 if there are patches of confluent staining

+1 if there is staining in the pupillary area

+1 if there are filaments