Excelencia en oftálmicos

Protocol for the study:

SOPH172-0919/I

Title: Phase I clinical study to evaluate the safety and tolerability of the PRO-172 ophthalmic solution, developed by Laboratorios Sophia, SA de CV, on the ocular surface of clinically healthy subjects.

Information on the molecule under study

Generic name: Bepotastine 1.5%
Distinctive name: PRO-172

Indication: Allergic conjunctivitis

Protocol information
Phase of the study: I
Version: 2.0
Version date: Nov 11, 2019

This protocol has been carried out in accordance with the principles of the Declaration of Helsinki and will be carried out in accordance with the Good
Clinical Practices and in compliance with ICH guidelines and current local legislation Study information

Sponsor: Sophia Laboratories, SA de CV

Changelog

Changes from version 1.0, dated September 23, 2019, to version 2.0, dated November 11, 2019

1. Page 57, first paragraph. The CIOMS reference has been updated from 2002 to 2016.
2. Page 60, third paragraph. The paragraph is deleted: In the event that a subject is illiterate, acceptance will be with your fingerprint, and in the event that the subject is not able to grant a adequate written informed consent, a representative of the subject “legally “authorized” may provide such consent by the subject in accordance with the laws and applicable regulations.

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Study leaders

The administrative structure of the sponsoring party, corresponding to Laboratorios Sophia, SA de CV

is shown in ***Table 1. Those responsible for the study***

Function	Name/Contact	Affiliation ¥
Medical Director of the study	[redacted]	Medical Director
Director of the study		Operations Manager Clinics
Team of Development Clinical		Medical Editor
Team of Development Clinical		Safety Pharmacologist Clinic
Team of Development Clinical		Biostatistics

¥ Employees of Laboratorios Sophia, SA de CV Av. Paseo del Norte No. 5255, Col. Guadalajara Technology Park, Carretera Guadalajara-Nogales Km13.5 CP 45010 Zapopan, Jalisco, Mexico Tel +52(33) 3000 4200

Table 1. Study leaders

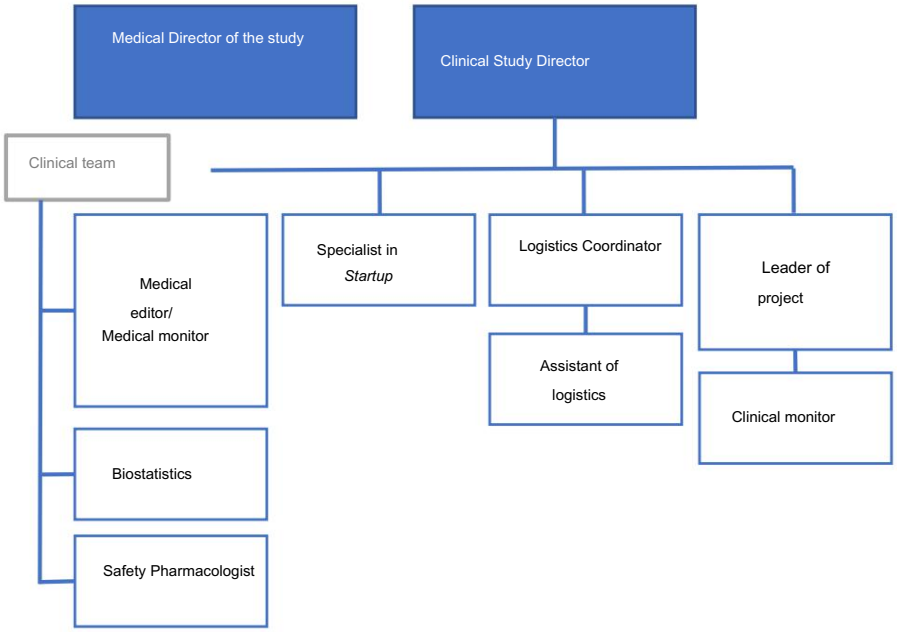


Figure 1. Administrative structure

Signature pages

From the sponsor

[redacted]

[redacted]

[redacted]

Researcher Agreement

I agree to conduct this clinical study according to the design and guidelines of this protocol, in compliance with the provisions of this protocol and in adherence to the accepted standards of Good Clinical Practices.

I agree to report all information or data in accordance with the provisions of the protocol, in particular, any adverse event. Also, I agree to handle clinical supplies, provided by the sponsor, strictly in accordance with this protocol.

I understand that the information that identifies me may be used by the sponsor. Because the information contained in this protocol and the Researcher's Manual is confidential, I understand that it is prohibited from sharing it with any third party, who is not involved in the approval, supervision or conducting the study. I will ensure that necessary precautions are taken to protect the information of loss, inadvertent disclosure or access by unauthorized third parties.

List of abbreviations

NSAIDs	Nonsteroidal anti-inflammatory drugs
AVcc	Visual acuity with correction
CEI	Research Ethics Committee
COFEPRIS	Federal Commission for the Protection against Sanitary Risks
IUD	Intrauterine device
EA	Adverse event
eCRF	Electronic Case Report *Form*
FCI	Informed consent form
FDA	United States Food and Drug Administration
IC	Confidence interval
IP	Principal Investigator
OD	Right eye
WHO	World Health Organization
YOU	Left eye
OU	Both eyes
PNA	Unanticipated problems
PI	Research products
QID	Four times a day
RAC	Conjunctival allergen challenge
RNEC	National Registry of Clinical Trials

1. Summary

1.1 Synopsis

<table>
<tr><td colspan="2">Title of the study:

Phase I clinical study, to evaluate the safety and tolerability of the PRO-172 ophthalmic solution, prepared
by Laboratorios Sophia, SA de CV on the ocular surface of clinically healthy subjects.</td></tr>
<tr><td>Study number:

SOPH172-0919/I</td><td>Creation date:

September 23, 2019</td></tr>
<tr><td>Protocol version:

2.0</td><td>Version date:

November 11, 2019</td></tr>
<tr><td>Therapeutic indication:

Antihistamine</td><td>Use:

Allergic conjunctivitis</td></tr>
<tr><td>Estimated duration of the study (from the first visit of the first patient to the preparation of the final report):
5 months</td><td>Clinical development phase: I</td></tr>
<tr><td colspan="2">Goals:

Main objective:

• Evaluate the safety and tolerability of the PRO-172 formulation manufactured by Sophia Laboratories SA de CV on the ocular surface of clinically healthy subjects.

Specific objectives:

• To evaluate the safety of PRO-172 ophthalmic solution through the incidence of events unexpected adverse events (AEs) related to the investigational product.

• To evaluate the tolerability of PRO-172 ophthalmic solution by means of the Index score Ocular Comfort (OC)</td></tr>
<tr><td colspan="2">Hypothesis:

H0= The PRO-172 ophthalmic solution is safe and tolerable in its ophthalmic application as it presents in less
10% of the study population experienced unexpected adverse events related to the product
investigation.</td></tr>
</table>

H1= PRO-172 ophthalmic solution is not safe and tolerable for ophthalmic application as it presents in more than 10% of the study population experienced unexpected adverse events related to the product investigation.

Study design:

Phase I clinical study, controlled, non-comparative, open, single-center.

Number of subjects (planned and analyzed):

Number of planned subjects: 22 evaluable subjects (both eyes)

Diagnosis and main inclusion criteria:

- Healthy subjects.

Selection criteria:

Inclusion criteria:

- Be clinically healthy.
- Have the capacity to voluntarily grant signed informed consent.
- Be able and willing to comply with scheduled visits, treatment plan, and other study procedures.
- Be between 18 and 45 years old.
- Women of childbearing potential must ensure continued use (started ÿ 30 days prior to signing the ICF) of a hormonal contraceptive method or intrauterine device (IUD) during the study period.
- Have corrected visual acuity (CCVA) of 20/30 or better in both eyes.
- Have vital signs within normal parameters.
- Have an intraocular pressure ÿ10 and ÿ 21 mmHg.

Exclusion criteria:

- Be a user of topical ophthalmic products of any kind.
- Being a user of medications or herbal products, by any other route of administration.
- For women: be pregnant, breastfeeding, or planning to become pregnant during the study period.
- Have participated in clinical research studies 90 days prior to inclusion in this study study.
- Have previously participated in this same study.
- Be a contact lens user who cannot discontinue use during the study.
- That they cannot follow lifestyle considerations.
- Having started using hormonal contraceptives or IUDs 30 days prior to inclusion in the present study.
- Have a history of any chronic-degenerative disease.
- Present inflammatory or infectious disease, active at the time of entering the study.
- Present unresolved injuries or traumas at the time of entering the study.
- Have a history of any type of eye surgery.
- Have undergone non-ophthalmological surgical procedures in the last 3 months.

Research Product (RP):

- PRO-172. Bepotastine 1.5% Ophthalmic Solution. Laboratorios Sophia, SA de CV Zapopan, Jalisco, Mexico.
- Dosage: 1 drop 4 times a day.
- Route of administration: Ophthalmic.

Duration of treatment:	**Subject's duration in the study:**
7 days	10 days

Evaluation criteria:

Primary outcome variables

- Incidence of unexpected AEs related to the investigational product. (Evaluation Time [ET]: days 8 and 10)

- ICO score (TE: day 8).

Secondary outcome variables:

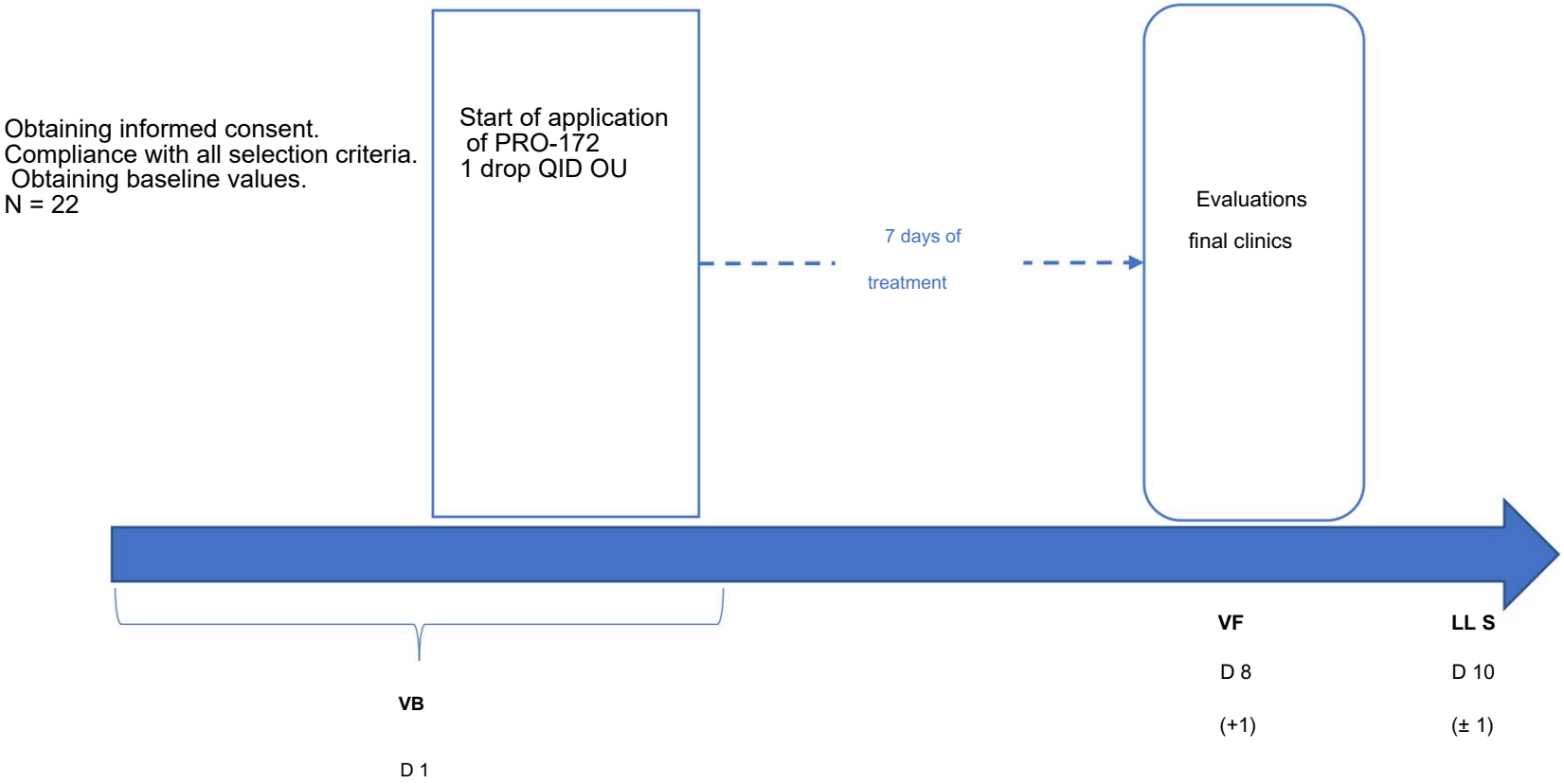
- Changes in Corrected Visual Acuity (CCVA) (TE: day 8).
- Changes in corneal and conjunctival staining with lissamine green (TE: day 8).
- Corneal and conjunctival staining changes with fluorescein (TE: day 8).
- Conjunctival hyperemia changes (TE: day 8).
- Incidence of chemosis (TE: day 8).

Statistical methodology

Data will be expressed using measures of central tendency: mean and standard deviation for quantitative variables. Qualitative variables will be presented as frequencies and percentages. Statistical analysis will be performed using the Wilcoxon rank test for quantitative variables. Differences between qualitative variables will be analyzed using the X2 (Chi-square) test or Fisher's exact test.

An $\alpha \leq 0.05$ will be considered significant.

1.2 Study diagram



VB=baseline visit, VF=final visit. Evaluation of final outcome variables., LI S=safety call., QID=Four times a day, OU=both eyes

In parentheses () is the allowed window period.

1.3 Study schedule

Procedures	VB **D 1**	VF **D 8 A +1**	LIS **D 10 ± 1**
FCI Signature	X		
Medical record	X		
Drug Evaluation Concomitant	X	X	
Urine pregnancy test	X	X	
Vital signs	X	X	
AVcc	X	X	
Integrity of the ocular surface (Staining and evaluation of conjunctival hyperemia and chemosis)	X	X	
Comprehensive ophthalmological evaluation	X	X	
PIO	X	X	
Eligibility criteria	X		
EA Assessment	X	X	X
Research Product Assignment (PI)	X		
Eye Comfort Index	X	X	
Delivery of the PI and start of intervention	X		
Delivery of the subject's diary	X		
Adherence assessment		X	
Return/Evaluation of the Subject's Diary		X	
Return of PI		X	

2. Introduction and Background

2.1 Theoretical framework

Allergic conjunctivitis is a pathology that presents with symptoms similar to infectious conjunctivitis: itching, Hyperemia, tearing, chemosis, and discharge are among the most common. They differ in etiology and management pharmacological. However, the common pathophysiological mechanism is the release of histamine by the mast cells and basophils with activation of central and peripheral receptors. [1, 2]

There are 4 types of histamine receptors: H1, H2, H3 and H4. They all belong to the family of receptors coupled to G proteins. [3, 4] The H1 receptor is the one that has the greatest participation in the immune response due to allergic processes. [3, 5] The binding of histamine to the H1 receptor generates the H1R complex, which It generates an increase in intracellular calcium, smooth muscle contraction and increased permeability. vascular. This physiological response generates hyperemia, itching and secretion. [1, 2] Despite the above, the Late responses appear to be unaffected by histamine, where cytokines have been implicated, interleukins (IL-5, IL-6, IL-8), prostaglandins and other inflammatory cells (eosinophils and lymphocytes). In addition, It can synergize with lipopolysaccharides and tumor necrosis factor alpha. If this response continues, will be released by eosinophils, cytotoxic proteins and cytokines that will perpetuate inflammation. [5, 6, 7]

The allergic inflammatory response provides an acute defense mechanism against toxins and infections. However, in allergic diseases, inflammation is activated inappropriately, which can cause structural damage to the affected tissue.[2]

Thus, allergic conjunctivitis is an abnormal inflammatory response of the conjunctiva to antigens of different origin. It can be classified as intermittent and persistent according to the presentation of the picture in a a specific time of year, although more precisely by the duration of the same. It is considered Persistent in cases where symptoms last longer than 4 weeks and intermittent in cases where symptoms last shorter than 4 weeks. to this period.[1]

The currently available treatment for allergic conjunctivitis can be non-pharmacological and pharmacological. The goal is to reduce associated symptoms. [8, 9]

Non-pharmacological treatment includes the use of ocular lubricants, physical aids, and hygiene measures.

Receiver	Characteristic function	General function
H1	Acute allergic reactions	Increases: • Itching • Pain • Vasodilation • Vascular permeability • Headache • Tachycardia • Bronchoconstriction • Stimulation of vagal afferent nerves in the airways
H2	Gastric acid secretion	Increases: • Gastric acid secretion • Vascular permeability • Headache • Tachycardia • Bronchodilation • Mucus production
H3	Modulation in neurotransmission	Prevents excessive bronchoconstriction, the itching is medium.
H4	Immunomodulator	Differentiation of myeloblasts and promyelocytes

Table 2. Function of histamine receptors.

Pharmacological treatment can be administered by different routes. The main therapies used are:

a) Corticosteroids
b) Topical decongestants
c) Systemic antihistamines
d) Topical antihistamines
e) Mast cell stabilizers
f) Non-steroidal anti-inflammatory drugs

The most effective treatment is corticosteroids, however, due to their adverse effects, Use is limited to severe or persistent cases. Despite the above, topical antihistamines are the most commonly used drugs and those with the greatest scientific evidence of their effectiveness for the treatment of allergic conjunctivitis. [10]

In Mexico there is no exact data on the presentation of allergic conjunctivitis, however, it is estimated a 42% prevalence of allergic diseases, rhinitis, asthma and conjunctivitis in the central part of the country. This group represents an absence from work and school of approximately 3 to 12 days. It also means a

high cost for health institutions and affects the sector that suffers from it, since it is estimated that between 10-30% of the income per person is allocated to drug treatment. [11]

In the United States, 15 to 40% of the population is affected by this disease. In the United Kingdom, it represents 15% of general medicine consultations and an estimated annual cost of 1 billion euros. [12, 13]

In 2015, Castillo et al. concluded that antihistamines and mast cell stabilizers had the Greater evidence regarding efficacy in treating the symptoms of allergic conjunctivitis.[14]

Bepotastine besylate is a selective H1 receptor antagonist and mast cell stabilizer drug, Belonging to the antihistamine family. It was approved for the treatment of allergic conjunctivitis by the FDA in 2009, in addition to being authorized in other countries such as Japan and Argentina. In addition to this experience, since 2000, it has been marketed in Japan for oral administration. [15]

2.2 Background on bepotastine

2.2.1 Pharmacology of bepotastine

It is a drug used in the treatment of allergic responses, although it is specifically found approved for the treatment of the signs and symptoms of allergic conjunctivitis.[16][17][18] It is found Available for oral and topical ophthalmic administration. In the countries where it is marketed, it is regulated to be purchased under prescription, unlike other OTC antihistamines. [19, 20, 21]

The main differences with other drugs in the same class lie in the frequency of dosing, the onset of action, bioavailability and low presence of sedative effects. [8, 9, 10]

Its pharmacological effect on allergic conjunctivitis is due to several mechanisms:

1) Selective H1 receptor antagonist . [21]
2) Mast cell stabilizer. [22]
3) Suppression of eosinophil infiltration.[22]
4) Probable inhibition of IL-5 secretion by mononuclear cells and suppression of the leukotriene B4-dependent allergic response. [23, 24]

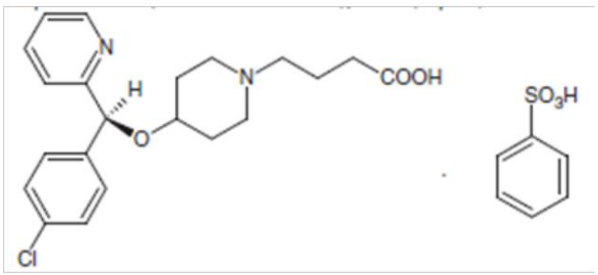


Figure 2. Chemical structure of bepotastine besylate

2.2.1.1 Pharmacokinetics in the eyeball

Route of administration: topical-ophthalmic.

Release: immediate.

Absorption: Highest concentrations appear after 1-2 hours of instillation. Cmax was 5.1 ± 2.5 ng/mL for 1% concentration and 7.3 ± 1.9 ng/mL for 1.5% concentration. This Cmax is three times lower than that reported for oral administration.

Distribution: Protein binding of approximately 55%. Low penetration into brain tissue. Has affinity reversible by melanin.

Metabolism: Minimal metabolism by enzymes of the cytochrome P450 pathway. In vitro studies have suggested a low interaction by microsomes CYP3A4, 2C9 and 2C19.

Elimination: The absorbed fraction is eliminated in the urine. However, the vast majority appears to be eliminated via the nasolacrimal route. After 24 hours of the last instillation, plasma concentrations are less than 2 ng/mL. It can also be eliminated by P-glycoprotein. [21] [25] [26] [27]

2.2.2 Efficacy of bepotastine

There are several clinical studies, reported in the literature, that demonstrate the efficacy of besilate Bepotastine 1.5%, in the treatment of symptoms and signs associated with allergic conjunctivitis. In these studies have been compared against placebo, Olopatadine and the same bepotastine, but in 1% concentration.

In the studies conducted by Abelson et al and Macejko et al, it was compared in an allergen challenge model conjunctival (RAC), the efficacy in reducing itching and conjunctival hyperemia of two concentrations of bepotastine (1% vs 1.5%), both were effective in reducing pruritus, however, although it was statistically significant decrease in conjunctival hyperemia, this was considered a reduction modest. [28, 16]

In a study conducted by Bergmann et al, they conducted two clinical studies, in which they compared the efficacy of bepotastine 1.5% vs placebo in a RAC model and determined that bepotastine significantly reduces Rapid and sustained, lasting up to 8 hours, itching. Other secondary signs of inflammation were also seen considerably decreased.[29]

2.2.3 Safety of bepotastine

Bepotastine besylate is an antihistamine with less sedation than other members of this class. pharmacological, due to its high selectivity for the H1 receptor (101 IC50nM) and its low activity on the H3.

In animal models, no respiratory or cardiological adverse events have been reported with the usual doses. Ophthalmic instillation has not generated histopathological and inflammatory changes in preclinical studies.

In healthy humans older than 3 years, no serious adverse events or deaths were reported following an application of 1 drop twice a day for 6 weeks. In addition, no changes in the number were reported endothelial cells, intraocular pressure, visual acuity and anterior and posterior segment structures.

The most common adverse event is dysgeusia.

It is categorized as C, because there is evidence of teratogenicity in animal models.
It is secreted in the breast milk of rats. However, this is unknown in humans.

Regarding carcinogenicity, it has not been reported after 2 years of exposure in rats and mice.

By oral administration the main adverse events that have been reported are:

- Drowsiness (59/4453 patients)
- Upper abdominal pain (6/4453 patients)
- Dry mouth (3 / 1153 patients)
- Facial edema and pharyngeal dryness (1/1153 patients)
- Urticaria (2/1316 patients) [21]

2.2.4 Summary of the pharmaceutical development of PRO-172

PRO-172 has been developed by Laboratorios Sophia, SA de CV. It has the physicochemical characterization and the accelerated and long-term stability protocol. A preclinical safety and toxicity in albino rabbits in New Zealand, with 60 days of application of PRO-172 BID. follow-up visits during the 60 days and a final visit, considered for the outcome variables. Safety variables included: conjunctival hyperemia, discharge, ocular surface staining, and incidence of adverse events; toxicity variables were histopathological changes in the cornea and conjunctiva. 172 was considered safe for ophthalmic application.

2.3 Background on the research

2.3.1 About the research question

Allergic conjunctivitis is an under-diagnosed disease because its clinical picture may be confused with other allergic pathologies. It affects 15 - 40% of the American population. [12] Decreases the quality of life and affects labor productivity, which has an important effect on increasing the cost for their treatment. In the United Kingdom, a decrease of 2.3 hours per week in the workday was reported occupational in patients with allergic conjunctivitis.[30]

The ideal treatment should be in accordance with the etiology and severity, however, it is important that it can be used concomitantly with other therapies, that is low cost, with a low event rate adverse effects, easy to access and easy to use by healthcare teams and patients.

The use of anhistamines in the treatment of allergic conjunctivitis blocks the H1 receptor of the histamine, decreasing the presentation of symptoms. Topical bepotastine is a treatment option, used in other countries, which has had few adverse events reported and a superior efficacy profile. other indicated pharmacological therapies.[19] .

2.3.2 From the development phase of the research product

As previously mentioned, ophthalmic formulations of bepotastine besilate are They are commercially available in Japan, the USA and Argentina, and therefore have clinical studies. and scientific evidence of its safety.

In addition, there is also evidence of its safety after oral administration of tablets. of bepotastine and nasal route of bepotastine nasal solution.

However, the PRO-172 formulation, developed by Laboratorios Sophia, SA de CV requires documentation its own safety and tolerability profile. No human studies have been previously conducted with this formulation, so the phase I clinical trial is indicated to evaluate said profile.

2.4 Risk-benefit assessment

2.4.1 Known potential risks

Bepotastine, as an active ingredient, has a known safety profile, already described in the literature, which which makes it a safe antihistamine. Its main expected adverse effects are dysgeusia, as well as heartburn. transient.

No other risks are anticipated with ophthalmic application of PRO-172.

2.4.2 Known potential benefits

In this phase of research, the known potential benefits of bepotastine, such as relief from Symptoms associated with allergic conjunctivitis will not be evaluated.

2.5 Problem statement

In the treatment of allergic conjunctivitis, the use of topical antihistamines has proven to be an option Effective in relieving symptoms. Bepotastine is an antihistamine whose efficacy and safety are known in different pharmacological formulations.

Laboratorios Sophia, SA de CV seeks to expand therapeutic options for symptom relief associated with allergic conjunctivitis. PRO-172 is a 1.5% bepotastine ophthalmic solution formulation for which we seek to know its clinical safety and tolerability profile.

2.6 Justification

The most widely used pharmacological therapy with the greatest scientific evidence is the receptor antagonists. histamine 1. However, in this therapeutic class there are differences due to their efficacy, risk of adverse events and pharmacokinetic and pharmacodynamic characteristics.

Bepotastine besilate 1.5%, developed by Laboratorios Sophia SA de CV, seeks to be an alternative to treatment for allergic conjunctivitis, based on the experience of its use in other populations. However, according to pharmacological development, it is required to document its safety profile and tolerability.

3. Objectives and hypotheses

3.1 Primary objective

To evaluate the safety and tolerability of the PRO-172 formulation manufactured by Laboratorios Sophia SA de CV on the ocular surface of clinically healthy subjects.

3.2 Specific objectives

- To evaluate the safety of PRO-172 ophthalmic solution through the incidence of adverse events (EA) unexpected adverse events related to the investigational product.

- To evaluate the tolerability of PRO-172 ophthalmic solution by means of the Index score Ocular Comfort (OC).

3.3 Secondary objectives

- To know the safety of the PRO-172 formulation manufactured by Laboratorios Sophia, SA de CV through changes in Avcc.

- To know the safety of the PRO-172 formulation manufactured by Laboratorios Sophia, SA de CV by changes in corneal and conjunctival staining with lissamine green.

- To know the safety of the PRO-172 formulation manufactured by Laboratorios Sophia, SA de CV by changes in corneal and conjunctival fluorescein staining.

- To know the safety of the PRO-172 formulation manufactured by Laboratorios Sophia, SA de CV through changes in conjunctival hyperemia.

- To know the safety of the PRO-172 formulation manufactured by Laboratorios Sophia, SA de CV by incidence of chemosis.

3.4 Hypothesis

3.4.1 Hypothesis

H0= The PRO-172 ophthalmic solution is safe and tolerable in its ophthalmic application as it presents in less than 10% of the study population unexpected adverse events related to the investigational product.

H1= PRO-172 ophthalmic solution is not safe and tolerable for ophthalmic application as it presents more than 10% of the study population unexpected adverse events related to the investigational product.

4. Study design

4.1 Design Overview

Phase I clinical trial, controlled, non-comparative, open, single-center

4.2 Justification of the study design

The study design (clinical trial) is considered the highest standard of quality in data when it comes to
seeks to explore the effect of an intervention. The pharmacological development phase (phase I) corresponds to the
The objective of the study is to evaluate safety and tolerability, so the intervention time is
short and the required sample size is smaller than that of an efficacy clinical trial. The presence of groups
parallels allows comparison between intervention groups on outcome variables.
Blinding was not considered for this study due to the characteristics of both products in
investigation

4.3 Expected duration

It is estimated that the total duration of the study, from the first visit of the first patient to the preparation of the final report, be it 5 months.

The planned recruitment period is 2 months. Considering that the proposed sample is 22 subjects,
The total average recruitment rate during the study should be no less than 0.37 subjects per day.

The approximate duration of each subject in the study is 10 days.

5. Study population

5.1 Eligibility criteria

5.1.1 Inclusion criteria

- Be clinically healthy
- Have the ability to voluntarily grant signed informed consent
- Be able and willing to comply with scheduled visits, treatment plan, and other study procedures

- Be between 18 and 45 years old.
- Women of childbearing potential must ensure continued use (started ÿ 30 days prior to signing the ICF) of a hormonal contraceptive method or intrauterine device (IUD) during the study period.

- Have corrected visual acuity of 20/30 or better in both eyes.
- Have vital signs within normal parameters.
- Have an intraocular pressure ÿ10 and ÿ 21 mmHg

5.1.2 Exclusion criteria

- Be a user of topical ophthalmic products of any kind.
- Being a user of medications or herbal products, by any other route of administration.
- In the case of women: being pregnant, breastfeeding or planning to become pregnant within of the study period.
- Have participated in clinical research studies 90 days prior to inclusion in this study study.
- Have previously participated in this same study.
- Be a contact lens user who cannot discontinue use during the study.
- That they cannot follow the lifestyle considerations described in section **5.3.**
- Having started using hormonal contraceptives or IUDs 30 days prior to inclusion in the present study.
- Have a history of any chronic-degenerative disease.
- Present inflammatory or infectious disease, active at the time of entering the study.
- Present unresolved injuries or traumas at the time of entering the study.
- Have a history of any type of eye surgery.
- Have undergone non-ophthalmological surgical procedures in the last 3 months.
- Be or have an immediate family member (e.g., spouse, parent/legal guardian, sibling, or child) who is a research site or sponsor staff member directly involved in this study.

5.2 Criteria for eliminating and replacing patients

- Withdrawal of the FCI letter.
- Presentation of a serious adverse event, whether or not related to the investigational product, which, in the opinion of the PI and/or sponsor, could affect the patient's ability to safely continue study procedures.

- Non-tolerability or hypersensitivity to any of the compounds used during the tests (fluorescein, lissamine green, tetracaine).

- Non-tolerability or hypersensitivity to any of the investigational drugs.

5.3 Lifestyle considerations

For the study, participants may need to modify some of their lifestyle activities.

to comply with the following:

- Refrain from smoking.
- Refrain from using electronic vaporizers.
- Avoid immersing yourself in water without eye protection *(goggles).*
- Avoid direct exposure to fans (including air conditioning vents) during activities that involve vision. 24 hours before your checkup visits.
- Maintain your sleep-wake cycle with which you enter the study.

5.4 Scrutiny failures

A screening failure is defined as those participants who agree to participate in the study,

giving their consent, but are not assigned to a treatment group, that is, they do not enter the

study. It is necessary to report at least the following information on counting errors:

- Demographic data.
- Details of the counting failure (specify whether due to eligibility criteria, which one, or some other reason for the failure).

- Presence of serious adverse events during the scrutiny.

The above is necessary to comply with the CONSORT *(Consolidated Standards of Reporting Trials)* guidelines for

the publication of results or to respond to potential questions from regulatory authorities.

Subjects who do not meet the eligibility criteria to participate in the study due to a factor

modifiable specific, could participate again in the scrutiny. The subjects in this case must

use the same initial counting number.

5.5 Recruitment and retention strategies

This is a Phase I study, which is planned to be conducted at one center. The selected center will be responsible.

from the recruitment of subjects.

The minimum expected recruitment rate is 0.37 subjects per day.

The duration of the subject's participation in the study is approximately 10 days, during which

You will only need to attend one visit after the baseline visit, so retention problems are not anticipated.

However, the subjects will be entitled to travel expenses for transportation and to carry out their visits.

Other strategies to improve subject retention include, but are not limited to:

- Clearly communicate the importance of the study and the benefits the population will obtain from its results.

- Make calls or send text messages to remind yourself of appointments or activities to do.
- Provide a printed calendar and ID card to remind you of upcoming appointments and activities, as well as their estimated duration.

- Offer flexible business hours.
- Systematic organization of the study procedures, so that the subject does not last longer than essential on your visit.
- Minimize subject waiting times.

All materials to be delivered to the subject or recruitment strategies implemented by the Centers will be submitted for approval by the relevant committees.

5.6 Procedure in case of loss of tracking

For this protocol, loss to follow-up is defined as those subjects who were randomized, who At some point they were active subjects in the study, but their final evaluation could not be completed.

In the event that the participating subject does not attend his appointment, the research center must make a call to find out the reason and will try to arrange a new appointment within the established window period or a unscheduled appointment. If an appointment cannot be made, the presence of a adverse events and reason for withdrawal from the study, as minimum data.

A loss to follow-up <10% is not considered to be a problem for the validity of the studies. results obtained. [31, 32]

5.7 Subject identification

Study subjects will be identified by a number and the initials of their name.

The initials of the study subject will be obtained by 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 If the person has two names or a compound surname, the first letter will always be used.

Example:

A. Arieh Daniel Mercado Carrizalez
a. Initials: AMC

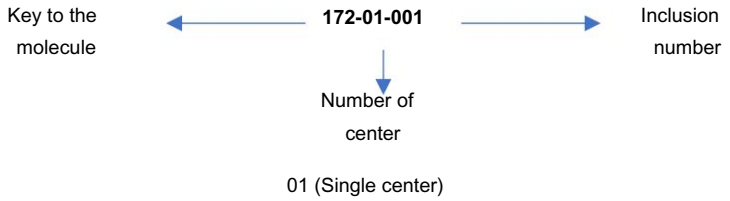
B. Juan De la Torre Orozco
b. Initials: JDO

At the screening stage (within the baseline visit) the participant number will be assigned to you in the form consecutive, using 3 consecutive digits. Once the subject has been selected, he or she will be assigned a number with which you will be identified throughout the study. This code will be made up of eight numbers in the following order from left to right:

- three digits of the molecule under study according to the name given by the sponsor.

• two digits corresponding to the research center number. • three digits of the consecutive number assigned to its inclusion in the research center.

Example:



6. Investigational product

6.1 Managed Products

6.1.1 Investigational Product

- Generic name: Bepotastine.
- Distinctive name: PRO-172.
- Active ingredients: Bepotastine besilate 1.5%.
- Pharmaceutical form: Ophthalmic solution.
- Presentation: multi-dose dropper bottle, 5 mL.
- Prepared by: Laboratorios Sophia, SA de CV
- Solution description: clear solution, free of visible particles.
- Packaging description: White bottle made of low-density polyethylene filled to 5mL.

6.1.2 Reference product

Non-comparative study.

6.1.2.1 Justification of the reference product

At this stage of the study, it is not essential to have a comparator. This is because the effects Side effects of ophthalmic formulations containing bepotastine have already been described in the literature. On the other hand, the primary objective is the search for unexpected AEs related to the PI, which does not justify using a comparator, the inclusion of a comparator would only mean greater exposure of healthy subjects to a drug.

6.1.3 Dose of the investigational product

One drop, both eyes (OU), four times a day, for 7 days.

Optimally, it is suggested to apply every 6 hours, however, it is not limiting. On days 2 to 7, every 4 hours is a reasonable spacing for subjects' waking period. On the basal day, one should consider space out applications as much as possible during the rest of the day.

There must be at least one hour between each application.

6.1.3.1 Justification of the dose

Published clinical studies of bepotastine evaluate efficacy and duration of action at 8 hours. Although 8 hours is still effective for controlling itching, the decrease in hyperemia has been less.
For this reason, and in order to evaluate a higher dosage in phase II, the aim is to evaluate the safety of the application 4 times a day.

6.2 Storage and handling of investigational products at the research center study

Delivery will be made through a courier service contracted by the sponsor, expressly selected for this purpose, to the address of the research center in accordance with the study plan.

The reception will be carried out by the assigned staff of the research team. They must verify the good condition of the primary packaging (box). If it shows alterations or defects in its integrity that from your judgment could have damaged the contents you must report it to the sponsor. If the package does not show significant defects will proceed to open it.

Inside you will need to find the receipt acknowledgment document and the temperature *data logger .* You must check that the recorded temperature complies with the specifications for transport and storage. It will verify the content (PI) with what is reported in the document. In case the document corresponds with The content will sign the receipt and send it to the sponsor. Otherwise, the sponsor will be notified.

Storage and safeguarding is the responsibility of the research center. The medication must be protected in a secure area with restricted access.

Storage temperature should be 2°C to 30°C.

The research center is required to record, in the designated format, the recorded temperature in the *data logger,* every day while the protocol is in force and has PIs. Said data They will be reviewed by the clinical monitor according to the record in the *data logger.*

In case of loss of material, this must be documented in the log of entries and exits along with a clear description of the mechanism by which the loss occurred.

Upon completion of the protocol, all study material will be recovered by the sponsor as part of the closing audit. The final delivery of material will be made by the principal investigator (PI) or the person designated by the latter for delivery of material at the end of the study.

Sponsor reserves the right to initiate civil and criminal actions against IP in case of failure to comply with undocumented material at the end of the study.

6.3 Concomitant treatments and medications not authorized during the study

The use of concomitant medications by any route of administration will not be permitted during the intervention period. Except as specified for the study procedures and the use of Hormonal contraceptives in women of childbearing age. The purpose of this restriction is to avoid interactions pharmacological agents that could alter the results of the variables evaluated.

Permitted medications:

- Ophthalmic:
  or Tetracaine 0.5%
  o Tropicamide 0.8% / Phenylephrine 5%

6.4 Procedure for monitoring and measuring adherence

For over four decades, there has been extensive research on the proper way to measure and quantify adherence to medications, however none has reached a consensus to establish as the gold standard, both in cross-sectional and longitudinal studies.[33][34][35][36][37][38][39] [40]

There are different procedures for measuring adherence to pharmacological interventions. The most common procedure involves self-reports, these include: patient interviews, Self-monitoring questionnaires and diaries. Their strengths are speed, flexibility, low cost, and ease of use. implementation; they have a high degree of specificity for non-adherence, however, the sensitivity and Reliability for adherence is low.[40][41]

Biochemical measurement of the drug, or its metabolite, is one of the methods that best confirms way the use of the drug. However, in addition to raising costs and being impractical, it is of little usefulness in the context of ophthalmic applications, since concentrations at the peripheral level could be undetectable; and samples from other tissues involve more invasive methods that would not be advisable. [40]

Medication counting is another way to measure adherence. Classically referred to as “medication count,” “pills” in ophthalmology translates to the weight of the bottle. This is a simple, inexpensive, and noninvasive method. The main disadvantages of this method are: 1. The application of the drug cannot be confirmed (could have been intentionally shot or instilled outside the eye) and 2. It depends on the subject bringing return the medicine.[40][41]

The approach with multiple adherence measurement procedures is recommended. Because it is not There is no ideal adherence measurement, it is appropriate to use more than one method when attempting to achieve results that resemble reality. Selecting two or more methods allows them to compensate each other their strengths and weaknesses, to more accurately capture adherence levels.[39]

The evaluation of the adhesion will be favored by means of the weight of the bottle and will be carried out as follows: taking into account the following information: the weight of the drop, the initial weight of the container, the final weight of the packaging and the calculation of the total applications. The following simplified formula will be used:

$$Ad = \frac{(P_i - P_f)100}{P_T}$$

Where:

Ad = adhesion

P_i = weight of the container delivered to the subject at the start

P_f = weight of the container returned by the subject

P_T = weight of the dosage indicated for the intervention

$$P_T = (P_g)G$$

Where:

P_g = weight of a drop of the intervention, determined by the research and development department

G = number of applications indicated for the intervention

Packaging that does not maintain its physical integrity will not be considered for the calculation of adhesion.

For cases where the packaging is not returned, or it has not retained its physical integrity, the adherence through the subject's diary, as follows:

$$Ad = (A_r)100/A_i$$

Ad = Adhesion

Ar = Registered applications

Ai = Applications indicated for the intervention

The research center will designate a person in charge of monitoring adherence through the diary, during Visits. Measuring adherence by weight will be the sponsor's responsibility.

There is no standardized parameter to define adequate adherence, it must be defined and delineated. by the objectives of the particular research.[40]

6.5 Strategies to improve adherence

1. The IP will sensitize the subject on the importance, in order to achieve the objectives of the study, of the correct application of the PI.
2. Direct questioning by the IP regarding the application of the PI.
3. Delivery of a printed calendar specifying the date of the visit and its activities.
4. Training in filling out and reviewing the subject's Diary.
5. If deemed necessary, text messages may be sent as reminders.
   The content of such messages must be previously approved by the IEC.

7. Methods and procedures of the study

7.1 From the research center

This study will be conducted at a research center previously evaluated by the sponsor. This center will be an institution or establishment where health research is carried out that complies with the current regulations.

The research center will be responsible for forming a multidisciplinary research team to Carry out the clinical study according to the protocol. It is their prerogative to design the organization and select of the staff who will perform the functions. However, it is the sponsor's requirement that the Researcher Principal (IP) is a specialist in ophthalmology.

Any person who is assigned, under his or her responsibility, a part of the study monitoring (co-investigator, sub-investigator, nurse, etc.) or a specific role of participation in the study (pharmacist, administrative assistant, study coordinator, etc.) must appear in the “Delegation of Responsibilities.”

The competence and training of all persons who have direct participation in the study activities must be verified before carrying out any activity related to the protocol. The above must be registered and documents constituting evidence of this competence and/or training must be be kept in the master file of the study. The competence and training of the personnel who have functions in the study, both at the central level and in the study centers, is the responsibility of the sponsor.

The sponsor must ensure that all staff from the study centers participating in the study, be adequately trained on it (research protocol, researcher's manual, amendments, standard operating procedures, etc.) and on the ICH Good Clinical Practices, before the start of your participation in the training. The training must be recorded in writing and those records must be filed in the master file of the study.

7.2 Clinical study registration

This clinical study will be registered by the sponsor in public clinical trial registries prior to its start (inclusion of the first patient): National Registry of Clinical Trials (RNEC) of the Federal Commission for the Protection against Health Risks (COFEPRIS) and in a WHO primary records platform. WHO primary records meet specific criteria for content, quality and

validity, accessibility, unique identification, technical capacity, and administration. The Registries WHO primary sources meet the requirements of the International Committee of Medical Journal Editors (ICMJE).

7.3 Outcome variables

7.3.1 Primary outcome variables

- Incidence of unexpected AEs related to the investigational product (TE 8 and 10).
- ICO score (TE 8).

7.3.2 Secondary outcome variables

- Changes in Corrected Visual Acuity (CCVA) (TE: day 8).
- Changes in corneal and conjunctival staining with lissamine green (TE: day 8).
- Corneal and conjunctival staining changes with fluorescein (TE: day 8).
- Conjunctival hyperemia changes (TE: day 8).
- Incidence of chemosis (TE: day 8).

7.3.3 Definition of variables, methods and scales to be used for measurement

Variable	Guy	Unit (Symbol)	Method of measurement	Worth normal	Time of assessment	Proof statistics
Primaries						
EA	Discreet	Number of cases (n)	Counting	0	VB, VF and LLS	ÿ2 or exact Fisher's
	Categorical nominal	Present/ absent	Observation	Absent		
Score of the ICO	Discreet	Points	Questionnaire	NA	VB, VF	Ranges of Wilcoxon
Secondary schools						
AVcc	Discreet	Fraction	Snellen chart	1	VB, VF	Ranges of Wilcoxon
Staining corneal and conjunctival with fluorescein	Ordinal	Degrees	Direct observation with lamp slit and blue filter cobalt, graduation Oxford scale	0	VB, VF	ÿ2 or exact Fisher's

Variable	Guy	Unit (Symbol)	Method of measurement	Worth normal	Time of assessment	Proof statistics
Staining corneal and conjunctival with green of lissamine	Ordinal	Degrees	Direct observation with lamp cleft, graduation scale Oxford	0	VB, VF	ÿ2 or exact Fisher's
Hyperemia conjunctival	Ordinal	Normal/ Very Light/ Light/ Moderate/ Severe	Observation direct. Classification of Efron.	Normal	VB, VF	ÿ2 or exact Fisher's
Chemosis	Categorical nominal	Present/ absent		Absent	VB, VF	ÿ2 or exact Fisher's

Table 3. Operational definition of variables

The variables, method and scales for their measurement are described in detail below. They are in order according to table 3.

7.3.3.1 Adverse events

As defined in section **8.2,** an AE is any unfavorable medical occurrence in a subject who is administer a PI, regardless of causal attribution.

The management of AEs will be carried out as described in the Adverse Events section.

The IP will record in the corresponding section of the electronic case report form (eCRF). in English *Case Report Form)* the AEs that the subjects of the study may present in addition to referring to it in the medical record.

For an adequate evaluation of the EA, in addition to the directed questioning, it is necessary to carry out in each Visit the Comprehensive Ophthalmological Evaluation which consists of: the ophthalmological examination of the eyelids and annexes; anterior segment and posterior segment that is performed in a routine ophthalmological examination, whose procedures are not specifically included in the study variables. The evaluation of pole posterior may be with direct or indirect ophthalmoscopy, with or without pharmacological mydriasis, at the discretion of the IP. An evaluation of the fundus will be performed to look for abnormalities that could alter the results of the study. The IOP will be measured in this evaluation, with the instrument of the IP's choice, it should be measured after the evaluation of the stains. The result of the assessment will be recorded in the clinical record. In the eCRF only Findings that are considered as such by the IP will be reported as AEs.

According to the available literature, the expected AEs for the use of PI are: dysgeusia, eye irritation, Headache, nasopharyngitis, dry eye, ocular itching, nasal congestion and rhinorrhea.[42]

7.3.3.2 ICO Score

The ICO is a questionnaire designed to measure ocular surface irritation with Rasch analysis for produce estimates on a linear interval scale (scores: 0-100). Similar to the index for Ocular surface diseases, the Ocular Comfort Index (OCI) assesses symptoms. The OCI contains items that focus on the discomfort associated with ocular surface alterations. Each of these The questions have two parts, which separately inquire about the frequency and severity of symptoms.[43]

The evaluator will give the questionnaire to the subject and allow him to answer it calmly without any kind of pressure and/or coercion, will only assist you if you have difficulty understanding any of the questions.

Management as AE: The ICO assesses symptoms, which may or may not be related to an AE. The score obtained from the ICO alone, should not be considered an EA.

7.3.3.3 Visual Acuity with correction

Visual acuity (VA) is a test of visual function. Spatial VA 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 objects separated.

Snellen notation is described as the distance at which the test is performed, divided by the distance to the which the letter is equivalent vertically to 5 minutes of arc. Thus, at 6 meters a letter 6/6 (20/20) is equivalent to 5 minutes of arc, a letter 6/12 (20/40) is equivalent to 10 minutes, and a letter 6/60 (20/200) is equivalent to 50 minutes. The Snellen fraction can also be expressed as a decimal (i.e. 20/20 = 1 and 20/40 = 0.5).
[44]

VA will be assessed at baseline, without refractive correction, using the Snellen chart. It will be placed in a place with adequate lighting, natural or artificial and at a distance of 3m from the subject to be evaluated. The visual acuity of each eye will be taken, starting with the right eye (RE) asking the subject to maintain both eyes open and using an occluder to cover the left eye (OS); the subject will read aloud the lines that the evaluator points out, the line of smallest letters that the evaluator can see will be noted by the evaluator as a fraction as the AV of OD in the clinical record. The OS is carried out using the same method.

Subsequently, the objective and subjective refractive correction of the subject will be performed. The result of the Subjective refraction will be reported as AVcc, and will be noted as a fraction in the clinical record and on the eCRF, In addition, the eCRF will record it as a decimal. By definition, the AVcc cannot be less than the VA.

Management as AE: A decrease of more than 2 lines on the Snellen chart should be reported and managed as EA.

7.3.3.4 Corneal and conjunctival staining with fluorescein

A drop of topical anesthetic will be instilled in the conjunctival fornix, then a drop will be applied. second drop on the tip of the fluorescein strip allowing it to sit on the strip for 5 seconds to elute the dye, shaking off the excess at the end. A small contact of the strip with the conjunctiva is made in the temporal fornix, while the patient looks up, without damaging the conjunctiva. It will be classified as according to the Oxford scale.[45]

The PI will record in the file and the eCRF the grade awarded for fluorescein staining of OD and OS respectively.

Management as AE: Corneal staining that is equal to or greater than grade III will be considered as AE.

7.3.3.5 Conjunctival staining with lissamine green

After the fluorescein examination, a drop of lissamine green will be applied to the tip of the strip. saline solution allowing it to sit on the strip for 5 seconds to elute the dye. A drop of the strip in the temporal fornix, while the patient looks up, without damaging the conjunctiva. It can be ask the patient to blink repeatedly to avoid accumulation in the conjunctival folds.
The scan should be performed between 1 and 4 minutes after instillation through a density filter. neutral or with the red-free filter. It will be graded according to the Oxford scale. [45]

The PI will record in the file and the eCRF the grade awarded for fluorescein staining of OD and OS respectively.

Management as AE: Corneal staining that is equal to or greater than grade III will be considered as AE.

7.3.3.6 Conjunctival hyperemia

Conjunctival hyperemia is defined as the simplest reaction of the conjunctiva to a stimulus, it is seen a red appearance secondary to vasodilation of the conjunctival vessels of varying intensity. It will be graded using the Efron scale. [46] See appendix.

Management as AE: Conjunctival hyperemias classified as grade 3 or higher will be considered as AE. superiors.

7.3.3.7 Chemosis

It is defined as 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 from the sclera in ÿ 1/3 of the total eyelid opening or if it exceeds the gray line. [47]

~~Handling as EA: Your~~ presence will be considered as an EA.

7.4 Study visits and activities program

7.4.1 Description of activities per visit

The procedures are listed in the order in which they are suggested to be performed, trying to maintain the consistency of assessments and, as far as possible, from the least invasive to the most invasive.

7.4.1.1 Baseline Visit

- Sign~~ature of the ICF:~~ refers to the signing of the written informed consent document. Without informed consent, none of the study procedures can be performed.

- ~~Medical record: refers~~ to the technical, clinical, and legal document that chronologically records the subject's health conditions, medical procedures, and other procedures performed on the subject. It includes anthropometric measurements, anamnesis, a comprehensive ophthalmological examination that allows determining the patient's eligibility, i.e., evaluation of both eyes and ocular adnexa, slit-lamp examination of the ocular surface and anterior segment, and fundoscopy. If the subject is taken from the study center's established population base, the existing medical record may be used; only one update is required.

- Eva~~luation of concomitant medications: refers to the IP quest~~ioning the subject, inquiring about the use of medications.

- Urin~~e pregnancy test: This refers to a rapid~~ pregnancy test performed on all women of childbearing age who wish to enter the study. By childbearing age, we mean women who have experienced menarche but have not yet experienced menopause. Menopause is defined as 12 months from the last menstrual period in women over 40 years of age, or who have undergone a hysterectomy or bilateral oophorectomy. Women of childbearing age using contraceptive methods, including bilateral tubal obstruction, must undergo a pregnancy test.

  This test will be performed by the IP or designated team member according to the instructions on the device provided by the sponsor.
- Vital ~~signs: refers to hea~~rt rate, respiratory rate, systemic blood pressure, and temperature. This information must be recorded in the patient's medical history and progress notes. • ccVA: See 7.3.3.2

- ICO: See 7.3.3.2
- Ocu~~lar surface stains: See 7.3.3.4 and 7.3~~.3.5
- Oph~~thalmological evaluation: See 7.~~3.3.1
- ~~Eligibility criteria: refers to the r~~eview by the PI, where it is confirmed that the subject can be included in the study by meeting the inclusion criteria and not meeting the exclusion criteria.

- PI A~~ssignment: Refers to~~ determining the intervention the patient will follow during the study. Since this is an open-label study, all eligible subjects will be assigned to PRO-172. However, assignment is the procedure by which the number of a given medication is linked to the subject's identification number. This assignment will be performed at the baseline visit (day 1).

- Deli~~very of the PI and start of intervention: Refers to~~ the delivery of the PI to the study patient by the research center.

- EA Assessment: See 7.3.3.1
- Delivery of patient materials and instructions for completion: This refers to the PI providing the subject with the subject's diary, identification card, and calendar, improving adherence. Staff assigned by the research center will provide the subject with prior training on how to complete the diary.

7.4.1.2 Final Visit

- Evaluation of concomitant medications: See 7.5.1.1 above
- Urine Pregnancy Test: See above 7.5.1.1
- Vital signs: See 7.5.1.1 above
- AVcc: See 7.3.3.2
- Ocular surface stains: See 7.3.3.4 and 7.3.3.5
- Comprehensive ophthalmologic evaluation: Ver7.3.3.1
- EA Assessment: See 7.3.3.1
- ICO: See 7.3.3.2
- Subject Diary Assessment: See 7.5.1.1
- Adhesion assessment: See 7.5.1.1
- Return of PI and Subject Diary: Refers to the return by the subject of the PI and subject diary to the research center.

7.4.2 Unscheduled follow-up visits

At the request of the patient or any other individual related to the study, visits may be carried out unscheduled follow-up visits for reporting adverse events. During these visits, the following must be Collect all relevant data on reported adverse events and, where appropriate, establish an appropriate management plan.

7.5 Data collection

7.5.1 Source documents

Source documents are all written or printed records derived from automated processes (for example, example: printouts of laboratory results issued by automated analysis equipment) where information is recorded for the first time and becomes part of the permanent records of the history of the patient. Examples of source documents include medical records, clinical progress notes, and reports. laboratory reports, office study reports, nursing notes, follow-up notes, surgical records, etc.

The IP is obliged to accept the monitoring of information related to the study, audits, review by part of ethics and research committees, and inspections by the health authority, this obligation involves direct access to source documents.

7.5.2 Electronic forms of data collection

All data relating to the protocol will be captured via an eCRF by team personnel.
of research. Data relating to the protocol should NOT be captured directly in the eCRF, but
which must be transcribed from the corresponding source document. This procedure allows the
Carrying out monitoring to verify the information captured in the eCRF. It is the responsibility of the
researcher that the information is transcribed to the eCRF in a correct, complete and timely manner.
understands that all eCRF forms captured and submitted for data analysis are approved by the
Researcher.

7.5.3 File

The data collected in this database is anonymous (it only stores the number
of the patient along with other information of interest). The program used for the capture and storage
of data covers the traceability requirements necessary for the execution of clinical studies. The data
collected will be stored by the sponsor or designated clinical research organization for
This and its storage will last for 10 years. The records of patient number assignment
They will remain in the participating institutions under the care of the IP or his/her work team and must be
protected for at least 5 years.

7.5.4 Unscheduled follow-up visits

At the request of the patient or any other individual related to the study, visits may be carried out
unscheduled follow-up visits for reporting adverse events. During these visits, the following must be
Collect all relevant data on reported adverse events and, where appropriate, establish
an appropriate management plan.

8. Event evaluation and management adverse

8.1 Regulation and standards on adverse events

The registration and reporting of adverse events will be carried out in accordance with the guidelines established in the NOM-220-SSA1-2016 which is in accordance with the international ICH E6 guidelines.

8.2 Definition of adverse event

According to the International Conference on Harmonization (ICH), an adverse event (AE) is any adverse medical occurrence in a patient undergoing clinical research who is administered a product pharmacist, regardless of causal attribution.

Therefore, an AE can be any of the following: any undesirable medical event that is temporally related to the use of a medical product, whether or not it is considered to be related to said product; any new disease or exacerbation of an existing disease (worsening the nature, frequency, or severity of a known condition); relapse of a medical condition Intermittent (e.g., headache) not present at baseline; some deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is related to the symptoms or that produce a change in the study treatment or concomitant treatment or discontinuation of the study drug.

8.3 Definitions relevant to the classification of adverse events

Severity (serious/not serious), also called seriousness (serious/not serious). It is defined as serious or grave. any event that: results in death, threatens life, requires hospitalization or prolongs the hospitalization, are a cause of permanent or significant disability or incapacity, are a cause of alterations or malformations in the newborn, other medically important conditions.

Severity (mild, moderate, or severe). Mild symptoms are those that occur with minimal symptoms, not require treatment or discontinuation of the medication; moderate, when they interfere with activities Common, non-life-threatening conditions require treatment and may or may not require discontinuation of the medication; severe, those that interfere with normal activities and require treatment pharmacological and discontinuation of the medication.

Causality. It is the relationship assigned between the medication and the adverse event: certainly caused by the drug, there is clear evidence of causality, ie the adverse event reappears with administration of the drug; probably caused by the drug, there is a high suspicion of causality but There is no direct evidence or it is considered unnecessary or dangerous, ie the reaction disappears when discontinue the medication; possibly caused by the medication, there is additional information that suggests that the cause may be due to another medication or disease; unlikely to be caused by the medication, there is a clear explanation of the origin due to the underlying disease or the use of another medication; conditional, data are lacking to issue a clear causality; not classifiable, those for which Once all possible information has been obtained about the adverse event, it remains unclassifiable.

8.4 Researcher Responsibilities

It is the Researcher's responsibility to perform the EA verification through questioning, reviewing the information recorded in the subject's diary, the relevant physical examination, the evaluation of progress, as well as such as appropriate medical and pharmacological management; as well as follow-up until resolution or outcome and final discharge of the EA, following the definitions determined in national and international regulations. [48] [49] [50]

In the event of an AE or any event that puts the health and well-being of the Subjects will be provided with relevant medical care either at the research center or will be referred to the Hospital Center with the greatest resolution power with which the research center has an agreement medical attention. The IP will notify the sponsor's clinical monitor, according to the times established in the national and international regulations. In the case of serious adverse events, the sponsor will be notified and will record the corresponding information in the eCRF and, in turn, will inform the CEI and the CI.

The attention of the EA will be carried out according to the event attention diagram (see **Figure 3. Attention of the adverse event).**

In the final report that will be written by the Clinical Team of the Department of Clinical Operations of Laboratories Sophia, SA de CV, the report of adverse events will be included in compliance with national and international regulations. current international. [49] [48]

If the research subject debuts during his/her participation in the study with any adverse event of chronic course, such as diabetes or systemic arterial hypertension, you will be referred to a health professional. competent health for your chronic treatment. The follow-up and completion of your participation will be as stipulated by the ICH.

8.4.1 Recording of adverse events in the electronic case report form

The EA registry considers:

- The subject's identification information such as: code, age, sex, left eye, right eye.
- Information about the type of AE to the PI or the study drug, as appropriate.
- Information on important dates:
    - o Date on which the EA occurs
    - o Date on which the IP is informed of the same
    - o Date of resolution or outcome, as applicable.
- Information on diagnosis and clinical management. If a lack of therapeutic response to the PI and/or investigational drug, must be reported as a serious adverse event within the period stipulated by current regulations. Include the therapy used in concomitant medications for the pharmacological management of the adverse event.
- Establish the outcome or resolution of the event:
    - o Patient recovered without sequelae
    - o Recovered patient with sequelae
    - or Patient not recovered
    - o Patient who died due to AE
    - o Patient who died and it is judged that the drug may have contributed
    - or Patient who died and this was not related to the product or medication in question investigation,
    - Or, indicate that the consequence of the event is unknown.
- Information about the investigational product or drug or the drug associated with the EA, RAM or SRAM. As applicable, information concerning generic name, distinctive name or code of the PI and/or investigational medicinal product, as appropriate according to the methodological design of the study, this is relevant in the case of blinded studies or those where placebo is used as comparators, since there are circumstances that justify opening the blind to determine whether the adverse event may be attributable to the active agent, the combination of active agents, or the substance(s) pharmacologically inert(s), such as vehicles or additives, as appropriate for the phase clinical research in which the development of the drug is located. It will also be necessary record the data concerning the batch number, manufacturing laboratory, expiration date, dose, route of administration, start and end dates of administration and/or consumption, reason for the prescription; depending on whether it is an investigational product or drug (protocol in which that the patient is currently participating in) or it is a medication that the subject is currently undergoing research

consumed for the treatment of underlying concomitant diseases or used for the management of any transient sign or symptom that does not correspond to the Natural History of the pathology that caused it your entry into the research protocol.

- Indicate the withdrawal or maintenance of the drug, PI or investigational drug, as appropriate. appropriate. Indicate whether when withdrawing the PI or investigational drug or suspected drug (if the event is caused) the adverse event disappears. Also indicate whether an adjustment is made to dose, if the event changes in intensity or severity, persistence of the reaction. It is It is important to indicate whether in those patients who are exposed again to the PI, medication in investigation or medication, which had previously been suspended, the AE reappears.
- Information regarding concomitant pharmacotherapy. Indicate the generic name, the dose, route of administration, start and end dates of use, as well as the reason for the prescription regardless of whether it is in accordance with the prescribing information or technical data sheet or is used outside of the regulations or what has been authorized by the local, national or regulatory entity international.
- Information on relevant clinical history. The analysis of the AE considers the information previously narrated, notwithstanding the clinical context in which said harmful phenomenon occurs in the participants of the clinical research protocol, is of special interest, so the information about previous conditions, hypersensitivity or allergy phenomena, previous surgical procedures, laboratory tests or office examinations that have been performed performed on the participant, etc., that the researcher deems appropriate to mention may do so.

8.4.2 Monitoring of adverse events

The IP will provide care and guidance for the EA presented by the participant until its outcome, according to what is referred to in the following section.

8.4.3 Procedures for a serious adverse event

The EA care process considers the following stages:

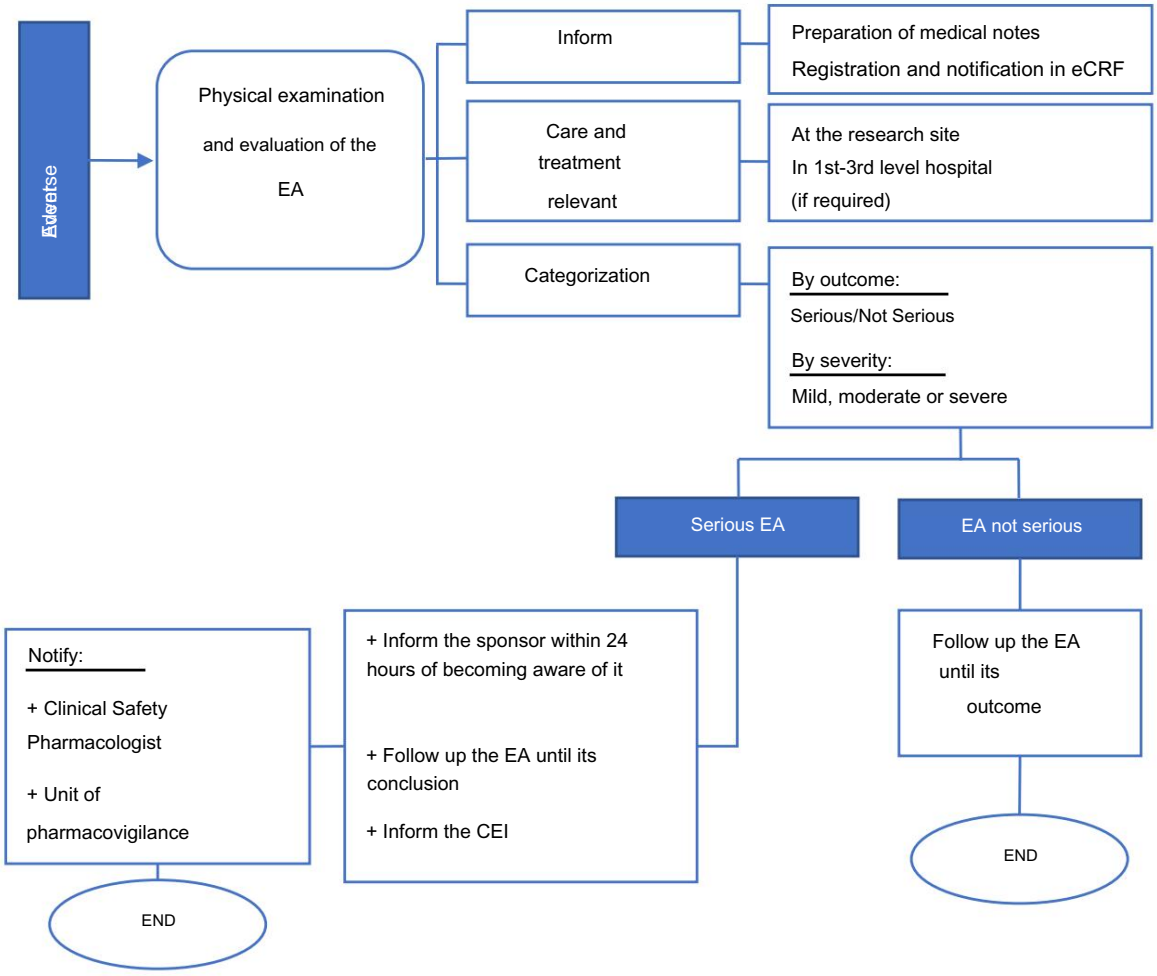


Figure 3. Adverse event care

During the development and conduction of this study, events may occur in the subject under investigation. harmful undesirable or adverse reactions, of medical implication, which do not necessarily have a causal relationship with the PI or investigational drug. These harmful phenomena may occur during the use of investigational medicinal products at doses authorized for use in humans, by a local, national or international regulatory body. However, there may be a suspicion that the IP or the investigational drug may cause any undesirable clinical manifestation. The AEs, ADRs or SRAs to one or several medications may occur during the systematic evaluation of participants (on days in that the clinical review is scheduled, according to the schedule of activities) or suddenly, in such a way that:

1. The researcher must be the first person to whom the patient notifies that he or she has developed or presented with any harmful clinical phenomenon during his or her participation in the present study.

2. Based on clinical judgment, the principal investigator will determine the appropriate course of treatment for the adverse event/reaction based on the relevant physical examination, history, etc., as well as the analysis of information available in the medical literature and the information contained in the investigator's manual, Prescribing Information, or the comparator drug's data sheet.

3. Such care may be provided at the research center or at the hospital with the highest capacity for treatment. Thus, if the patient is referred by the PI to a hospital, they will receive care through a referral system. The referral may be through a card identifying the subject as a study participant and linking them to the pre-established agreement with the institution, or through a referral medical note issued by the PI. Laboratorios Sophia, SA de CV, will pay the costs for medical care for participating patients when the adverse event is associated with or related to the PI or investigational drug.

4. Taking into account the clinical information collected, either during the care provided at the research center or provided by the treating physician(s) at the hospital, the IP will record the AE in his/her clinical note, noting the seriousness, intensity (mild, moderate, or severe), and relationship with the product or drug under investigation.

5. The PI must migrate the relevant data to the eCRF and its respective adverse event section. Therefore, in cases of serious adverse events, which must be reported within 24 hours of the PI becoming aware of them, the clinical monitor of the study is informed and, in turn, informs the Clinical Team and the UTFLS, so that the IEC is subsequently informed. Regarding non-serious adverse events, these will be recorded and appropriately addressed, and the corresponding regulatory entity will be informed about the safety profile of the PI or investigational drug in the final report of the clinical trial.

The recording of the outcome of the EA depends substantially on the follow-up that the IP carries out on the subject, since
Most harmful phenomena are expected (see safety profile section in the manual)
of the researcher), are of an ophthalmic nature, however, there may be systemic alterations. Therefore,
The researcher's judgment will consider the withdrawal of the participant or his/her continuation.

8.4.4 Causality Assessment

Causality assessment is the methodology used to estimate the probability of attributing to a
drug, investigational drug or PI, the observed adverse event. Consider categories
probabilistic according to the available evidence and the quality of the information, based on national regulations
pharmacovigilance.[48]

The Pharmacovigilance and Technovigilance Unit of Sophia Laboratories (UFTLS) can use the algorithm
of Karch and Lasagna modified by Naranjo referred to by Aramendi I, as a tool to facilitate the
Probabilistic categorization of causality. In this algorithm, different items are scored, which,
They allow a value to be assigned to the cause-effect relationship between the administration of the medication and the reaction
adverse. [51] See **Table 4. Karch and Lasagna algorithm modified by Naranjo.**

In such a way that the degree of certainty to establish the PI or investigational drug (according to

(as appropriate) as the causal agent of the harmful phenomenon that occurs to the subject of the clinical study.

It can also be indicated directly by the IP based on his clinical experience or through the

voluntary application of the aforementioned tool. However, it is important that the

researcher and the UFTLS take into account the following arguments in favor of the causal relationship:

a) Strength of association, which refers to the number of cases in relation to those exposed.

b) The consistency of the data, that is, the presence of a common characteristic or pattern.

c) The exposure-effect pattern, which determines the relationship with the site of appearance, time, dose and reversibility after suppression.

d) Biological plausibility, which refers to possible pharmacological or pathophysiological mechanisms involved in the development or presentation of the adverse event.

e) Experimental findings, for example, the appearance of anomalous metabolites or high levels of drug or the product of its biotransformation.

f) Analogy, which refers to the experience acquired with other related drugs, adverse reactions frequently produced by the same family of pharmacological agents.

g) Nature and characteristics of the data, i.e. objectivity, accuracy and validity of the documentation relevant. [52]

No.	Reagent	Score Yeah	No
1.	There are conclusive previous reports on adverse drug reaction, adverse event or suspected adverse reaction to medication	+1	0
2.	The adverse event occurred when the suspected drug was administered	+2	-1
3.	Adverse drug reaction, adverse event or suspected adverse drug reaction improved by discontinuing or administering a specific antagonist	+1	0
4.	Adverse drug reaction/adverse event/suspected adverse drug reaction reappeared upon administration of the investigational drug/product/investigational drug	+2	-1
5.	There are alternative causes that can provoke this reaction.	-1	+2
6.	The adverse reaction/adverse event/suspected adverse reaction to medication occurred after the placebo administration	-1	+1
7.	The drug was determined in blood or other fluids in toxic concentrations	+1	0
8.	The intensity of the adverse reaction/adverse event/suspected adverse drug reaction was higher with higher doses or lower with lower doses	+1	0
9.	The patient has had similar reactions to the investigational drug/product or medication in research, in the past	+1	0
10.	The adverse reaction/adverse event/suspected adverse reaction to medication was confirmed with some objective evidence	+1	0
	Total score	summation	

Probabilistic category based on the score obtained

.	The causal relationship is verified	ÿ,9
II	The ADR is likely due to the investigational drug or product	5 to 8
III	The ADR may be due to the investigational drug or product	1 to 4
IV	The causal relationship is doubtful	0

Each reagent receives a defined score and the final sum allows estimating the probabilistic category of the causal relationship. effect between the administration of the investigational product and the adverse reaction, adverse event, or suspected reaction adverse.

Table 4. Karch and Lasagna algorithm modified by Naranjo

8.5 Unanticipated Problems

Unanticipated problems (ANP) consider those situations that pose risks to the subjects.

Participants, in general, any incident, experience or outcome that meets all criteria

following:

- Unexpected in terms of its nature, severity, or frequency in relation to: 1) study-related documents such as the investigator's manual, study protocol, and informed consent form; and 2) the characteristics of the study population.

- Related or possibly related to your participation in the study (possibly related means that there is a reasonable possibility that the incident or results were caused by study procedures).

- Indicative that the research places participants at increased risk of harm (including physical, psychological, economic or social) than previously recognized.

8.5.1 PNA Report

The PI will be responsible for reporting PNAs to the sponsor, the IC, and the IEC. The report must contain the

following information:

- Study identification: protocol title and number, name of the PI and, where applicable, the center.
- Detailed description of the event, incident, experience or result.
- Explanation, justification of the reasons why the incident represents a PNA.
- Description of changes to the protocol or corrective actions taken or proposed in response to the PNA.

PNAs that are EAS must be reported to the IEC and the sponsor within the first 24 hours of

that the IP was aware of this.

Any other PNA will be reported to the CEI and the sponsor within the first 5 business days after the

IP became aware of this.

9. Study monitoring

The study sponsor is responsible for monitoring the study. Monitoring activities include:
but are not limited to: general safety monitoring, general study quality monitoring,
monitoring by study site, detection monitoring, reporting and follow-up of adverse events,
monitoring to resolve discrepancies in data capture, etc.

Responsibility for monitoring activities and ultimate responsibility for monitoring rests with the
sponsor.

Details of the monitoring activities are specified in a separate document from this protocol.
in a Monitoring Plan.

9.1 Monitoring of study centers

Monitoring of the research centers participating in the study will be carried out. For each center,
At least one initial visit and one closing visit must be carried out, which does not exclude the carrying out of one or more
several follow-up visits between those two mandatory visits.

The initial visit must be carried out before the inclusion of the first participant in that center; in it, the
The monitor will verify that the material to be used during the study has been received and that the personnel who
will participate in the study activities has been trained on the study, will also verify that
comply with applicable regulatory requirements and standard operating procedures.

At the follow-up visit(s), the monitor will review the study documents to
confirm that: the research protocol has been followed, standard procedures have been followed
applicable operating procedures, data filling has been complete and timely, and that event reports
adverse events have been carried out appropriately. At this visit the monitor will discuss the findings with the
researcher and will define the actions to be carried out.

The closing visit will take place at the end of the study, once the last participant from the site has been
discharged from monitoring. During this visit, the monitor will verify that the site has all the
documents needed to file, that all biological samples have been sent for analysis, that everything
the study drug (used and unused) has been recovered and shipped to the sponsor, and that all
unused material has been recovered.

Details on monitoring are set out in the corresponding plan.

9.2 Audit and quality control

To ensure compliance with GCP and all applicable regulatory requirements, Laboratories
Sophia, SA de CV may conduct quality assurance audits. Regulatory agencies
They could also conduct a regulatory review of this study.

Details of the audit process are set out separately in an Audit Plan.

9.2.1 Pre-study audit

Study centers included in the study will be subject to a pre-selection feasibility visit.
from the center, where it will be verified that they meet the minimum requirements indicated by the sponsor.

9.2.2 Audit during the conduct of the study

They may take place at any time before, during or after the conclusion of the study. If it is carried out
any audit or inspection, the researcher and the institution must agree to allow the
auditor/inspector has direct access to all relevant documents, and will allocate their time and that of their
staff to the auditor/inspector to discuss the findings and any relevant issues. In the event that the
If the audit has not been scheduled by the sponsor, the center must notify Laboratorios Sophia, SA
of CV immediately.

10. Statistical analysis

10.1 Data analysis

10.1.1 Statistical analysis

The statistical analysis will be performed by staff of Laboratorios Sophia, SA de CV. The program will be used SPSS statistical version 19.0 (IBM Corporation, Armonk, NY, USA).

Coding will be done using consecutive numbers. Data will be collected and sorted into an Excel spreadsheet (Microsoft® Office). The data will then be exported to the SPSS software platform. Variables will be categorized according to their nature.

10.1.2 Data interpretation

The Kolmogorov-Smirnov test will be performed to determine the distribution of the results obtained. [53]

The results of the continuous quantitative variables will be presented in measures of central tendency: mean, standard deviation and ranges.

The statistical analysis of continuous quantitative variables to find significant differences *(p)* will be as follows:

- Intra-group analysis: They will be determined by the Wilcoxon rank test, for the quantitative variables. [54]

The level of difference to consider significance will be an alpha (ÿ) of 0.05 or less.

The results of the nominal and ordinal qualitative variables will be presented in frequencies, proportions and percentages.

Statistical analysis to identify significant differences in qualitative variables will be performed by creating 2x2 contingency tables and will be carried out as follows:

- Intra-group analysis: Pearson's Chi-square (X2) test or Fisher's exact test on expected values under 5.

The level of difference to consider significance will be an alpha (ÿ) of 0.05 or less.

For adverse event reporting, all eyes of participants assigned to the intervention after the baseline visit will be considered. Results will be expressed as a percentage of subjects.

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

10.1.3 Procedure for handling missing data

The safety assessment will include in the analysis all those subjects (both eyes) who have been exposed at least once a year after the intervention, regardless of the visit at which they were eliminated from the study (ITT, intention-to-treat population).

10.1.4 Deviations from the statistical analysis plan

According to the sample size calculation to meet the objective of the study, 22 subjects are required. evaluable (both eyes). If this number is not met due to a loss of subjects greater than to the 20% contemplated in this protocol (loss to follow-up or withdrawal of FCI), the sponsor may replace these subjects.

The results obtained from the replaced subjects will continue to be used for the analysis of security and will be part of the ITT.

10.1.5 Subjects included in the analysis

Those subjects who meet an adherence ÿ75% will be included in the statistical analysis for meet the objective of the study, taken from the weight of the PI.

The investigational drug will be considered safe and tolerable when present in less than 10% of the study population unexpected adverse events related to the investigational product.

10.2 Sample size calculation

10.2.1 Calculated N

n= 22 evaluable subjects (both eyes)

10.2.2 Justification of the sample calculation

Although there are no references on sample calculation in phase I studies, it was considered relevant perform it according to the presence of Adverse Events (AE) referred to by Macejko et al., 2010, [16] in a trial A multicenter, double-blind, randomized, parallel-group controlled clinical trial was conducted. The trial evaluated the Efficacy and tolerability of a 1.5% bepotastine besilate ophthalmic solution (n=43) versus bepotastine 1.0% (n=44) and placebo (n=43), in 130 subjects in a conjunctival allergen challenge (CARC) model.

The intervention consisted of the application of 3 drops in each eye of each of the interventions (3 minutes after RAC), with measurements at 15 minutes, 8 and 16 hours post instillation.

The percentage of adverse events was 30% for the 1.5% bepotastine group, 47.5% for bepotastine 1% and 22.5% for placebo, so a non-inferiority margin of 10% was considered with the formulation proposed in this protocol (bepotastine 1.5%).[16]

The sample size was calculated using the equation for a proportion, [55] considering a power of 80% (ÿ), a significance level of 0.05 (ÿ) and a non-inferiority margin (ÿ) of 10%.

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

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

Where, ÿ is the non-inferiority margin (-10%).

The calculation to estimate the sample size and power was performed using the following equations.

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

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

Where;

n is the sample size,

p_0 is the reference proportion,

θ is the normal distribution function,

α s the Type I error

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

δ is the test margin.

According to the previous calculation, the result is 18 subjects, this calculation was increased by 20% considering possible losses. The total sample size required is 22 subjects, who will provide an eye for the analysis.

11. Ethical considerations

11.1 Approval of the committees

This study will be conducted in accordance with the standards of the Declaration of Helsinki, Medical Association 2013 World Cup. Nuremberg Code; Nuremberg Trials by the International Tribunal at Nuremberg, 1947. Belmont Report, National Commission for the Protection of Biomedical Research Subjects and Conduct, 1979. It will be conducted in accordance with the scientific and technical requirements necessary for registration of medicinal products for human use of the International Conference on Harmonization (The International Council for Harmonisation (ICH) Good Clinical Practice Guidelines. Ethical Guidelines International Organizations for Biomedical Research Involving Human Subjects of the Council for International Organizations of Medical Sciences (CIOMS, 2016). The Research Ethics Committee and the Research Committee will evaluate the protocol before carrying out the study and will issue their approval or possible modifications for its implementation, these Committees must be notified of any significant changes to the protocol. In addition to the above, the current regulations of the regulatory authority.

The personnel authorized by the sponsor will be subject to evaluation by the Research Ethics Committees, Research Committees, and when applicable to the Biosafety Committee, the essential documentation of the project research: research protocol, informed consent letter, researcher's manual, subject diary and patient material, as well as other additionally requested documents, according to the local, national or international requirements applicable by regulatory entities.

The study will not be started at the research center if the confidentiality agreements are not in place and economic proposal from each of the principal investigators, duly signed and without having previously obtained the favorable opinion and/or approval of the Research Ethics Committees, Research Committees, and when applicable, by the Biosafety Committee, corresponding.

The study will not be started without having met the local, national or international regulatory requirements. relevant and without having the corresponding health authorization.

The study is considered to be research with greater than minimum risk, according to Regulation of the General Health Law on Health Research, Title Two, Chapter I, Article 17, Section III, published in the Official Gazette of January 6, 19873

11.2 Amendments to the protocol

The amendment procedure will be relevant when there is a need to make any changes to a document that is part of the research project or protocol, derived from variations to the structure methodological, replacement of the principal investigator or identification of risks in the subjects of Research. Documents that may be amended include: protocol, letter of consent informed, researcher's manual, patient documents, measurement scales and schedule of activities.

Any amendment must be approved by the sponsor and/or the principal investigator, the document(s) amended, once reviewed and approved by the Research Ethics Committee and the Committee of Research or when applicable, by the Biosecurity Committee, (entities that issued the opinion initial favorable for the realization of the investigation) will be sent for authorization by the entity relevant regulatory.

Amendments that substantially modify the protocol, confer an additional or different risk to the research subjects, must be approved by the aforementioned Committees. It is the responsibility of the researcher take action in situations that require immediate action to avoid unnecessary harm to the study participants.

The principal investigator has the responsibility to communicate to the Research Ethics Committee any amendment to the protocol that could potentially affect the rights, safety or well-being of participants in the research. Likewise, you must report any situation or new knowledge that will show an increased risk to participants, premature termination or suspension of the study, reasons and the results obtained up to that point. You must also report on the conclusion of the study, upon completion of the research protocol.

11.3 Early termination of study

The study may be temporarily suspended or terminated prematurely if there is a cause sufficiently reasonable. Written notice, documenting the reason for the suspension or termination early, must be delivered by the party executing the suspension. The IP must inform as soon as possible to the study participants, the CI and the IEC, providing the reasons.

Situations in which suspension or early termination of the study will be considered include, but are not limited to: limit:

1. Presence of serious adverse events in more than 10% of participants in a group of study.

2. The regulatory authority (COFEPRIS) considered it due to security alerts.
3. The Sponsor determines it for its convenience or eventualities such as: support economic, manufacturing errors, etc.
4. Lower recruitment than stipulated.
5. Determination of unexpected risks to participants, which are significant or unacceptable.
6. Obtaining new relevant security information.
7. Insufficient adherence to protocol requirements.
8. The data obtained are not evaluable or are not sufficiently complete.
9. Determination that the primary objective has been achieved.
10. Determination of futility.

In case of suspension, the study can be resumed once the situations that have been corrected have been resolved. resulted in suspension; as long as this justification is sufficient for the sponsor, CI, CEI and regulatory authorities.

11.4 Informed consent

The FCI contains complete and understandable information about the study and the investigational product, in accordance with current applicable regulations and Good Clinical Practices.

The FCI will be considered a source document and will be archived as such. The principal investigator of the site is responsible for ensuring that all new versions of informed consent are submitted to the approvals that apply (the same ones to which the original informed consent letter was submitted) and that the most current approved version is the one presented to the study subjects.

11.4.1 Obtaining

Informed consent must be obtained before any procedure is performed on the subject. indicated in the protocol. For this purpose, the informed consent letter must be signed.

Written consent documents will incorporate the elements of informed consent described in the Declaration of Helsinki and the ICH Guideline for Good Clinical Practice and will be in compliance with all applicable laws and regulations.

The IP will provide the potential participant with all the information regarding the characteristics of the study, its potential benefits, risks, objectives and procedures thereof.

This information will be in a language that the subject understands, and it will be explained to the subject that he has the right to interrupt their participation in the study at any stage, without affecting the relationship with the

researcher and/or his/her future assistance. Informed consent will be submitted to the prospective participant; he or she must have sufficient time to analyze each and every aspect mentioned above and in case you have any questions, these will be clarified by the person in charge obtaining informed consent.

Once the participant agrees to participate in the study, he or she must sign and date the letter of informed consent in the presence of two witnesses who may or may not have a relationship with the subject of the study, who will participate during the informed consent process and will sign guaranteeing that the process is carried out prior to any study procedure, which was clearly explained the information of the study and any doubts were clarified.

The IP must also sign and date this consent.

The FCI must be signed in duplicate by all those involved, and two witnesses, one copy will be filed in the researcher's folder and the other will be given to the participant. The PI or delegated staff must document the process of obtaining Informed Consent through a detailed medical note, where the signed version, the date on which the document was signed and how the process was carried out are specified.

11.4.2 Special considerations

The procedures that will be performed during the study do not pose any additional risk that should be considered apart from the procedures listed for informed consent.

11.4.3 Modifications to informed consent

Any change to the “FCI” constitutes an amendment to this document and must be submitted for review. approval before the Research Ethics Committees, and if applicable before the Competent Authorities.

Such amendments may be implemented only after obtaining the written approval of the Research Ethics Committee and the Regulatory Entity (as applicable), with the exception of one amendment that is required to eliminate an immediate danger to the subjects of the study.

A re-consent process must be carried out for each subject affected by the amendment in the same conditions as those described above, in order to promptly communicate to this new information contained in the document. The subject will be given a signed original of the amendment and the The researcher will keep the second original.

11.5 Confidentiality

All documents and information provided to the research center by the sponsor are strictly confidential. The IP expressly agrees that the data regarding his or her professional experience and

clinic, provided to the sponsor in paper form and stored in electronic format, are for the sole purpose of use related to your activities with the sponsor of clinical studies, in accordance with the Good Clinical Practices.

The researcher agrees that he and his team members will use the information only within the framework of this study, to carry out the protocol. This agreement is mandatory as long as the information confidential information has not been disclosed to the public by the sponsor.

The clinical study protocol provided to the researcher may be used by the researcher and his team. to obtain informed consent from subjects for the study. The clinical study protocol, at just as any information taken from it must not be disclosed to other parties without authorization by sponsor's writing.

The researcher will not reveal any information without the prior written consent of Laboratories Sophia, SA de CV, except to representatives of the Competent Authorities, and only upon request of the same. In the latter case, the researcher is obliged to inform Laboratorios Sophia, SA de CV before to disclose the information to these authorities.

The researcher will complete and maintain a record of subject selection, as well as the identification and list of Enrollment of each of the subjects participating in the study. The researcher agrees to provide on-site access to the auditor and/or the representatives of the Competent Authorities. The information will be treated giving compliance with professional secrecy.

All eCRFs and communications related to study subjects will identify them only by their number. of identification of the subject under study. The information collected in this study will be exchanged between the sponsor and the research center, must be treated confidentially. The Health Authority, The IEC, the IC, the sponsor, the monitors/auditors and third-party auditors will be the only bodies authorized to review the study documentation. If publications arise from this project, research, in no case will they contain information on the identification of the study subjects. If publish the results of the study, no personal information of the study subjects will be revealed.

The protection of personal data will be in accordance with the corresponding current regulations.

11.6 Conflict of interest

The independence of the conduct of the study and its results from any current or external influence perceived is critical. For this reason, any current conflict of interest of any person who exercises a role in the design, conduct, analysis, publication, or any other aspect of this study will be declared. Furthermore,

Those individuals who have a perceived conflict of interest will be asked to handle it in a manner appropriate to their participation in the study.

11.6.1 Declaration of interests

The IP undertakes to make a declaration of financial interests, as well as conflict of interests prior to the start of the study.

11.7 Access to information

The final database of the study will be property of Laboratorios Sophia, SA de CV and its access will be restricted. The IP will not have access to this, except with prior written authorization from the sponsor.

The information obtained, which is relevant to the safety of the subjects participating in the study, must be shared immediately with the research center, so that it can in turn be notified to the subjects of the study.

11.8 Ancillary and post-study care

Once the study is completed and the adverse events are closed according to section 8, the sponsor does not will extend care to the research subject.

12. Biosecurity aspects

NO BIOSECURITY IMPLICATIONS

This protocol, entitled: “Phase I clinical study, to evaluate the safety and tolerability of PRO-172 ophthalmic solution, manufactured by Laboratorios Sophia, SA de CV on the ocular surface of clinically healthy subjects.”, and number: SOPH172-0919/I HAS NO BIOSECURITY IMPLICATIONS, since infectious biological material will NOT be used; pathogenic strains of bacteria or parasites; Viruses of any kind; radioactive material of any kind; animals and/or plant cells genetically modified; toxic, hazardous or explosive substances; any other material that puts at risk the health or physical integrity of the research center staff or subjects research or affect the environment. It is also declared that in this project no further research will be carried out carry out cell, tissue or organ transplant procedures, or cell therapy, nor will they be used laboratory, farm, or wildlife animals.

13.Publishing Policy

13.1 Final report

Once the statistical analysis is completed, the final report will be written with the results obtained, in charge from the Clinical Team of the Clinical Operations Department of Laboratorios Sophia, SA de CV Said The report will be prepared following the recommendations of the ICH E3 *Step 4* Guide.

13.2 Communication of results

Regardless of the results of the study, Laboratorios Sophia, SA de CV, is committed to communicate the final report of the study to the principal investigators and COFEPRIS. These results will also be shared with the research committee and the IEC. The IP will be responsible for communication to the research subjects.

Laboratorios Sophia, SA de CV will retain at all times the rights to the publication and dissemination of the information contained.

13.3 Publication of the results

Laboratorios Sophia, SA de CV, acting as the sponsor of the study, assumes full responsibility as to its function and retains exclusive property rights over the results of the study, the which you can use in any way you see fit.

The IP undertakes not to publish or communicate data collected from the study, unless it has the prior written agreement of Laboratorios Sophia, SA de CV Any manuscript derived from the data obtained with this protocol must be reviewed by the sponsor before any attempt to submit for publication in any scientific journal or conference

However, in case the sponsor is in the process of filing a patent application on the results of the study, the sponsor may delay its publication or communication of the results of the study. study until the date of registration or when it deems appropriate.

The assignment of authorship of publications, being the responsibility of the sponsor, will be the prerogative of this sponsor. Lastly, however, the express authorization of the persons invited to participate must be obtained. as authors. Authors have the right to review the manuscript prior to publication, as well as to make comments and suggestions in this regard, such comments must be submitted within the first 15 calendar days from the date the project is received.

14. Financing and insurance

14.1 Compensation to study participants

Subjects participating in the study will not receive financial compensation for their participation in the study. same. However, randomized subjects will receive financial support in the form of travel expenses in each scheduled visit to which they attend punctually. Said support, as well as the amount, will be specified in the informed consent letter.

14.2 Insurance for study participants

The subjects participating in the study will sign the informed consent letter, which specifies that Laboratorios Sophia, SA de CV agrees to pay for immediate treatment resulting from injuries or diseases caused by the investigational products until their resolution, according to the criteria doctor.

All study participants will be eligible for liability insurance coverage, contracted by Laboratorios Sophia, SA de CV The information of the contracted policy will be found in the informed consent letter. In case of a medical emergency, the research center must have with personnel, materials, equipment and procedures for immediate handling.

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16.Annexes

16.1 ICO

Eye Comfort Index

Identification card

Study No.: SOPH172-0919-I **Date:** / /

Subject's initials: **Subject No.:** 172-_____-_____

Directions:

This questionnaire was designed to rate the comfort of your eyes.

For each question, circle your answer.

Example: In the past week, how often were your eyes red?

Never						Always
0	1	2	3	4	5	6

There are no right or wrong answers. Don't spend too much time on each question.

1 In the past week, how often did your eyes feel *dry ?*

Never						Always
0	1	2	3	4	5	6

When your eyes felt *dry,* how severe was the sensation usually?

I haven't felt it						Severe
0	1	2	3	4	5	6

2 In the past week, how often did your eyes feel *gritty ?*

Never						Always
0	1	2	3	4	5	6

When your eyes felt *gritty,* typically, how intense was the sensation?

I haven't felt it						Severe
0	1	2	3	4	5	6

3 In the past week, how often did your eyes feel *throbbing ?*

Never						Always
0	1	2	3	4	5	6

When your eyes felt like *they were stinging,* how intense was the sensation usually?

I haven't felt it						Severe
0	1	2	3	4	5	6

4 In the past week, how often did your eyes feel *tired ?*

Never						Always
0	1	2	3	4	5	6

When your eyes felt *tired,* how intense was the feeling usually?

I haven't felt it						Severe
0	1	2	3	4	5	6

Sheet 1 of 2

Eye comfort index

5 In the past week, how often did your eyes feel *sore ?*

Never						**Always**
0	1	2	3	4	5	6

When your eyes felt *sore,* how severe was the sensation usually?

I haven't felt it						**Severe**
0	1	2	3	4	5	6

6 In the past week, how often did your eyes feel *itchy ?*

Never						**Always**
0	1	2	3	4	5	6

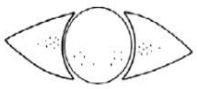
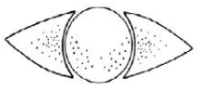
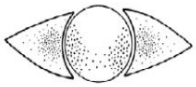
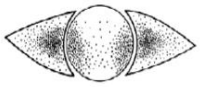
When your eyes felt *itchy ,* how intense was the sensation usually?

I haven't felt it						**Severe**
0	1	2	3	4	5	6

Ocular Comfort Index, translated from the Ocular Comfort Index available at: http:// iovs.arvohournals.org

Sheet 2 of 2

16.2 Oxford Scale

PANEL	Grade	Criteria
A 	0	Equal to or less than panel A
B 	I	Equal to or less than panel B, greater than A
C 	II	Equal to or less than panel C, greater than B
D 	III	Equal to or less than panel D, greater than C
E 	IV	Equal to or smaller than panel E, larger than D
>E	V	Larger than panel E

16.3 Efron Scale