Clinical study title:

Phase I clinical study to assess the safety and tolerability of Lagricel® Ofteno multi-dose ophthalmic solution compared to Lagricel® Ofteno, single-dose on the ocular surface of clinically healthy subjects

Study number: SOPH037-0119 / I

Protocol version: 1.0

Release Date: January 31, 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 Good Clinical Practices and in compliance with ICH guidelines and current local legislation

Sponsor: Sophia Laboratories, S.A of C.V

Content

Index of tables, tables and figures

Responsible for the study

The administrative structure of the sponsoring party, corresponding to Sophia Laboratories, S.A. of C.V. is shown in **Table 1. Responsible for the study**

Function	Name/ Contact	Membership ¥
Medical manager of study	MD Leopoldo Martín Baiza Durán leopoldo.baiza@sophia.com.mx	Medical and Regulatory Affairs Director
Study Director	QFB. Francisco García Vélez francisco.garcia@sophia.com.mx	Clinical Operations Manager
Clinical team	MD Oscar Olvera Montaño oscar.olvera@sophia.com.mx	Medical Editor
Clinical team	MD in C. Ricardo Alonso Llamas Velázquez ricardo.llamas@sophia.com.mx	Clinical Safety Pharmacologist
Clinical team	MD. in C. Patricia del Carmen Muñoz Villegas patricia.munoz@sophia.com.mx	Biostatistics

¥ Employees of Sophia Laboratories, S.A. of C.V Av. Paseo del Norte No.5255, Col. Guadalajara Technology Park, Carretera Guadalajara-Nogales Km13.5 C.P. 45010 Zapopan, Jalisco, Mexico Tel +52 (33) 3000 4200

Table 1. Responsible for the study

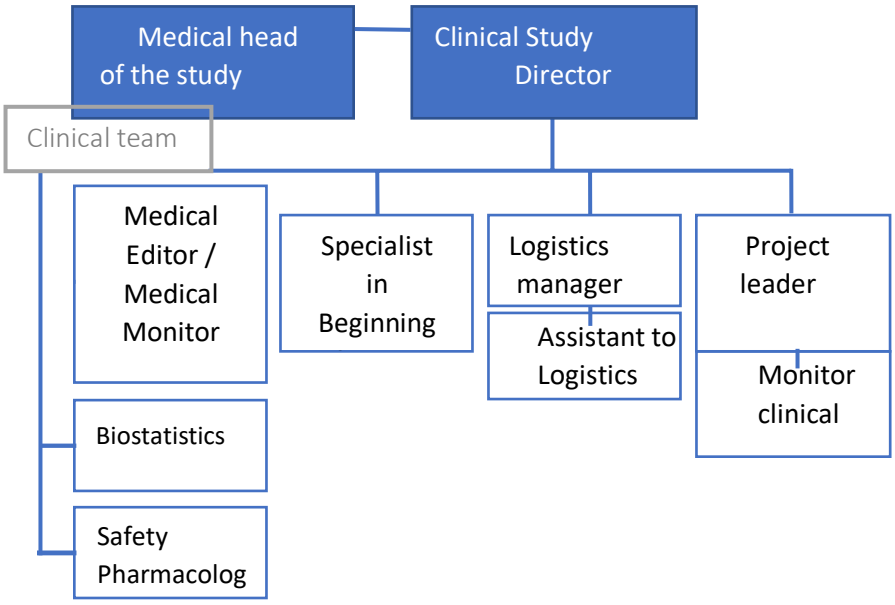


Figure 1. Administrative structure

Signature page

From the sponsor

Name: MD. Leopoldo Martín Baiza Durán Title: Medical head of the study	**Sign** **Date**

Name: QFB. Francisco García Vélez **Title:** Study Director	**SIgn** **Date**

Name: Oscar Olvera Montaño **Title:** Protocol author	**Sign** **Date**

Investigator Agreement

I agree to conduct this clinical study according to the design and guidelines of this protocol, abiding by the provisions of this protocol. I agree to conduct the study in compliance with the accepted standards of Good Clinical Practice. I agree to report all the 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 Investigator's Manual is confidential, I understand that it is prohibited to share it with any third party, who is not involved in the approval, supervision or conduct of the study. I will ensure that I take the necessary precautions to protect the information from loss, inadvertent disclosure or access by unauthorized third parties.

Name:	
	Sign
Title:	
	Date
Name of the centre:	
Geographic location (city / state / country)	

List of abbreviations

AV	Visual Acuity
BID	Twice a Day
CEI	Research Ethics Committee
COFEPRIS	Federal Commission for the Protection Against Sanitary Risks
CTO	Ocular Staining Qualification
DIU	Intrauterine Device
EA	Adverse Event
EEP	Punctate Epithelial Erosion
ESO	Ocular Surface Disease
FCI	Informed Consent Form
FDA	Food and Drug Administration of the United States of America
FERC	Electronic Case Report Form
HS	Sodium Hyaluronate
IC	Confidence Interval
ICO	Eye Comfort Index
IP	Principal Investigator
MAVC	Best Corrected Visual Acuity
OD	Right Eye
OMS	World Health Organization
OS	Left Eye
PNA	Unanticipated Problems
PI	Research Products
QID	Four Times a Day
RNEC	National Registry of Clinical Trials
SICCA	Sjögren International Clinical Collaboration Alliance
TE	Evaluation Time
TID	Three Times a Day
TFOS DEWS II	Workshop on Dry Eye of Tear Film and Ocular Surface Societies II

1. Summary

1.1 Synopsis

Study title: Phase I clinical study to evaluate the safety and tolerability of Lagricel® Ofteno multi-dose ophthalmic solution compared to Lagricel® Ofteno, single-dose on the ocular surface of clinically healthy subjects	
Study number: SOPH037-0119/I	**Creation date:** 31-Jan-19
Protocol version: 1.0	**Date Of the version:** 31-Jan-19
Therapeutic indication: Eye lubricant	**Use:** Dry Eye
Estimated duration of the study (from the first visit of the first patient to the preparation of the final report): 5 months	**Development phase:** I
Objectives: To evaluate the safety and tolerability of the multi-dose Lagricel® Ofteno formulation manufactured by Laboratorios Sophia S.A. de C.V. Over the surface of clinically healthy subjects.	
Hypothesis: H0 = Lagricel® Ofteno multi-dose ophthalmic solution has a safety and tolerability profile similar to Lagricel® Ofteno single-dose in healthy subjects. H1 = Lagricel® Ofteno multi-dose ophthalmic solution has a different safety and tolerability profile than Lagricel® Ofteno single-dose in healthy subjects.	
Study design: Phase I, single-center, controlled, parallel-group, open-label, randomized clinical trial.	
Number of subjects: n = 34 evaluable subjects 17 evaluable subjects per group (both eyes).	**Main inclusion criteria:** Clinically healthy subjects

Selection criteria:

Inclusion criteria:

- Be clinically healthy
- Have the ability to voluntarily grant your signed informed consent
- Be able and willing to comply with the scheduled visits, treatment plan and other study procedures
- Be between 18 to 45 years old.
- Women of childbearing age must ensure the continuation (started ≥ 30 days prior to signing the FCI) of use of a hormonal contraceptive method or intrauterine device (IUD) during the study period
- Have a best corrected visual acuity of 20/30 or better in both eyes.
- Have vital signs within normal parameters.
- Have an intraocular pressure ≥10 and ≤ 21 mmHg.

Exclusion criteria:

- Be a user of topical ophthalmic products of any kind.
- Being a user of medicines, or herbal products, by any other route of administration.
- In the case of women: be pregnant, breastfeeding or planning to become pregnant within the study period.
- Have participated in clinical research studies 90 days prior to inclusion in the present study.
- Have previously participated in this same study.
- Be a user of contact lenses and cannot suspend their use during the study.
- They cannot follow the lifestyle considerations described in section 5.3.
- Having started the use of 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 entry to the study.
- Present unresolved injuries or trauma at the time of study entry.
- Have a history of any type of eye surgery.
- Having undergone surgical procedures, not ophthalmological, in the last 3 months.
- Being or having an immediate family member (for example: spouse, parent / legal guardian, brother or son) who is part of the research site staff or the sponsor directly participating in this study.

Research Products (PI):

Investigational product, dose and route of administration:

- Lagricel® Ofteno Multidosis. Hyaluronate 0.4%. Ophthalmic solution. Sophia Laboratories, S.A. of C.V.
- Dosage: 1 drop 4 times a day, both eyes
- Route of administration: Ophthalmic

Comparator product, dose and route of administration:

- Lagricel® Ofteno Unidosis. Hyaluronate 0.4%. Ophthalmic solution. Sophia Laboratories, S.A. of C.V.
- Dosage: 1 drop 4 times a day, both eyes.
- Route of administration: Ophthalmic.

Treatment duration:	**Approximate duration of the subject in the study:**
7 days	10 days

Evaluation criteria:

Primary outcome variables:

o Incidence of adverse events (AE) (Evaluation Time: day 8 and 10).

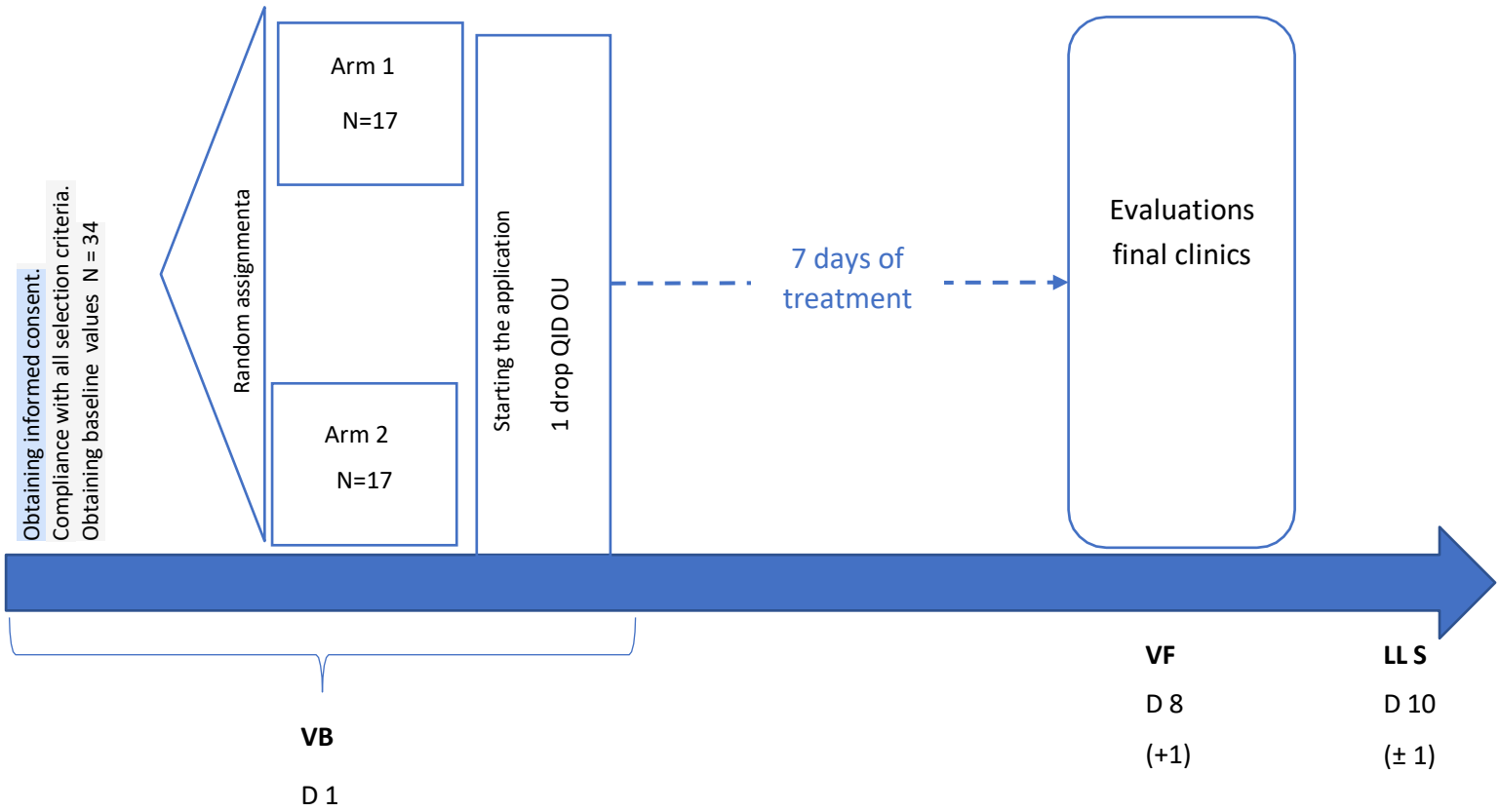
o Score of the Ocular Comfort Index (ICO) (TE: day 8).

Secondary outcome variables:

- o Changes in best corrected visual acuity (BCVA) (TE: day 8).
- o Changes in corneal and conjunctival staining with lysamine green (TE: 8).
- o Changes in corneal and conjunctival staining with fluorescein (TE: day 8).
- o Conjunctival hyperemia changes (TE: day 8).

○ Chemosis incidence (TE: day 8).
Statistical methodology: The data will be expressed with measures of central tendency: mean and standard deviation for the quantitative variables. The qualitative variables will be presented in frequencies and percentages. The statistical analysis will be carried out by means of the Mann-Whitney U test for the quantitative variables for the difference between the groups. The difference between the qualitative variables will be analyzed using X2 (Chi2) or Fisher's exact. An $\alpha \leq 0.05$ will be considered significant.

Study Diagram



VB = baseline visit

VF = final visit. Evaluation of final outcome variables.

Ll S= safety call

QID= four times a day.

OU= both eyes

In parentheses () is the allowed window period.

1.2 Study timeline

PROCEDURES	VB D 1	VF D 8 a +1	LLS D 10 ± 1
FCI signature	X		
Clinic history	X		
Drug Evaluation	X	X	
Concomitant	X	X	
Urine pregnancy test	X	X	
MAVC	X	X	
Integrity of the ocular surface (Staining and evaluation of hyperemia and chemosis conjunctival)	X	X	
Comprehensive ophthalmological evaluation	X	X	
PIO	X	X	
Eligibility criteria	X		
EA evaluation	X	X	X
Research Product Allocation (PI)	X		
Eye Comfort Index	X	X	
Delivery of the PI and start of intervention	X		
Subject's Daily Delivery	X		
Assessment of adherence		X	
Return / Evaluation of Subject Diary		X	
Return of PI		X	

2. Introduction and Background

2.1 Theoretical framework

Currently, dry eye is defined as a multifactorial disease of the ocular surface, characterized by a loss of homeostasis in the tear film that is accompanied by ocular symptoms, in which the instability and hyperosmolarity of the ocular surface, inflammation and ocular surface damage, as well as neurosensory abnormalities play etiological roles. [1]

Dry eye is a common disease; the initial report of the TFOS DEWS I epidemiology subcommittee concluded that the worldwide prevalence of dry eye in individuals over 50 years of age was between 5-30%. [2] One of the main challenges of epidemiological studies has been the lack of a standardization of the definition and classification of dry eye. Despite the efforts of TFOS DEWS I and TFOS DEWS II to standardize these criteria, this has not yet been achieved. The report of the TFOS DEWS II epidemiology subcommittee marked a prevalence of 5-50% in studies involving symptoms, with or without signs; for studies in which the diagnosis was based mainly on signs, the prevalence was even higher, reaching up to 75%. [3]

The incidence of the disease has been reported in few studies. The Beaver Dam Eye Study established, in a Caucasian population aged 48-91 years, that 13.3% (95% CI 12.0 - 14.7%) of the individuals develop symptomatic dry eye at 5 years and 21.6% (95% CI 19.9 - 23.3%) to 10 years. Age being a risk factor for increased incidence with an odds ratio of 1.2x (1.1 - 1.3) for each increase of 10 years. [4]

Although there is no formal study on the prevalence of the disease in Latin American countries, various reports coincide in suggesting that there is a higher prevalence of severe symptoms and clinical diagnosis of dry eye in the Hispanic population when compared to the Caucasian population. [5] [6]

The current definition of the TFOS DEWS II does not indicate that the presence of any specific sign is necessary for its diagnosis; on the contrary, it emphasizes the homeostasis of the tear film. Tear film plays an essential role in lubricating and protecting the ocular surface, as well as maintaining a smooth refractive surface for optimal visual performance. [7]

Physiologically, homeostasis describes the state of equilibrium in the body with respect to its different functions and the chemical composition of fluids and tissues. When applied to dry eye, the concept recognizes the potential for the many changes that can occur in the tear film and ocular surface in response to one or more underlying causes of dry eye. [7, 8] Altered homeostasis is considered to be the unifying characteristic that describes the fundamental process in the development of dry eye.

The most current classification of dry eye attempts to eliminate any perception of exclusivity, by indicating that the diagnoses of aqueous deficit and evaporative dry eye exist as a continuum rather than as separate entities.

The elements of each must be considered in diagnosis and treatment. [1]

This classification system incorporates evaluation elements to provide clarity to the diagnosis, from which various etiologies can be considered and appropriate treatment plans can be established. Appropriate treatment of Ocular Surface Diseases (ESO) with a differential diagnosis masquerading as dry eye increases the options for successful treatment and allows any coexisting component of the condition attributable to dry eye to be adequately revealed and managed.

Figure 2 incorporates a clinical decision algorithm based on current knowledge of the pathophysiology of dry eye..

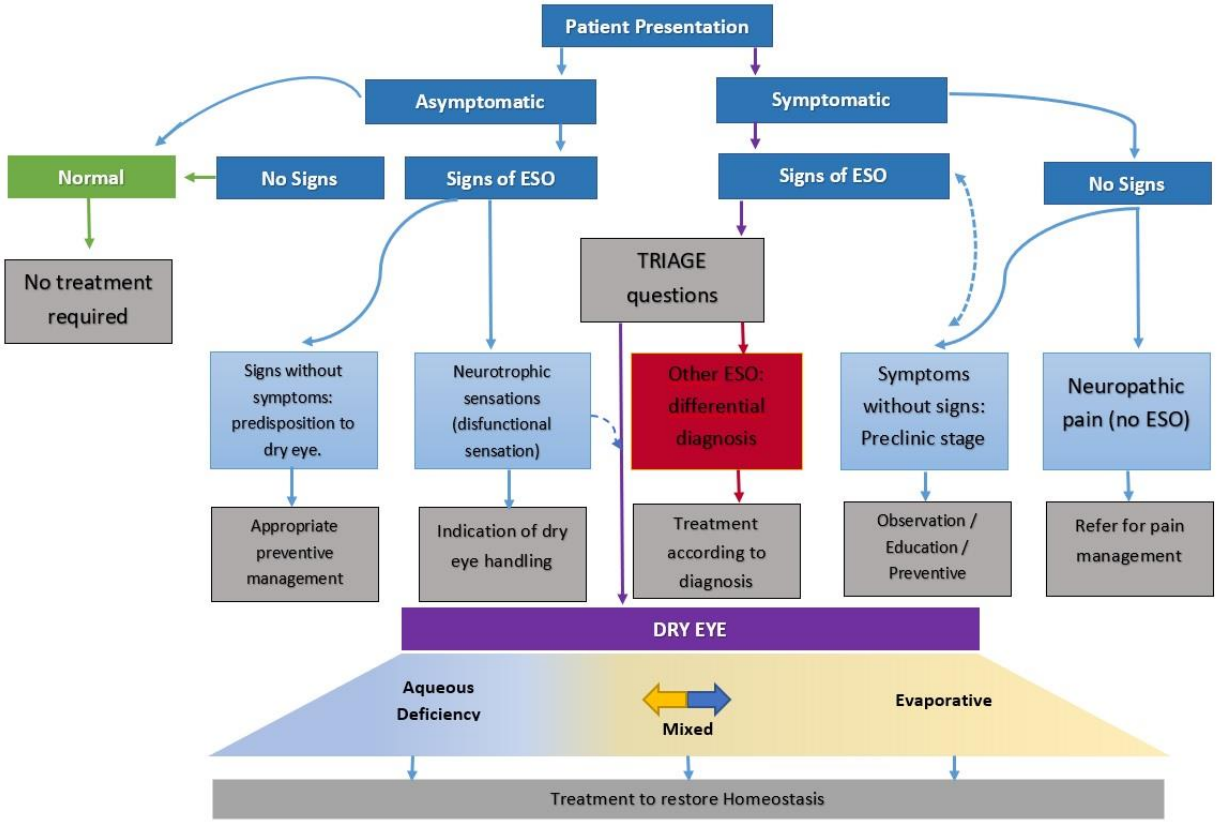


Figure 2. Classification of dry eye

Adapted from TFOS DEWS II Definition and Classification Report [1]

The replacement of tears with eye lubricants is traditionally considered a mainstay of dry eye treatment and there are numerous topical formulations available. These products without pharmacological action are often called "artificial tears" that, as their name suggests, try to replace and / or supplement the natural tear film. However, these products do not act on the underlying pathophysiology of dry eye, and the mechanisms of any palliative action are generally poorly understood. [9]

Tear substitutes consist of various products, which normally aim to act on one or more of the layers of the tear film. The wide variety of properties of these ocular lubricants has been described in other works. [10, 11, 12, 13, 14]

Eye lubricants are considered largely safe, although there are some reported side effects, mainly blurred vision, varying levels of "eye discomfort", and foreign body sensation [15].
There are relatively few randomized controlled trials that have compared the relative superiority of a certain product against other products for the treatment of dry eye. [16] A recent Cochrane systematic review, which sought to assess the effect of eye lubricants for the treatment of dry eye, included 43 randomized controlled trials that had compared various lubricant formulations with no treatment or with placebo.[15] The main outcome measure was patient-reported symptoms. The authors reported that the overall quality of the evidence was low for the different tear supplement formulas compared in the review, and concluded that although artificial tears may be effective in treating dry eye, there remains a need for future research to allow solid conclusions to be drawn about the effectiveness of ophthalmic lubricant formulations.

The management of dry eye is complicated due to its multifactorial etiology. Developing the simple doctrine that "diagnosis precedes treatment" means that clinicians must do their best to identify the degree to which ESOs contribute to the presentation of patients. This aspect of determining the main causative factors of dry eye is critical for proper management.

Figure 3 presents, schematically, an approach to managing dry eye. Before selecting the appropriate treatment to be carried out, one should ask questions and perform diagnostic tests in order to determine that the patient really has dry eye and if he or she shows more signs of ESO in general. After the diagnosis is confirmed, the severity of the disease, together with the determination of the etiological subtype, will allow the development of an appropriate treatment plan.

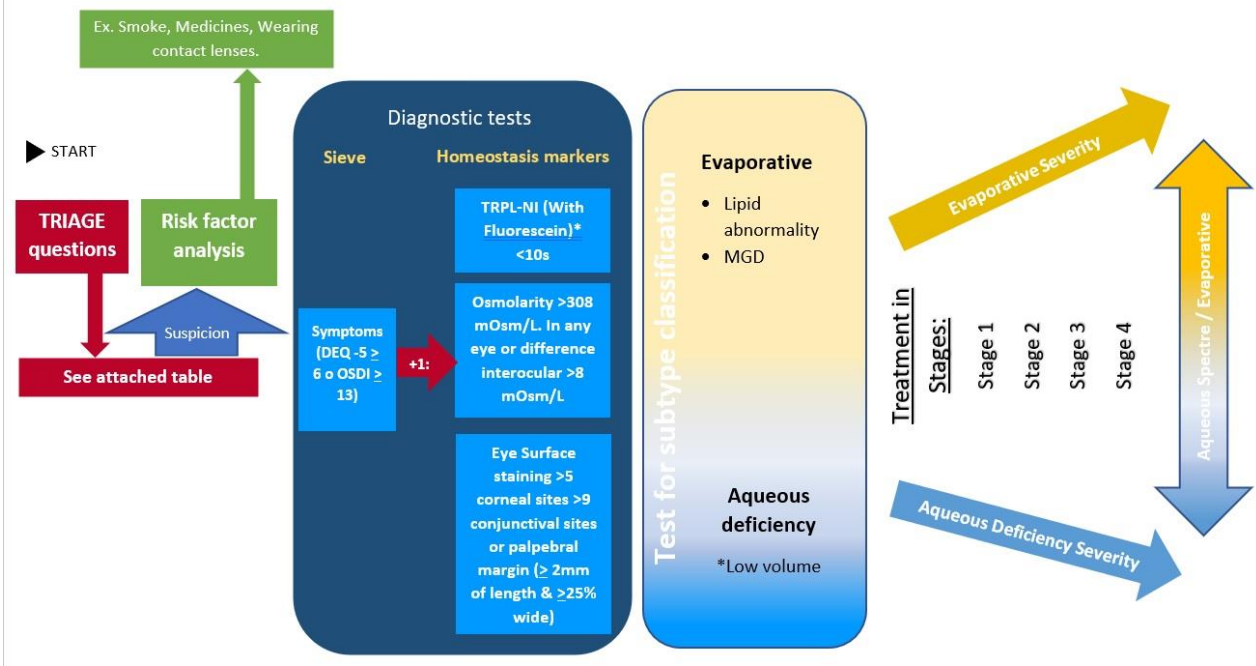


Figure 3. Diagnosis and management of dry eye*

Fluorescein is used when TRPL-NI is not available. * If more than one homeostasis marker test is performed, the order should be: TRPL-NI, osmolarity, TRPL with fluorescein and staining. Adapted from TFOS DEWS II Management and Treatment Report

• How severe is the eye discomfort? • Do you have dry mouth or have you had in some gland? • How long have your symptoms lasted, were there any triggers? • Has your vision been affected, does it clear when you blink? • Are the symptoms or redness much worse in one eye than in the other? • Do your eyes itch, appear swollen, crusty, or have a discharge? • Do you wear contact lenses? • Have you recently been diagnosed with a general illness, or do you take any type of medication? + Detailed examination of the eye

Table 1. Triage questions

Stage 1: • Education according to the disease, its management, treatment and prognosis • Modification of the local environment • Education according to dietary modifications • Identification and modification / elimination of offending topical and systemic medications • Eye lubricants • Eyelid hygiene and warm compresses Stage 2: If the above options are inappropriate, consider the following: • Treatment for Demodex • Tear preservation o Occlusion of lacrimal points o Wet chamber goggles • Night treatments (eg ointments) • Physical warming and expression of meibomian glands • Pulsed light therapy • Prescription of: Antibiotics or their combination with steroids in the palpebral margins o Topical steroids (limited duration) o Topical secretagogues o Topical immunomodulators o Topical LFA-1 antagonists o Topical macrolides or tetracyclines Stage 3: • Oral secretagogues • Autologous serum • Therapeutic contact lenses Stage 4: • Topical steroids (extended duration) • Amniotic membrane grafts • Surgical occlusion of lacrimal points • Other surgical approaches.

Table 2. Stages of dry eye treatment

Treatment algorithms are often built to recommend a sequence of treatments according to the

stage of the disease, but this is not possible for dry eye, as it is a complex condition that varies from patient to patient. gravity as in character. However, with the intention of helping ophthalmologists create a logical and evidence-based approach to treatment, the treatment algorithm shown in Table 2 was proposed within the framework of the TFOS DEWS II. For patients who do not respond to a certain level, or that show greater severity, the next level is recommended and, in some cases, previous treatment can continue, in addition to any new treatment. In general, the approach is to start with low-risk and commonly available conventional treatments, such as eye lubricants for the early stages of the disease, and progress to more advanced treatments for more severe forms.

2.2 Background on the product under study

2.2.1 Pharmacology of the product in research.

Sodium hyaluronate (HS) is a glycosaminoglycan with viscoelastic rheology. It is made up of repeating units of N-acetyl-D-glucosamine and sodium-D-glucuronate. [17] HS has a great capacity to retain water, this is one of its characteristics that is present in a large number of formulations of artificial tears, as it improves ocular hydration and reduces surface friction. [18]

HS is a derivative of hyaluronic acid and shares many of its beneficial properties. In addition to water retention, which makes it a good humectant and lubricant, HS is hypoosmolar. This hypoosmolar characteristic allows it to decrease the osmolarity of the tear and mucinoid filaments. [19]

2.2.2 Effectiveness of the product in research

The efficacy of HS 0.15% has been determined in the treatment of patients with dry eye syndrome, using 1 drop every 4 hours in each eye for 30 days, likewise the authors demonstrated that this pharmacological agent reduces inflammatory markers expressed by the cells of the corneal surface (macrophages and T lymphocytes), restores the tear film, which leads to a decrease in corneal inflammation. [20]

In another clinical trial, the efficacy of 0.18% HS was evaluated in the treatment of dry eye and it was shown that it is more efficient than 1% carboxymethylcellulose, without the differences measured in each group being statistically significant. Using fluorescein staining as a corneal status marker, it was determined that HS restores the corneal surface faster and reduces dry eye symptoms. [21]

Hyo L et al., Evaluated the efficacy of a hypotonic formulation of HS 0.18% in the treatment of dry eye. The study included 30 patients with mild dry eye syndrome, divided into: Group 1: Made up of 15 patients who received HS 0.1% (300 mOsm / l) free of isotonic preservative 1 drop 4 times a day for 90 days, Group 2 : Consisting of 15 patients who received HS 0.18% (150 mOsm / l) free of hypotonic preservative 1 drop 4 times a day for 90 days. Likewise, 30 patients with moderate dry eye syndrome participated in the study, divided into: Group 3: 15 patients exposed to isotonic 0.1% HS (1 drop 4 times a day) + 0.1% fluorometholone (2 times a day) + 0.05% cyclosporine (2 times a day). Group 4: 15 patients exposed to hypotonic 0.18% HS (1 drop 4 times a day) + 0.1% fluorometholone (2 times a day) + 0.05% cyclosporine (2 times a day). The results showed that the

use of HS at 0.1% and 0.18% are equally effective for the treatment of mild to moderate dry eye syndrome at the end of 90 days of intervention, considering the stability of the tear film and improvement of the surface corneal. [22]

2.2.3 Safety of the product in research

The safety of Lagricel® Ofteno has been evaluated in clinical studies. In a phase II clinical study, its safety and efficacy were evaluated, compared to 0.2% polyacrylic acid gel (Viscotears®), after LASIK surgery. This was a prospective, randomized, controlled study, including 30 patients, who received the study drug TID for 28 days. Outcome variables included: red eye, foreign body sensation, dry sensation, pain, photophobia, BCVA, conjunctival hyperemia, integrity of the corneal surface, corneal opacity, rose bengal staining, and findings in the periocular area and fundus . No statistically significant differences were found between the groups. [23]

In another randomized, crossover, controlled clinical study in 20 patients, the efficacy in reducing the signs and symptoms associated with dry eye disease was tested. [24]

A phase IV clinical study was recently concluded in which the effect of bromfenac ophthalmic solution 0.09% on conjunctival hyperemia in patients with pterygium, administered twice daily, compared to placebo, was concluded. Both groups used Lagricel® Ofteno TID concomitantly. The results demonstrated the efficacy of both arms in reducing hyperemia and symptoms associated with pterygium, being statistically significant when compared to baseline values. In turn, the bromfenac group was statistically superior to the placebo group. No AE related to Lagricel® Ofteno were reported. [25]

2.2.4 Summary of the pharmaceutical development of the product in research

Lagricel® Ofteno multi-dose has been developed by Sophia Laboratories, S.A. of C.V. It has the physicochemical characterization and the protocol of accelerated and long-term stabilities. The formulation is identical to that of Lagricel® Ofteno single-dose in a multi-dose presentation.

2.3 Research background

2.3.1 From the research question

There is no previous information on Lagricel® Ofteno multi-dose in clinical studies. However, the efficacy and tolerability of single-dose Lagricel® Ofteno has been previously evaluated in two single-center clinical studies. [23, 25, 24].

In the three clinical studies of Lagricel® Ofteno single-dose outcomes, TRPL, comfort, blurred vision and the incidence of AD were evaluated as outcome variables. Lagricel® Ofteno single dose was well tolerated and final results were consistently better when compared to baseline values.

2.4 Risk benefit assessment

2.4.1 Known potential risks

Eye lubricants are safe formulations. The HS has a known security profile. The diagnostic tests considered in the study design are also considered safe.

Only anticipated with the use of ophthalmic applications: burning, foreign body sensation and blurred vision. Which are of mild intensity and transitory, with a post-instillation duration of no more than one minute.

2.4.2 Known potential benefits

As they are healthy subjects, no potential benefits for the subjects are expected. An improvement in eye comfort may occur, however, it may not be significant.

The benefits of the study will be to document the safety profile of Lagricel® Ofteno multi-dose.

2.5 Statement of the problem

Although the pathogenesis of dry eye is multiple and its semiotics variable, the different phases of treatment have the use of ocular lubricants as a common denominator. There is a great variety of topical lubricants, with different wetting agents; however, there is no evidence that one is better than another.

Although ocular lubricants have not been shown to be sufficient to completely resolve the ocular surface alteration and inflammation seen in patients with dry eye, they have been shown to be effective in providing protection to the ocular surface and reducing symptoms and clinical findings.

Lagricel® Ofteno, obtains from HS its viscoelastic, hypoosmolar and water retention properties, to function as an effective lubricant that protects the ocular surface and reconstitutes the tear film, without the association of a preservative.

2.6 Justification

Patients with dry eye, regardless of its etiology and degree of severity, will have to use ocular lubricants to reduce symptoms and improve their quality of life.

Ocular lubricants constitute the first line of treatment for ocular symptoms related to dry eye in healthy referring subjects, with a prevalence of 5 to 35% in those older than 50 years. [26] If we add to this those who report occasional symptoms or that depend on some work or occupational situation and who will use it for intermittent periods throughout their lives, the spectrum of the population that will have access to these drugs is very extensive. It is estimated that 50% of patients diagnosed with dry eye without concomitant diseases will use more than 2 types of ophthalmic solutions in 5 years of treatment.

For this reason, preservative-free lubricants have gained importance, to reduce the deleterious effect of the accumulated dose of preservatives. One of the disadvantages of preservative-free

ophthalmic products is the single-dose presentation, which makes the treatment more expensive for various reasons, including the loss of the product. With the development of new technologies, it has been possible to create a new generation of preservative-free products in multi-dose presentation.

Lagricel® Ofteno multi-dose is a preservative-free lubricant in multi-dose presentation which requires documentation of its safety and efficacy profile.

2.3 Objectives and Hypotheses

2.3.1 Primary objectives

To evaluate the safety and tolerability of the multi-dose Lagricel® Ofteno formulation manufactured by Sophia Laboratories S.A. of C.V. on the ocular surface of clinically healthy subjects.

2.3.2 Specific objectives

- • Compare the safety of the Lagricel® Ofteno multi-dose formulation against Lagricel® Ofteno unit doses manufactured by Sophia Laboratories S.A. of C.V. through the incidence of AD.
- • Compare the tolerability of the Lagricel® Ofteno multi-dose formulation against Lagricel® Ofteno unit-dose manufactured by Sophia Laboratories S.A. of C.V. using the ICO score.

2.3.3 Secondary objectives

• Compare the safety of the Lagricel® Ofteno multi-dose formulation against Lagricel® Ofteno unit doses manufactured by Sophia Laboratories S.A. of C.V. through changes in CV.

• Compare the safety of the Lagricel® Ofteno multi-dose formulation against Lagricel® Ofteno unit doses manufactured by Sophia Laboratories S.A. of C.V. by changes of corneal and conjunctival staining with lysamine green.

• Compare the safety of the Lagricel® Ofteno multi-dose formulation against Lagricel® Ofteno unit doses manufactured by Sophia Laboratories S.A. of C.V. by changes in corneal and conjunctival staining with fluorescein.

• Compare the safety of the Lagricel® Ofteno multi-dose formulation against Lagricel® Ofteno unit doses manufactured by Sophia Laboratories S.A. of C.V. by changes in conjunctival hyperemia.

• Compare the safety of the Lagricel® Ofteno multi-dose formulation against Lagricel® Ofteno unit doses manufactured by Sophia Laboratories S.A. of C.V. through the incidence of chemosis

2.3.4 Hypotheses

H0 = Lagricel® Ofteno multi-dose ophthalmic solution has a safety and tolerability profile similar to Lagricel® Ofteno single-dose in healthy subjects.
H1 = Lagricel® Ofteno multi-dose ophthalmic solution has a different safety and tolerability profile than Lagricel® Ofteno single-dose in healthy subjects

2.4 Study design

2.4.1 Description overall design

Phase I, single-center, controlled, parallel-group, open-label, randomized clinical trial.

2.4.2 Justification of the study design

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

2.4.3 Expected duration

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

The planned recruitment period is 3 months. Considering that the proposed sample is 34 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.

2.5 Study population

2.5.1 Elegibility criteria

2.5.1.1 Inclusion criteria

- Be clinically healthy

- Have the ability to voluntarily grant your signed informed consent

- Be able and willing to comply with the scheduled visits, treatment plan and other study procedures

- Be between 18 to 45 years old.

- Women of childbearing age must ensure the continuation (started ≥ 30 days prior to signing the FCI) of use of a hormonal contraceptive method or intrauterine device (IUD) during the study period

- Have a best corrected visual acuity of 20/30 or better in both eyes.

- Have vital signs within normal parameters.

- Have an intraocular pressure ≥10 and ≤ 21 mmHg

2.5.1.2 Exclusion Criteria

- Be a user of topical ophthalmic products of any kind.
- Being a user of medicines, or herbal products, by any other route of administration.
- In the case of women: be pregnant, breastfeeding or planning to become pregnant within the study period.
- Have participated in clinical research studies 90 days prior to inclusion in the present study.
- Have previously participated in this same study.
- Be a user of contact lenses and cannot suspend their use during the study.
- They cannot follow the lifestyle considerations described in section 5.3.
- Having started the use of 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 entry to the study.
- Present unresolved injuries or trauma at the time of study entry.
- Have a history of any type of eye surgery.
- Having undergone surgical procedures, not ophthalmological, in the last 3 months.
- Being or having an immediate family member (for example: spouse, parent / legal guardian, brother or child) who is part of the research site staff or the sponsor directly participating in this study.

2.5.2 Elimination Criteria and Substitution of subjects

5.2.1 Elimination criteria

- Withdrawal of the FCI letter.
- Presentation of a serious adverse event related or not to the investigational product, which at the discretion of the PI and / or the sponsor could affect the patient's ability to continue with the study procedures safely.
- Non-tolerability or hypersensitivity to any of the compounds used during the tests (fluorescein, green lysamine, tetracaine).
- Non-tolerability or hypersensitivity to any of the drugs under investigation.

5.3.1 Subtitution of sujects

The sponsor, with prior authorization from the research ethics committees, may decide to replace the subjects who withdraw their CRF or those who present loss of follow-up, in case it is necessary to balance the study groups so that they are evaluable.

2.5.3 Lifestyle considerations

For the study, participants may have to modify some lifestyle activities to meet the following:
- Refrain from tobacco use.
- Refrain from the use of electronic vaporizers.
- Avoid submerging in water without eye protection (goggles-protective glasses).
- Avoid direct exposure to fans (including air conditioning vents) during activities involving sight. 24 hours before your review visits.
- Maintain your sleep-wake cycle with which you enter the study.

2.5.4 Counting failures

A scrutiny failure is defined as those participants who agree to participate in the study, giving their consent, but who are not assigned to a treatment group, that is, they do not enter the study. The following information on scrutiny failures must be reported at a minimum:

- Demographic data.

- Details of the scrutiny failure (specify if it is due to the eligibility criteria, to which, or some other reason for the failure).

- Presence of serious adverse events during the scrutiny.

This is necessary to comply with the CONSORT (Consolidated Standards of Reporting Trials) guidelines for the publication of results or to answer possible questions from the regulatory authorities.

Subjects who do not meet the eligibility criteria to participate in the study due to a specific modifiable factor may be eligible for re-scrutiny. Subjects in this case must use the same initial scrutiny number.

2.5.5 Recruitment and retention strategies

This is a phase I study, which is planned to be conducted in 1 center. The selected center will be responsible for the recruitment of the 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 they will only have to attend one visit after the baseline, so no retention problems are anticipated. However, the subjects will be creditors of a travel allowance for transportation and to fulfill their visits. Other strategies to improve subject retention include, but are not limited to:

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

- Make calls or send text messages to remember appointments or activities to do.

- Provide a printed calendar and an identification card in order to remember appointments and activities to be carried out, in addition to the estimated time of their duration.

- Offer flexible service hours.

- Systematic organization of the study procedures, so that the subject does not last longer than necessary during his visit.

- Minimize the waiting times of the subject. All the materials to be delivered to de subject or recruitment strategies implemented by the Centers, will be submitted for approval bye the corresponding committees.

2.5.6 Procedure in case of loss of follow-up

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

In the event that the participating subject does not attend their appointment, the research center must make a call to find out the reason and will try to make a new appointment within the established window period or an unscheduled appointment. In the event that it is not possible to make an appointment, the presence of adverse events and the reason for leaving the study will be asked, as minimal data.

It is considered that a loss to follow-up <10% does not represent a problem for the validity of the results obtained. [27, 28]

2.5.7 Identification of the subject

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

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

Example:

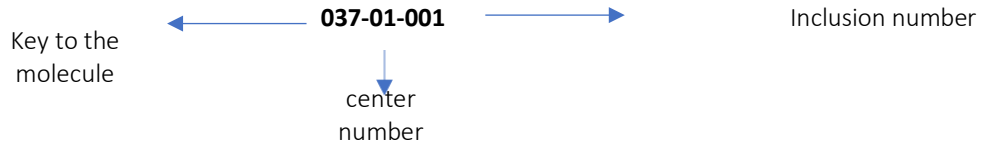
A. Arieh Daniel Mercado Carrizalez
   a. Initials: AMC

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

In the scrutiny stage (within the baseline visit) the participant number will be assigned consecutively, using 3 consecutive digits. Once the subject has been selected, he will be assigned a number with which he 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 by the sponsor.
- two digits corresponding to the research center number..
- three digits of the consecutive number assigned to their inclusion in the research center.

Example:



2.6 Investigational product

2.6.1 Managed Products

2.6.1.1 Investigational Product

- Generic name: Sodium Hyaluronate
- Distinctive name: Lagricel® Ofteno multi-dose (PRO-037)
- Active principles: Sodium Hyaluronate 0.4%.
- Excipients: sodium chloride, monobasic sodium phosphate monohydrate, anhydrous dibasic sodium phosphate, water for the manufacture of injections.
- Pharmaceutical form: Ophthalmic solution
- Presentation: multi-dose dropper bottle.
- Prepared by: Sophia Laboratories S.A. of C.V.
- Description of the solution: clear solution, free of visible particles.
- Description of the container: White bottle with a capacity of 10 mL, made of low-density polyethylene.

2.6.1.2 Reference product

- Generic name: Sodium Hyaluronate
- Distinctive name: Lagricel® Ofteno unit dose
- Active principles: Sodium Hyaluronate 0.4%.
- Excipients: sodium chloride, monobasic sodium phosphate monohydrate, anhydrous dibasic sodium phosphate, water for the manufacture of injections.
- Pharmaceutical form: Ophthalmic solution
- Presentation: Single dose vial.
- Prepared by: Sophia Laboratories S.A. of C.V.
- Description of the solution: clear solution, free of visible particles.
- Description of the container: transparent vial with a capacity of 0.5mL.

2.6.1.2.1 Justification of the reference product

Lagricel® Ofteno unit dose is a commercially available lubricant, with a previously described safety and efficacy profile.

2.6.1.3 Dosage of Investigational Products

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

2.6.1.3.1 Dose justification

Ophthalmic lubricants are generally prescribed as needed (pro re nata [PRN]). [29] However, the study by Asbell et al compared the efficacy of QID versus PRN. Their results showed that, although there was no difference in clinical signs, the QID group had greater improvement in symptoms. [30] For this reason it is proposed as a posology for this study.

6.2 Storage and handling of research products in the study center.

The delivery will be made by means of a courier service hired by the sponsor, expressly selected for this purpose, to the address of the research center according to the study plan.

The reception will be carried out by the assigned personnel of the investigation team. You must verify the good condition of the primary packaging (box). In the event that it shows alterations or defects in its integrity that from its judgment could have damaged the content, it must report it to the sponsor. If the package does not show significant defects, proceed to open it.

Inside you must locate the acknowledgment of receipt document and the temperature data logger. You should check that the registered temperature complies with what is specified 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, they will sign the receipt and send it to the sponsor. Otherwise, it will notify the sponsor.

Storage and protection is the responsibility of the research center. The medicine must be kept in a secure area with restricted access.

The storage temperature should be no more than 30 ° C.

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

In the event of material loss, it must be documented in the entry and exit log together with a clear description of the mechanism by which the loss occurred.

Upon completion of the protocol, all study material will be retrieved by the sponsor as part of the closing audit. The final delivery of material will be made by the principal investigator or the person designated by him to deliver the material at the end of the study.

The sponsor reserves the right to initiate civil and criminal actions against the principal investigator in the event of a lack of undocumented material at the end of the study.

6.3 Unauthorized concomitant treatments and medications during the study

The use of concomitant medications by any route of administration will not be allowed during the intervention period. Except those specified for the study procedures. The objective of this restriction is to avoid pharmacological interactions that could alter the results of the variables evaluated.
Allowed drugs:

- Ophthalmic:
    - o Tetracaine 0.5%

- Tropicamide 0.8% /Phenylephrine 5%

6.4 Procedure to monitor and measure adherence

For more than four decades, numerous investigations have been conducted on the appropriate way to measure and quantify adherence to medications, however none has reached a consensus to establish itself as the gold standard, both in cross-sectional and longitudinal studies. [31, 32, 33, 34, 35, 36, 37, 38]

There are different procedures to measure adherence to pharmacological interventions. The most common procedure involves self-reports, these include: patient interviews, questionnaires and self-monitoring diaries. Its strengths are speed, flexibility, low cost and ease of implementation; they have a high degree of specificity for non-adherence, however, the sensitivity and reliability for adherence is low. [38, 39]

Biochemical measurement of the drug, or its metabolite, is one of the methods that best confirms the use of the drug. However, in addition to being costly and impractical, it is of little use in the context of ophthalmic applications, as concentrations at the peripheral level could be undetectable; and samples from other tissues involve more invasive methods that would not be advisable. [38]
Counting medication is another way to measure adherence. Classically referred to as "pill count", in ophthalmology it translates to the weight of the bottle. This is a simple, inexpensive, and non-invasive method. The main disadvantages of this method are: 1. The application of the drug cannot be confirmed (it may have been intentionally thrown or instilled out of the eye) and 2. Depends on the subject bringing the medication back. [38, 39]

The approach with multiple adherence measurement procedures is recommended. Because there is no ideal adherence measurement, it is appropriate to use more than one method when trying to achieve realistic results. Selecting two or more methods allows their strengths and weaknesses to be offset, to more accurately capture adherence levels. [37]

Due to the characteristics of the containers, the evaluation of adherence will be favored through the subject's diary. The following simplified formula will be used:

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

$Ad = Adhesion$

$Ar = Registered\ applications$

$Ai = Applications\ indicated\ for\ the\ products\ under\ investigation$

There is no standardized parameter to define adequate adherence, it must be defined and delineated by the objectives of the particular research. [38]

For this study, it will be considered that a minimum adherence of 70% is what is necessary to meet the research objectives. Therefore, subjects who present an adherence of less than 70% will not be considered for the efficacy analysis, they will only enter the safety analysis.

6.5 Strategies to improve adherence

1. The IP will sensitize the subject on the importance, to achieve the objectives of the study, of the correct application of the IP.
2. Direct questioning by the IP about the application of the IP.
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 these messages must be previously approved by the CEI.

7. Study methods and procedures

7.1 From the research center

The present study will be carried out in 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 current regulations.

The research center will be responsible for forming a multidisciplinary research team to execute the clinical study according to protocol. It is their prerogative to design the organization and select the personnel who will carry out the functions. However, it is the sponsor's need for the Principal Investigator (PI) to be an ophthalmology specialist.

Any person who is appointed, under their responsibility, a part of the study follow-up (co-investigator, sub-investigator, nurse, etc.) or a specific role for participation in the study (pharmacist, administrative assistant, study coordinator, etc.) It must appear in the "Delegation of Responsibilities".

The competence and training of any person who has direct participation in the study activities must be verified before carrying out any activity related to the protocol. The foregoing must be recorded and the documents that constitute evidence of this competence and / or training must 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 the personnel of the study centers participating in the study are adequately trained on the study (research protocol, investigator's manual, amendments, standard operating procedures, etc.) and on the Good Clinical Practices of the ICH, before the start of your participation in it. Training must be recorded in writing and those records must be filed in the study master file.

Clinical study registration

This clinical study will be registered by the sponsor in public registries of clinical trials before its initiation (inclusion of the first patient): National Registry of Clinical Trials (RNEC) of the Federal Commission for the Protection against Sanitary Risks (COFEPRIS) and on a platform WHO primary registry. WHO Primary Registries meet specific criteria for content, quality and validity, accessibility, unique identification, technical capacity, and administration. WHO Primary Registries meet the requirements of the International Committee of Medical Journal Editors (ICMJE).

7.2 Randomization and Blinding

Subject randomization will be carried out using a computerized assignment system. After signing the FCI, the patient will receive a patient number with which all their information will be coded pseudo anonymously during collection and completely anonymized during analysis.

The generation will be carried out by a third party, authorized by Sophia Laboratories S.A. of C.V., through its electronic system. The information for this third party will be in the file.

Although it is an open study, the secondary container will be masked.

PIs will be identified by means of labels in accordance with current and applicable regulations, they must contain at least:

- Name, address and telephone number of the sponsor.
- Pharmaceutical form and route of administration.
- Lot Number.
- Legend "Exclusively for clinical studies"
- Date of Expiry.

7.3 Outcomes Variables

7.3.1 Primary outcome Variables

- Incidence of adverse events (AE) (Evaluation Time: day 8 and 10).
- Score of the Ocular Comfort Index (ICO) (TE: day 8).

7.3.2 Secundary outcome variables

-Changes in the BCVA (TE: day 8).
-Changes in corneal and conjunctival staining with lysamine green (TE: 8).
-Changes in corneal and conjunctival staining 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 their measurement

Variable	Type	Unit (Symbol)	Method of measurement	normal value	evaluation time	statistical test
Primary						
Adverse events	Discreet Categorical nominal	Number of cases (n) Present/ absent	Counting Observation	0 Absent	VB, V1, VF y LLS	U de Mann-Whitney χ2 or exact by Fisher
Score of	Discreet	Points	Questionnaire	NA	VB, VF	U de Mann-Whitney
Secondary						
MAVC	Discreet	Fraction	Poster of Snellen	1	VB, V1 y VF	U de Mann-Whitney
Corneal and conjunctival fluorescein staining	Ordinal	Levels	Direct observation with slit lamp and cobalt blue filter, Oxford scale graduation	0	VB, V1 y VF	χ2 or exact by Fisher
Corneal and conjunctival staining with lysamine green	Ordinal	Levels	Direct observation with slit lamp, Oxford scale graduation	0	VB, V1 y VF	χ2 or exact by Fisher
Conjunctival hyperemia	Ordinal	Normal / Very Mild / Mild / Moderate / Severe	Direct observation. Clasification of Efron.	Normal	VB, V1 y VF	χ2 or exact by Fisher
Chemosis	Categorical nominal	Present / absent		Absent	VB, V1 y VF	χ2 or exact by Fisher

Table 2. Defoperational definition of variables

The variables, the method and scales for their measurement are described in detail below. They are in order according to Table 2

7.3.3.1 Adverse events

As defined in section 8.2, an AE is any unfavorable medical occurrence in a subject to whom an PI is administered, regardless of the causal attribution.

The management of AEs will be carried out according to what is described in the Adverse Events section.

The IP will register in the corresponding section of the FERC the AE that the study subjects present in addition to referring it in the clinical file.

For an adequate evaluation of the AE, in addition to the directed questioning, it is necessary to carry out at each visit the Ophthalmological Ophthalmological Evaluation of the eyelids and attachments; anterior segment and posterior segment that is performed in a routine ophthalmological examination, whose procedures are not specifically included in the study variables. The posterior pole evaluation can be with direct or indirect ophthalmoscopy, with or without pharmacological mydriasis, at the discretion of the PI. An evaluation of the fundus will be carried out in search of abnormalities that alter the result of the study. The IOP will be measured in this evaluation, with the instrument of choice of the PI, it should be measured after the evaluation of the stains. The result of the assessment will be recorded in the clinical file. In the FERC, only the findings that are considered by the IP will be reported as EA.

Expected AEs for the use of IPs are: blurred vision, burning, eye irritation, foreign body sensation and sticky eyelash sensation. They are expected to be transient, lasting no more than 30 seconds after PI instillation, and to be of mild intensity..

7.3.3.2 ICO score

The ICO is a questionnaire designed to measure the irritation of the ocular surface with Rasch analysis to produce estimates on a linear interval scale (scores: 0-100). Similar to the index for ocular surface diseases, the ocular comfort index (ICO) assesses symptoms. The ICO contains items that focus on discomfort associated with ocular surface disturbances. Each of these questions has two parts, which separately inquire about the frequency and severity of symptoms. [40]

The evaluator will deliver the questionnaire to the subject and will allow him to answer it calmly without any pressure and / or coercion, he will only assist him if he has 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 Best Corrected Visual Acuity

Visual acuity (VA) is a test of visual function. Spatial AV is the ability to distinguish separate elements of an object and identify them as a whole. It is quantified as the minimum angle of separation (located at the nodal point of the eye) between two objects that allows them to be perceived as separate objects.

Snellen's notation is described as the distance at which the test is performed, divided by the distance at which the letter is vertically equal to 5 arc minutes. Thus, at 6 meters a letter 6/6 (20/20) is equivalent to 5 arc minutes, 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 (that is, 20/20 = 1 and 20/40 = 0.5). [41]

VA will be evaluated baseline, without refractive correction with the Snellen chart. Which will be located in a place with adequate natural or artificial lighting 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 (OD) asking the subject to keep both eyes open and using an occluder to cover the left eye (OS); The subject will read aloud the lines that the evaluator indicates, the line of smallest letters that can be seen will be noted by the evaluator in fraction as the VA of OD in the clinical record. The OS is proceeded with the same method.

Subsequently, the subject's objective and subjective refractive correction will be carried out. The result of the subjective refraction will be reported as BCVA, it will be noted in fraction in the clinical record and in the FERC, also in the FERC it will be noted in decimal. By definition, BCVA cannot be lower than VA.

Handling as EA: a decrease of more than 2 lines in the Snellen chart should be reported and handled as EA.

7.3.3.4 Corneal and conjunctival fluorescein staining

A drop of topical anesthetic will be instilled in the conjunctival cul-de-sac, then a second drop will be applied to the tip of the fluorescein strip allowing it to settle 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 cul-de-sac, while the patient looks up, without damaging the conjunctiva. It will be graded according to the Oxford scale. [42]

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

Management as AE: corneal stains that are equal to or greater than grade III will be considered as AE.

7.3.3.5 Conjunctival staining with lysamine green

After the fluorescein check, a drop of saline will be applied to the tip of the lysamine green strip, allowing it to settle on the strip for 5 seconds to elute the dye. A drop of the strip is instilled into the temporal cul-de-sac, while the patient looks up, without damaging the conjunctiva. The patient may be asked to blink repeatedly to avoid accumulation in the conjunctival folds. The examination should be done 1 to 4 minutes after instillation through a neutral density filter or with the filter free of red. It will be graded according to the Oxford scale. [42]

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

Management as AE: corneal stains that are equal to or greater than grade III will be considered as AE.

7.3.3.6 Conjunctival hiperemia

Conjunctival hyperemia is defined as the simplest reaction of the conjunctiva to a stimulus, a red appearance is seen secondary to the vasodilation of the conjunctiva vessels of variable intensity. You will graduate using the Efron scale. [43] See annex.

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

7.3.3.7 Chemosis

It is defined as conjunctival edema, the result of an inflammatory reaction. It is qualified as present or absent. The evaluator will use a narrow beam of light at 60 ° and will measure if the conjunctiva separates from the sclera by ≥ 1/3 of the total lid opening or if it exceeds the gray line. [44]

Handling as EA: your presence will be considered as an EA.

7.4 Program of visits and study activities

7.4.1 Description of activities per visit

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

7.4.1.1 Basal visit

- -FCI Signature: refers to the signature of the written informed consent document. Without obtaining informed consent, it is not possible to perform any of the study procedures
- -Clinical history: refers to the technical, clinical and legal document in which the subject's health conditions, medical acts and other procedures performed on the subject are chronologically recorded. It includes anthropometric measurements, anamnesis, comprehensive ophthalmological examination that allows discerning the eligibility of the patient, that is, evaluation of both eyes of ocular attachments, slit lamp examination of the ocular surface and anterior segment, and funduscopy. If the subject is taken from the established population base of the study center, the existing clinical history may be used, only an update being required.
- -Evaluation of concomitant medications: refers to the questioning by the PI of the subject, inquiring about the use of medications.
- -Pregnancy test in urine: It refers to the realization of a rapid pregnancy test in all women of childbearing age who wish to enter the study. By childbearing age we understand women who have had their menarche and have not had their menopause. Menopause is defined as 12 months from the last menstruation in women over 40 years of age, or who have undergone a bilateral hysterectomy or oophorectomy. Women of childbearing potential with contraceptive methods including bilateral tubal obstruction should undergo a pregnancy test. This test will be performed by the IP or the designated team person in accordance with the instructions of the device provided by the sponsor
- -Vital signs: refers to the taking of heart rate, respiratory rate, systemic blood pressure and temperature. This information must be contained in the patient's medical record and the progress notes of the patient's clinical record.
- -MAVC: See 7.4.3.2
- -ICO: See 7.4.3.2
- -Ocular surface stains: See 7.4.3.4 and 7.4.3.5
- -Ophthalmological evaluation: See 7.4.3.1
- -Eligibility criteria: refers to the review by the PI, where it verifies that the subject can be included in the study by meeting the inclusion criteria and not meeting the exclusion criteria. See 5.1

-Assignment of PI: It refers to determining the intervention that the patient will follow during the study. It will be carried out according to section 7.3. This assignment will be made at the baseline visit (day 1).

-Delivery of the PI and start of intervention: It refers to the delivery of the PI to the study patient, by the research center. See

-Evaluation of EA: See 7.4.3.1

-Delivery of patient material and filling instructions: It refers to the delivery by the IP to the subject of the subject's diary, identification card and calendar, improving adherence. The assigned personnel will carry out a previous training to the subject, on the filling of the diary.

7.4.1.2 Final Visit

- -Evaluation of concomitant medications: See further 7.5.1.1
- -Pregnancy test in urine: See above 7.5.1.1
- -Vital signs: See above 7.5.1.1
- -MAVC: See 7.4.3.2
- -Ocular surface stains: See 7.4.3.4 and 7.4.3.5
- -Integral ophthalmological evaluation: Ver7.4.3.1
- -Evaluation of EA: See 7.4.3.1
- -ICO: See 7.4.3.2
- -Evaluation of the Subject's Diary: See 7.5.1.1
- -Evaluation of adherence: See 7.5.1.1
- -Return of PI and subject's diary: refers to the return by the subject, of the PI and the subject's 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, unscheduled follow-up visits may be carried out to report adverse events. During these visits, all pertinent data on reported adverse events should be collected and, where appropriate, an appropriate management plan should be established.

7.5 Data collection

7.5.1 Source documents

Source documents are all written or printed records derived from automated processes (for example: prints of laboratory results issued by automated analysis equipment) where the information is recorded for the first time and which is part of the permanent records of the history of the patient. Examples of source documents are the medical history, the clinical progress notes, the laboratory reports, the cabinet study reports, the nursing notes, the follow-up notes, the surgery records, etc.
The IP agrees to accept the monitoring of information related to the study, audits, review by ethics and research committees, and inspections by the health authority, this obligation implies direct access to source documents.

7.5.2 Electronic forms of data collection

All data related to the protocol will be captured through an electronic form of case report (FERC) by the staff of the investigation team. The data related to the protocol should NOT be captured directly in the FERC, but must be transcribed from the corresponding source document. This procedure allows monitoring to verify the information captured in the FERC. It is the responsibility of the researcher that the information is transcribed to the FERC in a correct, complete and timely manner. It is understood that all FERC forms captured and submitted for data analysis are approved by the Investigator.

7.5.3 File

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

8. Assessment and management of adverse events

8.1 Regulation and regulations on adverse events

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

8.2 Definition of adverse event

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

Therefore, an AE can be any of the following: any unfavorable and unintended disease, symptom or sign (including an abnormal laboratory finding) that is temporarily related to the use of a medical product, whether or not it is considered related with said product; any new disease or exacerbation of an existing disease (worsening of the nature, frequency, or severity of a known condition); relapse of an intermittent medical condition (eg, headache) not present at baseline; any deterioration in a laboratory value or other clinical test (eg, electrocardiogram [ECG], X-ray) that is related to symptoms or that results in a change in study treatment or concomitant treatment or discontinuation of study drug.

8.3 Definitions relevant to the classification of adverse events

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

Severity (mild, moderate or severe). Those that present with minimal symptoms are mild, do not require treatment or suspension of the medication; moderate, when they interfere with normal activities, without threatening the patient's life, require treatment and may or may not require discontinuation of the medication; severe, those that interfere with normal activities and require drug treatment and discontinuation of medication.

Causality. It is the relationship that is assigned between the drug and the adverse event: certainly caused by the drug, there is clear evidence of causality, i.e. the adverse event reappears with the administration of the drug; Probably caused by the drug, there is a high suspicion of causation but there is no direct evidence or it is considered unnecessary or dangerous, i.e. the reaction disappears when the drug is stopped; possibly caused by the drug, there is additional information to suggest that the cause may be due to another drug or disease; unlikely to be caused by the drug, there is a

clear explanation of the origin due to the underlying disease or the use of another drug; conditional, missing data to issue clear causality; not classifiable, those for which once all the possible information on the adverse event has been obtained, it continues to be unclassifiable.

8.4 Investigator responsibilities

It is the Investigator's responsibility to verify AE through questioning, reviewing the information recorded in the subject's diary, the pertinent physical examination, the evaluation of evolution, as well as the appropriate medical and pharmacological management; as well as follow up until the resolution or outcome and definitive discharge of the EA, following the definitions determined in the national and international regulations. [45] [46] [47]

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

The attention of the AE will be carried out according to the diagram of attention to the event (see **Figure 4. Attention to the adverse event**).

In the final report to be drawn up by the Clinical Team of the Department of Clinical Operations of Laboratorios Sophia, S.A. de C.V., the report of adverse events will be included in compliance with current national and international regulations. [46] [45]

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

8.4.1 Recording of adverse events in the electronic form of case report

EA registration considers:

- The identification information of the subject such as: subject number, age, sex, and if applicable specify the eye.
- Information about the causality of the AE, its relationship to PIs, or to another drug related to the study, as appropriate.
- The information of important dates:
  o Date the EA occurs
  o Date in which the IP is aware of it
  o Date of resolution or outcome, as applicable.
- Diagnosis information and clinical management.

- If a lack of therapeutic response to PIs is detected, it must be reported as a serious adverse event within the term stipulated by current regulations. Include in concomitant medications the therapy used for the pharmacological management of the adverse event.
- Establish the outcome or resolution of the event:
  o Recovered / resolved without sequelae
  o Recovered / resolved with sequelae
  o Not recovered / Not resolved
  o Patient who presented death due to AD
  o Patient who died and it is judged that the drug may have contributed
  o Patient who died and this is not related to the product or drug under investigation,
  o Unknown
- Information about the product or investigational drug or the drug associated with AD, RAM or SRAM. As applicable, the information concerning the generic name, distinctive name or IP code and / or investigational drug must be recorded, as appropriate according to the methodological design of the study, this is relevant in the case of blinded studies or in those where they are used. placebo as comparators, since there are circumstances that justify opening the blind to determine if the adverse event may be attributable to the active agent, the combination of active agents, or to the pharmacologically inert substance (s), as they can be the vehicle or additives, according to the clinical research phase in which the development of the drug is located. Likewise, it will be necessary to record the data concerning the batch number, manufacturer laboratory, expiration date, dose, route of administration, start and end dates of administration and / or consumption, reason for the prescription; according to whether it is a product or drug under investigation (protocol in which the patient currently participates) or is a drug that the research subject consumes for the treatment of underlying concomitant diseases or uses for the management of any sign or transitory symptom that does not correspond to the Natural History of the pathology that motivated their entry into the research protocol.
- -Indicate the withdrawal or maintenance of the medication, as appropriate. Indicate if the withdrawal of the PI or investigational drug or suspected drug (causing the event) disappears the adverse event. Likewise, indicate if a dose adjustment is made, if the event changes in intensity or seriousness, persistence of the reaction. It is important to indicate if in those subjects who are exposed again to the drug, which had previously been suspended, the AE reappears.

- -The information regarding concomitant pharmacotherapy. Indicate the generic name, the dose, the route of administration, the start and end dates of its 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 it is used outside the regulations or of what the local, national or international regulatory entity has authorized.

-The information of the relevant clinical history. The AE analysis considers the previously narrated information, despite 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 phenomena or allergy, previous surgical procedures, laboratory analysis or office examinations that have been performed on the participant, etc., that the researcher deems appropriate to mention may do so.

8.4.2 Adverse event monitoring

The IP will provide the attention and follow-up of 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 AE care process considers the following stages:

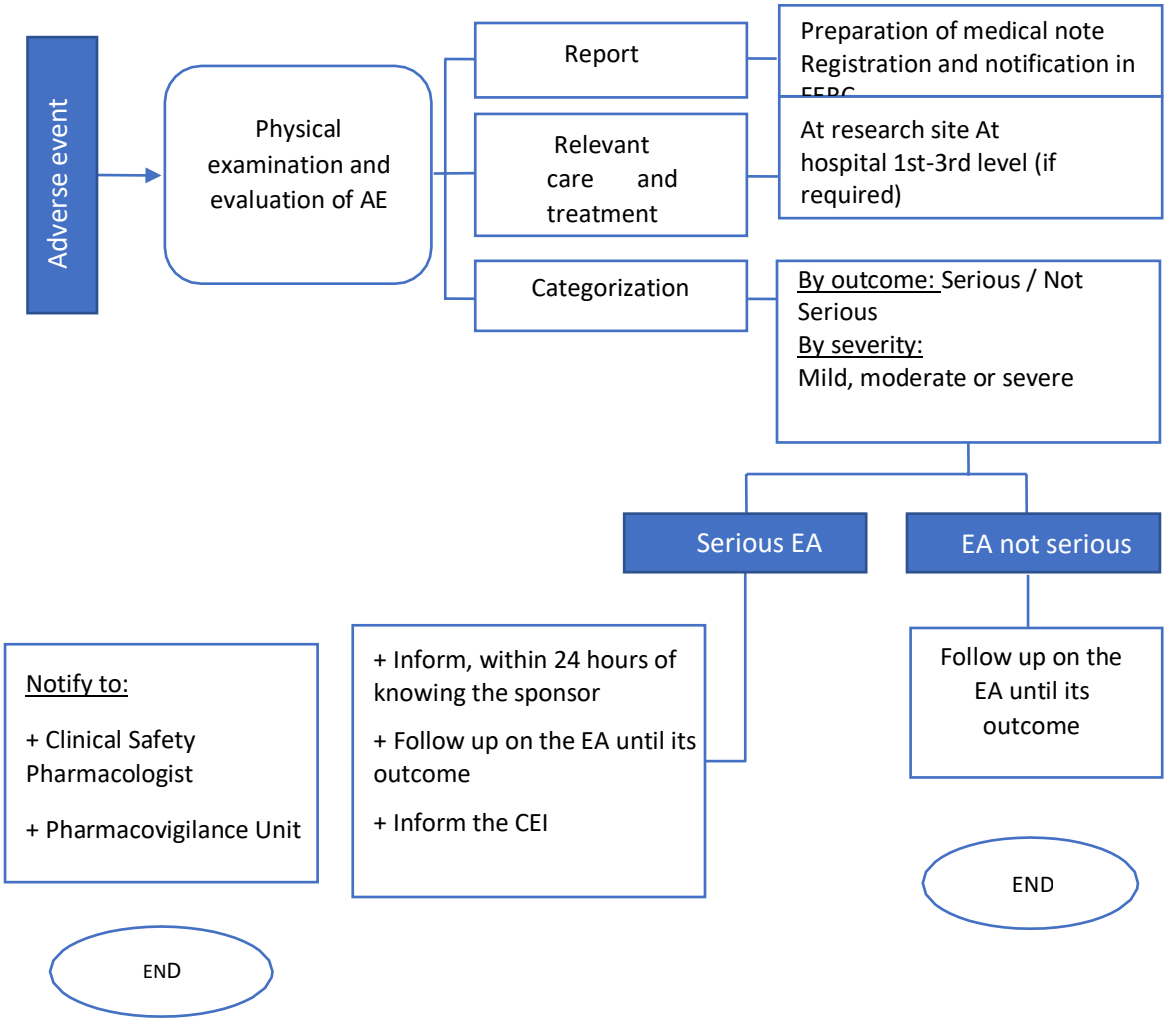


Figure 4. Attention to the adverse event

During the development and conduct of the present study, undesirable harmful events or adverse reactions, of medical implication, may occur in the research subject, which do not necessarily have a causal relationship with PIs. These harmful phenomena can occur during the use of investigational drugs at authorized doses, for use in humans, by a local, national or international regulatory entity. However, the PI or the investigational drug may be suspected of causing some unwanted clinical

manifestation. AE, ADR or ARS to one or more medications can occur during the systematic evaluation of the participants (on the days when 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 has developed or presented any harmful phenomenon of a clinical nature during his participation in this study.
2. According to her clinical judgment; Based on the pertinent physical examination, questioning, etc., as well as the analysis of the information available in the medical literature and what is referred to in the investigator's manual, Prescribing information, or the comparator drug's technical sheet, the principal investigator determines the relevant attention to the damaging event / reaction.
3. This care can be in the research center or in the hospital with the highest resolution power. In such a way that, in the event that the patient is sent by the IP to a hospital, he / she assists through a referral system. The referral can be with a card that identifies the subject as a study participant and links him to the pre-established agreement with the institution, or through a medical reference note issued by the IP. Laboratorios Sophia, S.A. de C.V., will pay the expenses for the medical care of the participating patient, when the adverse event is associated or is related to the PI or investigational drug.
4. Taking the clinical information collected, either during the care provided at the research center or that provided by the treating physician (s) at the hospital, the IP will record the AE in their clinical note, recording the seriousness, intensity (mild, moderate, or severe) and relationship to the investigational product or drug.
5. The IP must migrate the relevant data to the FERC and its respective adverse event section. By virtue of the fact that, in cases of serious adverse events, the clinical monitor of the study must be notified within 24 hours after knowledge of the same, so that in turn it informs the Clinical Team and the UTFLS, and that subsequently find out to the CEI. Regarding non-serious adverse events, these will be recorded and treated appropriately 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 AE depends substantially on the follow-up that the PI performs on the subject, since it is expected that most of the harmful phenomena (see section of the safety profile in paragraph 5.3 and in the investigator's manual) are of an ophthalmic nature. however, there may be systemic alterations. Therefore, in the opinion of the researcher, the withdrawal of the participant or their permanence will be considered.

8.4.4 Assessment of causality

Causality assessment is called the methodology used to estimate the probability of attributing the observed adverse event to a drug. It considers probabilistic categories according to the available evidence and the quality of the information, based on the national pharmacovigilance regulations. [45]

The Pharmacovigilance and Technovigilance Unit of Sophia Laboratories (UFTLS) can use the Karch and Lasagna algorithm 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 allow assigning a value to the cause-effect relationship between the administration of the drug and the adverse reaction. [48] See **Table 3. Karch and Lasagna algorithm modified by Naranjo.**

No.	Reagent	Score	
		Yes	**No**
1.	There are previous conclusive reports on adverse drug reaction, adverse event or suspected adverse drug reaction	+1	0
2.	The adverse event appeared when the suspect drug was administered	+2	-1
3.	Adverse drug reaction, adverse event, or suspected adverse drug reaction improved upon suspension or administration of a specific antagonist	+1	0
4.	Adverse drug reaction / adverse event / suspected adverse drug reaction reappeared when drug / investigational product / investigational drug was administered	+2	-1
5.	There are alternative causes that can cause this reaction	-1	+2
6.	Adverse reaction / adverse event / suspected adverse drug reaction occurred after administration of placebo	-1	+1
7.	Drug was determined in blood or other fluids at 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 / drug or investigational drug in the past	+1	0
10.	The adverse reaction / adverse event / suspected adverse drug reaction was confirmed with some objective evidence	+1	0
	Total score	summatio	
	Probabilistic category based on the score obtained		
I	The causal relationship is verified	≥,9	
II	The ADR is likely due to the investigational drug or product	5 a 8	
III	The ADR may be due to the investigational drug or product	1 a 4	
IV	The causal relationship is doubtful	0	

Each item receives a defined score and the final sum allows estimating the probabilistic category of the cause-effect relationship between the administration of the product under investigation and the adverse reaction, adverse event or suspected adverse reaction.

Table 3. Karch and Lasagna algorithm modified by Naranjo

In such a way that the degree of certainty to establish PI as the causal agent of the harmful phenomenon that happens to the subject of the clinical study. It can also be indicated directly by the IP based on their clinical experience or through the voluntary application of the previously

mentioned 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 the possible pharmacological or pathophysiological mechanisms involved in the development or presentation of the adverse event.
e) Experimental findings, for example, the appearance of abnormal metabolites or high levels of the 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, that is, objectivity, accuracy and validity of the relevant documentation. [49]

8.5 Unanticipated problems

Unanticipated problems (PNA) consider those situations that pose risks to the participating subjects, in general, any incident, experience or result that meets all the following criteria:

- Unexpected in terms of its nature, severity or frequency in relation to: 1) the documents related to the study such as the investigator's manual, study protocol and informed consent format; and 2) the characteristics of the population being studied.
- Related or possibly related to your participation in the study (possibly related means that there is a reasonable possibility that the incident, or results, was caused by procedures specific to the study).
- Indicative that the research places the participants at a greater risk of harm (including physical, psychological, economic or social) than previously recognized.

8.5.1 PNAs report

The IP will be responsible for reporting NAPs to the sponsor, the IC, the CEI. The report must contain the following information:

• Study identification: protocol title and number, IP name and, where appropriate, the center.

• Detailed description of the event, incident, experience or result.

• Explanation, justification of the reasons why the incident represents a PNA.

• Description of the changes to the protocol or corrective actions taken or proposed in response to the NIP.

The NAPs that are EAS must be reported to the CEI and the sponsor within the first 24 hours that the IP became aware of this.

Any other NAP will be reported to the CEI and the sponsor in the first 5 business days, after the IP became aware of it.

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 tracking of adverse events, monitoring for resolution of capture discrepances data, etc.
Responsibility for monitoring activities and ultimate responsibility for monitoring rests with the sponsor.
The details of the monitoring activities are specified in a separate document of 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 performance of one or more follow-up visits between these two mandatory visits.

The initial visit must be carried out before the inclusion of the first participant in that center; In it, 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 have been trained on the study, and will also verify that the regulatory requirements and standardized procedures of applicable operation.

At the follow-up visit (s), the monitor will review the study documents to confirm that: the investigation protocol and applicable standard operating procedures are being followed, the data is complete and timely, and that reports of adverse events are being carried out appropriately. At each visit, the monitor will discuss the findings with the researcher and define the actions to be taken.

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

Details about monitoring are set out in the corresponding plan.

9.2 Audit and quality control

To guarantee compliance with the GCP and with all applicable regulatory requirements, Sophia Laboratories S.A. of C.V. could carry out quality assurance audits. Regulatory agencies could also carry out a regulatory inspection of this study.

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

9.2.1 Pre-study Audit

The study centers included in the study will be subject to a feasibility visit prior to the selection of the center, where it will be verified that they meet the minimum requirements indicated by the sponsor.

9.2.2 Audit while conducting the study

They may take place at any time before, during or after the conclusion of the study. If any audit or inspection is performed, the investigator and the institution should agree to allow the auditor / inspector to have direct access to all relevant documents, and will allocate their time and that of their staff to the auditor / inspector to discuss the findings. findings and any pertinent issues. In the event that the audit has not been scheduled by the sponsor, the center must notify Sophia Laboratories S.A. of C.V. immediately.

10. Statistical analysis

10.1 Data Analysis

10.1.1 Statistical analysis

The statistical analysis will be carried out by personnel from Sophia Laboratories S.A. of C.V. The statistical program SPSS version 19.0 (IBM Corporation, Armonk, NY, USA) will be used.

Designated staff will be blinded to intervention groups. Coding will be done using consecutive numbers for each intervention group.

The data will be collected and arranged in a spreadsheet of the Excel program (Microsoft® Office). Later the data will be exported to the platform of the SPSS program. The variables will be categorized according to their nature.

10.1.2 Interpretation of data

The Kolmogorov-Smirnov tests will be carried out to know if the distribution presents normality in the results obtained in each study group. [fifty]

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

The statistical analysis of the continuous quantitative variables to find significant differences ($p < 0.05$) will be as follows:

- • Intra-group analysis: they will be determined using the Wilcoxon rank test for quantitative variables. [51]
-
- • Between-group analysis: The differences between the groups will be analyzed using the Mann-Whitney U test.

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

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

The statistical analysis to identify significant differences of the qualitative variables will be carried out by creating 2x2 contingency tables and will be carried out as follows:

• Intragroup difference: McNemar test. [52] Which is applied to 2 × 2 contingency tables with a dichotomous trait, with pairs of matched subjects, to determine if the marginal frequencies of row and column are equal (marginal homogeneity).

• Difference between groups: Pearson's Chi-square test (X2) or Fisher's exact test in expected values less than 5.

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

For the reporting of adverse events, all the eyes of those participants who were randomly assigned to an intervention group after the baseline visit will be considered. The results will be expressed in number of subjects.

The final report of the results will be shown in tables or graphs, as appropriate.

10.1.3 Procedure for handling missing data

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

10.1.4 Deviations from the statistical analysis plan

According to the calculation of the sample size to meet the objective of the study, 34 evaluable subjects (17 subjects per arm / both eyes) are required. If this number is not met due to the loss of subjects greater than 20% contemplated in this protocol (loss of follow-up or withdrawal of ICF), in order to balance the treatment groups, the sponsor may substitute these subjects.

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

10.1.5 Subjects included in the analysis

Those subjects who comply with an adherence ≥75% will be included in the statistical analysis to fulfill the objective of the study, taken from the subject's diary.

The investigational drug will be considered safe and effective when there are no clinical and statistical differences in all the primary outcome variables, with respect to its comparator (Lagricel® Ofteno, unit dose).

10.2 Calculation of sample size

10.2.1 Number of subjects calculated

n = 34 evaluable subjects (both eyes) 17 subjects per arm.
17 subjects (both eyes) are estimated per treatment arm.

10.2.2 Justification of the sample calculation

Although there are no references on the calculation of the sample size in phase I studies, it was considered pertinent to perform it according to the safety results of a phase I study, carried out with three ocular lubricants (Humylub Ofteno® PF, Xyel® Ofteno and Systane® Ultra). [53]

The reference study was a single-center, randomized, 1: 1: 1, parallel group, blinded clinical trial. In total, 30 ophthalmologically and clinically healthy subjects were enrolled and included in the safety analyzes.

PRO-037 (Lagricel® Ofteno, multi-dose) is expected to be not inferior to its comparator (Lagricel® Ofteno, single-dose), based on the following working hypotheses:

$$H_0: \varepsilon > \delta$$

$$H_0: \varepsilon \leq \delta$$

Where μA - μB = ε, the true difference of the means between the test treatment (Lagricel® Ofteno, multi-dose) and the active control (Lagricel® Ofteno unit-dose). Where δ is the margin of non-inferiority, and the relationship between the sample sizes of the two groups is given by:

$$k = \frac{n_A}{n_B}$$

The calculations were made using the equation for two proportions, considering a power of 80% (β), a significance level of 0.05 (α) and a non-inferiority margin (δ) of 5%. [54]

$$n_B = \left(\frac{p_A(1-p_A)}{k} + p_B(1-p_B)\right)\left(\frac{z_{1-\alpha} + z_{1-\beta}}{p_A - p_B - \delta}\right)^2$$

In the reference study, after 10 days of treatment (1 drop / 4 times a day), 28 AE were reported in 14 subjects out of a total of 30 subjects exposed to any of the three interventions (46.67%). Without observing statistical differences in the incidence of AE between the three treatment arms (p = 0.788), 19 of the AE were ocular, where burning was the most common, followed by pruritus. Other ocular AE reported were discharge, SCE, and dry eye sensation.

The percentage of ocular AE reported in the study was considered, with respect to the total AE for the three treatments. As it is an ocular lubricant, a similar proportion of ocular AE is expected in ophthalmologically and clinically healthy subjects (50%).

The calculated sample was 56 eyes (28 eyes / arm; 14 subjects / arm), increasing the calculation by 20% considering possible losses, 17 subjects / arm (both eyes) are estimated.

11. Ethical Considerations

11.1 Approval of committees

This study will be carried out according to the standards of the Declaration of Helsinki, World Medical Association 2013. Nüremberg Code; Trial of Nüremberg by the International Tribunal of Nüremberg, 1947. Belmont Report, National Commission for the Protection of Subjects of Biomedical and Behavioral Research, 1979. It will be conducted in adherence to the scientific and technical requirements necessary for the registration of drugs for use Human Rights of the International Conference on Harmonization (ICH) Good Clinical Practice Guide. International Ethical Guidelines for Biomedical Research in Human Beings of the Council for International Organizations of Medical Sciences (CIOMS, 2002). International Ethical Guidelines for epidemiological studies of the Council for International Organizations of Medical Sciences (CIOMS, 2008). 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 performance, these Committees must be notified of any significant change to the protocol. In addition to the above, the current regulations of the regulatory authority will also be complied with.

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

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

The study will not begin without having fulfilled the pertinent local, national or international regulatory requirements and without having the corresponding sanitary authorization.

The study is considered as an investigation with a risk greater than the minimum, in accordance with the Regulations of the General Health Law on Research for Health, Second Title, Chapter I, Article 17, Section III, published in the Official Gazette of the January 6 - 1987[3]

11.2 Amendments to the protocol

The amendment procedure will be relevant when there is a need to make any change to a document that is part of the research project or protocol, derived from variations in the methodological structure, replacement of the main researcher or in the face of the identification of risks in the research subjects . The documents subject to amendment will be: protocol, letter of informed consent, investigator's manual, documents for the patient, measurement scales and schedule of

activities.

Any amendment must be approved by the sponsor and / or the principal investigator, the amended document (s), once reviewed and approved by the Research Ethics Committee and the Research Committee or when applicable, by The Biosafety Committee, (entities that issued the initial favorable opinion to carry out the research) will be sent for authorization by COFEPRIS.

The 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 investigator to take action in situations that require immediate action to avoid unnecessary harm to study participants.

The principal investigator has the responsibility of communicating to the Research Ethics Committee any amendment to the protocol that could eventually affect the rights, safety or well-being of the research participants. Likewise, she must find out any situation or new knowledge that will show a greater risk for the participants, the termination or premature suspension of the study, the reasons and the results obtained up to that moment. Likewise, you must inform about the conclusion of the study, when completing the research protocol.

11.3 Early termination of the study

The study may be temporarily suspended or terminated prematurely if there is a sufficiently reasonable cause. The written notification, documenting the reason for the suspension or early termination, must be delivered by the party executing the suspension. The PI should promptly inform the study participants, the IC and the REC, providing the reasons.

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

1. The presence of serious adverse events in more than 10% of the participants in a study group.
2. The regulatory authority (COFEPRIS) considered it for security alerts.
3. The Sponsor determined it for their convenience or eventualities such as: economic support, manufacturing errors, etc.
4. The determination of unexpected risks for participants, which are significant or unacceptable.
5. Obtaining new relevant safety information.
6. Insufficient adherence to the requirements of the protocol.
7. The data obtained are not evaluable or are not sufficiently complete.
8. The determination that the primary objective has been achieved.
9. The futility determination.

In case of suspension, the study can be resumed once the situations that led to the suspension have been corrected; 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 on the study and the research product, in accordance with current applicable regulations and Good Clinical Practices.

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

11.4.1 Obtaining

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

The written consent documents will incorporate the elements of informed consent outlined in the Declaration of Helsinki and the ICH Guide to 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.

This information will be in a language understandable to the subject, it will be explained to the subject that they have the right to interrupt their participation in the study at any stage, without affecting the relationship with the researcher and / or their future assistance. The informed consent will be put to the consideration of the possible participant; This must have enough time to analyze each and every one of the aspects mentioned above and in case of any doubt, it will be clarified by the person in charge of obtaining informed consent.

Once the participant agrees to participate in the study, the participant must sign and date the informed consent letter in the presence of two witnesses who are related or not with the study subject, who will participate during the informed consent process and will sign endorsing that the process was carried out prior to any study procedure, that the study information was clearly explained and doubts were clarified, if any.

In the event that a subject is illiterate, acceptance will be with his or her fingerprint, and in the event that the subject is not able to grant adequate written informed consent, a representative of the subject "legally authorized" may provide such consent by the subject in accordance with applicable laws and regulations.

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 investigator's folder and the other will be delivered to the participant. The IP or delegated staff must document the process of obtaining Informed Consent through a detailed medical note, specifying the signed version, date the document was signed and how the process was carried out..

11.4.2 Special Considerations

The procedures that will be performed during the conduct of the study do not pose an 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 approval to the Research Ethics Committees, and if applicable, to 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 an amendment that is required to eliminate an immediate danger to the study subjects.

A re-consent process must be carried out for each subject affected by the amendment under the same conditions as those described above, in order to promptly communicate the new information contained in the document to them. The subject will be given a signed original of the amendment and the investigator 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 on their professional and clinical experience, provided to the sponsor on paper and stored in electronic format, are only for use related to their activities with the sponsor of clinical studies, in accordance with Good Clinical Practice.

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

The clinical study protocol provided to the investigator may be used by himself and by his team to obtain the informed consent of the subjects for the study. The clinical study protocol, as well as any information taken from it, should not be disclosed to other parties without the written permission of the sponsor.

The researcher will not reveal any information without the prior written consent of Sophia Laboratories S.A. of C.V., except to the representatives of the Competent Authorities, and only by request of the same. In the latter case, the researcher undertakes to inform Sophia Laboratories S.A. of C.V. before disclosing the information to these authorities.

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

All FERCs and communications related to study subjects will identify them only by the study subject identification number. The information collected in this study will be exchanged between the sponsor and the research center, it must be treated confidentially. The Health Authority, the CEI, 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 research project, in no case will they contain information on the identification of the study subjects. If study results are published, personal information of study subjects will not be disclosed.

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

11.6 Conflict of interest

The independence of the conduct of the study and its results from any actual or perceived external influences is critical. For this reason, any current conflict of interest of any person who plays a role in the design, conduct, analysis, publication or any aspect of this study will be declared. Furthermore, those people 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 a conflict of interest, prior to the start of the study.

11.7 Access to information

The final database of the study will be owned by Sophia Laboratories S.A. of C.V. and your access will be restricted. The IP will not have access to it, except with the prior written authorization of the sponsor.

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

11.8 Ancillary and post-study care

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

12. Biosecurity aspects

NO BIOSECURITY IMPLICATIONS

This protocol, with title: "Phase I clinical study, to evaluate the safety and tolerability of Lagricel® Ofteno multi-dose ophthalmic solution compared to Lagricel® Ofteno, single-dose on the ocular surface of clinically healthy subjects", and number: SOPH037-0119 / I DOES NOT HAVE BIOSECURITY IMPLICATIONS, since infectious-contagious biological material will NOT be used; pathogenic strains of bacteria or parasites; virus of any kind; radioactive material of any kind; genetically modified animals and / or cells and / or plants; toxic, dangerous or explosive substances; any other material that endangers the health or physical integrity of the research center staff or the research subjects or affects the environment. Likewise, it is declared that this project will not carry out cell, tissue or organ transplantation or cell therapy procedures, nor will laboratory, farm or wildlife animals be used.

13. Publishing policy

13.1 Final report

Once the statistical analysis is completed, the final report will be drawn up with the results obtained, by the Clinical Team of the Department of Clinical Operations of Sophia Laboratories S.A. of C.V. Said report will be prepared following the recommendations of the ICH E3 Step 4 Guide.

13.2 Communication of results

Regardless of the results in the study, Sophia Laboratories S.A. of C.V., is committed to communicating the final report of the study to the principal investigators and to COFEPRIS. These results will also be shared with the research committee and the CEI. The communication to the research subjects will be the responsibility of the IP.

Sophia Laboratories S.A. of C.V. will maintain at all times the rights to the publication and disclosure of the information contained.

13.3 Publication of results.

Sophia Laboratories S.A. of C.V., acting as the sponsor of the study, assumes full responsibility for its function and retains the exclusive property rights over the results of the study, which it may use in the manner it deems appropriate.

The IP undertakes not to publish or communicate data collected from the study, unless it has the prior written agreement of Sophia Laboratories S.A. of C.V. All manuscripts derived from the data obtained with this protocol must be reviewed by the sponsor before any attempt to submit them for publication in any journal or scientific congress.

However, if 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 study results until the date of registration or when it deems appropriate.

The assignments of authorship of publications, responsibility of the sponsor, will be the prerogative of the latter. However, you must have the express authorization of the people who are invited to participate as authors. Authors have the right to review the manuscript prior to its publication, as well as to issue comments and suggestions in this regard, said comments must be delivered within the first 15 calendar days from the date the project is received.

14. Financing and Insurance

14.1 Compensation to study participants

The subjects who participate in the study will not receive financial compensation for their participation in it. However, randomized subjects will receive financial support for travel expenses at each scheduled visit to which they attend on time. Said support, as well as the amount. will be specified in the FCI.

14.2 Insurance for study participants

The subjects participating in the study will sign the informed consent form, which specifies that Sophia Laboratories S.A. of C.V. You agree to pay for immediate treatment resulting from injury or illness caused by the investigational products until resolution, in accordance with medical judgment.

All study participants will be entitled to the coverage of a liability policy, contracted by Sophia Laboratories S.A. of C.V. The information of the contracted policy will be available to the research centers. In the event of a medical emergency, the research center must have personnel, material, equipment and procedures for immediate management.

15. Annexes

15.1 ICO

Eye Comfort Index

Identification file

Study No. SOPH037-0119-I **Date:** / /

Initials of the subject: _____ **No. of subject:** 037- -

Indications:

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						Forever
0	1	2	3	4	5	6

There are no right or wrong answers. Don't take too long on each question.

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

Never						Forever
0	1	2	3	4	5	6

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

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						Forever
0	1	2	3	4	5	6

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

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

3 3 In the past week, how often did your eyes sting ?

Never						Forever
0	1	2	3	4	5	6

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

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						Forever
0	1	2	3	4	5	6

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

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						Forever
0	1	2	3	4	5	

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

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

6 In the past week, how often did your eyes itch?

Never						Forever
0	1	2	3	4	5	

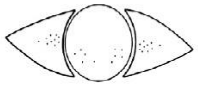
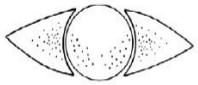
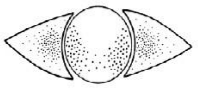
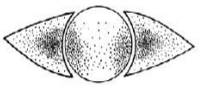
When your eyes were itchy, usually how intense was the sensation?

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

15.2 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 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 less than panel E, greater than D
>E	V	Greater than panel E

15.3 Efron scale

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