Creation date: february 2017

Phase I clinical study to evaluate the safety and tolerability of PRO-165 ophthalmic gel versus Artelac® Nightime Gel on the ocular surface of ophthalmologically and clinically healthy subjects

Protocol code:SOPH165-0217/I

Protocol version:4.0

Version date: 21/Jan/2022

Clinical Trial ID: NCT04704531

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

1. Summary

<table>
<tr><td colspan="2">Title of the study:
Estudio clínico fase I, para evaluar la seguridad y tolerabilidad del gel oftálmico PRO-165 versus Artelac® Nightime Gel, en la superficie ocular de sujetos oftalmológica y clínicamente sanos.</td></tr>
<tr><td>Protocol code:
SOPH165-0217/I</td><td>Creation date:
February 7, 2017</td></tr>
<tr><td>Protocol version:
4.0</td><td>Version date:
January 21, 2022</td></tr>
<tr><td colspan="2">Therapeutic indication:
Eye lubricant</td></tr>
<tr><td>Study period:
4 months</td><td>Development phase: I</td></tr>
<tr><td colspan="2">Aim:
To evaluate the safety and tolerability of the PRO-165 formulation on the ocular surface of ophthalmologically and clinically healthy subjects.</td></tr>
<tr><td colspan="2">Hypothesis:
PRO-165 ophthalmic gel presents a safety and tolerability profile similar to Artelac ® Nightime Gel in ophthalmologically and clinically healthy subjects.</td></tr>
<tr><td colspan="2">Methodology:
Phase I, controlled, parallel-group, double-blind, randomized, exploratory clinical study.</td></tr>
<tr><td colspan="2">Number of patients:
32 subjects, divided into 2 groups [16 subjects (16 eyes) exposed per group]</td></tr>
<tr><td colspan="2">Diagnosis and main inclusion criteria:
- Systemically and ophthalmologically healthy subjects
- Signed informed consent.
- Age between 18 and 45 years.
- Both sexes
- Blood tests [complete blood count (CBC), three-element blood chemistry (BC), and liver function tests (LFTs)] within normal parameters
- Visual capacity 20/30 or better</td></tr>
<tr><td colspan="2">Test product, dose and route of administration,
- PRO-165 Sodium hyaluronate 0.2% ophthalmic gel. Manufactured by Laboratorios Sophia , SA de CV, Zapopan, Jalisco, Mexico.
▪ Dosage: One drop of gel, 4 times a day during the waking period, in the fornix of the right eye.</td></tr>
</table>

▪ Route of administration: ophthalmic
Treatment duration: 10 days
Reference product, dosage and route of administration: 1. **Artelac ® Nightime Gel.** Carbomer 0.2%, ophthalmic gel. Made in Germany by: Dr. Gerhard Mann Chem Pharm. Fabrik GmbH Brunsbütteler Damm 165-173 D-13581, Berlin, Germany . Imported and marketed by: Bausch & Lomb México, SA de CV, Av. Michoacán No. 20, Warehouse 10, Section F; Renovación Neighborhood; Iztapalapa District, Zip Code 09209; Mexico City
Evaluation criteria: **Primary safety outcome variables:** - Presence of adverse events. **Secondary outcome variables:** - Tear film break-up time - Vital signs: HR, RR, SBP. - Posterior segment - Intraocular pressure. - Visual capacity. - Laboratory tests: BHc , QS and PFH. - Ocular surface stains. **Primary tolerability outcome variables:** - Eye comfort index
Statistical methodology: Data will be expressed using measures of central tendency. Qualitative variables will be presented as frequencies, proportions, and/or percentages. Statistical analysis will be performed using the Kruskal-Wallis test for quantitative variables. Differences between qualitative variables will be analyzed using the X^2 test or Fisher's exact test. An alpha ≤ 0.05 will be considered significant.

2. Content

Index of tables and figures

3. Index of abbreviations

ALT	Alanine transferase
AST	A spartate transferase
BAK	Benzalkonium Chloride, (for its acronym in English *Benzalkonium chloride* .)
BD	Direct bilirubin
BI	Indirect bilirubin
BHc	Complete blood count
GCP	Good Clinical Practices
BT	Total bilirubin
CV	Visual capacity
ICC	Informed Consent Letter
CEI	Research Ethics Committee
CI	Informed consent
CRF	*Case Report* Form *Form*)
DEWS International Workshop on	*Dry* Eye *Eye Workshop*)
AE/EAS	Adverse event/serious adverse event
FDA	*Food and Drug* Administration *Administration*)
FC	Heart rate
RR	Respiratory rate
GAG	Glycosaminoglycans
ICH	*International Conference* on Harmonization (ICH) *on Harmonization*)
ICO	Eye Comfort Index
IP	Principal Investigator of the clinical study
ITF	*International Task* Force on Dry Eye *Force*)
PFH	Liver function tests
IOP	Intraocular pressure
QS	Blood chemistry
TAS	Systemic blood pressure

TF	Fluorescein staining
TVL	Lissamine green stain
ULF	Functional Lacrimal Unit

4. Administrative structure of the study

The administrative structure of the sponsoring party, corresponding to Laboratorios Sophia , SA de CV is shown in **Table 1Administrative structure**

Function	Name / Contact	Affiliation [¥]
Medical Director of the study	[redacted]	Medical and Regulatory Affairs Director
Operations Manager		Regional Clinical Research Manager
Studio Director		Medical Manager
Clinical Development Team		Chief of Medical Affairs Operations
Clinical Development Team		Biostatistics Manager

[¥] Employees of Laboratorios Sophia , SA de CV Av. Paseo del Norte No. 5255, Col. Guadalajara Technology Park, Guadalajara-Nogales Highway Km13.5 C.P45010 Zapopan, Jalisco, Mexico Tel +52 (33) 3000 4200

Table 1Administrative structure

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5. Introduction

5.1 Theoretical framework

Dry eye disease (DED) *Eye Eye disease*) is a common ocular condition that significantly diminishes quality of life and affects 6–34% of the adult population worldwide. [1] [2]Although there are no formal studies on the prevalence of the disease in Latin American countries, several reports suggest a higher prevalence of severe symptoms and clinical diagnosis of DED in the Hispanic population compared to the Caucasian population.[2] [3]

DED is a tear film disorder that results in damage to the ocular surface and is associated with symptoms of ocular discomfort. DED has also been called *keratoconjunctivitis. sicca* (KCS), sicca syndrome , xerophthalmia, dry eye syndrome, ocular surface disease, tear film dysfunction syndrome (TPDS), or simply dry eye. Strictly speaking, some of these terms are not synonymous, since, for example, DED can occur without keratitis, KCS; this protocol will use TPDS as [4] [5]*a synonym for DED, assuming that they are interchangeable concepts and adopting the definition of the 2007 International Dry* Eye Workshop (DEWS). *Eye Workshop*):

> *Dry eye is a multifactorial disorder of the tear film and ocular surface that causes symptoms of discomfort, visual disturbances, and tear film instability with potential damage to the ocular surface. It is accompanied by increased tear film osmolarity and inflammation of the ocular surface.* [4]

LPDS is an alteration of the lacrimal functional unit (LFU), an integral system comprising the lacrimal glands, ocular surface (cornea, conjunctiva and meibomian glands), eyelids and the afferent and efferent nervous network that interconnects them. [6]

This LFU controls the main components of the tear film and regulates them in response to environmental, endocrinological, and cortical influences. Its main function is to preserve the integrity of the tear film, the transparency of the cornea, and the quality of the image projected onto the retina. [6] [7] [8] [9]

Damage or disruption to any component of the UFL can destabilize the tear film and lead to ocular surface disease manifested as PLDS. Tear film stability, a hallmark of a normal eye, is threatened when interactions between tear film-stabilizing components are compromised by decreased secretion, delayed clearance, and altered tear composition. Inflammation is a secondary consequence. Reflex tear secretion, in response to irritation, is considered the initial compensatory mechanism, but over time, inflammation accompanying secretory dysfunction and decreased corneal sensitivity compromises the reflex response and results in further tear film instability. Disruption of the UFL is considered to play a critical role in the development of various forms of dry eye. [4]

The tear film is a highly specialized and carefully structured moisturizing layer that covers the cornea and conjunctiva. It has been classically described as a trilaminar structure composed of a lipid surface layer, an aqueous intermediate layer, and an internal mucinous layer . [10]Currently, it is considered a hydrated gel with a concentration gradient of its components, mucin, water/electrolytes, proteins, and other components such as immunoglobulins. [7]The tear film has four main functions: 1) Maintain a regular optical surface, 2) Prevent friction between the structures of the ocular surface, 3) Nourish the cornea, and 4) First line of defense against ocular surface infections.[11]

Based on models of the tear film's "microstructure" and its interface with ocular surface cells, the mucin layer should always be present in a healthy tear film. [10]This layer provides support for the rest of the tear film on the ocular surface, helping to keep it moist and lubricated. [12]The epithelial cell layer of the conjunctiva includes goblet cells, which secrete mucin. These cells are the main source of mucin for the tear film. [11]

Within the framework of the DEWS, the etiopathogenic classification of PLDS was established, which is summarized in **Figure 1**This classification aims to provide a more up-to-date understanding of PLDS. It is divided into two main classes: aqueous deficiency and evaporative. The aqueous deficiency category primarily refers to a failure of tear secretion. The evaporative class has been subdivided to distinguish between causes that depend on intrinsic conditions of the eyelids and ocular surface and those that arise from extrinsic influences.

PLDS can begin in either class, but these are not mutually exclusive. It is recognized that a disease can begin in one major class and coexist or even lead to events that produce PLDS through a mechanism in another class. This is part of a vicious cycle of interactions that can amplify severity. An example of this is that all forms of PLDS cause goblet cell loss, which over time will contribute to a loss of tear film stability, surface damage, and evaporative water loss. [4]

Many pathophysiological mechanisms of PLPS stimulate the sensory nerves of the cornea, which is why PLPS is described as a "symptomatic disease." [13] [14] [15]In most patients, there is a relationship between symptoms and clinical signs; however, it is also recognized that in some patients, the severity of symptoms does not correspond to the clinical signs of the disease. [14] [16] [17]

Classifying PLPS according to severity is currently challenging, as there is no gold standard for determining its severity; however, disease severity is one of the most relevant factors when considering therapeutic options for PLPS. [18]In 2006, a panel of specialists called the Delphi Panel issued a severity classification, later adopted by the DEWS. Severity was classified into four levels, based on the increasing frequency and intensity of various signs and symptoms. [18]See **Table 2**

There are other systems for classifying the severity of PLDS referred to by other authors, [19] [20] [21] [22]including the *European Consensus algorithm of the ODISSEY group,* which classifies discordant PLDS cases as severe, which are therefore more difficult to classify. [23]

In addition to the most highly correlated diagnostic methods for PLDS (OSDI, TRL, Schirmer test), conjunctival impression cytology (CIC) has recently been used. CIC is a minimally invasive technique that evaluates the characteristics of goblet cells. This technique can be used for diagnostic purposes, to elucidate the mechanism of the disease, and to evaluate treatment efficacy. [24]

Figure 1Classification of SDPL by etiology

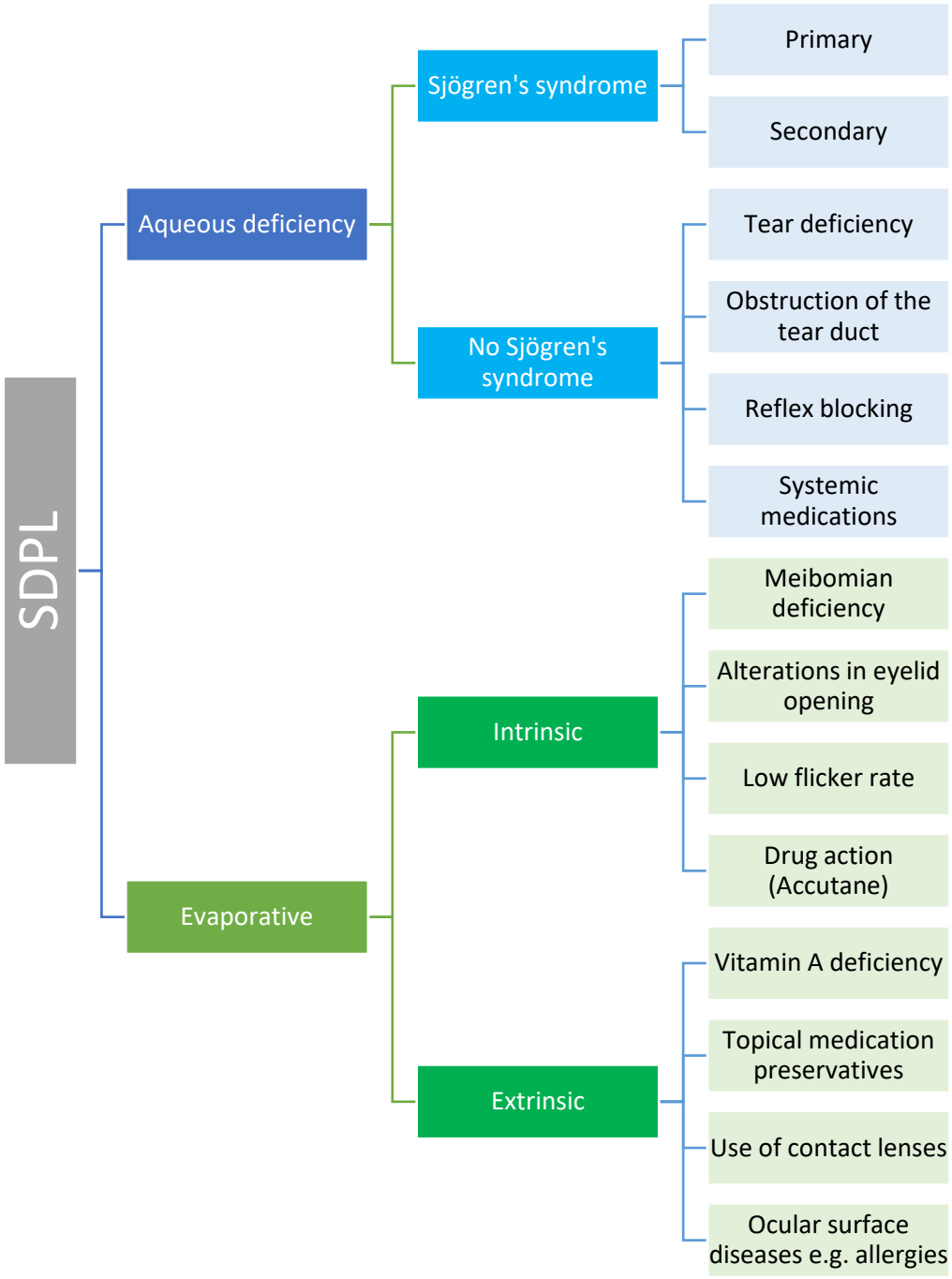


Table 2Classification of SDPL by severity

Degree	1 Light	2 Moderate	3 Severe	4* Disabling
Discomfort, severity and frequency	Mild and/or episodic; occurs under environmental stress	Moderate episodic or chronic, with or without stress	Frequent or constant severe without stress	Severe and/or disabling and constant
Visual symptoms	None or mild episodic fatigue	Annoying and/or limiting episodic	Chronic and/or constant limiting discomfort	Constant and/or possibly disabling
Conjunctival injection	None to mild	None to mild	+	+/++
Conjunctival staining	None to mild	Variable	Moderate to marked	Marked
Corneal staining	None to mild	Variable	Marked center	Severe and widespread punctate erosion
Tear/corneal signs	None	Light debris, decreased meniscus	Filamentous keratitis, mucus aggregation, increased debris in tears	Filamentous keratitis, mucus aggregation, increased debris in tears, ulcer
Meibomian glands / eyelids	Meibomitis present variably	Meibomitis present variably	Frequent	Trichiasis , keratinization, symblepharon
TRL	Variable	≤ 10	≤ 5	Immediate
Schirmer I	Variable	≤ 10	≤ 5	≤ 2

*Must have signs and symptoms.
Adapted from Behrens A, Doyle JJ, Stern L, et al.[18]

The treatment currently available for SDPL can be divided into:

a) Tear supplements: lubricants.
b) Tear retention: tear punctum occlusion, contact lenses.
c) Stimulation of secretion: secretagogues .
d) Biological substitutes: autologous serum, salivary gland autotransplant.
e) Anti-inflammatory drugs: cyclosporine, steroids, tetracyclines.
f) Essential fatty acids
g) Environmental strategies

Recommended practices in dry eye by the American Academy of Ophthalmology and the Delphi Panel of the International Task Force Force , ITF) on the treatment of dry eye, favored, in turn, by the DEWS, are based on the severity of the disease See **Table 3**. The recommendations may be modified by the ophthalmologist, based on clinical experience and the individual profile of his patient. [18] [25] [26]

Table 3Treatment recommendations for LPDS

Level 1: Education and dietary and environmental modifications Elimination of systemic medications that alter UFL Lubricants Eyelid treatment
Level 2: If level 1 treatments are insufficient, add: Anti-inflammatories Tetracyclines Tear plugs Secretagogues
Level 3: If level 2 treatments are insufficient, add: Autologous serum Contact lenses Permanent occlusion of tear ducts
Level 4: If level 3 treatments are insufficient, add: Systemic anti-inflammatories Surgery (tarsorrhaphy, transplantation: mucous membrane, salivary gland, amniotic membrane)
Modified from the ITF [18]

The primary goal of caring for patients with PLDS is to improve ocular comfort and quality of life, as well as to return the ocular surface and tear film to a state of homeostasis. Although symptoms are rarely eliminated, they can often be reduced, resulting in improved quality of life. [26]

Ocular lubricants are the first line of treatment for PLDS and a constant at all treatment levels. They are characterized as hypotonic or isotonic solutions containing electrolytes, surfactants, and various types of viscosifying agents. The main variables in ocular lubricant formulations relate to the selection or concentration of electrolytes, osmolarity, the type of viscopolymer system, and the presence or absence of preservatives. [26]

5.2 Background

5.2.1 Sodium hyaluronate

It is a biopolymer, a disaccharide of the GAG family, formed by the alternating sequence of N-acetyl-D-glucosamine and glucuronate in linear chains. In physiological solvents, they form spirals; their configuration is determined by their viscosity. It is a constituent of the extracellular matrix, connective tissue, vitreous humor, umbilical cord, synovial fluid, skin, etc. It can be composed of more than 10,000 disaccharide pairs. At concentrations above 0.1%, sodium hyaluronate forms a network. The diffusion rate through the network is inversely related to the size of the polysaccharide molecules, which are stable. Proteoglycans contribute to providing mechanical and elastic properties. Numerous authors have reported that HS has a high water-retaining capacity; it has been established that 1 g of HS can retain up to 6 L of water. [28]

Sodium hyaluronate is synthesized on the inner surface of the plasma membrane as a linear polymer, in contrast to other GAGs, which are synthesized by enzymes in the Golgi apparatus. The

enzymes responsible for the synthesis of sodium hyaluronate are hyaluronate and glucosyltransferases , which coordinately polymerize and translocate sodium hyaluronate outside the cell into the extracellular matrix. [29]

5.2.1.1 Pharmacokinetics in the eyeball

Route of administration: Ophthalmic.

Release: immediate.

Absorption: No absorption of HS through the cornea has been reported when applied to the ocular surface. Pharmacokinetic studies conducted in patients with dry eye showed that the HS solution reached its maximum concentration within 10 minutes and is widely distributed across the ocular surface.

Metabolism: It is biotransformed by hyaluronidases.

Elimination: It is eliminated from this compartment through the lacrimal sac and tear duct without intraocular absorption, in approximately 45 minutes. [30]Based on the results of preclinical research in rabbits conducted by Laboratorios Sophia SA de CV, the ocular half-life correlates with the volume of the formula.

5.3 Problem Statement

There are few effective treatments for PLDS. Clinical development of new treatments is slow due to the multiple pathogenesis of PLDS and its variable semiotics. The different treatment phases have a common denominator: the use of ocular lubricants.

Although there is a wide variety of topical lubricants, with different viscosifying agents, 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 PLDS, they have been shown to provide protection to the ocular surface and reduce symptoms and clinical findings.

Sodium hyaluronate (SHN) is a biopolymer, glycosaminoglycan (GAG), a constituent of the extracellular matrix. It provides PRO-165 with viscoelastic and water-retaining properties, enabling it to function as an effective lubricant that protects the ocular surface and reconstructs the tear film. Formulating it as an ophthalmic gel can provide a longer dwell time, promoting prolonged lubrication. Currently, the range of lubricants in ophthalmic gels is not as extensive as that of solutions. Therefore, adding a new option to this group of pharmaceutical formulations will contribute to improved care for patients with PLDS.

5.4 Justification

Patients with LPDS, regardless of its etiology and severity, will need to use ocular lubricants to reduce symptoms and improve their quality of life.

Ocular lubricants are the first-line treatment for ocular symptoms related to tear film dysfunction in self-reported healthy subjects, with a prevalence of 5% to 35% in those over 50 years of age. [32]If we add to this the number of patients who report occasional symptoms or symptoms that are dependent on a work or occupational situation and who will use them intermittently throughout their lives, the population spectrum that will have access to these medications is very broad. It is

estimated that 50% of patients diagnosed with tear film dysfunction without concomitant diseases will use more than two types of ophthalmic solutions in 5 years of treatment.

PRO-165 is an ophthalmic gel lubricant formulation for which a safety profile must be documented.

5.5 Objectives and hypotheses

5.5.1 General Objective

To evaluate the safety and tolerability of the PRO-165 formulation on the ocular surface of ophthalmologically and clinically healthy subjects.

5.5.2 Specific objectives

- To describe the safety of PRO-165 ophthalmic gel by presenting adverse events.

5.5.3 Secondary Objectives

- To describe the safety of PRO-165 ophthalmic gel through changes in intraocular pressure.
- To describe the safety of PRO-165 ophthalmic gel through changes in visual ability.
- To describe the safety of PRO-165 ophthalmic gel through changes in laboratory testing.
- To describe the safety of PRO-165 ophthalmic gel when evaluating ocular surface stains
- To describe the safety of PRO-165 ophthalmic gel through changes in tear break-up time.
- To describe the safety of PRO-165 ophthalmic gel through changes in vital signs.
- To describe the tolerability of PRO-165 ophthalmic gel by the presence of the symptoms: burning, foreign body sensation, and itching.

5.5.4 Hypothesis

H_0 PRO-165 ophthalmic gel presents a safety and tolerability profile similar to Artelac ® Nightime Gel in ophthalmologically and clinically healthy subjects

H_1 PRO-165 ophthalmic gel presents a different safety and tolerability profile than Artelac ® Nightime Gel in ophthalmologically and clinically healthy subjects.

5.6 Study design and plan

Phase I, controlled, parallel-group, double-blind, randomized, exploratory clinical trial.

5.6.1 Discussion of the study design

The study design (clinical trial) is considered the highest standard of data quality when exploring the effect of an intervention. The drug development phase (Phase I) corresponds to the study objective, which is to evaluate safety and tolerability. Therefore, the intervention time is short and the required sample size is smaller than that of an efficacy clinical trial. The presence of parallel groups allows for comparisons between intervention groups on outcome variables. Blinding and randomization reduce biases that occur with other designs, e.g., selection bias, assessment bias, among others.

The selection of Artelac ® Nightime Gel was based on the need to compare PRO-165 with a treatment with the same formulation and the same indication as PRO-165. Although they do not share the same active ingredients, this does not limit their comparability, as no pharmacological action is expected from either treatment. Since there is no ophthalmic gel with the same concentration of the active ingredient as PRO-165, and since comparison with placebo is not feasible due to technical difficulties, Artelac ® Nightime Gel is an option for conducting a comparative Phase I study.

6. Materials and methods. Participants, interventions, and variables

6.1 Study center

This study will be conducted in properly equipped and registered ophthalmology offices. Depending on the sponsor's needs, these offices may be private or public, attached to a hospital or clinic, or independent.

6.1.1 Organization of the center

Each study center will have a principal investigator (PI). The PI is the ophthalmology specialist leading the clinical study.

The PI is responsible for forming a multidisciplinary research team to execute the clinical study according to the protocol, under his or her scientific guidance. The PI is responsible for designing the organization of his or her center and selecting the personnel who will perform these functions. However, the minimum organization of the research team requested by the sponsor requires the following: a sub-investigator , study coordinator, and pharmacist. (See **Figure 2Minimum organization of the center**.)

Any person designated by the PI as responsible for monitoring the study (coinvestigator, sub-investigator, nurse, etc.) or for a specific role in the study (pharmacist, administrative assistant, study coordinator, etc.) must be listed on the “Delegation of Responsibilities” form.

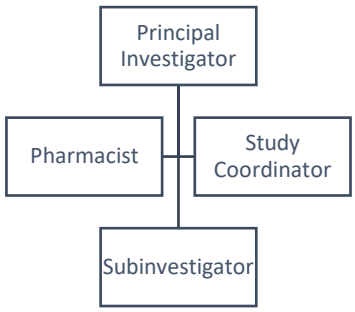


Figure 2Minimum organization of the center

The "Delegation of Responsibilities" and the "Center Organizational Chart" must be submitted to the sponsor before the start of the study and updated if the members or their responsibilities change.

6.1.2 Documentation to be delivered to the sponsor

The IP must submit to the sponsor, before the start of the study:

- Updated *curriculum vitae* , in Spanish, dated and signed (maximum 10 pages), of the IP and the staff that make up the center's organizational chart.

- Copy of academic certifications from the IP (degree and specialty diploma in ophthalmology; federal professional licenses)

- A copy of academic certifications of the highest degree obtained by each member of your research team, which support their ability to perform the delegated functions.

- Copy of the notice of operation or similar issued by the corresponding regulatory entity (when applicable)

- A valid certificate of good clinical practice. If the issuing institution does not specify the validity period in the certificate, the certificate issue date must not be more than one year old.

6.1.3 Closure of the center

The closure of the center will be agreed upon in advance by the sponsor and the PI, once the last visit of the last enrolled subject has been completed. The closure process will be in accordance with the sponsor's internal operating procedures.

It is the sponsor's prerogative to close a study center prematurely; they must inform the IP of the reasons for the closure.

6.2 Eligibility criteria

6.2.1 Inclusion criteria

- Signed informed consent.
- Systemically and ophthalmologically healthy subjects evaluated during the medical history.
- Age between 18 and 45 years.
- Both sexes.
- Blood tests [complete blood count (CBC), three-element blood chemistry (BC), and liver function tests (LFTs)] within normal parameters specified by the reference laboratory with a lower and upper margin of 10%.
- Vital signs are within normal limits. (Resting vital signs: blood pressure ≤ 139/89 mmHg , heart rate 60-100 beats per minute, and respiratory rate 12-24 breaths per minute)
- Visual capacity 20/30 or better, in both eyes.
- Intraocular pressure ≥11 and ≤ 21 mmHg .

6.2.2 Exclusion criteria

6.2.2.1 General criteria

- Subjects with a history of hypersensitivity to any of the components of the investigational products.
- Subjects who are users of topical ophthalmic medications of any pharmacological group.
- Subjects who use medications by any other route of administration.
- Pregnant or breastfeeding women.
- Women with no history of bilateral tubal obstruction , oophorectomy or hysterectomy, who do not ensure a hormonal contraceptive method or intrauterine device during the study period.
- Subjects with participation in clinical research studies 90 days prior to inclusion in this study.
- Known diagnosis of liver disease
- Inability to attend or respond to assessments conducted at each visit.
- Positive smoking (specified as cigarette consumption regardless of quantity and frequency)
- Positive alcoholism (specified as the consumption of alcoholic beverages, regardless of quantity and frequency, during the study intervention period).
- Contact lens wearers.

6.2.2.2 Medical and therapeutic criteria

- History of any chronic-degenerative disease.
- Inflammatory or infectious disease, active at the time of entering the study.

- Unresolved injuries or trauma at the time of study entry.

6.2.3 Elimination criteria

- Withdrawal of the consent letter under information.
- Presentation of a serious adverse event.
- Non-tolerability or hypersensitivity to any of the compounds used during the tests (fluorescein, lissamine green , tetracaine)
- Non-tolerability or hypersensitivity to any of the investigational drugs.
- Adherence < 50% determined by subject's diary.

6.2.4 Subject identification

Patients in the study will be identified by a number and their initials.

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

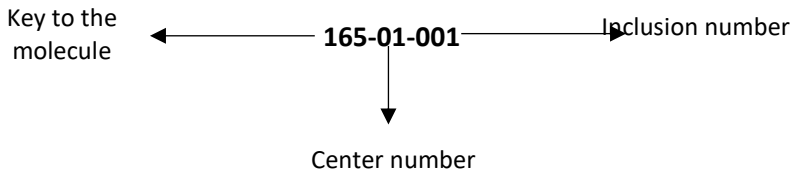
Example:

1. Arieh Daniel Mercado Carrizalez
    a. Initials: AMC
2. Juan De la Torre O Rozco
    a. Initials: JDO

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

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

Example:



6.3 Intervention

6.3.1 Treatments administered

6.3.1.1 Treatment under study

- **PRO-165**
    - Active ingredients (lubricant): sodium hyaluronate 0.2%
    - Pharmaceutical form: Ophthalmic gel
    - Prepared by: Laboratorios Sophia , SA de CV
    - Dosage: One drop of gel, 4 times a day during the waking period, in the fornix of the right eye.

- Formulation description: Clear gel, free of visible particles.
- Packaging description: Sterile multi-dose tube, low-density polyethylene and aluminum polylaminate with high-density polyethylene cap.

Table 4Qualitative -quantitative formulation of PRO -165

Agent type	Amount mg/ mL	Function
Sodium hyaluronate	2.0	Active ingredient
Chondroitin sulfate	Not shown	Viscosant
Polyoxylated Castor Oil 35	Not shown	Solubilizer
Polyethylene glycol 8000 [1]	Not shown	Cosolvent
Edetate disodium dihydrate	Not shown	Chelating agent
Cetrimide	Not shown	Conservative
Glycerin	Not shown	Osmoregulator
Sodium hydroxide	Not shown	pH adjustment
Homopolymer carbomer type B [2]	Not shown	Gelling agent
Polycarbophil [3]	Not shown	Gelling agent
Water for the preparation of injectables cbp [4]	Not shown	Vehicle

Qualitative and quantitative formulation of the investigational product PRO-165. The concentration of the active ingredient is shown, as well as the substances that act as additives. (1) Synonym of Carbowax ® (2) Synonym of Carbopol® 974P NF Polymer, USP (3) Synonym of Noveon ® AA-1 Polycarbofil , USP (4) as much as is sufficient for

6.3.1.2 Reference treatment

- **Artelac ® Nightime Gel**
- Active ingredients: Carbomer 0.2%
- Pharmaceutical form: Ophthalmic gel
- Prepared by: Dr. Gerhard Mann Chem Pharm. Fabrik GmbH Brunsbütteler Damm 165-173 D-13581, Berlin, Germany . Imported and marketed by: Bausch & Lomb México, SA de CV, Av. Michoacán No. 20, Warehouse 10, Section F; Renovación Neighborhood; Iztapalapa, Zip Code 09209; Mexico City, Mexico City.
- Dosage : One drop of gel, 4 times a day during the waking period, in the fornix of the right eye.
- Solution description: Clear gel, free of visible particles.
- Packaging description: Sterile multi-dose tube.
- Characterization: The characterization, stability, and formulation of the comparator will be supported by its packaging, lot number, and IPP, a copy of which will be kept in the study's master folder.

6.3.2 Strategies to improve adherence and procedure to monitor adherence

Adherence to the intervention is essential to achieve the objectives of clinical research. Adherence is defined as: "the extent to which people's behavior (including medication intake) corresponds to

the instructions of the health service provider." [33]The safety profile of a product may be under- or overvalued due to poor adherence.

The strategies to be carried out to improve adherence are:

1. Direct questioning by the IP regarding the application of the intervention.
2. At the IP's discretion, reminder messages or calls may be sent.
3. Delivery of a printed schedule specifying the date of the visit and its activities
4. Subject's diary.

6.3.2.1 Procedure for monitoring adherence

For more than four decades, numerous studies have been conducted on the appropriate way to measure and quantify medication adherence, but none have reached a consensus that could serve as the gold standard, whether in cross-sectional or longitudinal studies. [34] [35] [36] [37] [38] [39] [40] [41]

There are different procedures for measuring adherence to pharmacological interventions. The most common procedure involves self-reports , which include patient interviews, questionnaires, and self-monitoring diaries. Their strengths are speed, flexibility, low cost, and ease of implementation; they have a high degree of specificity for non-adherence, but their sensitivity and reliability for adherence are low. [41] [42]

Biochemical measurement of the drug, or its metabolite, is one of the methods that best confirms drug use. However, in addition to being costly and impractical, it is of little use in ophthalmic applications, as peripheral concentrations may be undetectable; and samples from other tissues require more invasive methods that would be inadvisable. [41]

Medication counting is another way to measure adherence. Classically referred to as "pill counting," in ophthalmology it is translated as the weight of the bottle. This is a simple, inexpensive, and noninvasive method. The main disadvantages of this method are: 1. It cannot confirm medication application (it could have been intentionally dropped or instilled outside the eye), and 2. It depends on the subject bringing the medication back. [41] [42]

A multi-method approach to adherence measurement is recommended. Because there is no ideal adherence measure, it is appropriate to use more than one method when aiming to achieve results that resemble reality. Selecting two or more methods allows for balancing their strengths and weaknesses, thus more accurately capturing adherence levels. [40]

Adherence assessment will be facilitated by the subject's diary and will be performed as follows:

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

Ad = Adhesion
A_r = Registered applications
A_i = Applications indicated for the intervention

Final adherence will be determined by the average adherence from each visit. Overall adherence (all subjects) will be determined by the average of each subject's final adherence.

Adherence to the procedure, taking into account weight, will be calculated as follows: the weight of the empty tube, the weight of the drop, the weight of the tube with its contents, the total amount of gel to be applied during the entire procedure, and the total weight of the gel applied. The following simplified formula will be used:

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

Where:
Ad = adhesion
P_i = weight of the tube delivered to the subject at the start
P_f = weight of the tube returned by the subject
P_T = weight of the dosage indicated for the intervention

$$P_T = (P_g)G$$

Where:
P_g = weight of a drop of the intervention, determined by the research and development department
G = number of applications indicated for the intervention

It will not be considered for the calculation of adhesion if the tube does not maintain its physical integrity.

There is no standardized parameter to define adequate adherence; it must be defined and outlined by the objectives of the particular research. [41]

Calculating adhesion by weight is not chosen as the ideal way to monitor adhesion, due to the difficulty in standardizing the amount of product per application, due to the characteristics of the formulation (gel).

6.3.3 Concomitant treatments and interventions permitted and prohibited during the study

The use of concomitant medications by any route of administration will not be permitted during the intervention period, except for those specified for the study procedures. The objective of this restriction is to avoid drug interactions that could alter the results of the evaluated variables.

6.3.4 Treatment management

The interventions will be provided by Laboratorios Sophia , SA de CV, for the research center. They will be labeled, reconciled, and weighed beforehand. Treatment management will be the responsibility of the researcher or a designated member of their team.

6.3.4.1 Delivery and receipt

Delivery will be made in sealed cardboard boxes by courier or directly by sponsor staff to the research center's address, according to the study plan.

Reception will be handled exclusively by the research center team, including the researcher. They must verify the condition of the primary packaging (the box). If it shows alterations or defects in its integrity that, in their opinion, could have damaged the contents, they must report this to the sponsor. If the package shows no significant defects, they will open it.

Inside, you must locate the receipt acknowledgment document and the temperature and humidity *data logger* . You must verify that the recorded temperature and humidity comply with the specifications for transport and storage (see section 6.3.4.2 Storage). You will verify the content (interventions) with what is reported in the document. If the document corresponds to the content, you will sign the receipt and send it to the sponsor. If not, you will notify the sponsor.

At the study center, staff assigned by the PI will administer the appropriate treatment to admitted subjects, sufficient for the study period. This treatment will be administered at the baseline visit. The center must record the medication administered.

6.3.4.2 Storage

The medication must be stored in a secure area with restricted access.

Storage temperature should be at room temperature, no more than 30º Celsius.

The research center is required to record the temperature and humidity recorded in the *data logger , using the format designated by the sponsor* . This record must include the current temperature and humidity, as well as the minimum and maximum values for each. This must be done at least once a day on weekdays.

These data will be compared by the clinical monitor according to the record in the *data logger* .

6.3.4.3 Return

Research subjects will return their medications to the staff designated by the PI at the center during the final visit. The return will be made by the research center upon the sponsor's instructions. Prior to return, the research center must conduct a count of the assigned medication and the remaining medication to create an inventory that will be used to complete the final medication return form.

6.4 Outcome variables

6.4.1.1 Primary outcome variables

- Security
  - Presence of adverse events.
- Tolerability
  - Eye comfort index

6.4.1.2 Secondary outcome variables

- Tear film break-up time
- Vital signs: HR, RR, SBP.
- Posterior segment
- Quality questionnaire
- Intraocular pressure.
- Visual capacity.
- Laboratory tests: BHc , QS and PFH.
- Ocular surface stains.

6.4.3 Methods and scales to be used for measuring the variables

Variable	Unit	Symbol	Guy	Measurement method	Normal value
Age	Years	--	Continued	Calculation from the date of birth	NA
Gender	Female / Male	F / M	Nominal	Direct questioning	NA
Adverse events	Number of cases	n	Discreet	Counting	NA
Intraocular pressure	Millimeters of mercury	mmHg	Continued	Goldman applanation tonometry	11 - 21

Variable	Unit	Symbol	Guy	Measurement method	Normal value
Visual capacity	Fraction	Snellen	Nominal	Primer	20/20
Tear break-up time	Seconds	s	Continued	Direct count	> 10
Eye comfort index	Points	--	Discreet	Questionnaire	NA
Adverse events	Present / Absent	--	Nominal	Comprehensive assessment	Absent
Vital signs					
Heart rate	Beats per minute	bpm	Discreet	Auscultation	60 – 100
Respiratory rate	Breaths per minute	rpm	Discreet	Auscultation	12 – 24
Systemic blood pressure	Millimeters of mercury	mmHg	Continued	Non-invasive auscultatory measurement	< 120 / 80
Anterior segment					
Ocular surface stains	Degrees	--	Discreet	Direct observation with fluorescein and lissamine green staining	Oxford Scale
Ophthalmological signs and symptoms					
Blood count [1]					
Erythrocytes		M/ uL	Continued		
Hemoglobin	Grams per deciliter	g/ dL	Continued		
Hematocrit	Percentage	%	Continued		
VGM	Femtoliters	fL	Continued		
HCM	picograms	pg	Continued		
CMHbG	Grams per deciliter	g/ dL	Continued		
Leukocytes	Thousands per liter units	Thousand/ uL	Continued		
Platelets	Thousands per liter units	Thousand/ uL	Continued		
Myelocytes	Percentage	%	Discreet		
Metamyelocytes	Percentage	%	Discreet		
Bands	Percentage	%	Discreet		
Segmented	Percentage	%	Discreet		
Lymphocytes	Percentage	%	Discreet		

Variable	Unit	Symbol	Guy	Measurement method	Normal value
Monocytes	Percentage	%	Discreet		
Eosinophils	Percentage	%	Discreet		
Basophils	Percentage	%	Discreet		
Blastos	Percentage	%	Discreet		
Blood chemistry [1]					
Glucose	Milligrams per deciliter	mg/ dL	Continued		
Urea	Milligrams per deciliter	mg/ dL	Continued		
Creatinine	Milligrams per deciliter	mg/ dL	Continued		
Liver function tests [1]					
Alanine transferase	Units per liter	U/L	Continued		
Aspartate transferase	Units per liter	U/L	Continued		
Total bilirubin	Milligrams per deciliter	mg/ dL	Continued		
Direct bilirubin	Milligrams per deciliter	mg/ dL	Continued		
Indirect bilirubin	Milligrams per deciliter	mg/ dL	Continued		

[1] The measurement method and normal values will be designated by the clinical analysis laboratory designated by the sponsor.

Table 5Scales to be used

The methods and scales that will be used to measure the variables are described below, which are in strict alphabetical order:

6.4.3.1 Visual capacity

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

Snellen notation is described as the distance at which the test is performed divided by the distance at which the letter is vertically equivalent to 5 minutes of arc. Thus, at 6 meters, a letter 6/6 (20/20) is equivalent to 5 minutes of arc, a letter 6/12 (20/40) is equivalent to 10 minutes, and a letter 6/60 (20/200) is equivalent to 50 minutes. The Snellen fraction can also be expressed as a decimal (i.e., 20/20 = 1 and 20/40 = 0.5). [43]

VA will be assessed at baseline, without refractive correction, using the Snellen chart. This chart will be placed in a location with adequate natural or artificial lighting and at a distance of 3 m from the subject being assessed. Visual acuity will be measured in each eye, starting with the right eye (RE),

asking the subject to keep both eyes open and using an occluder to cover the left eye (LE); the subject will read aloud the lines indicated by the evaluator. The evaluator will record the smallest line of letters visible as the RE VA in the clinical record. The LE is then assessed using the same method.

The subject's best refractive correction will then be performed, and the examination will be repeated using the obtained refraction. This result will be reported as CV, entered as a fraction in the clinical record and on the Case Report Form (CRF), and will also be entered as a decimal on the CRF. By definition, the CV cannot be less than the VA.

6.4.3.2 Eye comfort index

This questionnaire is designed to measure ocular surface irritation using 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 (OCI) assesses symptoms. The OCI contains six items that focus on discomfort associated with the ocular surface. Each of these questions has two parts, which separately inquire about the frequency and severity of symptoms. [44]See Appendix 14.1 Eye comfort index

The evaluator will give the questionnaire to the subject and allow them to answer it calmly without any pressure or coercion. They will only assist them if they have difficulty understanding any of the questions.

Ocular surface stains

- *Lissamine green staining .*
  A drop of topical anesthetic will be instilled into the conjunctival fornix. A second drop will then be applied to the tip of the lissamine green strip and allowed to run into the fornix. It is essential to rapidly assess the staining, sequentially, first in the OD and then the OS, so that the observed patterns are equally bright. [19]See Appendix 14.2 Oxford Scale
- *Fluorescein staining.*
  A drop of topical anesthetic will be instilled in the conjunctival fornix. A second drop will then be applied to the tip of the fluorescein strip and allowed to run into the fornix. It is essential to rapidly assess the staining, sequentially, first in the OD and then the OS, so that the observed patterns are equally bright. This assessment will be performed using a cobalt blue filter. [19]See Appendix 14.2 Oxford Scale

For both stains, the value obtained according to the Oxford scale will be recorded in the CRF.

6.4.3.4 Presence of adverse events

The management of AEs will be carried out according to what is described in section 9.3 Adverse events

The IP will record any AEs presented by the study subjects in the corresponding section of the CRF, in addition to mentioning them in their essential document.

The IP must perform a complete ophthalmologic examination of the ocular surface, anterior segment, and posterior segment. Any pathological changes found must be reported in accordance with the AD management guidelines.

6.4.3.5 Intraocular pressure

Tonometry is the objective measurement of IOP, based primarily on the force required to flatten the cornea or the degree of corneal indentation produced by a fixed force. Goldman tonometry, based on the Imbert-Fick principle, is considered the gold standard for IOP measurement.

[43]Tonometry is performed after instillation of a drop of topical anesthetic (tetracaine 0.5%), fluorescein, and the use of a cobalt blue filter (after evaluating corneal surface staining). These measurements are recorded in the clinical record and on the CRF.

6.4.3.6 Vital signs

The vital signs to be assessed (HR, RR and SBP) may be measured by an assistant duly designated in the center's organization and the delegation of responsibilities. The technique to be used for HR and RR will be counting repetitions in one minute by direct auscultation with a stethoscope.

SBP should be measured after 5 minutes of rest on the left arm. The instrument may be manual or automatic, as the PI deems appropriate. All measurements must be performed under equal conditions. Three measurements will be taken, with a minimum interval of 5 minutes between measurements, and recorded in the patient record. The average will also be recorded on the grade and the CRF.

6.4.3.7 Tear film break-up time

One of the first aspects of the tear film to change when there is a change in the ocular surface is its stability. In general, if the corneal or conjunctival surface is damaged, it is unlikely that a stable tear film can be maintained.

The most common method for assessing tear film stability is fluorescein-based TRL. Once fluorescein is instilled, the patient is asked not to blink using the cobalt blue filter. The fluorescein-stained precorneal layer will shift to less fluorescent or non-fluorescent regions. The time elapsed from the last blink until these regions appear is the TRL. It is reported in seconds in the clinical record and on the CRF.

6.4.3.8 Pregnancy test

This refers to the performance of a rapid pregnancy test in all women of childbearing age who wish to enter the study. By childbearing age, we mean women who have not experienced menopause. For the purposes of this study, menopause is defined as 12 months from the last menstrual period in women over 40 years of age or who have undergone a hysterectomy or bilateral oophorectomy. Women of childbearing age using contraceptive methods, including bilateral tubal obstruction , must undergo a pregnancy test. This test will be performed by the PI or a designated team member according to the instructions for the device provided by the sponsor. When applicable, the performance, result, and date must be recorded on the CRF. If not applicable, the reason must be noted.

6.4.3.9 Laboratory tests

The PI will generate the order for the BH, QS, and LFT studies, to be performed by the clinical laboratory designated by the sponsor. The clinical laboratory will provide the PI with the results for evaluation and recording. The normal parameters to be considered will be the ranges established by the laboratory; however , the PI's clinical judgment will prevail in determining whether the results are normal or abnormal.

6.4.4 Time of measurements

Measurements of the primary and secondary outcome variables will be performed and evaluated for each visit, according to the following:

Baseline Visit / Day 0.

Some of these measurements will be performed at the screening visit to complete the eligibility criteria (see Study schedule and diagram), at the discretion of the PI, and if no more than 10 days have passed, they may be taken to complete the baseline visit data.

1. Visual capacity.
2. Intraocular pressure.
3. Eye comfort index
4. Ocular surface evaluation
    a. Includes stains
    b. TRL
5. Adverse event evaluation.
6. Vital signs.
7. Evaluation of laboratory test results

Visit 1 / Day 5.
It can be done in a period of ± 2 days in relation to day 5 of application.

1. Visual capacity.
2. Intraocular pressure.
3. Ocular surface evaluation
    a. Includes stains
    b. TRL
4. Vital signs.
5. Adverse event evaluation.

Final Visit / Day 11.
It can be done in a period + 1 day in relation to the 11th day of the start of application, not before the 11th day since the 10 days of application would not be met.

1. Visual capacity.
2. Intraocular pressure.
3. Eye comfort index
4. Ocular surface evaluation
    a. Includes stains
    b. TRL
5. Vital signs.
6. Evaluation of adverse events.

Safety Call / Day 13.
It can be carried out within a period of ± 1 day in relation to the 13th day from the start of application.

1. Ask about the presence of any adverse events.
2. Evaluation of laboratory test results

6.5 Study schedule and diagram

Procedures	*Scrutiny* Day 0 - X to	Baseline Visit Day 0	Visit 1 Day 5 ± 2	Final Visit Day 11 at + 1	Security Call Day 13 ± 1
CI Signature	X				
Medical record	X				
Ophthalmological clinical history	X				
Laboratory sample collection	X			X	
Laboratory Test Review		X			X
Pregnancy test	X			X	
Eligibility criteria	X	X [b]			
Assignment		X			
Delivery of intervention		X [c]			
Return of intervention				X	
Adherence assessment			X	X	
Adverse events			X	X	X
Intraocular pressure	X	X [1]	X	X	
Visual capacity	X	X [1]	X	X	
TRL	X	X [1]	X	X	
Ocular surface stains	X	X [1]	X	X	
Vital signs	X	X [1]	X	X	
Eye Comfort Index		X		X	
Submission of the subject's diary		X	X		
Return/Evaluation of the Subject's Diary			X	X	
Return and Evaluation of the quality questionnaire				X	
Subject continuity assessment			X		

[The] screening visit may be up to 10 days prior to the baseline visit; if this is exceeded, the subject will not be allowed to enter.
[b] These criteria will be completed with the results of the laboratory tests and those collected during the scrutiny visit.
[c] The instruction will be given to start the application the following day.
[1] They can be taken from the screening visit, as long as no more than 10 days have passed; it is the IP's prerogative to measure them again at the baseline visit.

6.5.1 Procedures to be performed per visit

6.5.1.1 Scrutiny visit

- Signature of informed consent: refers to the signing of the written informed consent document. See 10.3 Consent
- General and ophthalmological medical history: refers to the technical, clinical, and legal document that chronologically records the patient's health conditions, medical procedures, and other procedures performed on the patient. It includes a comprehensive ophthalmological history and examination to determine the patient's eligibility, i.e., evaluation of both eyes and ocular adnexa, slit-lamp examination of the ocular surface and anterior segment, and fundoscopy . If the patient is recruited from the study center's established office, the existing medical history may be used; only one update is required.
- Laboratory sampling: see 6.4.3.9 Laboratory tests.
- Pregnancy test: see 6.4.3.8 Pregnancy test.
- Eligibility criteria: Refers to the PI's review, which verifies that the subject can be included in the study if they meet the inclusion criteria and do not meet the exclusion criteria. See 6.2 Eligibility criteria
- Intraocular pressure: see 6.4.3.5 Intraocular pressure
- Visual capacity: see 6.4.3.1 Visual capacity
- TRL: see 6.4.3.7 Tear film break-up time
- Ocular surface stains: see Ocular surface stains
- Vital signs: see 6.4.3.6 Vital signs

6.5.1.2 Baseline visit

- Laboratory Test Review: Refers to the PI's review and analysis of the BHc , QS, and PFH results. See 6.4.3.9 Laboratory tests.
- Eligibility criteria: The laboratory results will determine the subject's profile for inclusion or exclusion.
- Assignment: This refers to determining the intervention the patient will follow during the study. This will be done according to section 7. Methods. Intervention allocation . This assignment will be done at the baseline visit (day 0) and will be accompanied by the indication to begin the treatment period the following day (day 1).
- Delivery of intervention: Refers to the delivery of the investigational product to the study patient by the research center. This will be carried out in accordance with sections 6.3.1 Treatments administeredand 6.3.4.1 Delivery and receipt.
- Variable Assessment: Data from the assessment of the variables listed below may be taken from the scrutiny visit, as long as it is not taken more than 7 days prior to this visit. It is the IP's prerogative to decide whether to use the information from the scrutiny visit or repeat the assessments during this visit.
    - Intraocular pressure
    - Visual capacity
    - TRL
    - Ocular surface stains
    - Vital signs
- Eye comfort index: see 6.4.3.2 Eye comfort index
- Delivery of the subject's diary: Refers to the delivery by the IP to the subject of the subject's diary instrument.

6.5.1.3 Visit 1

- Adherence assessment: refers to the assessment carried out by the IP in accordance with section 6.3.2.1 Procedure for monitoring adherence
- Adverse events: see 6.4.3.4 Presence of adverse events
- Intraocular pressure: see 6.4.3.5 Intraocular pressure
- Visual capacity: see 6.4.3.1 Visual capacity
- TRL: see 6.4.3.7 Tear film break-up time
- Ocular surface stains: see Ocular surface stains
- Vital signs: see 6.4.3.6 Vital signs
- Submission of the subject's diary: see 6.5.1.2 Baseline visit
- Return/Review of Subject Diary: Refers to the subject handing over the subject diary to the PI. The PI will review the diary to ensure it is complete correctly, assess post-instillation symptoms , and record the applications.
- Subject Continuance Assessment: Refers to the PI's determination of the subject's desire to continue participating in the study.

6.5.1.4 Final Visit

- Laboratory sampling: see 6.4.3.9 Laboratory tests
- Pregnancy test: see 6.4.3.8 Pregnancy test
- Return of intervention: see 6.5.1.3 Visit 1.
- Adherence assessment: refers to the assessment carried out by the IP in accordance with section
- Adverse events: see 6.4.3.4 Presence of adverse events
- Intraocular pressure: see 6.4.3.5 Intraocular pressure
- Visual capacity: see 6.4.3.1 Visual capacity
- TRL: see 6.4.3.7 Tear film break-up time
- Ocular surface stains: see Ocular surface stains
- Vital signs: see 6.4.3.6 Vital signs
- Eye comfort index: see 6.4.3.2 Eye comfort index
- Subject diary return/evaluation: see 6.5.1.3 Visit 1.
- Return/evaluation of the quality questionnaire: refers to the submission of the quality questionnaire to the IP by the subject.

6.5.1.5 Safety call

- Adverse events: see 6.4.3.4 Presence of adverse events
- Laboratory test review: see 6.5.1.2 Baseline visit

6.5.2 Study diagram

An enrollment time of 30 days is estimated for the entire sample.

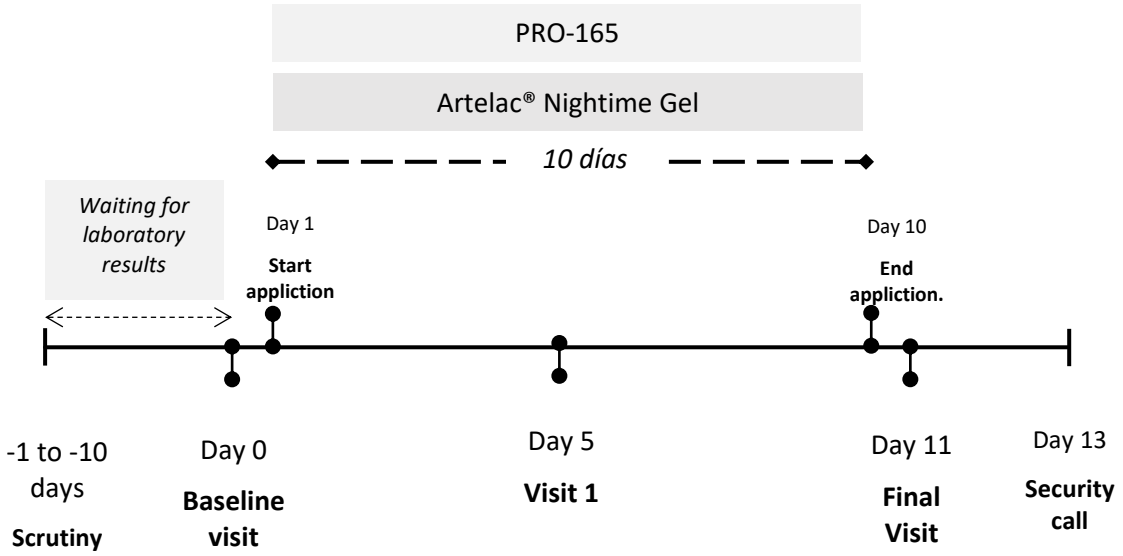


Figure 3Study diagram

6.6 Sample size

A total size of 32 subjects is estimated, distributed in 2 intervention groups. [16 subjects (16 eyes) per group]

6.6.1 Sample size calculation

There are no references on the calculation of the sample size in phase I studies, and the formulation of Humylub Ofteno® has not reported any adverse events in its periodic safety reports. Therefore, it was considered appropriate to base the calculations on previous phase I studies conducted by Laboratories . Sophia , SA de CV [45, 46, 47, 48].

The calculation was based on the adverse event presentation reported by Christ T., in a randomized, single-blind, parallel-group controlled clinical trial evaluating the efficacy and tolerability of a 5% dexpanthenol ophthalmic gel versus a 5% panthenol ointment in 48 subjects with corneal erosion, UV-induced keratoconjunctivitis, or similar conditions. The intervention consisted of applying 1 cm of the gel and ointment for 4 and 3 days, respectively.[49]

The percentage of good tolerance reported with the gel was 25%, so it is expected that no more than 10% of subjects will report poor tolerance with the formulation proposed in this protocol.

The sample size was calculated using the formula for proportions

$$n = p\,(1-p)\left(\frac{Z_{1-\alpha+}\,Z_{1-\beta}}{p-p0-\ \delta}\right)^2$$

With a statistical confidence of 95% corresponding to type I error, equal to 1.96, with a power of 90%, corresponding to type II error, equal to 0.84.

According to the previous calculation, the result is 26 subjects, which was increased by 20% to account for probable losses. The total required sample size is **32 subjects** . Therefore, each group will consist of 16 subjects, each of whom will contribute an eye to the analysis.

6.7 Recruitment

It is recommended that during the development of this research protocol, the principal investigator request approval from the Research Ethics Committee and the Research Committee, as well as authorization from the relevant regulatory body, to publish or disseminate in mass media the invitation to participate in the study to those individuals who meet the eligibility criteria.

It is possible to discuss with other health professionals the opportunity for healthy subjects to be evaluated by an ophthalmologist at no cost, as well as undergo office examinations that will allow for a more precise determination of their clinical ocular status by participating in a clinical research protocol sponsored by Laboratorios Sophia SA de CV.

7. Methods. Intervention allocation

7.1 Generating the assignment sequence

Two strata will be used for the intervention groups, which will be balanced for each research center. The allocation will be 1:1. Data will be generated through a validated electronic system from an external provider, previously evaluated and authorized by Laboratorios Sophia SA de CV. Information regarding this provider will be found in the study's master folder.

7.2 Blinding mechanism

Blinding will be performed by personnel assigned by the Clinical Operations Management of Laboratorios Sophia SA de CV. This will consist of identical labeling for both interventions. This will prevent the PI, the study subject, and all unauthorized individuals from identifying which intervention each container belongs to.

7.3 Implementation

The sequence will be generated using an electronic randomization system. This system will be contracted by Laboratorios Sophia , SA de CV to a third party. Information about this third party will be found in the study's master folder.

7.4 Blinding (Masking)

Blinding will be performed on the subject and principal investigator. Furthermore, the statistical analysis will be performed blindly for the partial and final analyses.

Blinding will be carried out using identical labels. These, in compliance with current and applicable regulations, must contain at least:

- Name, address and telephone number of the sponsor
- Pharmaceutical form and route of administration
- Batch number
- Legend “Exclusively for clinical studies”
- Expiration date

7.4.1 Opening the blind

Blinding may be opened in the following cases:

1. Presence of a serious adverse event.
2. Safety alert for the use of the drugs under study.

3. In the event that the sponsor determines it for any security reason or other reason that it deems appropriate.

8. Methods. Data collection, management, and analysis

8.1 Data collection methods

The sponsor will assign a clinical monitor to the research site, who will be authorized to monitor, review, procure, and ensure that the quality of the information obtained from participants is reliable and trustworthy. The monitor will schedule periodic visits to the research sites to review source documents and corroborate the information captured in the case report form (CRF). The monitor will be trained in the study protocol information (objective, visits, procedures, accepted range of values, etc.). If the data are not identical between the two records, the clinical monitor will generate a discrepancy, which must be resolved by the research site within the timeframe the sponsor deems reasonable to meet the objectives of the clinical study. Discrepancies will be corrected in accordance with Good Documentation Practices.

The data recorded in the CRF will be reviewed by Laboratorios Sophia , SA de CV personnel trained in ophthalmology, clinical, and pharmacology, who will have the authority to generate discrepancies in the event that the data do not adhere to the provisions of the research protocol or put participants at risk.

Once all discrepancies generated by the clinical monitoring team and clinical staff have been resolved , the data will be downloaded into an electronic database (Excel spreadsheet) by personnel designated by the sponsor. A new review of the data will be conducted to verify its accuracy, and new discrepancies may be generated if deemed necessary.

The generated database will be safeguarded by the sponsor and will only be accessible to designated personnel.

8.1.1 Strategies for completing the follow-up

- You will be clearly informed of the importance of the study and the benefits the population will gain from its results.
- Transportation assistance will be provided to enable participants to attend their visits.
- A printed calendar will be provided to remind participants of their appointments and upcoming activities, as well as their estimated duration.
- If the participating subject does not attend their appointment, the research site will call to determine the reason and will attempt to schedule a new appointment within the established window or an unscheduled appointment. (If an appointment cannot be scheduled, the presence of adverse events and the reason for discontinuing the study will be asked as minimum information.)

8.2 Data Management

The subject's medical record (including clinical notes, examination results, etc.), as well as the subject's diary, and the ICO questionnaire are considered source data.

The PI or their designated team member will complete the Case Report Form (CRF) as well as all other documents provided by the sponsor (e.g., treatment management documents).

A CRF was designed to record the data required by the protocol and collected by the researcher at each visit.

In the case of self-assessment questionnaires, the principal investigator or the person responsible for completing them is not permitted to modify what was written by the study subject.

Data entry at the center will be performed by the researcher, or a designated person from their team, after completing the Medical Record. The researcher or a designated person from their team will be trained in completing the CRF.

All corrections to the CRF data must be made by the researcher or a designated person on his or her team according to the instructions provided.

To ensure data confidentiality and security, usernames and passwords will be used to restrict system access to authorized personnel only.

The monitor must ensure that all information on the CRF has been completed. After comparing the data with the source documents, the monitor will ask the investigator to make any necessary corrections or clarifications so that the responses and closure can be completed as quickly as possible.

The Scientific Committee of Laboratorios Sophia , SA de CV will conduct the final medical-scientific review and issue guidelines for freezing the database.

8.3 Statistical methodology

8.3.1 Analysis of primary and secondary outcome variables

Statistical analysis will be performed by Sophia Laboratories staff . SPSS version 19 (IBM Corporation , Armonk , NY, USA) will be used.

The designated personnel will be blinded to the intervention groups. Coding will be performed using consecutive numbers for each intervention group.

The data will be collected and organized in an Excel spreadsheet. They will then be exported to the SPSS software platform. The variables will be categorized according to their nature.

The results of continuous quantitative variables will be expressed and presented using measures of central tendency and dispersion (mean, standard deviation, and ranges **,** as appropriate). Nominal and ordinal qualitative variables will be presented using frequencies, proportions, and/or percentages. See **Table 5Scales to be**

Kolmogorov-Smirnov test will be performed to determine whether the distribution is normal in the results obtained in each study group [50].

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

- Intra-group analysis : will be determined by the Wilcoxon rank test, for quantitative variables [51]
- Between-group analysis : Kruskal-Wallis test [52]. This nonparametric test is used to determine whether a group of data comes from the same population. Intuitively, it is identical to ANOVA with the data replaced by categories. For quantitative variables, the Student t *statistic is used* .

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

The results of the nominal and ordinal qualitative variables will be presented as frequencies, proportions, and percentages. See Table 1 (section 6.4.3).

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

- Intra-group difference : McNemar [53]'s test . This test is applied to 2x2 contingency tables with a dichotomous trait, with matched subject pairs, to determine whether the row and column marginal frequencies are equal (marginal homogeneity).

- Difference between groups : Pearson's $\chi^{2\ test}$ (or Fisher's exact test).

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

For adverse event reporting, all eyes of participants randomized to an intervention group after the baseline visit will be considered. Results will be expressed as the number of cases (eyes).

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

The investigational drug will be considered safe and tolerable when there are no clinical or statistical differences in all primary outcome variables compared to its comparators.

Subjects with an adherence rate greater than 60% will be included in the statistical analysis to meet the study objective, based on the subject's diary. However, even if the subject's diary indicates adherence greater than 60%, if the adherence calculated by weight is less than 30%, the subject will not be included. The minimum dose necessary to obtain a pharmacological effect (lubricant/1 gel application per day) and the presence of adverse events (exposure) were considered sufficient to meet the overall design objective, in accordance with the pharmacological characteristics of the investigational product.

8.3.2 Additional analyses

No additional analyses beyond those previously described are planned. However, these may be performed if specific safety aspects of an intervention need to be analyzed during the study, maintaining blinding until the study's completion.

8.3.3 Population analysis and missing data handling

An intention-to-treat analysis will be performed, including data from participants who completed at least visit 1.

9. Methods. Monitoring

9.1 Data Monitoring

The purpose of monitoring visits is to confirm that studies sponsored by Laboratorios Sophia , SA de CV are conducted in accordance with the ethical principles established in the Declaration of Helsinki, with Good Clinical Practices, and with applicable regulatory requirements. The site monitor must verify compliance with the protocol, amendment(s), review accounting records for the investigational product, and verify that the site personnel and facilities are adequate for conducting the study.

The researcher must ensure that sufficient time, space, and qualified personnel are available for monitoring visits.

In order to conduct the monitoring review, it is mandatory to provide direct access to all source data and data related to the study site. The monitor will conduct a review of the CRF and a Source Document Verification (SDV). SDV refers to the verification of records in the CRF by comparing them with the source data that the researcher will make available for this purpose.

Regarding the CRF, the monitor will mark the completed and approved screens on each visit if the electronic platform is used.

In accordance with applicable regulations, Good Clinical Practices, and the procedures of Laboratorios Sophia , SA de CV, Laboratorios Sophia , SA de CV monitors will contact the site prior to the start of the study to review the protocol, regulatory, ethical, and Laboratorios Sophia , SA de CV requirements with site personnel. When reviewing procedures for data collection, the discussion will also include the identification, agreement, and documentation of individual data for which the records in the CRF will serve as source documents.

Laboratorios Sophia , SA de CV will monitor the study to verify, among other things, that:

- The data is authentic, correct and complete.
- The safety and rights of the subjects are being protected.
- The study is being conducted in accordance with the currently approved protocol, any other study agreements, Good Clinical Practices, and all applicable regulatory requirements.

The investigator and the head of the medical institution (when applicable) agree to allow the monitor direct access to all relevant documents.

Study monitoring visits will be conducted at regular intervals, depending on the recruitment rate, under arrangements between the investigator and the sponsor. All information related to these visits will be treated as strictly confidential.

Upon premature completion or discontinuation of the study, the monitor will conduct site closure activities with the investigator or site personnel, as appropriate, in accordance with applicable regulations, Good Clinical Practices, and Laboratorios Sophia , SA de CV procedures.

After the study is closed, the investigator must maintain all study records on-site in a secure location. Records must be maintained to allow for easy and timely retrieval, when necessary (e.g., during an audit or inspection). Laboratorios Sophia , SA de CV will inform the investigator/institution of the length of time these records must be retained in order to comply with all applicable regulatory requirements. However, the investigator/institution must seek written approval from the sponsor before disposing of these records. The minimum retention period will satisfy the most stringent standard applicable to that study site, as set forth in GCP, any institutional requirements, or applicable laws or regulations, or the standards/procedures of Laboratorios Sophia , SA de CV.

The researcher/institution must notify Laboratorios Sophia , SA de CV of any changes in archiving arrangements including, but not limited to, the following: archiving in an off-site facility, transfer of ownership of records in the event the researcher leaves the site.

9.2 Preliminary analysis and early termination of the study

If a partial analysis is required, as described in section 8.3.2, this will allow the sponsor to make a decision about early termination of the study if the safety of the participants is compromised.

Early termination of the study will be considered in the following cases:

1. Presence of serious adverse events in more than 5% of participants in any intervention group.
2. The competent authority (COFEPRIS) considers it as security alerts.
3. The Sponsor determines this for its convenience or eventualities such as: financial support, manufacturing errors, etc.
4. Lower recruitment than expected.

If the decision is to terminate the clinical study early, the research center will be notified within the first 24 hours, using the available means of communication. The corresponding authority and the Ethics Committees involved will also be informed.

The research center is required to inform subjects participating in the clinical study within 24 hours of receiving the information from the sponsor. All subjects involved in any phase of the study must be informed.

The outcome of the preliminary evaluation will be the responsibility of the Clinical Operations Management and the Medical Directorate of Laboratorios Sophia , SA de CV, which will have the authority to determine the fate of this protocol, as they deem appropriate.

9.3 Adverse events

9.3.1 Researcher Responsibilities

Conduct adverse event verification through questioning, a relevant physical examination, assessment of progress, as well as appropriate medical and pharmacological management, resolution or outcome, and final discharge following the definitions established in national and international regulations.[54] [55] [56]

In the event of adverse events or any occurrence that puts the health and well-being of patients at risk, appropriate medical care will be provided, either at the research site or by referring the patient to the Hospital Center with the highest resolution capacity with which the researcher's site and/or the researcher has a medical care agreement. The researcher will notify the sponsor's clinical monitor, in accordance with the times established in national and international regulations. In the case of serious adverse events, the sponsor will be notified and the corresponding information will be recorded in the case report form, and in turn, the Research Ethics Committee and the Research Committee will be informed.

The care of adverse events will be carried out according to the event care diagram (see **Figure 4Adverse event care**)

The final report to be drafted by the Scientific Committee of the Clinical Operations Department of Laboratorios Sophia , SA de CV, will include a report on adverse events in compliance with current national and international regulations. [55] [54]

9.3.1.1 Recording adverse events on the Case Report Form

The adverse event registry considers information concerning the participating patient's identification data such as code, age, sex, left eye, right eye.

Information about the type of adverse event, adverse reaction, or suspected adverse reaction to the investigational product or study drug, as applicable. The date on which the adverse event occurred is reported, as well as the date on which the Investigator became aware of it, and the date of resolution or outcome, as applicable. The clinical diagnosis is indicated. Include among concomitant medications the therapy used for the pharmacological management of the adverse

event, suspected adverse reaction, or adverse reaction. Record the outcome or resolution of the event: patient recovered without sequelae, with sequelae, or not recovered. Patient who died due to the adverse reaction/adverse event; patient who died and it is judged that the drug may have contributed; patient who died and the death was not related to the investigational product or drug; or indicate that the consequence of the event is unknown.

Record information about the investigational product or drug, or the drug associated with the adverse event, adverse reaction, or suspected adverse reaction. As applicable, information concerning the generic name, distinctive name, or code of the investigational product 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 those where placebo is used as a comparator, since there are circumstances that justify opening the blind to determine whether the adverse event, adverse reaction, or suspected adverse reaction may be attributable to the active agent, combination of active agents, or pharmacologically inert substance(s), such as vehicles or additives, as appropriate to the phase of clinical research in which the development of the drug is located. It will also be necessary to record data concerning the batch number, manufacturing laboratory, expiration date, dose, route of administration, start and end dates of administration and/or consumption, reason for the prescription; depending on whether it is a product or medication under investigation (protocol in which the patient is currently participating) or a medication that the subject under investigation consumes for the treatment of concomitant underlying diseases or uses for the management of some temporary sign or symptom that does not correspond to the Natural History of the pathology that motivated his/her entry into the research protocol.

Record the withdrawal or discontinuation of the drug, investigational product, or investigational drug, as appropriate. Indicate whether the adverse event disappears upon withdrawal of the investigational product, investigational drug, or suspected drug (of causing the event). Also indicate whether a dose adjustment is made, if the event changes in intensity or severity, and if the reaction persists. It is important to note that in patients who are re-exposed to the investigational product, investigational drug, or drug, which had previously been discontinued, if the adverse reaction or event reappears .

Regarding concomitant pharmacotherapy, indicate the generic name, dose, route of administration, start and end dates, and the reason for the prescription, regardless of whether it is in accordance with the prescribing information or the data sheet or if it is used outside the regulations or as authorized by the local, national, or international regulatory body.

Regarding relevant clinical history. The analysis of the adverse event, adverse reaction, or suspected adverse reaction takes into account the previously described information. However, the clinical context in which the adverse event occurs in the participants of the clinical research protocol is of special interest. Therefore, information about previous conditions, hypersensitivity or allergy symptoms, previous surgical procedures, laboratory tests or examinations performed on the participant, etc., that the researcher deems appropriate may be mentioned. If there is not enough space in the case report form, the information from the clinical note may be supplemented in the clinical record.

9.3.1.2 Monitoring of adverse events

The PI will provide care and management of the participant's AE until its resolution, as described in the following section. If the participant develops a chronic adverse event during the study, the patient will only be monitored for 30 days after the last pharmacological intervention.

9.3.1.3 Procedures for a serious adverse event

The adverse event handling process considers the following stages:

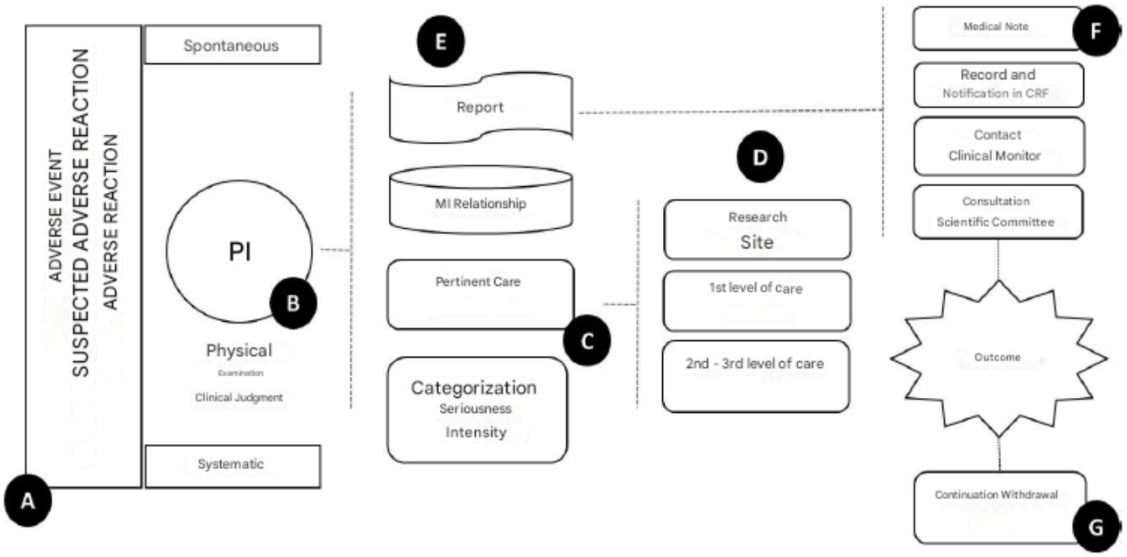


Figure 4 Adverse event care

A. During the development and conduct of this clinical research, undesirable harmful events or adverse reactions of medical significance may occur in the participating patient, which do not necessarily have a causal relationship with the investigational product or investigational drug. These harmful phenomena may occur during the use of investigational drugs, unintentionally, at doses authorized for use in humans by a local, national, or international regulatory entity, whether for prophylaxis, diagnosis, treatment, or for the modification of a physiological process. However, it may be suspected that the investigational product, the investigational drug, or the placebo may cause some unwanted clinical manifestation. Adverse events, adverse reactions, or suspected adverse reactions to one or more drugs may occur during the systematic evaluation of participants (on the days in which the clinical review is scheduled, according to the schedule of activities) or suddenly, in such a way that,
B. The researcher must be the first person to whom the patient notifies that he or she has developed or experienced any harmful clinical phenomenon during his or her participation in this research protocol.
C. In accordance with his or 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 that referred to in the investigator's manual, Prescribing Information or the comparator drug's data sheet, the principal investigator determines the appropriate treatment for the adverse event/reaction; whether
D. at the research site or at the hospital with the highest resolution power (1st, 2nd or 3rd level of medical care). So that, in case the patient is referred by the Researcher to a hospital, he/she attends through a referral system, it may be with an identification card that the patient belongs to the present investigation and there is an office or folio number, which belongs to the emergency care agreement with the health institution with the highest resolution power or a medical reference note issued by the principal investigator is given to the participating patient so that appropriate care is provided. It should be noted that the

Sponsor of the study, Laboratorios Sophia , SA de CV, will pay the expenses for the medical care of the participating patient, only if the adverse event, adverse reaction or suspected adverse reaction to a medication is associated or related to the investigational product or investigational medication.

E. Taking the clinical information collected, either during the care provided at the research site or that provided by the treating physician(s) at the hospital, the principal investigator records the adverse event, suspected adverse reaction or adverse reaction to medication in his/her clinical note in the clinical record, recording the seriousness, intensity (mild, moderate or severe), relationship with the product or medication under investigation, as well as:
F. The migration of relevant data to the case report format and its respective adverse event section, indicating the pertinent information, already referred to in section 9.3.1.1. This is because in cases of serious adverse events, which must be reported within 24 hours after the principal investigator becomes aware of them, the clinical monitor of the study is informed, so that he or she, in turn, informs the Scientific Committee and the Pharmacovigilance Department of the sponsor, and subsequently informs the Research Ethics Committee. Regarding non-serious adverse events, these will be recorded and appropriately addressed, and the corresponding regulatory entity will be informed about the safety profile of the investigational product or investigational drug in the final report of the clinical trial.
G. The recording of the outcome of the adverse event, suspected adverse reaction, or adverse reaction to medication depends substantially on the principal investigator's monitoring of the participant, since the majority of adverse phenomena are expected to be ophthalmic in nature (see the safety profile section in section 5.3 and in the investigator's manual). However, systemic alterations may exist. Therefore, at the investigator's discretion, the participant's withdrawal or retention will be considered, in accordance with the provisions of section 6.2.2 Exclusion criteriaof this research protocol.

9.3.1.4 Causality Assessment

Causality assessment, the methodology used to estimate the probability of attributing an adverse reaction, a suspected adverse reaction, or an observed adverse event to a drug, investigational drug, or investigational product, considers probabilistic categories based on the available evidence and the quality of the information, in accordance with national pharmacovigilance regulations. [54]As a tool to facilitate the probabilistic categorization of causality, the principal investigator may use the Karch and Lasagna algorithm , modified by Naranjo, which rates different items to assign a value to the cause-effect relationship between the administration of the drug and the adverse reaction. [57]See **Table 6Karch and Lasagna algorithm modified by Naranjo**

Karch and Lasagna algorithm modified by Naranjo

No .	Reagent	Score	
		Yeah	No
1.	There are conclusive previous reports on adverse drug reaction, adverse event or suspected adverse drug reaction	+1	0
2.	The adverse event occurred when the suspected drug was administered	+2	-1

Karch and Lasagna algorithm modified by Naranjo			
No .	Reagent	Score	
		Yea h	No
3.	The adverse drug reaction, adverse event, or suspected adverse drug reaction improved upon discontinuation or administration of a specific antagonist	+1	0
4.	The adverse drug reaction/adverse event/suspected adverse drug reaction recurred upon administration of the investigational drug/investigational product/investigational drug	+2	-1
5.	There are alternative causes that can provoke this reaction.	-1	+2
6.	The adverse reaction/adverse event/suspected adverse drug reaction occurred after placebo administration	-1	+1
7.	The drug was determined in blood or other fluids in toxic concentrations	+1	0
8.	The intensity of the adverse reaction/adverse event/suspected adverse drug reaction was greater with higher doses or less with lower doses	+1	0
9.	The patient has had similar reactions to the investigational drug/product 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		**Addition**	
Probabilistic category based on the score obtained			
Yo	The causal relationship is verified	≥ ,9	
II	The ADR is likely due to the investigational drug or product	5 to 8	
III	The ADR may be due to the investigational drug or product	1 to 4	
IV	The causal relationship is doubtful	0	

The items considered by the Karch and Lasagna algorithm , modified by Naranjo, are shown. 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 investigational drug/product/drug and the adverse reaction, adverse event, or suspected adverse reaction. Note that if the information is unavailable, a score of zero is recorded.

Table 6Karch and Lasagna algorithm modified by Naranjo

Thus, the degree of certainty for establishing the investigational product or investigational drug (as applicable) as the causal agent of the harmful event occurring to the participating patient may be indicated directly by the principal investigator based on their clinical experience or through the voluntary application of the aforementioned tool. However, it is important for the investigator to consider the following arguments in favor of a causal relationship:

a) Strength of association that 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 onset, time, dose and reversibility after suppression.
d) Biological plausibility: 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 anomalous metabolites or high levels of drug or its biotransformation product.
f) Analogy: experience acquired with other related drugs, adverse reactions frequently produced by the same family of pharmacological agents.
g) Nature and characteristics of the data: objectivity, accuracy and validity of the relevant documentation. [58]

9.3.2 Sponsor Responsibilities

The sponsor will be responsible for and cover the costs arising from medical care for adverse events related to the investigational product (see section 11. Financing and insurance).

9.4 Audit

To ensure compliance with GCP and all applicable regulatory requirements, Laboratorios Sophia , SA de CV may conduct a quality assurance audit. Regulatory agencies and research and ethics committees may also conduct an inspection of this study.

9.4.1 Pre-study audit

The research centers included in the study will be subject to a pre-study visit prior to center selection, where they will be verified to meet the minimum requirements indicated by the sponsor.

9.4.2 Audit/Inspection during the conduct of the study

They may take place at any time before, during, or after the conclusion of the study. If an audit or inspection is conducted, the researcher and the institution must agree to allow the auditor/inspector direct access to all relevant documents and must allocate their own and staff time to the auditor/inspector to discuss the findings and any pertinent issues. If the audit is conducted by a regulatory agency or committee, the researcher must notify the auditor/inspector immediately.

10. Ethical considerations

10.1 Approval of committees

This study will be conducted in accordance with the standards of the “Declaration of Helsinki”, World Medical Association 2013. “ Nuremberg Code”; Nuremberg Trial by the International Tribunal of Nuremberg , 1947. “Belmont Report”, National Commission for the Protection of Subjects of Biomedical and Conduct Research, 1979. It will be conducted in accordance with the scientific and technical requirements necessary for the registration of medicines for human use of the “International Conference on Harmonization” (The International Council for Harmonisation (ICH) Guideline for Good Clinical Practice. “International Ethical Guidelines for Biomedical Research Involving Human Subjects of the Council for International Organizations of Medical Sciences ” of Medical Sciences , CIOMS, 2002). “International Ethical Guidelines” for Epidemiological Studies of the Council for International Organizations of Medical Sciences of Medical Sciences , CIOMS, 2008).

The Research Ethics Committee and the Research Committee will evaluate the protocol before conducting the study and will issue their approval or any possible modifications for its

implementation. These Committees must be notified of any significant changes to the protocol. In addition to the above, the current regulations issued by the Ministry of Health must also be complied with. General Health Law, NOM 012 Mexican Official Standard NOM-012-SSA3-2012, which establishes the criteria for the execution of health research projects in human beings. The study is considered research with greater than minimum risk according to the Regulations of the General Health Law on Health Research, Title Two, Chapter I, Article 17, Category III, published in the Official Gazette on January 6, 1987.

The principal investigators, study coordinators or personnel authorized by the sponsor will submit for evaluation by the Research Ethics Committees, Research Committees, and when applicable, the Biosafety Committee, the essential documentation of the research project: research protocol, informed consent letter, researcher's manual, subject diary, as well as those requested, additionally, in accordance with the local, national or international requirements applicable by the regulatory entities.

The study will not be initiated at the research site without the confidentiality agreements and financial proposals from each of the principal investigators, duly signed, and without having previously obtained the favorable opinion and/or approval of the corresponding Research Ethics Committees, Research Committees, and, when applicable, the Biosafety Committee.

The study will not begin without meeting the relevant local, national, or international regulatory requirements and obtaining the appropriate health authorization.

10.2 Amendments to the protocol

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

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 for the conduct of the research), will be sent for authorization by the relevant regulatory entity.

Amendments that substantially modify the protocol or impose additional or different risks on research subjects must be approved by the aforementioned Committees. It is the investigator's responsibility to take measures in situations requiring immediate action to prevent unnecessary harm to study participants.

The principal investigator is responsible for communicating to the Research Ethics Committee any amendments to the protocol that could affect the rights, safety, or well-being of the research participants. They must also report any situation or new knowledge that indicates an increased risk to the participants, the premature termination or suspension of the study, the reasons for it, and the results obtained to that point. They must also report the conclusion of the study upon completion of the research protocol.

The list of amendments, and where necessary, the list of errata issued, will be included in the final research report.

10.3 Consent

10.3.1 Obtaining

Informed consent must be obtained before the subject undergoes any procedure indicated in the protocol.

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

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

This information will be provided in a language understandable to the subject. The subject will be explained that they have the right to discontinue their participation in the study at any stage, without affecting their relationship with the researcher and/or their future participation. Informed consent will be presented to the potential participant; they must have sufficient time to review each and every aspect mentioned above. Any questions they may have will be clarified by the person responsible for obtaining informed consent.

Once the participant agrees to participate in the study, he or she must sign and date the informed consent letter in the presence of two witnesses, whether or not related to the study subject. These witnesses will participate in the informed consent process and sign, confirming that the process was carried out prior to any study procedure, that the study information was clearly explained, and that any questions were clarified.

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 capable of providing adequate written informed consent, a “legally authorized” representative of the subject may provide such consent for the subject in accordance with applicable laws and regulations.

The IP must also sign and date this consent.

Informed consent must be signed in duplicate by all parties involved, and two witnesses. One copy will be filed in the subject's file and the other will be given to the participant. The PI must document the date the informed consent was signed in the subject's medical record.

10.3.2 Special considerations

The auxiliary studies that will be performed during the study (laboratory tests) do not pose an additional risk that should be considered apart from the procedures listed in the informed consent.

10.3.3 Modification to informed consent

Changes to the “informed consent” constitute an amendment to this document and must be submitted for approval to the Research Ethics Committees and, if applicable, to the Competent Authorities.

The amendment shall include a copy of the new version in the language(s) of the country.

Such amendments may be implemented only after obtaining written approval from the Research Ethics Committee and the Regulatory Body (as applicable), except for an amendment that is required to eliminate an immediate danger to the study subjects.

Each subject affected by the amendment must complete, date, and sign two originals of the new version. The subject will be given one signed original of the amendment, and the researcher will retain the second original.

10.4 Confidentiality

All documents and information provided to the investigator by the sponsor are strictly confidential. The investigator expressly agrees that the data regarding his or her professional and clinical experience, provided to the sponsor on paper and stored electronically, are solely for use in connection with his or her activities with the clinical trial sponsor, in accordance with Good Clinical Practice. The investigator agrees that he or she and his or her team members will use the information only within the framework of this study, to carry out the protocol. This agreement is binding as long as the confidential information has not been publicly disclosed by the sponsor. The clinical trial protocol provided to the investigator may be used by the investigator and his or her colleagues to obtain informed consent from the subjects for the study. The clinical trial protocol, as well as any information derived from it, must not be disclosed to other parties without the sponsor's written authorization.

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

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

10.5 Declaration of interests

The IP agrees to declare his or her financial interests and conflicts of interest prior to the start of the study.

10.6 Access to information

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

10.7 Ancillary and post-study care

Once the study is completed and adverse events are closed according to section 9.3 Adverse events, the sponsor will not extend care to the research subject.

10.8 Biosecurity aspects

NO BIOSECURITY IMPLICATIONS

The present protocol, entitled: “Phase I clinical study to evaluate the safety and tolerability of PRO-165 ophthalmic gel versus Artelac ® Nightime Gel, on the ocular surface of ophthalmologically and clinically healthy subjects”, and number:SOPH165-0217/I IT HAS NO BIOSECURITY IMPLICATIONS, since no infectious-contagious biological material will be used; pathogenic strains of bacteria or parasites; viruses of any type; radioactive material of any kind; genetically modified animals and/or

cells and/or plants; toxic, hazardous, or explosive substances; or any other material that puts the health or physical integrity of the research center staff or research subjects at risk, or affects the environment. It is also declared that no cell, tissue, or organ transplant procedures, or cell therapy, will be carried out in this project, nor will laboratory, farm, or wildlife animals be used.

10.9 Final report and publication of results

10.9.1 Final report

Once the statistical analysis is completed, a final report will be written with the results obtained, by the Scientific Committee of the Clinical Operations Department of Laboratorios Sophia , SA de CV. This report will be prepared following the recommendations of the ICH E3 *Step 4 Guide.*

10.9.2 Communication of results

Regardless of the results of the study, Laboratorios Sophia , SA de CV, is committed to communicating the final report of the study to the principal investigators and the corresponding regulatory entities in the countries with participating research centers. The company maintains at all times the rights to publish and disclose the information contained therein.

10.9.3 Publication of results

Laboratorios Sophia , SA de CV, acting as the sponsor of the study, assumes full responsibility for its role and retains exclusive property rights over the study results, which it may use in any manner it deems appropriate.

The PI agrees not to publish or communicate data collected only in one center or in part of the centers before the publication of the complete results of the study, unless there is prior written agreement from Laboratorios Sophia , SA de CV.

Any draft publication and/or communication related to the study and/or the results obtained during or after the study's completion must be submitted to the participating physician researchers at least 30 days in the case of a publication and 15 days in the case of an abstract, before the scheduled date for the communication and/or presentation of a publication. The physician researchers must comment on the draft within 15 days in the case of a publication and 7 days in the case of an abstract, from the date the draft is received.

However, if the sponsor is in the process of filing a patent application for the results of the study, the sponsor may delay publication or communication of the study results until the date of registration.

11. Financing and insurance

11. 1 Compensation to study participants

Subjects participating in the study will not receive financial compensation for their participation. However, subjects will receive travel expenses for each scheduled visit they attend on time. This amount, as well as the amount, will be specified in the informed consent form.

11.2 Study insurance

In accordance with current local regulations, Laboratorios Sophia SA de CV has contracted a civil liability insurance policy to fulfill its responsibility to provide the medical treatment and compensation to which a subject would be legally entitled in the event of damages directly caused by this research.

In the event of a medical emergency, the research center must have the personnel, materials, equipment, and procedures for its immediate management.

12. Bibliographic references

[1] J. Clegg, J. Guest, A. Lehman and e. al, "The annual cost of dry eye syndrome in France, Germany, Italy, Spain, Sweden and the United Kingdom among patients managed by ophthalmologists.," *Ophthalmic Epidemiol,* vol. 13, pp. 263-274, 2006.

[2] International Dry Eye WorkShop 2007, "The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye Workshop.," *Ocul Surf,* vol. 5, pp. 93-107, 2007.

[3] M. Hom and P. De Land, "Prevalence and severity of symptomatic dry eyes in Hispanics," *Optom Vis Sci,* vol. 82, no. 3, pp. 206-208, 2005.

[4] International Dry Eye WorkShop 2007, "The definition and classification of dry eye disease: report of the definition and classification subcommittee of the international Dry Eye WorkShop," *Ocul Surf,* vol. 5, no. 2, pp. 75-92, 2007.

[5] S. Phadatare, M. Momin, P. Nighojkar, S. Askarkar and K. Singh, "A Comprehensive Review on Dry Eye Disease: Diagnosis, Medical Management, Recent Developments, and Future Challenges," *Adv in Pharm,* 2015.

[6] M. Stern, R. Beuerman, R. Fox and e. al, «The pathology of dry eye; the interaction," *Cornea,* vol. 17, pp. 584-589, 1998.

[7] S. Plugfelder, A. Solomon and M. Stern, "The diagnosis and management of dry eye: a twenty-five year review," *Cornea,* vol. 19, pp. 644-649, 2000.

[8] R. Beuerman, A. Mircheff, S. Pflugfelder, and M. Stern, "The lacrimal function unit," from *Dry eye and ocular surface disorders* , New York, Marcel Dekker, 2004.

[9] M. Stern, J. Gao, K. Siemarko and e. al, "The role of the lacrimal functional unit in the pathophysiology of dry eye.," *Exp Eye Res,* vol. 78, pp. 406-409, 2004.

[10] J. Craig, "Structure and function of the preocular tear film," from *The tear film, structure, function and clinical examination* , Oxford, Butterworth-Heinemann, 202, pp. 18-50.

[11] D. Dartt, "Formation and function of the tear film," from *Adler's Physiology of the eye* , St Louis MO, Saunders-Elsevier, 2011, pp. 350-362.

[12] M. Doughty, "The corneal and conjunctival surfaces in relation to the tear film," from *The tear film, structure, function and clinical examination* , Oxford, Butterworth-Heineman, 2002, pp. 1-17.

[13] C. Belmonte, M. Acosta and J. Gallar, "Neural basis of sensation in intact and injured corneas," *Exp Eye Res,* vol. 78, pp. 513-525, 2004.

[14] C. Begley, R. Chalmers, L. Abetz and e. al, "The relationship between habitual patient-reported symptoms and clinical signs among patients with dry eye of varying severity," *Invest Ophthalmol Vis Sci,* vol. 44, pp. 4753-4761, 2003.

[15] P. Roshental and D. Borsook, «The corneal pain system. Part I: the missing piece of the dry eye puzzle," *Ocul Surf,* vol. 10, pp. 2-14, 2012.

[16] O. Schein, J. Tielsch, B. Munoz and e. al, "Relation between signs and symptoms of dry eye in the elderly," *Ophthalmology,* vol. 104, pp. 1395-1401, 1997.

[17] K. Nichols, N. JJ and G. Mitchell, "The lack of association between signs and symptoms in patients with dry eye disease," *Cornea,* vol. 23, pp. 762-770, 2004.

[18] A. Behrens, J. Doyle, L. Stern and e. al., « Dysfunctional tear syndrome study group. Dysfunctional tear syndrome: a Delphi approach to treatment recommendations.," *Cornea,* vol. 25, pp. 900-907, 2006.

[19] International Dry Eye WorkShop 2007, "Methodologies to diagnose and monitor dry eye disease," *Ocul Surf,* vol. 5, no. 2, pp. 108-152, 2007.

[20] J. Murube, J. Benitez del Castillo, L. Chenghou and e. al, "The Madrid triple classification system.," *Arch Soc Esp Oftalmol,* vol. 78, p. 587–593., 2003.

[21] J. Murube, J. Nemeth, H. Hoh and e. al., "The triple classification of dry eye for practical clinical use," *Eur J Ophthalmol,* vol. 15, pp. 660-667, 2005.

[22] Y. Uchino, M. Uchino, M. Dogru and e. al., "Changes in dry eye diagnostic status following implementation of revised Japanese dry eye diagnostic criteria," *Jpn J Ophthalmol,* vol. 5, pp. 8-13, 2012.

[23] C. Baudouin, P. Aragona, G. Van Setten, M. Rolando and e. al., "Diagnosing the severity of dry eye: a clear and practical algorithm," *Br J Ophtalmol,* vol. 98, no. 9, pp. 1168-1176, 2014.

[24] E. Lopin, T. Deveney and P. Asbell, "Impression cytology: recent advances and applications in dry eye disease," *Ocul Surf,* vol. 7, no. 2, pp. 93-110, 2009.

[25] A. Matoba, D. Harris, D. Mark and e. al, "Dry eye syndrome," American Academy of Ophthalmology, 2003.

[26] International Dry Eye WorkShop (2007), "Management and Therapy of Dry Eye Disease: Report of the Management and Therapy Subcommittee of the International Dry Eye WorkShop (2007)," *Ocul Surf,* vol. 5, no. 2, pp. 163-178, 2007.

[27] Sophia Laboratories, SA de CV, «Periodic Safety Report of Humylub Ofteno(r)», Zapopan, Jalisco, 2012.

[28] W. Sutherland, "Novel and established applications of microbial polysaccharides.," *Trends Biotechnol,* vol. 16, pp. 41-46, 1998.

[29] KT Yamada T, "Microbial synthesis of hyaluronan and chitin: New approaches.," *J Biosci Bioeng,* vol. 99, pp. 521-528, 2005.

[30] G. Snibson, J. Greaves, J. Prydal, C. Wilson and A. Bron, “Precorneal residence times of sodium hyaluronate solutions studied by quantitative gamma scintigraphy.,” *Eye,* vol. 4, pp. 594-602, 1998.

[31] M. Kaido, M. Uchino, N. Yokoi, Y. Uchino and e. al, “Dry-eye screening by using a functional visual acuity measurement system: the Osaka Study,” *Invest Ophthalmol Vis Sci,* vol. 55, no. 5, pp. 3275-3281, 2014.

[32] E. Sabaté, “Adherence to Long-Term Therapies: Evidence for Action,” World Health Organization, Geneva, Switzerland, 2003.

[33] L. Gordis, "General concepts for use of markers in clinical trials," *Control Clin Trials,* vol. 5, pp. 481-487, 1984.

[34] M. Mattson and L. Friedman, “Issues in medication adherence assessment in clinical trials of the National Heart, Lung, and Blood Institute,” *Control Clin Trials,* vol. 5, pp. 488-496, 1984.

[35] S. Norell, “Methods in assessing drug compliance,” *Acta Med Scand,* vol. S 683, pp. 34-50, 1984.

[36] P. Rudd, R. Byyny, V. Zachary and e. al, “Pill count measures of compliance in a drug trial: variability and suitability,” *Am J Hypertens,* vol. 1, pp. 309-312, 1988.

[37] K. Farmer, “Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice,” *Clin Ther,* vol. 21, pp. 1074-1090, 1999.

[38] H. Liu, C. Golin, L. Miller and e. al, "A comparison study of multiple measures of adherence to HIV protease inhibitors," *Ann Intern Med,* vol. 134, pp. 968-977, 2001.

[39] W. Lam and P. Fresco, “Medication Adherence Measures: An Overview,” *BioMed Research International,* vol. 2015, 2015.

[40] M. Vitolins, C. Rand, S. Rapp, P. Ribisl, and M. Sevick, “Measuring Adherence to Behavioral and Medical Interventions,” *Controll Clin Trial,* vol. 21, pp. 188S-194S, 2000.

[41] J. Lee, K. Grace, T. Foster, M. Crawley and e. al, “How should we measure medication adherence in clinical trials and practice?” *Ther and Clin Risk Manag,* vol. 3, no. 4, pp. 685-690, 2007.

[42] J. Kanski, Clinical Ophthalmology, Barcelona: Elsevier, 2009.

[43] M. Michel, W. Sickenberg and H. Pult, “The effectiveness of questionnaires in the determination of contact lens induced dry eye,” *Ophthal Physiol Opt,* vol. 29, pp. 479-486, 2009.

[44] Laboratorios Sophia, SA de CV, «NATIONAL CLINICAL TRIALS REGISTRY (RNEC)», COFEPRIS, [Online]. Available: http://189.254.115.252/Resoluciones/Consultas/ConWebRegEnsayosClinicosDetalle.asp?idsolicitud=1499. [Last accessed: 25 01 2018].

[45] Laboratorios Sophia, SA de CV, "NATIONAL CLINICAL TRIALS REGISTRY (RNEC)," COFEPRIS, [Online]. Available:

http://189.254.115.252/Resoluciones/Consultas/ConWebRegEnsayosClinicos.asp. [Last accessed: 25 01 2018].

[46] Sophia Laboratories, SA de CV, "NATIONAL CLINICAL TRIALS REGISTRY (RNEC)," COFEPRIS, [Online]. Available: http://189.254.115.252/Resoluciones/Consultas/ConWebRegEnsayosClinicos.asp. [Last accessed: 25 01 2018].

[47] Laboratorios Sophia, SA de CV, "NATIONAL CLINICAL TRIALS REGISTRY (RNEC)," COFEPRIS, [Online]. Available: http://189.254.115.252/Resoluciones/Consultas/ConWebRegEnsayosClinicos.asp. [Last accessed: 25 01 2018].

[48] T. Christ, "Treatment of corneal erosion with a new ophthalmic gel containing panthenol," *Spektrum Augenheilkd,* vol. 8, no. 5, pp. 224-226, 1994.

[49] A. Haffajee, S. Socransky and J. Lindhe., "Comparison of statistical methods of analysis of data from clinical periodontal trials.," *Journal of Clinical Periodontology,* vol. 10, pp. 247-256, 1983.

[50] R. Woolson, "Wilcoxon signed-rank test.," *Wiley Encuclopedia of Clinical Trials.,* pp. 1-3, 2008.

[51] N. Salkind, Encyclopedia of research design, Thousand Oaks, CA: SAGE Publications Ltd, 2010.

[52] B. Klingenberg and A. Agresti, "Multivariate extension of McNemar's test.," *Biometrics.,* vol. 62, pp. 921-928, 2006.

[53] Mexican Ministry of Health, «Official Mexican Standard NOM-220-SSA1-2012, Installation and operation of pharmacovigilance.,» *Official Gazette,* 2013.

[54] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A," *ICH Harmonized Tripartite Guideline,* vol. 4 version, 1994.

[55] International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, "General Considerations for Clinical Trials," *ICH Topic E8,* 1998.

[56] I. Aramendi, L. Ardao, M. Oyarzun, M. Pérez, I. Olmos, and M. Frontini, "Drug-Related Problems in Patients Hospitalized at Vilardebó Hospital," *Rev Psiquiatr Urug,* vol. 75, no. 2, pp. 123–133, 2011.

[57] R. Meyboom, A. Egberts, I. Edwards, Y. Hekster, F. Koning and Gribnau, "Principles of signal detection in pharmacovigilance.," *Drug Safety,* vol. 16, pp. 355-365, 1997.

[58] N. Efron, "Grading scales for contact lens complications," *Ophtalmic Physiol Opt,* vol. 18, pp. 182-186, 1998.

[59] European Group of Graves Orbitopathy, «Eugogo,» ETA, [Online]. Available: http://www.eugogo.eu/_downloads/clincial_evaluation/CHEMOSIS-GO.pdf. [Last accessed: 11 April 2016].

[60] The United States Pharmacopeial Convention, “Chondroitin Sulfate Sodium,” Revision Bulletin, 2015.

13. Signature Page

13.1 Signatures of the sponsor's representatives

Name:	
[redacted]	**Signature**
Qualification:	
Medical Director of the study	**Date**

Name:	
[redacted]	**Signature**
Qualification:	
Director of the study	**Date**

Name:	
[redacted]	**Signature**
Qualification:	
Developer of the current version of the protocol	**Date**

13.2 Researcher

I agree to conduct this clinical study according to the design and guidelines of this protocol, adhering to the provisions of this protocol. I agree to conduct the study in accordance with accepted standards of Good Clinical Practice. I agree to report all information and data in accordance with the protocol, particularly any adverse events. I also agree to manage 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 sharing it with any third party not involved in the approval, supervision, or conduct of the study is prohibited. I will ensure that necessary precautions are taken to protect the information from loss, inadvertent disclosure, or access by unauthorized parties.

Name:	
	Signature
Qualification:	
	Date

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14. Annexes

14.1 Ocular comfort index

Eye Comfort Index

Identification card

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

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

Directions:

This questionnaire was designed to rate the comfort of your eyes.
For each question, circle your answer.

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

Never						Always
0	1	2	3	4	5	6

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

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

Never						Always
0	1	2	3	4	5	6

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

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

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

Never						Always
0	1	2	3	4	5	6

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

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

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

Never						Always
0	1	2	3	4	5	6

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

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

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

Never						Always
0	1	2	3	4	5	6

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

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

Sheet 1 of 2

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

Never						Always
0	1	2	3	4	5	6

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

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

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

Never						Always
0	1	2	3	4	5	6

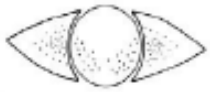
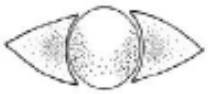
When your eyes felt *itchy ,* how intense was the sensation usually?

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

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

Sheet 2 of 2

14.2 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 panel A
C 	II	Equal to or less than panel C, greater than panel B
D 	III	Equal to or less than panel D, greater than C
E 	IV	Equal to or less than panel E, greater than panel D
>E	V	Greater than panel E