CONFIDENTIAL

Creation date: August 2016

Phase I clinical study, to evaluate the safety and tolerability of the ophthalmic gel PRO-167 versus Corneregel® on the ocular surface of ophthalmological and clinically healthy subjects

Protocol code: SOPH167-0816 / I
Protocol version: 1.0
Date of the version: 08/08/2016
Registration: 173301410A0062/2017

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

1. Summary

<table>
<tr><td colspan="2">Title of the study:
Phase I clinical study, to evaluate the safety and tolerability of the ophthalmic gel PRO-167 versus Corneregel®, on the ocular surface of ophthalmological and clinically healthy subjects.</td></tr>
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SOPH167-0816/I</td><td>Creation date:
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1.0</td><td>Date of the version:
08/08/2016</td></tr>
<tr><td colspan="2">Therapeutic indication:
Reepithelizing of the corneal surface</td></tr>
<tr><td>Study period:
3 to 4 months</td><td>Development phase: I</td></tr>
<tr><td colspan="2">Goals:
To evaluate the safety and tolerability of the ophthalmic gel PRO-167 manufactured by Sophia Laboratories S.A. of C.V. on the ocular surface of clinically healthy subjects.</td></tr>
<tr><td colspan="2">Hypothesis:
Ophthalmic gel PRO-167 has a safety and tolerability profile similar to that of its comparator in healthy subjects.</td></tr>
<tr><td colspan="2">Methodology:
Phase I clinical trial, controlled, of parallel groups, double blind, randomized, exploratory.</td></tr>
<tr><td colspan="2">Number of patients:
24 subjects, divided into 2 groups [12 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 to 45 years.
- Both genders.
- Blood tests [complete blood count (BHc), three element blood chemistry (QS) and liver function tests (PFH)] within normal parameters.
- Visual capacity 20/30 or better.</td></tr>
<tr><td colspan="2">Test product, dose and route of administration, lot number:
- PRO-167. Dexpanthenol 5%. Ophthalmic gel produced by Sophia Laboratories A.S. of V.C., Zapopan, Jalisco, Mexico.
- Dose: a strip approximately 1 cm long, 4 times a day during the period of vigil, in the bottom of the right eye sac.</td></tr>
</table>

- Route of administration: ophtalmic.
Duration of treatment: 10 days
Reference product, dose and route of administration, lot: - Corneregel®. Dexpanthenol 5%. Ophthalmic gel developed by Bausch & Lomb, Berlin, Germany. ▪ Dose: a strip approximately 1 cm long, 4 times a day during the period of vigil, in the bottom of the right eye sac. ▪ Route of administration: ophthalmic
Evaluation criteria: - Density of goblet cells. - Epithelial defects in cornea and conjunctiva. - Presence of adverse events. **Secondary outcome variables:** - Intraocular pressure. - Visual ability - Break time of the tear film. - Laboratory tests: BHc, QS and PFH. - Ophthalmological signs: conjunctival hyperemia, chemosis. - Life signs: FC, FR, TAS. - Subsequent segment. - Quality questionnaire. **Primary outcome variables of tolerability:** - Burning. - Foreign body sensation. - Itching. - Eye comfort index.
Statistical methodology: The data will be expressed with measures of central tendency: mean and standard deviation for the quantitative variables. The qualitative variables will be presented in frequencies and percentages. The statistical analysis will be carried out through the Mann-Whitney U-test for quantitative variables. The difference between the qualitative variables will be analyzed by means of X2 (Chi2). An alpha ≤ 0.05 will be considered significant.

2. Content

Index of tables and figures

3. Index of abbreviations

ALT **Alanino transferase**

AST **Aspartate transferase**

BAK **Benzalkonium chloride, (for its acronym in English Benzalkonium chloride.)**

BD **Direct bilirubin**

BI **Indirect bilirubin**

BHc **Complete blood count**

BPC **Good clinical practices**

BT **Total Bilirubin**

CV **Visual capacity**

CCI **informed consent letter**

CIC **Cytology by conjunctival impression**

IEC **Research Ethics Committee**

CI **Informed Consent**

CRF **Case Report Form (Case Report Form)**

EA/EAS **Adverse event / serious adverse event**

FDA **Food and Drug Administration (Food and Drug Administration)**

FC **Heart rate**

FR **Respiratory frequency**

ICH **International Conference on Harmonization (for its acronym in English International Conference on Harmonization)**

ICO **Eye comfort index**

IP **Principal investigator of the clinical study**

PFH **Liver function tests**

IOP **intraocular pressure**

TAS **Systemic blood pressure**

TF **Fluorescein staining**

TVL **Green lysine stain**

QS **Blood chemistry**

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4. Administrative structure of the study

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

Function	Name/ Contact	Afilliation ¥
Medical responsible for the study	Dr. Leopoldo Martín Baiza Durán leopoldo.baiza@sophia.com.mx	Medical Director and Regulatory Affairs
Director of the study	Dr. Aldo Arturo Oregón Miranda aldo.oregon@sophia.com.mx	Clinical Operations Manager
Scientific Comittee	Dr. Oscar Olvera Montaño oscar.olvera@sophia.com.mx	Ophthalmologist Investigator
Scientific Comittee	Dr. en C. Arieh Roldán Mercado Sesma arieh.mercado@sophia.com.mx	Biostatist
Scientific Comittee	Dr. en C. Ricardo Alonso Llamas Velázquez ricardo.llamas@sophia.com.mx	Clinical pharmacologist
Coordinator of regulatory procedures	LN. Ana Isabel Alcaraz Ledón ana.alcaraz@sophia.com.mx	Specialist in the beginning of clinical studies
Monitoring coordinator	QFB Virginia Manuela Villa Félix virgina.villa@sophia.com.mx	Monitor coordinator
International monitor	M. en F. Sandra Carolina Gómez Méndez sandra.gomez@sophia.com.mx	Senior Monitor
Monitor	QFB Jessica Lizette Mejía Gutiérrez jessica.mejia@sophia.com.mx	Senior Monitor
Monitor	LP María Angela González Ávila maria.gonzalez@sophia.com.mx	Junior Monitor
Monitor	QFB Lizeth de Jesús Pérez Lerma lizeth.perez@sophia.com.mx	Junior Monitor
Monitor	LN Pilar Carolina Castro Mata pilar.castro@sophia.com.mx	Junior Monitor
Administrative Assistant	LAET Maira Alejandra Ramírez Velazco alejandra.ramirez@sophia.com.mx	Clinical Operations Assistant

¥ Employees of Sophia Laboratories, S.A. of C.V Av. Paseo del Norte No.5255, Col. Guadalajara Technology Park, Carretera Guadalajara-Nogales Km13.5 C.P45010 Zapopan, Jalisco, Mexico Tel +52 (33) 3000 4200

Table 1. Administrative structure

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5. Introduction

5.1 Theoretical framework

1. The cornea has a fundamental role in the optics of vision. It has physiological and histopathological characteristics that no other tissue possesses: it is avascular, it is considered the most sensitive tissue, it is transparent and curved to achieve an optimal refraction of light.
2. These special characteristics are due to the cellular organization and strict regulation of the aqueous content. The cornea is formed by three types of cells:

3. Epithelial.

4. Stroms.

5. Endothelial.

The epithelial cells comprise the outermost layer. Its main function is to serve as a barrier between the external world and the internal environment. This cellular group is formed by a well-defined laminar structure from the basement membrane and outwardly by basal cells, winged cells and superficial cells, respectively. On the other hand, the components of the corneal stroma include: type I and IV, laminin and fibronectin. [1] [2]

The turnover of epithelial cells is estimated between 1-2 weeks, however, only the cells of the basal layer have mitotic activity. The stability and dynamics of the corneal epithelium is maintained by three processes: 1) proliferation of basal epithelial cells; 2) centripetal movement of the cells of the periphery and 3) desquamation or loss of the outer epithelial cells. [1] In addition, of these mechanisms, the stem cells in the limbus region are complemented by epithelial cells. When the stem cells of the limbus are deficient, the epithelial cells are unable to cover the defects, this causes the conjunctival cells to migrate to the cornea. A process that is accompanied, in addition to neovascularization. [1] [3]

Cell-cell and cell-substrate adhesion is maintained by integrins α5β1, α5 and β4. In addition there are two types of contact in cell adhesion, union adhesions and non-union adhesions, which participate in the structure and repair of the corneal epithelium. [1] [4] In turn, there are 4 types of union accessions: a) gap junctions; b) zonula occludens (tight junctions); c) desmosomes; and d) zonula adherens. [1] On the other hand, non-union adhesions use integrins and specific ligands such as the intercellular adhesion molecule-1 (ICAM-1, for its acronym in English intercellular adhesion molecule-1). All these components maintain the integrity of the corneal epithelium, coupled with a complex signaling through integrins, cytokines, growth factors and nerve stimuli. [1] [2] [5]

Repair of corneal wounds

Corneal wounds are all those disruptions in the continuity of some of the strata that make up the corneal tissue. They are due to constant or abrupt traumas, elective or not, for example, refractive surgeries. [6] [7] Damage to the corneal epithelium leads to the formation of edema, the activation of fibroblasts, and the infiltration of inflammatory cells into the stroma. This response derives in the loss of transparency and integrity of the cornea. Nevertheless, these changes in integrity activate repair mechanisms to restore homeostasis and function. [2] [1] [8]

The process in the repair of epithelial wounds includes three mechanisms which are grouped into two phases:

1. **Initial phase**: it is characterized by a cellular and subcellular rearrangement. Its objective is to initiate the **migration** of epithelial cells to edge of the wound. During this phase there is no mitotic activity.

2. **Closing phase:** involves cell **proliferation and differentiation.** Some authors mention that the stratification of the epithelial layers is part of this phase. [2]

Unlike the skin, the corneal epithelium does not undergo keratinization during differentiation. It is essential that the cell-cell adhesion be re-established before the epithelium begins its barrier function. During these phases they participate directly and indirectly, in a cascade of orchestrally organized signaling, multiple cells, cytokines, molecules (peptides or proteins in their majority), receptors and factors that promote the precise repair of the corneal tissue. [1] [2] See Table 1.

This intricate molecular pathway has points of pharmacological interest, which are being explored to promote or inhibit this physiological process. [9]

Molecule	Function
EGF, *Epidermal growth factor*	Start the migration and proliferation. Activates the NF-κB pathway.
HGF, *Hepatocyte growth factor*	Stimulates epithelial cells. Activates P38-MAP. Promotes the expression of markers for stem cells.
KGF, *Keratinocyte growth factor*	It acts on limbic cells. Increases proliferation of the limbal epithelium by MAP kinases, PI3K, P70S6.
IGF, *Insulin-like growth factor*	Stimulates cell differentiation in the limbus.
TGF-β, *Transforming growth factor*	Stimulates the proliferation of stromal fibroblasts. Increase the repair speed. TGF-β1 and 2 have antagonistic effects to EGF, HGF and KGF in vitro
PDGF, *Platelet-derived growth factor*	Regulate the migration and proliferation of keratocytes in the presence of fibronectin
NGF, *Nerve growth factor*	Modulates DNA synthesis, migration and tissue organization. Inhibits proliferation
OGF, *Opioid growth factor*	Modulate migration. Modulates the differentiation of keratocytes. Stimulates migration in epithelial and stromal cells.
Tβ$_4$, *Thymosin- β$_4$*	Promotes re-epithelialization Decreases inflammation It inhibits apoptosis. It protects corneal endothelial cells from UV radiation and oxidative stress.
IL-6 y 10, *interleukin-6, 10*	Improve migration
P2Y-P2X, *Purinergic receptors*	Participates in the migration by means of the rearrangement of actin in the cytoskeleton
TLRH, *Toll-like receptor*	Improves migration and proliferation. Modulates inflammation through NF-κB, MAP, AP-1
ROCK, *Rho-associated protein cinase*	Participate in differentiation, proliferation. It also participates in the reorganization of the cytoskeleton cell-cell and cell-matrix adhesion

NF, nuclear factor, MAP, mitogen-activated protein, PI3K, phosphatidylinositol-3-kinase, ADN, ácido desoxirribonucleico, AP-1, activator protein-1.

Table 2. Cells, molecules, factors and cytokines involved in corneal repair

Corneal alterations: ulcers and abrasions

Any alteration in the morphological and histopathological structure of the cornea modifies its function. Ulcers and abrasions are among the most common defects, which can progress to permanent tissue damage and consequently transient or permanent visual defects. [10] [11]

Corneal abrasions are histological disruptions that affect only epithelial cells. In contrast, in ulcers, the stromal layer is also affected. The etiology is diverse and involves mechanical, chemical, infectious and intrinsic agents, in a general way. The severity will depend on the time of exposure to the etiologic factor, the characteristics of this, the cell layers affected and the time in which the treatment is granted. [12] [13] Nevertheless, once the damage occurs, an immune response is initiated to repair the damage in order to recover the function and histological characteristics of the cornea.

The treatment currently available for corneal injuries can be divided into:

1. Doctor

a) Antibiotics: tetracycline, doxycycline, minocycline.
b) Tissue inhibitor of MMP, ilomastat.
c) Steroids
d) Autologous serum
e) Lubricants: dexpanthenol.
f) Growth factors: FGF, EFG.
g) Ascorbic acid and citrate.
h) Immunomodulators.

2. Surgical

According to Tuli et al, [7] all corneal ulcers, except those in which the etiology is an autoimmune disease, should be treated with lubricants.

The main objective in the care of patients with corneal injuries is to recover the morphology of the cellular strata and maintain function.

Eye lubricants are a safe, accessible, inexpensive and easy to use option, in most cases. They allow the recovery of the corneal surface with a low risk of serious adverse events. In addition, they are a minimally invasive therapy that can be combined with other types of therapies.

5.2 Definition of the problem and fundamental reason

Corneal lesions (ulcers and abrasions) are common pathologies, according to a WHO report in 2001 in the countries of emerging economies, which in a large percentage are treated by doctors not ophthalmologists. [14] [15] Although in its majority, the evolution is not catastrophic, it is important to determine the etiology and give a timely treatment, since it is estimated that the average cost of care is 600 dollars, in the case of uncomplicated ulcers. [16] Nevertheless, the true impact occurs when the treatment is not timely and appropriate, because the complications usually end in blindness.

The ideal treatment should be according to the etiology and severity, nevertheless, it is important that it can be used concomitantly with other therapies, that it is low cost, with a low rate of adverse events, easily accessible and that it can be used easily by health teams and patients.

The use of dexpanthenol in the repair of wounds is a feasible option in relation to ease of use and cost in the Mexican population. According to its participation in the inflammatory process establishing relationships with molecules (TGF, EGF) and cells (fibroblasts, epithelium), it has therapeutic advantages, which would increase treatment options. [17]

5.3 Background

In Mexico there are no exact data on the presentation of corneal lesions. Notwithstanding, worldwide, an incidence of corneal lesions (ulcers and abrasions) is estimated at between 1.5 and 2 million of the population per year. [18] Coupled with a high cost of treatment, these alterations pose a challenge for the health systems of any country. However, the most significant impact lies in the complications that may arise if the treatment is not timely and adequate.

The repair of corneal tissue is a complex and orderly process, where multiple molecules and cells of the immune system interact with the different cellular strata of the cornea. During this signaling network it is possible to identify key points, which can be modified pharmacologically, in order to accelerate, improve or inhibit the repair response.

Dexpanthenol (vitamin B5) has been widely used in the cosmetic industry in products for the skin, hair, mucous membranes and eyes. Its main application route is topical. [19] In Ophthalmology, it has been used as an ocular lubricant due to its hygroscopic properties.

In a randomized, controlled clinical trial conducted in Germany, the efficacy and tolerance of a gel versus a dexpanthenol ointment was evaluated. The study population (n = 48) was composed of patients with corneal erosions, keratoconjunctivitis due to UV radiation or similar corneal conditions. The intervention consisted in the administration of 1 cm of the gel and the ointment 4 and 3 times a day for 14 days, respectively. Corneal erosion staging was performed (≤ 10%,> 10 but <25%, ≥25 but ≤ 50%,> 50%), subjective symptoms were evaluated with an ordinal scale (0 = non-existent, 1 = minimum, 2 = moderate, 3 = intense) and objective symptoms (conjunctival injection, ciliary injection, photophobia, lacrimation, blepharospasm, edema-corneal opacity and epithelial defects, on days 0, 3, 8 and 14.

In the evaluation of day 3, 50 vs 45% of the subjects, of the group with gel and ointment, presented corneal erosions less than 10% with reference to the basal size, respectively. At the final visit, all the erosions were less than 10% of the size, in both groups, with a tendency to be faster in the decrease in size in the gel group. Regarding the symptoms, they were reported non-existent in both groups during the final evaluation. Tolerance was reported as very good by the patients. However, in the group with ointment there was a higher incidence of alterations in vision, compared with the gel group. [20]

In 1996, Martin Göbbels and Dorothea Groβ, published the results of a double-blind, controlled, randomized clinical trial conducted in 50 subjects with dry eye, divided into two groups, which were administered five drops per day of tears artificial with and without dexpanthenol for 6 weeks. The outcome variables were measured before and after the intervention. Corneal permeability was evaluated by means of fluorophotometry and the Schirmer test. In addition, staining with Bengal rose and lacrimal rupture time was performed. All subjects made a subjective evaluation of complaints (tolerability).

After 6 weeks of intervention, the epithelial permeability of the cornea was better, in the group with dexpanthenol, compared to the other group. The other parameters did not show differences. [21]

In another double blind, randomized clinical trial, the efficacy of a dexpanthenol plus vitamin A ointment and a gel based on a hemodialysis free of calf blood proteins was evaluated and compared. We included 54 subjects with superficial corneal lesions due to foreign metallic bodies. After the removal of the foreign body and the debris, an exploration of the anterior segment with a slit lamp was performed. The depth of the corneal lesion was classified (superficial, medium and deep) and the percentage of damaged area was calculated by planimetry. The intervention consisted in the application, single dose, of the gel with dexpanthenol + vitamin A or the hemodialysis in the conjunctival cul-de-sac. Subsequently, the eye was bandaged. The control review was performed 24 hours later and, if necessary, during the following days. Healing was defined as a reduction of the initial corneal injury in less than 5% of the total.

No statistical difference was observed between the groups 24 hours after the intervention. Nevertheless, 81.3% of the subjects who used the gel with dexpanthenol + vitamin A showed healing in corneal lesions of 1-6 mm2. In those lesions of 7 - 26 mm2, the greatest recovery appeared on day 2 (72%). [22]

Raczynska et al, made a comparison between a gel and a solution (drops) of dexpanthenol, using as a model conjunctival and corneal lesions in the postoperative period. The groups were conformed by 40 eyes, which received the active intervention and the placebo. Among the reported results it is mentioned that from the second day, after the surgery, an improvement was observed in the repair of the lesion (disappearance of the edema and conjunctival congestion), in the group that received dexpanthenol. In addition, the edges of the wound improved and the tendency to close. [2. 3]

In that same year (2003), the group from the University of Gdańsk (Poland) evaluated a dexpanthenol gel placed, during the examination of the retina, on the contact surface of a three-lens Goldmann-type lens. The sample size was 84 eyes, divided according to the intervention: dexpanthenol exploration group (n = 42) and exploration group with 3% methylcellulose (n = 42). The ophthalmological variables to be evaluated were conjunctival congestion, edema and defects of the corneal epithelium. In addition, the transparency of the molecules under investigation was evaluated. The result showed less congestion of the conjunctiva and a greater facility to perform the exploration procedure with the use of dexpanthenol compared to the group with methylcellulose. [24]

Smolle et al. Developed a randomized clinical trial in 92 subjects undergoing elective surgery under general anesthesia. The objective was to compare the perioperative ocular comfort and in vitro bacterial growth of a 0.2% carbomero hydrogel against a dexpanthenol and vitamin A ointment. The intervention consisted in the application of 40 mg ointment (n = 46) and instillation of two hydrogel drops (n = 46) after anesthesia.

The ocular comfort was evaluated using an ordinal scale ("yes", "rather yes", "rather no", "no") by means of a questionnaire which contained the following reagents: burning sensation / itching, dry eye , foreign body sensation, blurred vision and perception. An ophthalmological examination was performed to identify conjunctival inflammation (lacrimation, hyperemia), palpebral adhesion (difficulty to open the eyelids before a verbal command) and palpebral edema. The bacterial growth was evaluated, after the inoculation of 10 mL of S. aureus (10 2 bacteria for 14 hours at 37 ° C) in 1

gram of the hydrogel and the ointment (incubation for 24 hours), by means of the number of forming units of colonies (UFC).

After the surgery none of the participants presented corneal abrasions. There were no significant differences between the groups in relation to the sensation of burning, itching and dry eyes. The patients who received the ointment reported a greater presence in the sensation of foreign body, blurred vision and palpebral adherence compared with those who received the hydrogel solution ($p < 0.001$). In relation to bacterial growth, the hydrogel group presented 17 CFU more compared with ointment and control. [25]

Reepithelialization and complete restoration of the superficial layer of the corneal epithelium was achieved between day 7 and 14. In the cases of severe epitheliopathies, the repair was not complete. [26]

5.3.1 Dexpanthenol 5 %

It is a component of animal tissues. It participates in the synthesis of fatty acids, porphyrins and acetylcholine, in the release of ATP from carbohydrates. It is also part of the degradation of fatty acids, sterols and steroid hormones. It is an essential component in food. [19]

In ophthalmology it is classified as a lubricant, due to its properties in water retention. The pharmaceutical forms in which it is marketed are: gel, ointment and solution. [27] [28] [29]

Its pharmacological effect in the repair of wounds, is due to several mechanisms:

1) Conversion into pantothenic acid, a component of coenzyme A, which participates in the metabolism of epithelial cells. [30]

2) Increase in the gene expression of cytokines, mainly IL-6 that participates in reepithelialization, granulation and wound closure. [30]

3) Promotes the proliferation and migration of fibroblasts. [17]

4) Increase in gene expression of CCR-1 (chemokine receptor-1, chemokine receptor-1) which promotes the migration of macrophages and neutrophils in the area of the wound. [17]

5) Increase in MCP-1 (Monocyte chemotactic protein-1, for its acronym in English, monocyte chemotactic protein-1). [17]

6) Increase in TGF-B. [17]

7) Increase antioxidant levels (reduced glutathione, coenzyme A). [31] [32]

5.3.1.1 Eyeball pharmacokinetics

Route of administration: topical-ophthalmic.

Release: immediate.

Absorption: no absorption of dexpanthenol has been reported through any ocular tissue or through the epithelium of the skin into the systemic circulation. [19]

Metabolism: It is not described in ophthalmology. Systemically, dexpanthenol is degraded in pantothenic acid, due to enzymatic oxidation, in the liver. In the eye, metabolism is likely to occur at the corneal level, without allowing absorption by cytochrome enzymes located in this region (CYP1B1, CYP2A6, CYP2C8, CYP2D6, CYPE1, CYP3A4, CYP4B1, CYP4V2). [19] [33] [34]

Elimination: Occurs with the kinetics of the flicker and dissolved in the tear film.

There are no data on the area under the curve, Cmax, T1 / 2.

5.4 Justification

The risk of developing a corneal lesion increases in the population that is of productive age, due to the use of instruments, tools, machines and substances typical of work activity. Nevertheless, those patients undergoing surgery with prolonged times in the procedure are also at risk. In addition to the characteristics of the corneal tissue, as the ocular layer that has contact with the environment and its repair mechanisms.

The severity of the injury will depend on the etiology and treatment. Nevertheless, the cost of care and the complications that can be triggered make corneal injuries a challenge for doctors and health systems.

The treatment of corneal lesions (erosions and ulcers) should be timely, effective, easily accessible, economically available and according to the etiology. In most cases, the first treatment option should be pharmacological management (lubricants), within which there is a wide variety of medications.

Dexpanthenol as a lubricant or ocular reepititelizer has demonstrated its efficacy and safety in the healing of the corneal epithelium in different clinical situations. It is a well tolerated option, easily accessible and that can be used in most corneal injuries, regardless of the etiology.

According to its pharmacological properties, its absorption is almost null and its metabolism is wide, it can be used several times a day without the risk of developing serious adverse events. Its pharmacodynamics allows it to act by different mechanisms and interact with the various molecules in the repair of the cell layers that make up the cornea.

According to the pharmacological development and the design of the present protocol, the PRO-167 molecule is a formulation which requires the documentation of its safety profile.

5.5 Objectives and hypothesis

5.5.1 General Objective

To evaluate the safety and tolerability of the ophthalmic gel PRO-167 on the ocular surface.

5.5.2 Specific objectives

- Describe the safety of the ophthalmic gel PRO-167 by means of the density of goblet cells
- Describe the safety of the ophthalmic gel PRO-167 by means of changes in ocular surface stains.

- Describe the safety of the ophthalmic gel PRO-167 by means of changes in intraocular pressure.

- Describe the safety of the ophthalmic gel PRO-167 by means of changes in laboratory tests.

- Describe the safety of the ophthalmic gel PRO-167 by means of changes in vital signs.

- Describe the safety of the ophthalmic gel PRO-167 by means of changes in visual ability.

- Describe the safety of the ophthalmic gel PRO-167 by means of changes in the time of tear rupture.

- Describe the safety of the ophthalmic gel PRO-167 by means of changes in the ocular comfort index.

- Describe the safety of the ophthalmic gel PRO-167 by means of changes in the posterior segment.

- Describe the safety of the ophthalmic gel PRO-167 by means of changes in ophthalmological signs and symptoms.

- Describe the safety of the ophthalmic gel PRO-167 when assessing the integrity of the anterior segment by means of the green lysine stain.

- Describe the safety of the ophthalmic gel PRO-167 by means of the presentation of adverse events.

5.5.3 Hypothesis

Ha Ophthalmic gel PRO-167 presents a safety and tolerability profile similar to the comparator in healthy subjects.

Ho Ophthalmic gel PRO-167 presents a safety and tolerability profile different from the comparator in healthy subjects.

5.6 Design and plan of the study

Clinical trial, phase I, controlled, parallel groups, double blind randomization, exploratory.

5.6.1 Discussion of the study design

The design of the study (clinical trial) is considered the highest quality standard in the data when it is sought to explore the effect of an intervention. The phase of pharmacological development (phase I) corresponds to the objective of the study which is to assess safety and tolerability, so that the intervention time is short and the sample size required is less than that of a clinical efficacy trial. The presence of parallel groups allows the comparison between the intervention groups on the outcome variables. Blinding and randomization allows to reduce biases that are incurred with other designs, e.g. Selection bias, evaluation bias, among others.

6. Material and methods. Participants, interventions and variables

6.1 Study Center

The present study will be performed in ophthalmology offices duly equipped and registered for their proper functioning. According to the needs of the sponsor, these may be private or public, be attached to a hospital or clinic or be independent.

6.1.1 Organization of the center

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

The PI is responsible for forming a multidisciplinary research team to carry out the clinical study according to protocol, under its scientific guidance. It is the prerogative of the IP the design of the organization of its center and the selection of the personnel that will perform the functions. However, the minimum organization of the research team requested by the sponsor requires the figure of sub-researcher, study coordinator and pharmacist. (**See Figure 1 Minimum organization of the center**)

Any person to whom the PI designates, under his / her responsibility, a part of the follow-up of the study (co-investigator, under-researcher, nurse, etc.) or a specific function of participation in the study (pharmacist, administrative assistant, study coordinator, etc.) should appear in the "Delegation of Responsibilities" format.

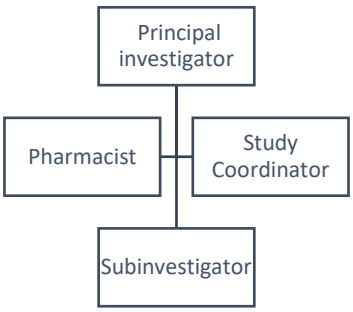


Figure 1 Minimum organization of the center

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

6.1.2 Documentation to be delivered to the sponsor

The PI must deliver to the sponsor, before the start of the study:

- Curriculum vitae updated, in Spanish, dated and signed (maximum 10 pages), of the IP and the staff that integrates its organizational chart of the center.

- Copy of IP academic certifications (degree certificate and specialty diploma in ophthalmology, federal professional certificates)

- Copy of academic certifications of the maximum degree obtained, from each one of the members of your research team, that cover their capacity to perform the delegated functions.

- Copy of operating notice or similar issued by corresponding regulatory entity (When applicable)

- Certificate of good clinical practice in force. If the issuing institution does not specify the validity period in the certificate, the date of issue of the certificate must not exceed one year

6.1.3 Closure of the center

The closing of the center will be carried out once the last visit of the last included subject previously agreed between the sponsor and the IP has been made. The closing process will be according to the internal operating procedures of the sponsor.

It is the prerogative of the sponsor to prematurely close a study center, it must inform the IP 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 clinical history.
- Age between 18 to 45 years.
- Both genders.
- Blood tests [complete blood count (BHc), three element blood chemistry (QS) and liver function tests (PFH)] within normal parameters specified by the reference laboratory with a lower and upper margin of 10%.
- Vital signs within normal parameters.
- 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 research products.

- Subject users of topical ophthalmic medications of any pharmacological group.

- Subject users of medication by any other route of administration.

- Pregnant or lactating women.

- Women without a history of hysterectomy, oophorectomy, 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 the present study.

- Diagnosis of liver disease or elevation to three times the normal upper value of any of the following liver enzymes: aspartate transferase (AST), alanine transferase (ALT) or bilirubin.

- Inability to attend or answer the evaluations made in each of the visits.

- Positive smoking (specified as cigarette consumption regardless of amount and frequency)

- Positive alcoholism (specified as the consumption of alcoholic beverages, regardless of quantity and frequency, during the study intervention period).

- Contact lens users.

6.2.2.2 Medical and therapeutic criteria

6.2.3 Elimination criteria

- Withdrawal of the consent letter under information.
- Presentation of a serious adverse event.
- No tolerability or hypersensitivity to any of the compounds used during the tests (fluorescein, green lysine, tetracaine)
- No tolerability or hypersensitivity to any of the investigational drugs.
- Adherence <50% determined by the diary of the subject.

6.2.4 Identification of the subject

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

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

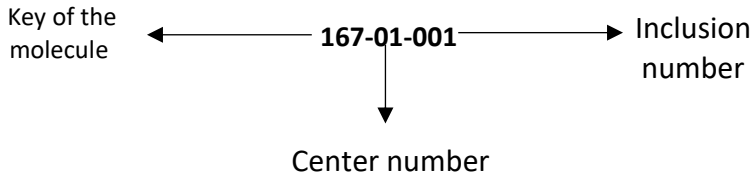
Example:

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

In the counting stage, the participant number will be assigned consecutively, using 3 consecutive digits. Once the subject has been selected, he will be assigned a number with which he will be identified throughout the study. Said code will be integrated with eight numbers in the following order from left to right:

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

Example:



6.3 Intervention

6.3.1 Managed treatments

6.3.1.1 Treatment under study

- PRO-167
  - Active ingredients: Dexpanthenol 5%
  - Pharmaceutical form: Ophthalmic gel.
  - Prepared by: Sophia Laboratories A.S. of V.C.
  - Posology: a strip approximately 1 cm long, 4 times a day during the waking period, in the bottom of the right eye sac.
  - Description of the formulation: transparent gel, free of visible particles.
  - Description of the packaging: sterile multi-dose tube, low density polyethylene polyethylene and aluminum with high density polyethylene lid.

Table 3. Quali-quantitative formulation of PRO-167

Type of agent	Amount mg/mL	Function
Dexpanthenol	50.0	Active principle (lubricant)
Boric acid	2.00	Active principle
Sodium Borate decahydrate	without showing	additive
Polysorbate 80	without showing	additive
Sorbitol	without showing	additive
Potassium chloride	without showing	additive
Sodium chloride	without showing	additive
Magnesium Chloride hexahydrate	without showing	additive
Water for the preparation of injectables c.b.p.	1.00	Vehicle

Quali-quantitative formulation of the product under investigation PRO-167. The concentration of the active principles is shown, as well as the substances that act as a buffer additive.

6.3.1.2 Reference treatment

- **Corneregel®**
  - Active ingredients: Dexpanthenol 5%
  - Pharmaceutical form: Ophthalmic gel
  - Prepared by: Bausch & Lomb.
  - Posology: a strip approximately 1 cm long, 4 times a day during the waking period, in the bottom of the right eye sac.
  - Description of container: sterile multi-dose tuve
  -

6.3.2 Strategies to improve adherence and procedure to monitor adherence

1. Each visit the research subject will return the assigned tube in order to evaluate the adherence by weigh
2. Direct questioning by the PI about the application of the intervention.

3. At the discretion of the IP, messages may be sent or reminder calls made.
4. Delivery of a printed chronogram specifying the date of the visit and its activities
5. Journal of the subject.

6.3.2.1 Procedure to monitor adherence

Before delivering the medication to the research subject, the pharmacist must weigh the tubes to be delivered. After the return of the medication by the subject will also carry out the weighing. Guidelines to follow for weighing:

o The pharmacist will use the scale provided by the sponsor
o Place the tube in the center of the balance. You will get the result of the measurement.
o It will remove the tube from the balance and put it back, confirming that the measurement is the same. If it is different, it will weigh one more time and take the average of the 3 measurements
o Record the result in the log and the CRF provided by the sponsor

Adherence to the intervention will be calculated considering: the weight of the empty tube, the weight of the strip, the weight of the tube with the content, the calculation of the total gel to be applied during the entire intervention time and the total weight of the applied gel . 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 posology indicated for the intervention

$$P_T = (P_g)G$$

where:
P_g= weight of a 1 cm strip of the intervention, determined by the research and development department
G = number of applications indicated for the intervention

Adherence will be estimated at each visit where the research subject returns the intervention. Only tubes without apparent physical damage will be considered for the calculation. This result will allow the PI to determine if the subject continues in the study according to the stipulations of the elimination criteria.

The evaluation of the adherence by means of the diary of the subject will be carried out in the following way:

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

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

The final (overall) adhesion will be determined by the average of the adherence of each of the visits.

It will not be considered for the calculation of final adherence if the subject did not return the tube in two subsequent visits.

The balance will be provided by Sophia Laboratories, S.A de C.V. You must take shelter in a locked place. It will be placed on a smooth surface (table), avoiding the movement and the change of place as much as possible. The surface of the balance must be kept clean. The maintenance of the same must be according to the manufacturer's specifications. Its use is exclusive for protocol procedures. It is the IP's responsibility to safeguard and correct use.

6.3.3 Treatments and concomitant interventions allowed and prohibited during the study

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

6.3.4 Treatment management

The interventions will be provided by Sophia Laboratories A.S. of V.C., for each research center. They will be labeled, reconciled and weighed previously. The handling of the treatment will be under the responsibility of the investigator or a designated member of his team.

6.3.4.1 Delivery and reception

The delivery will be made in closed cardboard boxes by means of a courier service or directly by the sponsor's staff to the address of the research center according to the study plan.

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

Inside you must locate the acknowledgment document and the logger (data logger) of temperature and humidity. You should check that the registered temperature and humidity comply with the specifications for transport and shelter (see section 6.3.4.2 Storage). Verify the content (interventions) with what is reported in the document. In case the document corresponds to the content, it will sign the receipt and send it to the sponsor. Otherwise, notify the sponsor.

In the study center, the personnel assigned by the PI will deliver the corresponding treatment to the subjects admitted, sufficient for the period to be covered. Delivery will be made in stages, medication will be delivered at the baseline visit and visit 1. The center must register the medicine delivered

6.3.4.2 Storage

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

The storage temperature should be at room temperature to no more than 25º Celsius.

The research center has the obligation to record, in the format designated by the sponsor, the temperature and humidity registered in the data logger. This record should include the current temperature and humidity, as well as the minimum and maximum of each of these. It must be done at least once a day, on business days.

Said data will be compared by the clinical monitor according to the registration in the data logger.

6.3.4.3 Return

The research subjects will return to the staff indicated by the IP in the center their treatments in visits 1 and final. The refund will be made by the research center when the sponsor indicates it. Prior to the return the research center must make a count of the assigned medication and the remaining medication, with the aim of creating an inventory which serves for the final filling of the return form of the medication.

6.4 Outcome variables

6.4.1 Security variables

6.4.1.1 Primary outcome variables

- Globet cell density
- Epithelial defects in cornea and conjunctiva.
- Presence of adverse events.

6.4.1.2 Primary outcome variables of tolerability

- Burning
- Foreign body sensation
- Itching
- Eye comfort index

6.4.1.3 Secondary outcome variables

- Intraocular pressure
- Visual ability
- Laboratory tests: BHc, QS and PFH.
- Ophthalmological signs: conjunctival hyperemia, chemosis.
- Rupture time of the tear film
- Life signs: FC, FR, TAS.
- Subsequent segment
- Quality questionnaire

6.4.2 Efficacy variables

6.4.2.1 Primary outcome variables

It does not apply because it is a phase I study

6.4.2.2 Secondary outcome variables

It does not apply because it is a phase I study

6.4.3 Methods and scales to be used for the measurement of the variables

Variable	Unit	Symbolo	Type	Method of measurement	Normal value
Age	years	--	Continuous	Calculation from the day of birth	NA
Gender	Female/ Male	F / M	Nominal	Direct questioning	NA
Adverse events	Number of cases	n	Discreet	Conteo	NA
Intraocular presure	Milimeters of mercury	mmHg	Continuous	Goldman´s applanation tonometry	11 - 21
Visual ability	Fraction	Snellen	Nominal	Chart	
Tear rupture time	Seconds	s	Continuous	Direct counting	> 10
Eye confort index	Points	--	Discreet	Questioning	
Adverse events	Present / Absent	--	Nominal	Comprehensive assessment	Absent
Goblet cell density	Cells per square milimeter	Cel/mm^2	Continuous	Citology per impression	> 500 cell/mm^2
Vital signs					
Heart rate	Beats per minute	lpm	Discreet	Auscultation	60 – 100
Breathing frequency	Breaths per minute	rpm	Discreet	Auscultation	12 – 24
Systemic blood pressure	Milimeters of mercury	mmHg	Continuous	Non-invasive auscultatory measurement	< 120 / 80
anterior segment					
Epithelial defects	Degrees	--	Discreet	Direct observation with green lysine and fluorescein stains	Oxford Scale
Ophthalmologic signs and symptoms					
Conjunctival hiperemia	Normal / Very Light / Mild / Moderate / Severe	--	Ordinal	Direct observation. Classification of Efron	Normal
Chemosis	Present / Away	--	Nominal	Direct observation	Absent
Burning	Severity: Absent, very mild, mild,	--	Nominal	Direct questioning	Absent

Variable	Unit	Symbolo	Type	Method of measurement	Normal value
	moderate and severe Frequency: At all times, almost at all times, 50% of the time, almost in no time, at any time.				
Foreign body sensation	Severity: Absent, very mild, mild, moderate and severe Frequency: At all times, almost at all times, 50% of the time, almost in no time, at any time	--	Nominal	Direct questioning	Absent
Pruritus	Severity: Absent, very mild, mild, moderate and severe Frequency: At all times, almost at all times, 50% of the time, almost in no time, at any time	--	Nominal	Direct questioning	Absent
Post-application symptoms					
Burning	Present / Away	--	Nominal	Journal of the subject	Absent
Sensación de cuerpo extraño	Present / Away	--	Nominal	Journal of the subject	Absent
Prurito	Present / Away	--	Nominal	Journal of the subject	Absent
Ojo rojo (síntoma)	Present / Away	--	Nominal	Journal of the subject	Absent
posterior segment					
Macula	Normal / Abnormal	--	Nominal	Direct observation	Normal
Optical disk integrity	Normal / Abnormal	--	Nominal	Direct observation	Normal
Blood count					
Erythrocytes		M/uL	Continuous		

Variable	Unit	Symbolo	Type	Method of measurement	Normal value
Hemoglobin	Grams over deciliter	g/dL	Continuous		
Hematocrit	Porcentage	%	Continuous		
VGM	Femto liters	fL	Continuous		
HCM	picograms	pg	Continuous		
CMHbG	Grams over deciliter	g/dL	Continuous		
Leukocytes	Thousands per liter units	Mil/uL	Continuous		
Platelets	Thousands per liter units	Mil/uL	Continuous		
Myelocytos	Porcentage	%	Discreet		
Metamyelocytos	Porcentage	%	Discreet		
Bands	Porcentage	%	Discreet		
Segmented	Porcentage	%	Discreet		
Lymphocytes	Porcentage	%	Discreet		
Monocytes	Porcentage	%	Discreet		
Eosinophils	Porcentage	%	Discreet		
Basophils	Porcentage	%	Discretet		
Blastos	Porcentage	%	Discreet		
Blood chemistry					
Glucose	Milligrams on deciliter	mg/dL	Continuous		
Urea	Milligrams on deciliter	mg/dL	Continuous		
Creatinine	Milligrams on deciliter	mg/dL	Continuous		
Liver function tests					
Alanine transferase	Units on liter	U/L	Continuous		
Aspartate transferase	Units on liter	U/L	Continuous		
Total Bilirrubin	Milligrams on deciliter	mg/dL	Continuous		
Direct Bilirrubin	Milligrams on deciliter	mg/dL	Continuous		

Variable	Unit	Symbolo	Type	Method of measurement	Normal value
Indirect Bilirrubin	Milligrams on deciliter	mg/dL	Continuous		

Table 4. Scales to be used

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

6.4.3.1 Visual ability

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 separation angle (located at the nodal point of the eye) between two objects that allows perceiving them as separate objects.

Snellen's notation is described as the distance at which the test is performed, divided by the distance at which the letter is vertically equivalent to 5 arc minutes. Thus, at 6 meters a letter 6/6 (20/20) equals 5 minutes of arc, a letter 6/12 (20/40) equals 10 minutes, and a letter 6/60 (20/200) equals 50 minutes The Snellen fraction can also be expressed as a decimal (ie 20/20 = 1 and 20/40 = 0.5). [38]

The VA will be evaluated basally, without refractive correction with the Snellen chart. Which will be located in a place with adequate lighting, natural or artificial and at a distance of 3m from the subject to be evaluated. The visual acuity of each eye will be taken, starting with a right eye (DO) asking the subject to keep both eyes open and using an occluder to cover the left eye (OS); the subject will read aloud the lines that the evaluator points out, the line of smaller letters that he reaches to see will be annotated by the fractional evaluator as the DO of the DO in the clinical record. Proceed to the OS with the same method.

Subsequently the best refractive correction of the subject will be made and the examination will be repeated using the obtained refraction. This result will be reported as CV, it will be written in fraction in the clinical file and in the CRF, in addition in the CRF it will be written in decimal. By definition, the CV can not be inferior to the AV.

6.4.3.2 Goblet cell density (Cytology per impression)

The density of goblet cells in the conjunctiva can be a reflection of the severity of alteration in the ocular surface. [39] It has been determined that the normal density is greater than 500 cel / mm2. [40] Impression cytology refers to the application of a cellulose acetate filter to the ocular surface to remove the superficial layers of the epithelium; these removed cells can be subjected to histological, immunohistological or molecular analysis. [41]

The cytology per impression of the conjunctiva will be done by the researcher using the device provided by the sponsor for this purpose, which may consist of a circular cell of approximately 10 mm in diameter, with a cellulose acetate filter millicell. After ocular surface anesthesia, with topical tetracaine, the researcher will ask the subject to expose the temporal surface of the eye to be evaluated and gently press the cell on the temporal conjunctiva (2 to 3 mm of the sclerocorneal limbus) for 5 seconds and remove the cell with a peeling technique (**Illustration 1. Cytology per impression**). Immediately fix with diethyl ether spray with one or two shots at 15 cm distance. The investigator will contact the Courier, within the first 24 hours, after the appointment designated by the sponsor for the shipment of the samples to histopathological analysis. You must complete the

requisition form provided by the investigator and attach it to the mailing. The format will consist of three sheets (1 original and 2 copies) which will be assigned as follows: original sheet for the Courier, 1 copy will be collected by the monitor and 1 copy will remain in the research center and will be filed in the corresponding folder to each research subject.

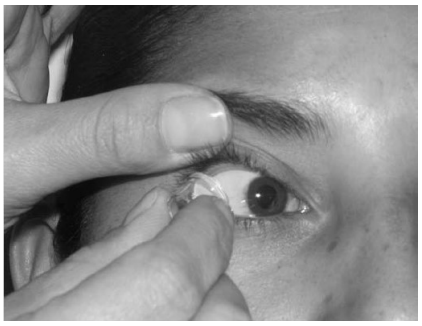


Illustration 1. Cytology per impression

The data of the histopathological report to be recorded in the CRF are: density of goblet cells and degree of squamous metaplasia according to the Nelson scale. (**See Table 5**)

In the visits required to perform this procedure, it will be done prior to the use of ocular surface stains.

Table 5. Nelson classification

Grade	Detail description of the epithelial cells	Characteristics of goblet cells
0	Small and round cells; Large nuclei, 1: 2 ratio with nuclear cytoplasm	Abundant goblet cells (> 500 cells / mm2), globose and oval with an intense PAS-positive staining of the cytoplasm.
1	Slightly enlarged cells; smaller nuclei, 1: 3 ratio with nuclear cytoplasm	Marked decrease in the number of goblet cells (350 to 500 cells / mm2) but still maintain their globose and oval shape and intense staining
2	Enlarged and polygonal cells; small nuclei, ratio 1: 4 to 1: 5 with nuclear cytoplasm	Marked decrease in the number of goblet cells (100 to 350 cells / mm2), less intense PAS - positive with poorly defined cell borders
3	Even larger and polygonal cells; small and pyknotic nuclei, 1: 6 ratio with nuclear cytoplasm	Few goblet cells (<100 cells / mm2)

Adapted from Nelson & Wright [24] [42]

6.4.3.3 Eye comfort index

It is a questionnaire designed to measure the irritation of the ocular surface with Rasch analysis to produce estimates on a linear scale of intervals (ratings: 0-100). Similar to the index for ocular surface diseases, the ocular comfort index (ICO) evaluates symptoms. The ICO contains 8 items (one positive and eight negative) that focus on the discomfort associated with alterations of the ocular

surface. Each of these questions has two parts, which inquire separately the frequency and severity of the symptoms. [43] See annex 13.1 Eye comfort index.

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

6.4.3.4 Eye surface integrity: conjunctival hyperemia and chemosis

This will be done by means of biomicroscopy using the slit lamp of the research center. A full assessment of the previous segment will be made, which will be recorded in the clinical file. The lighting techniques used will be at the discretion of the IP.

The variables that will be registered in this protocol are:

Conjunctival hyperemia.
It is defined as the simplest reaction of the conjunctiva to a stimulus, a red appearance secondary to the vasodilation of the conjunctival vessels of variable intensity. He will graduate using the Efron scale. [44] See annex 13.2 Efron scale for conjunctival hyperemia

- *Chemosis*.
- It is defined as conjunctival edema, the result of an inflammatory reaction. It is qualified as present or absent. The evaluator will use a narrow beam of light at 60 ° and will measure if the conjunctiva separates from the sclera at ≥ 1/3 of the total palpebral opening or if it exceeds the gray line. [43]

6.4.3.4.1 Stains

• Staining with green lysine and fluorescein
A drop of topical anesthetic will be instilled in the conjunctival cul-de-sac, then a second drop will be applied to the tip of the strip of green lysine and fluorescein and it will be allowed to slip towards the bottom of the sac. It is essential to quickly evaluate the staining, in sequence, first in the DO and then the OS, so that the observed patterns are equally bright. [19] See Annex 13.3 Oxford Scale
The value obtained according to the Oxford scale will be registered in the CRF.

6.4.3.5 Presence of adverse events

The management of the EAs will be done according to what is described in section 9.3 Adverse events. The PI will register in the corresponding section of the CRF the EA that the subjects of the study will present, as well as referring it in their essential document.

6.4.3.6 Intraocular pressure

Tonometry is the objective measure of IOP, based primarily on the force required to flatten the cornea or the degree of corneal indentation produced by a fixed force. Goldman's tonometry is based on the Imbert-Fick principle. [38] The tonometry will be performed, after instillation of a drop of topical anesthetic (tetracaine 0.5%), with fluorescein and the use of the cobalt blue filter (after evaluation of the corneal surface staining). Three shots will be taken, which will be registered in the clinical file and the average will be registered in the CRF.

6.4.3.7 posterior segment

The evaluation of the posterior segment will be carried out under medication mydriasis (tropicamide 0.8% / phenylephrine 5%), in the slit lamp with an aerial loupe (at the choice of the PI). An integral assessment of the fundus (including optic disk, posterior pole and periphery) will be performed in

search of abnormalities that alter the study result. The result of the assessment will be recorded in the clinical file. In the CRF the assessment of the macula and optic nerve as normal, abnormal or abnormality that does not affect will be registered.

6.4.3.8 Vital signs

The vital signs to be evaluated (FC, FR and TAS) can be measured by an assistant duly indicated in the organization of the center and the delegation of responsibilities, the technique to be used for the FC and FR will be with the count of repetitions in one minute by Direct auscultation with stethoscope.

The SBP should be measured with 5 minutes of previous rest, in the left arm. The instrument can be manual or automatic according to the IP. It is necessary that all measurements are equal in circumstances. 3 measurements will be made, with a minimum interval of 5 minutes between them. The IP will record the average in the note and the CRF.

6.4.3.9 Ocular symptomatology

The subject will be questioned directly about the presence in general (since the last visit) of the following symptoms: burning, foreign body sensation and pruritus. Respond about the severity and frequency of symptoms such as:

Severity: Absent (0), very mild (1), mild (2), moderate (3) and severe (4)
Frequency: At all times (4), almost at all times (3), 50% of the time (2), almost at no time (1), at any time (0).
The number corresponding to each symptom will be registered in the CRF.
Post-application symptomology:

The subject will be requested, that in the subject's daily instrument, after registering the application of the product under investigation, mark YES or NO according to the presence of the following symptoms: burning, sensation of a foreign body, red eye and pruritus

6.4.3.10 Breaking time of the tear film

One of the first aspects of the tear film that changes when there is an alteration to 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 to evaluate the stability of the tear film is the evaluation of TRL with fluorescein. Once the fluorescein is instilled, with the cobalt blue filter the patient is asked not to blink. The precorneal colored fluorescein layer will change to less fluorescent or non-fluorescent regions. The time that elapses from the last blink until the appearance of these regions is the TRL. It will be reported in seconds, in the clinical file and in the CRF.

6.4.3.11 Pregnancy test

It refers to the performance of a rapid pregnancy test in all women of childbearing age who wish to enter the study. By fertile age we understand women who have not had their menopause, defined as 12 months since the last menstrual period in women over 40 years of age; or those who underwent bilateral hysterectomy or oophorectomy. Women of childbearing age with contraceptive methods including bilateral tubal obstruction should be tested for pregnancy. This test will be carried out by the IP or the designated team person according to the instructions of the device delivered by the sponsor. When applicable, the completion, result and date must be registered in the CRF. If you do not apply, you must write down the reason

6.4.3.12 Lab tests

The PI will deliver to the subject the order of the studies of BH, QS and PFH, to be carried out in the clinical laboratory designated by the sponsor. The clinical laboratory will deliver to the IP the results for its assessment and registration. The normal parameters to be considered will be the ranges established by the laboratory, nevertheless the clinical criterion of the PI will prevail in the decision of normality or abnormality of the results.

6.4.4 Measurement time

The measurements of the variables of primary and secondary outcome will be made and evaluated for each visit, according to the following:

Scrutiny Visit

Some of these measurements should be complemented with those of the baseline visit and thus meet the eligibility criteria (see Schedule and study diagram), at the discretion of the PI.

1. Signature of informed consent.
2. General and ophthalmological clinical history.
3. Laboratory sample taking.
4. Pregnancy test.
5. Review of selection criteria
6. Visual ability
7. Density of goblet cells (Cytology per impression)
8. Intraocular pressure.
9. Eye comfort index
10. Evaluation of ocular signs and symptoms
11. Integrity of ocular surface

a. Epithelial defects (TF and TVL)
b. TRL

12. Subsequent segment evaluation.
13. Vital signs

Basal Visit / Day 0.

Some of these measurements will be taken at the screening visit to complete the eligibility criteria (see Schedule and study diagram), at the discretion of the PI, they may be taken to complete the data of the baseline visit.

1. Visual ability
2. Density of goblet cells (Cytology per impression)
3. Intraocular pressure.
4. Eye comfort index
5. Evaluation of ocular signs and symptoms
6. Integrity of ocular surface
    a. Epithelial defects (TF and TVL)
    b. TRL
7. Subsequent segment evaluation.
8. Vital signs
9. Evaluation of results of laboratory tests

Visit 1 / Day 3

It can be done in a period ± 1 day in relation to day 3 of application.

1. Visual ability
2. Intraocular pressure.
3. Evaluation of ocular signs and symptoms
4. Integrity of ocular surface
    a. Epithelial defects (TF and TVL)
    b. TRL
5. Vital signs
6. Delivery of quality questionnaire.
7. Evaluation of adverse events.

Final Visit / Day 11.
It can be done in a period ± 1 day in relation to the 11th day of the start of application.

1. Visual ability
2. Density of goblet cells (Cytology per impression)
3. Intraocular pressure.
4. Eye comfort index
5. Evaluation of ocular signs and symptoms
6. Integrity of ocular surface
    a. Epithelial defects (TF and TVL)
    b. TRL
7. Subsequent segment evaluation.
8. Vital signs
9. Return and evaluation of quality questionnaire.
10. Evaluation of adverse events

Security call / Day 13.
It can be done in a period ± 1 day in relation to the 13th day of the start of application.

1. Ask about the presence of an adverse event.
2. Evaluation of results of laboratory test

6.5 Timeline and study diagram

Procedures	*scrutiny*	Basal visit	Visit 1	Final visit	Call Security
		Day 0	Day 3 ± 1	Day 11 ± 1	Day 13 ± 1
CI signature	X				
clinic history	X				
Ophthalmological clinical history	X				
Laboratory sample taking	X			X	
Laboratory tests review		X			X
Pregnancy test	X			X	
Eligibility criteria	X	X[a]			
Assignment		X			
Delivery of intervention		X	X		
Return of intervention			X	X	
Adherence evaluation			X	X	
Adverse events			X	X	X
Intraocular pressure	X	X[1]	X	X	
Visual ability	X	X[1]	X	X	
TRL	X	X[1]	X	X	
Epithelial defects (TF and TVL)	X	X[1]	X	X	
Eye signs and symptoms	X	X[1]	X	X	
Posterior Segment	X	X[1]		X	
Vital signs	X	X[1]	X	X	
Ocular Comfort Index		X		X	
Goblet cell density (cytology by impression)		X		X	
Daily delivery of the subject		X	X		
Return / Evaluation of the subject's Journal			X	X	
Delivery Quality Questionnaire		X			
Return and Evaluation of the quality questionnaire				X	
Continuity evaluation of the subject		X	X	X	

a The eligibility criteria will be completed with the revision of the laboratory exams. 1 These measurements may be taken from the result of the screening visit, if it does not exceed the previous 7 days. It is the prerogative of the PI to decide whether to repeat the measurements 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 clinical history: refers to the technical, clinical and legal document in which the patient's health conditions, medical acts and other procedures performed on the patient are recorded chronologically. It includes the anamnesis and comprehensive ophthalmological exploration that allows to discern the patient's eligibility. If the patient is taken from the established consultation of the study center, he / she will be able to use the existing clinical history, only having to perform an update.
- Taking laboratory samples: see 6.4.3.12 Laboratory tests.
- Pregnancy test: see 6.4.3.11 Pregnancy test.
- Eligibility criteria: refers to the review by the IP, where it states that the subject can be included in the study by meeting the inclusion criteria and not meeting the exclusion criteria. See 6.2 Eligibility criteria
- Intraocular pressure: see 6.4.3.6 Intraocular pressure
- Visual ability: see 6.4.3.1 Visual capacity
- TRL: see 6.4.3.10 Rupture time of the tear film
- Epithelial defects (TVL and TF): see 6.4.3.4.1 Stains
- Eye signs and symptoms: see 6.4.3.4 Eye surface integrity: and 6.4.3.9 Ocular symptomatology
- Posterior segment: see 6.4.3.7 Posterior segment
- Vital signs: see 6.4.3.8 Vital signs

6.5.1.2 Basal visit

- Review of laboratory tests: refers to the review and analysis by the IP of the results of the BH, QS and PFH. See 6.4.3.12 Laboratory tests.
- Eligibility criteria: with the laboratory results, the subject's profile will be finalized for inclusion or not.
- Assignment: It refers to determining the intervention that the patient will follow during the study. It will be done according to section 7. Methods. Assignment of the intervention. This assignment will be made at the baseline visit (day 0) and will go along with the indication to start the treatment period the next day (day 1).
- Delivery of intervention: Refers to the delivery of the product under investigation to the patient of the study, by the research center. It will be done according to sections 6.3.1 Managed treatments and 6.3.4.1 Delivery and reception.
- Evaluation of variables: The data of the evaluation of the variables listed below can be taken from the scrutiny visit, as long as it does not exceed 7 days prior to this visit. It is the IP's prerogative to decide whether to use the information from the screening visit or to repeat the evaluations on this visit.
  o Intraocular pressure
  o Visual capacity
  o TRL
  o Epithelial defects (TF and TVL)
  o Eye signs and symptoms
  o Subsequent segment
  o vital signs

- Eye comfort index: see 6.4.3.3 Eye comfort index
- Density of goblet cells (cytology per impression): see 6.4.3.2 Density of goblet cells (cytology per impression)
- Delivery of the subject's diary: It refers to the delivery by the IP to the subject, the subject's daily instrument.
- Delivery of quality questionnaire: It refers to the delivery by the IP to the subject, the quality questionnaire instrument.

6.5.1.3 Visit 1

- Intervention delivery: see 6.5.1.2 Baseline visit
- Return of intervention: refers to the return of research products to the center by the research subject.
- Evaluation of adherence: refers to the assessment made by the IP according to section 6.3.2.1 Procedure to monitor adherence
- Adverse events: see 6.4.3.5 Presence of adverse events
- Intraocular pressure: see 6.4.3.6 Intraocular pressure
- Visual ability: see 6.4.3.1 Visual capacity
- TRL: see 6.4.3.10 Rupture time of the tear film
- Epithelial defects (TF and TVL): see 6.4.3.4.1 Stains
- Eye signs and symptoms: see 6.4.3.4 Eye surface integrity: and 6.4.3.9 Ocular symptomatology
- Vital signs: see 6.4.3.8 Vital signs
- Submission of the subject's diary: see 6.5.1.2 Baseline visit
- Return / daily evaluation of the subject: refers to the delivery of the subject's diary to the IP by the subject. The IP will review the diary to assess its correct filler, evaluate the post-application symptomatology and the registration of the applications.
- Continuity assessment of the subject: refers to the determination by the PI and desire of the subject to continue with their participation in the study.

6.5.1.4 Final visit

- Laboratory sample taking: see 6.4.3.12 Laboratory tests
- Pregnancy test: see 6.4.3.11 Pregnancy test
- Return of intervention: see 6.5.1.3 Visit 1.
- Adherence evaluation: see 6.5.1.3 Visit 1
- Adverse events: see 6.4.3.5 Presence of adverse events
- Intraocular pressure: see 6.4.3.6 Intraocular pressure
- Visual ability: see 6.4.3.1 Visual capacity
- TRL: see 6.4.3.10 Rupture time of the tear film
- Epithelial defects (TF and TVL): see 6.4.3.4.1 Stains
- Eye signs and symptoms: see 6.4.3.4 Eye surface integrity: and 6.4.3.9 Ocular symptomatology
- Subsequent segment: see 6.4.3.7 Subsequent segment
- Vital signs: see 6.4.3.8 Vital signs
- Eye comfort index: see 6.4.3.3 Eye comfort index
- Density of goblet cells (cytology per impression): see 6.4.3.2 Goblet cell density (Cytology per impression)
- Return / daily evaluation of the subject: see 6.5.1.3 Visit 1.

- Return / evaluation of the quality questionnaire: refers to the delivery of the quality questionnaire to the IP by the subject.

6.5.1.5 Security call

- Adverse events: see 6.4.3.5 Presence of adverse events
- Review of laboratory tests: see 6.5.1.2 Baseline visit

6.5.2 Diagram of the study

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

In order to increase the safety of the participants with the use of the products under investigation, a partial analysis will be carried out following a modification to the Fibonacci method. This methodology will consist of including 33% of the total sample size (4 subjects per group, n = 8), which will complete all the visits and procedures described. Once this group of 8 subjects has finished their participation in the clinical study, a blinded analysis will be carried out. During the period in which this sub-analysis is carried out, the inclusion of new participants will be restricted. Inclusion will resume when the sponsor notifies the research center.

In addition to safety, therapeutic adherence will be evaluated and problems related to procedures will be resolved, should they arise.

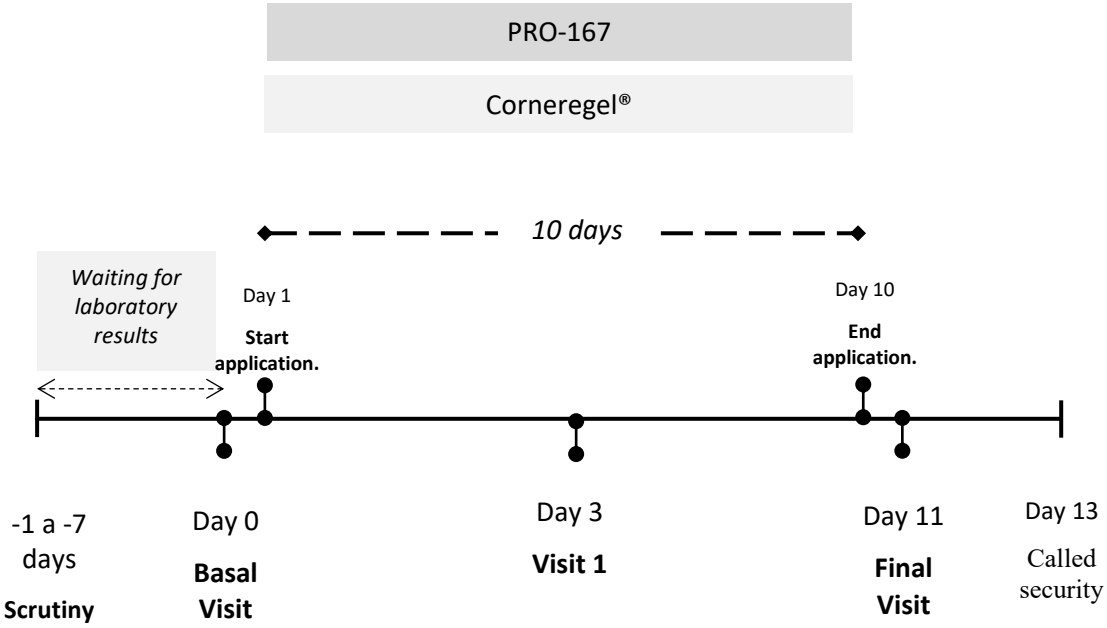


Figure 1. Diagram of the study

6.6 Sample size

A total size of 24 subjects is estimated, divided into 2 intervention groups. (12 subjects per group)

6.6.1 Calculation of the sample size

Although there are no references on the calculation of the sample size in phase I studies, it was considered pertinent to perform it according to the presentation of adverse events referred by Christ T, in a randomized controlled trial of parallel groups, single blind, with randomization where

it was evaluated the efficacy and tolerance of a 5% dexpanthenol ophthalmic gel versus a 5% panthenol ointment in 48 subjects with corneal erosion, keratoconjunctivitis by UV radiation or similar conditions. The intervention consisted in the application of 1 cm of the gel and the ointment during 4 and 3 days, respectively. [20]

The percentage of good tolerance that was presented with the gel was 25%, so it is expected that no more than 10% of the subjects report a bad 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 the type I error, equal to 1.96, with a power of 80%, corresponding to the type II error, equal 0.84.

According to the previous calculation, the result is 19 subjects, which was increased by 20% for the probable losses. The total sample size required is 24 subjects. Therefore, each group will consist of 12 subjects, who will provide an eye for analysis.

6.7 Recruitment

It is recommended that during the development of this research protocol, the principal investigator requests the approval of the Research Ethics Committee and the Research Committee, as well as the authorization to the relevant regulatory entity, to publish or disseminate in the mass media, the invitation to participate in the study to those people 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 cabinet exams that will allow the more accurate determination of their ocular clinical status by participating in a sponsored clinical research protocol. by Sophia Laboratories SA of C.V.

7. Methods. Assignment of the intervention

7.1 Generation of the allocation sequence

The random numbers will be generated through the online tool: www.randomization.com

Two strata corresponding to the intervention groups will be used, which will be balanced for a research center. The allocation will be 1: 1.

7.2 Blinding mechanism

Blinding will be performed by personnel assigned by the Clinical Operations Management of Sophia Laboratories S.A de C.V. Which will consist in the elimination of the primary label (commercial) in the case of Corneregel® and the placement of a label identical to the other interventions. Because the tube in which Corneregel® is packaged differs in the color and shape of the lid used by the PRO-

167, a masking will be made in the secondary packaging which will be identical for the two interventions.

7.3 Implementation

The allocation sequence will be generated by personnel assigned by the Clinical Operations Management of Sophia Laboratories S.A de C.V. The research center will receive a set of envelopes which will contain the intervention number individually. The envelopes will be identical on the outside. Each of these envelopes will be shown to the participants for their election by the principal investigator or by a designated member of their team.

7.4 Blinding (Masking)

The blinding will correspond to the research subject and the principal investigator. In addition, the statistical analysis will be carried out in a blinded manner for the partial and final analysis.

The masking will be done using boxes in the secondary packaging identical in the two groups. Blinding for the research subject and the researcher will be done by replacing the commercial labels in the case of the comparator in the tubes and the use of identical labels that contain the assignment number.

7.4.1 Opening of blinding

Blinding may be opened in the following cases:

1. Presence of a serious adverse event.
2. Safety alarm due to the use of the drugs under study.
3. In case the sponsor determines it for any security reason or other reason that it considers pertinent

8. Methods Collection, administration and data analysis

8.1 Methods of data collection

A clinical monitor will be assigned to each research center, which will be authorized to monitor, review, procure and ensure that the quality of the information obtained from the participants is reliable and trustworthy. Each monitor will schedule periodic visits to the research centers in order to review the source documents and corroborate the information captured in the case report format (CRF). All clinical monitors will be trained in relation to the information of the study protocol (objective, visits, procedures, range of accepted values, etc.). In the event that the data are not identical between the two registers, the clinical monitor will generate a discrepancy, which must be resolved by the research center in time that the sponsor deems reasonable to meet the objectives of the clinical study. The correction of the discrepancies will be made according to the Good Documentation Practices.

The data registered in the CRF will be reviewed by personnel of Sophia Laboratories SA de CV, trained in the ophthalmological, clinical and pharmacological area, which will have the power to generate discrepancies in the event that the data do not comply with the stipulations of the research protocol or put participants at risk.

Once all discrepancies generated by the team of clinical monitors and clinical staff have been resolved, the data will be downloaded into an electronic database (Excel Sheet) by personnel

designated by the sponsor. A new review of the data will be carried out to corroborate the fidelity of the same and new discrepancies may be generated in case it was considered.

The database generated will be safeguarded by the sponsor and will only have personal access designated by the same.

8.1.1 Strategies to complete the follow-up

- You will be clearly informed of the importance of the study and the benefits that the population will obtain from the results of the study.
- Transportation assistance will be provided in order for the participant to attend their visits.
- Calls, messages or a printed calendar will be made in order to remind the participant of their appointments and the activities that will be carried out, in addition to the estimated duration of the same.
- In case the participant does not attend his appointment, the research center must make a call to know the reason and try to arrange a new appointment within the established window period or an unscheduled appointment.
- In case it is not possible to make an appointment, it will be asked about the presence of adverse events and the reason for leaving the study, as minimum data.

8.2 Data management

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

The PI or the designated person of your team will fill out the Case Report Format (CRF) with all other documents provided by the sponsor (for example, documents related to the handling of the treatment).

A CRF was designed to record the data that are required in the protocol and that the researcher collects in each of the visits.

In the case of self-assessment questionnaires, it is not permissible for the principal investigator or person responsible for filling in to modify what was written by the subject of the study.

The data capture in the investigator's site will be done by the investigator or the designated person of his team after performing the Medical File. The researcher or a designated person of your team will be trained in filling the CRF.

All corrections to the CRF data should be made by the investigator or the designated person of your team in accordance with the instructions provided.

To ensure the confidentiality and security of the data, user names and access codes will be used to restrict access to the system only to authorized personnel.

The monitor must ensure that all the data has been filled in the CRF. After comparing the data against the source documents, the monitor will ask the researcher to make the necessary correction / clarification, so that they are answered and closed as quickly as possible.

The Scientific Committee of Laboratories Sophia S.A. of C.V. will give the latest medical-scientific review, and will set the pattern to freeze the database.

8.3 Statistical methodology

8.3.1 Analysis of primary and secondary outcome variables

The statistical analysis will be carried out by personnel of Sophia Laboratories. The statistical program SPSS version 19 (IBM Corporation, Armonk, NY, USA) will be used.

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

The data will be collected and sorted in an excel sheet. Later they will be exported to the platform of the SPSS program. The variables will be categorized according to their nature.

The result of the continuous quantitative variables will be presented in measures of central tendency: mean, standard deviation and ranges. See Table 4. Scales to be used

The normal distribution of the results will be obtained by the Kolmogorov-Smirnov test.

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

- Intra-group analysis: Wilcoxon rank test.
- Inter-group analysis: Mann-Whitney U test.

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

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

The statistical analysis to identify significant differences of the **qualitative variables** will be done creating 2x2 contingency tables and it will be carried out in the following way:

- Intra-group difference: McNemar or Pearson test.
- Difference between groups: test $\chi 2$ (Chi-square) of Pearson.

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

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

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

It will be considered that the investigational drug is safe and tolerable when there are no clinical and statistical differences in all the variables of primary outcome, with respect to its comparator.

Those subjects who comply with an adherence greater than 60% will be included in the statistical analysis to meet the objective of the study. It was considered that from the minimum dose necessary to obtain a pharmacological effect (reepithelizer / 1 cm per day) and the presence of adverse events (exposure) is sufficient to meet the overall design objective, according to the pharmacological characteristics of the product in investigation.

8.3.2 Additional analyzes

A partial analysis will be carried out with the objective of evaluating safety and adherence once 4 subjects per group (33% of the sample size) have completed all the visits and study procedures. Non-

parametric statistics will be used and the same mechanisms described will be used for the total analysis of the data.

8.3.3 Population analysis and management of missing data

An analysis will be carried out by intent to treat where the data of the participants that have fulfilled two visits will be included (Basal Visit and visit 1).

9. Methods Monitoring

9.1 Data monitoring

Monitoring visits by a site monitor of Sophia Laboratories S.A. of C.V. are intended to confirm that studies sponsored by Sophia Laboratories S.A. of C.V. they are conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and with the applicable regulatory requirements (verifying a continuous compliance with the protocol, amendment or amendments, reviewing accounting records of the product under investigation, verifying that the personnel of the site and the facilities remain adequate to carry out the study).

The researcher must ensure that they have sufficient time, space and qualified personnel for the monitoring visits.

In order to carry out the monitoring review, it is mandatory to provide direct access to all source data and those related to the study site. The monitor will conduct a review of the CRF and a Verification of Source Documents (VDF). By VDF means the verification of the records in the CRF through its comparison with the source data that the researcher will make available for this purpose.

Regarding the CRF, the monitor will mark in each visit the screens completed and approved in case of use of electronic platform.

In accordance with the applicable regulations, Good Clinical Practices, and the procedures of Sophia Laboratories A.S. of V.C. The monitors of Sophia Laboratories A.S. of V.C. they will contact the site before the start of the study to review the protocol, the regulatory and ethical requirements of Sophia Laboratories, S.A. with the staff of the site. of C.V. When reviewing the procedures for data collection, the conversation will also include the identification, agreement and documentation of the individual data for which the records in the CRF serve as source documents.

Sophia Laboratories A.S. of V.C. 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 carried out in accordance with the currently approved protocol, any other study agreement, Good Clinical Practices and all applicable regulatory requirements.

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

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

Upon completion or early termination of the study, the monitor will carry out site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, Good Clinical Practices, and Sophia Laboratory procedures. , SA of C.V.

After the study is closed, the researcher must keep all study records on the site in a safe place. Records should be maintained to allow easy and timely recovery, when necessary (for example, in an audit or inspection). Sophia Laboratories A.S. of V.C. will inform the investigator / institution the period of time they will have to retain these records, in order to comply with all applicable regulatory requirements. However, the investigator / institution must seek the written approval of the sponsor before proceeding to the elimination of these records. The minimum retention time will satisfy the most stringent standard applicable to that site for the study, in accordance with the provisions of the PCBs, any institutional requirements or the applicable laws or regulations, or the standards / procedures of Sophia Laboratories A.S. of V.C. The researcher / institution must notify Sophia Laboratories A.S. of V.C. Of any change in file arrangements including, without limitation, the following: file in an off-site facility, transfer of ownership of records in the event the investigator leaves the site.

9.2 Preliminary analysis and early termination of the study

The partial analysis described in section **8.3.2 Additional analyzes** will allow the sponsor to make a decision about the early termination of the study in the event that the safety of the participants is compromised.

The early termination of the study will be considered in the following cases:

1. Presence of serious adverse events in more than 5% of the participants in each intervention group.
2. The competent authority (COFEPRIS) considers it for security alerts.
3. The Sponsor determined it for his convenience or eventualities such as: economic support, manufacturing errors, etc.
4. Lack of recruitment as expected.

In case the decision is the early termination of the clinical study, all the research centers will be informed within the first 24 hours by the available communication channels. Likewise, the corresponding authority in each country will be informed (if applicable) and the Ethics Committees involved.

Each research center has the obligation to inform the subjects that participate in the clinical study in a period no longer than 24 hours, after receiving the information from the sponsor. You must inform all the subjects involved in any phase of the study.

The result of the preliminary evaluation will be in charge of the Clinical Operations Management and the Medical Management of Sophia Laboratories A.S. of V.C., which will have the faculty to determine the destiny of the present protocol, according to judge convenient.

9.3 Adverse events

9.3.1 Investigator's responsibilities

Perform the verification of adverse events through questioning, relevant physical examination, assessment of evolution, as well as adequate medical and pharmacological management, resolution or outcome and final discharge following the definitions determined in national and international regulations. [45] [46] [47]

In case of adverse events or any event that puts the health and well-being of the patients at risk, appropriate medical attention will be provided, either at the research site or will be referred to the Hospital Center with greater resolving power with which the researcher and / or researcher site have medical care agreement. The researcher will notify the clinical monitor of the sponsor, according to the times established in the national and international regulations. In the case of serious adverse events, notify the sponsor and record the corresponding information in the case report form and in turn inform the Research Ethics Committee to the Research Committee.

The attention of the adverse events will be made according to the diagram of attention of the event (see Figure 3. Attention of the adverse event)

In the final report to be drafted by the Scientific Committee of the Department of Clinical Operations of Sophia Laboratories A.S. of V.C., will include the report of adverse events in compliance with current national and international regulations. [46] [47]

9.3.1.1 Record of adverse events in the Case Report Form

The registry of adverse events considers the information concerning the identification data of the participating patient as code, age, sex, left eye, right eye.

Information about the type of adverse event, adverse reaction or suspected adverse reaction to the product under investigation or to the study medication, as appropriate. The date on which the adverse event occurs is reported, as well as in which the Investigator is aware of it, date of resolution or outcome, as applicable. The clinical diagnosis is indicated. Include in concomitant medications the therapy used for the pharmacological management of the adverse event, suspected adverse reaction, adverse reaction. Record the outcome or resolution of the event: patient recovered without sequelae, with sequelae, not recovered. Patient who presented death due to adverse reaction / adverse event, patient who presented death and it is judged that the drug could have contributed, patient who presented death and this is not related to the investigational product or drug, or indicate that it was not He knows what the consequence of the event is.

Consign information about the product or drug under investigation or the drug associated with the adverse event, adverse reaction or suspected adverse reaction. As applicable, information concerning generic denomination, distinctive denomination or product code in research and / or investigational medication should be recorded, as appropriate according to the methodological design of the study, this is relevant in the case of blinded studies or those where they use placebo as comparators, since there are circumstances that justify opening the cecum to determine if the adverse event, the adverse reaction or suspected adverse reaction may be attributable to the active agent, the combination of active agents, or the substance (s). s) pharmacologically inert (s), such as vehicles or additives, as appropriate the phase of clinical research in which the development of the drug is located. It will also be necessary to record the data concerning the batch number, manufacturer laboratory, expiration date, dosage, route of administration, start and end dates of administration and / or consumption, reason for the prescription; according to whether it is a

product or investigational medicine (protocol in which the patient currently participates) or is a medicine that the subject under investigation consumes for the treatment of basic concomitant diseases or used for the management of any sign or transient symptom that does not correspond to the Natural History of the pathology that motivated its entry into the research protocol.

Record the withdrawal or maintenance of the medication, investigational product or investigational medication, as appropriate. Indicate if the adverse event disappears when the investigational product or investigational medication or suspicious medication is removed (to provoke the event). Also indicate if a dose adjustment is made, if the event changes in terms of intensity or seriousness, persistence of the reaction. It is important to indicate that in those patients who are exposed again to the investigational product, investigational medication or medication, which had previously been suspended, if the adverse reaction or adverse event reappears.

Regarding concomitant pharmacotherapy. Indicate the generic name, the dose, the route of administration, start and end dates of its use, as well as the reason for the prescription regardless if it is consistent with the information to prescribe or technical data sheet or is used outside the regulations or of what the local, national or international regulatory entity has authorized.

Concerning the relevant clinical antecedents. The analysis of the adverse event, adverse reaction or suspicion of adverse reaction considers the information previously reported, notwithstanding the clinical context in which said harmful phenomenon occurs in the participants of the clinical research protocol, it is of special interest, so that the information about previous ailments, hypersensitivity or allergy phenomena, previous surgical procedures, laboratory analysis or cabinet exams that have been practiced on the participant, etc., that the researcher deems convenient to mention may do so. If you have enough space in the case report format, you can complement the information of your clinical note in the clinical file.

9.3.1.2 Follow up of adverse events

The IP will provide the attention and guidance of the EA that the participant presents until the outcome of the same, according to what is referred to in the following section.

9.3.1.3 Procedures for a serious adverse event

The process of attention of the adverse event considers the following stages:

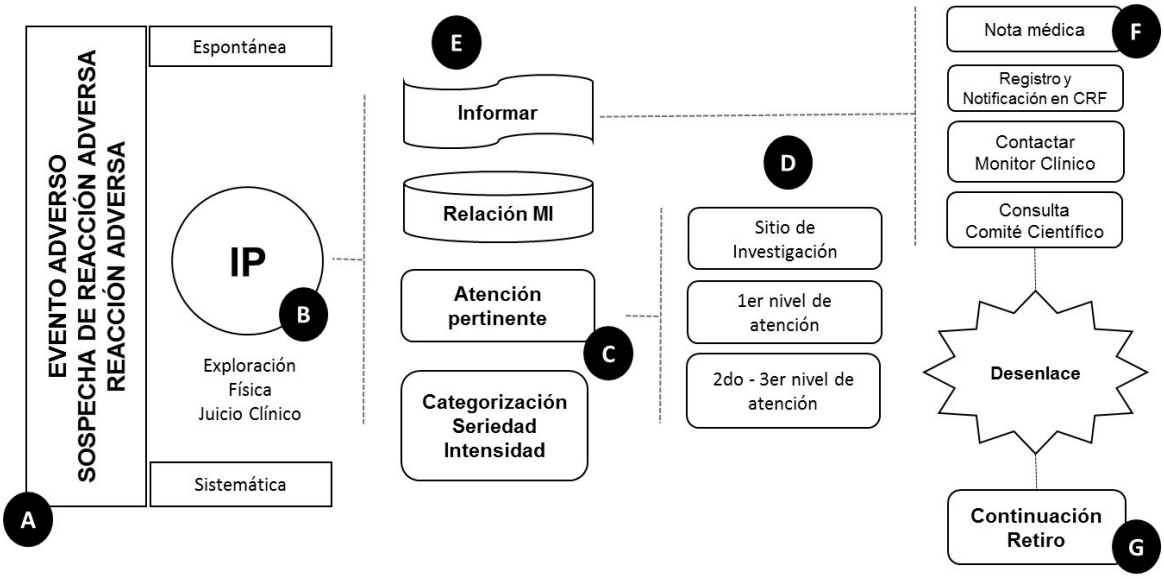


Figure 3. Attention to the adverse event

A. During the development and conduct of the present clinical research, undesirable damaging events or adverse reactions, of medical implication, which do not necessarily have a causal relationship with the investigational product or investigational medication, may occur in the participant patient. These harmful phenomena can 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 some physiological process. However, it can be suspected that the investigational product or the investigational drug or the placebo cause some unwanted clinical manifestation. Adverse events, adverse reactions or suspected adverse reactions to one or several medications can occur during the systematic evaluation of the participants (on the days when the clinical review is scheduled, according to the schedule of activities) or suddenly, as such way that,
B. The investigator must be the first person to whom the patient reports that they have developed or presented a harmful clinical phenomenon during their participation in this research protocol.
C. According to your clinical judgment; on the basis of the pertinent physical examination, interrogation, etc., as well as the analysis of the information available in the medical literature and that referred to in the investigator's manual, information to prescribe or technical data sheet of the comparator drug, the principal investigator determines the relevant attention of the event / harmful reaction; either
D. In the research site or in the hospital with the greatest resolving power (1st, 2nd or 3rd level of medical attention). In such a way that, in case the patient is sent by the Investigator to a hospital, he / she attends by means of a reference system, it can be with an identification card that the patient belongs to the present investigation and there is an official number or folio, which pertains to the emergency care agreement with the health institution with the greatest resolving power, or a medical reference note issued by the principal investigator, so that appropriate care is given to the participating patient. It should be noted that the Study Sponsor, Sophia Laboratories, S.A. C.V., will pay the expenses for the medical care of the participating patient, only if the adverse event, adverse reaction or suspected adverse

reaction to medication is associated or found in relation to the investigational product or investigational medication.

E. Taking the clinical information collected, either during the care provided at the research site or provided by the treating physician (s) in the hospital, the principal investigator records the adverse event, suspected reaction adverse or adverse reaction to medication in your clinical note of the clinical record, indicating the seriousness, intensity (mild, moderate or severe), relationship with the investigational product or medication, as well as:
F. The migration of the relevant data to the case report format and to its respective adverse event section; noting the pertinent information, already referred to in section 9.3.1.1., this in virtue of the fact that in cases of serious adverse events, which must be notified in less than 24 hours after the moment in which the principal investigator has knowledge of the same, the clinical monitor of the study is informed, so that in turn he / she informs the Scientific Committee and the Pharmacovigilance Department of the sponsor and later he / she informs the Research Ethics Committee. Regarding non-serious adverse events, these will be recorded and adequately addressed and the corresponding regulatory entity will be informed about the safety profile of the investigational product or investigational medication in the final report of the clinical trial.

The record of the outcome of the adverse event, suspicion of adverse reaction or adverse reaction to medication depends substantially on the follow-up that the principal investigator makes to the participant, since most of the harmful phenomena are expected, consult section of the safety profile in number 5.3 and in the researcher's manual, they are ophthalmic in nature, however there may be systemic alterations. Therefore, in the opinion of the researcher, the withdrawal or permanence of the participant will be considered, according to the provisions of section 6.2.2 Exclusion criteria of the present research protocol.

9.3.1.4 Causality evaluation

The assessment of the causality, the methodology used to estimate the probability of attributing to a drug, investigational drug or investigational product the adverse reaction, the suspicion of the same or the observed adverse event, considers probabilistic categories, according to the evidence available and the quality of information, based on national pharmacovigilance regulations. [47] As a tool to facilitate the probabilistic categorization of causality, the principal investigator can use the algorithm of Karch and Lasagna modified by Naranjo referred by Aramendi I, 2011 in which different items are qualified which allow assigning a value to the relationship cause-effect between the administration of the drug and the adverse reaction. [48] **See Table 6. Algorithm of Karch and Lasagna modified by Naranjo**

Algorithm of Karch and Lasagna modified by Naranjo			
No.	**Reagent**	**Score**	
		yes	**No**
1.	There are previous conclusive reports about the adverse drug reaction, adverse event or suspected adverse drug reaction	+1	0
2.	The adverse event appeared when the suspected drug was administered	+2	-1
3.	Adverse reaction to medication, adverse event or suspected adverse drug reaction improved upon discontinuation or administration of a specific antagonist	+1	0
4.	Adverse reaction to medication / adverse event / suspected adverse drug reaction reappeared when administering the drug / investigational product / investigational medication	+2	-1
5.	There are alternative causes that may cause this reaction	-1	+2
6.	Adverse reaction / adverse event / suspected adverse drug reaction occurred after placebo administration	-1	+1
7.	The drug was determined in blood or other liquids in toxic concentrations	+1	0
8.	The intensity of the adverse reaction / adverse event / suspected adverse drug reaction was higher with higher doses or lower with lower doses	+1	0
9.	The patient has had similar reactions with the drug / product under investigation or investigational medication, in the past	+1	0
10.	Adverse reaction / adverse event / suspected adverse reaction to medication was confirmed with some objective evidence	+1	0
	Totalscore	summation	
Probabilistic category based on the score obtained			
I	The causal relationship is checked	≥,9	
II	It is likely that ADR is due to the drug or product under investigation	5 a 8	
III	It is possible that the RAM is due to the drug or product under investigation	1 a 4	
IV	The causal relationship is doubtful	0	

The reagents considered by the algorithm of Karch and Lasagna modified by Naranjo where each one receives a defined score are shown and the final summation allows estimating the probabilistic category of the cause-effect relationship between the administration of the drug / product in research / investigational medicine and the adverse reaction, adverse event or suspected adverse reaction. Consider that if the information is not available, a score equal to zero is recorded.

Table 6. Algorithm of Karch and Lasagna modified by Naranjo

In such a way that the degree of certainty to establish the investigational product or investigational medication (as appropriate) as the causal agent of the harmful phenomenon that befalls the participating patient, can be directly indicated by the principal investigator based on his or her clinical experience or well through the voluntary application of the tool mentioned previously. However, it is important that the researcher take into account the following arguments in favor of the causal relationship:

a) Force of association that refers to the number of cases in relation to those exposed.
b) The consistency of the data, ie 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) The biological plausibility: which refers to the possible pharmacological or physiopathological mechanisms involved in the development or presentation of the adverse event.
e) Experimental findings: for example the appearance of anomalous metabolites or high levels of drug or the product of its biotransformation.
f) Analogy: 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. [49]

9.3.2 Responsibilities of the sponsor

The sponsor will be responsible, and will cover the expenses derived from medical attention to adverse events related to the product under investigation.

9.4 Audit

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

9.4.1 Pre-study audit

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

9.4.2 Audit / Inspection during the conduction 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 performed, the investigator and the institution should agree to allow the auditor / inspector direct access to all relevant documents, and will allocate their time and that of their staff to the auditor / inspector to discuss the findings and any relevant problems.

10. Ethical considerations

10.1 Approval of the committees

The present study will be conducted according to the standards of the Declaration of Helsinki, World Medical Association 2013. Nuremberg Code; Nuremberg Trial by the International Court of Nuremberg, 1947. Belmont Report, National Commission for the Protection of Subjects of

Biomedical Research and Conduct, 1979. Will be conducted in accordance with the scientific and technical requirements necessary for the registration of medicines for use of the International Conference on Harmonization (The International Council for Harmonization, ICH) Guide to Good Clinical Practices. International Ethical Guidelines for Biomedical Research in Human Beings of the Council for International Organizations of Medical Sciences (Council for International Organizations of Medical Sciences, CIOMS, 2002). International Ethical Guidelines for epidemiological studies of the Council for International Organizations of Medical Sciences (Council for International Organizations 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 possible modifications for its realization, these Committees should be notified of any significant changes to the protocol. In addition to the above, the current regulations issued by the Ministry of Health will also be complied with. General Health Law, NOM 012 Official Mexican Standard NOM-012-SSA3-2012, Which establishes the criteria for the execution of research projects for human health. The study is considered as an investigation with a risk greater than the minimum according to the Regulation of the General Health Law on Health Research, Title Two, Chapter I, Article 17, Category III, published in the Official Gazette on 6 January 1987

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

The study will not start in the research site if you do not have the confidentiality agreements and economic proposal of each of the principal investigators, duly signed and without having previously obtained the favorable opinion and / or the approval of the Committees of Ethics in Research, Research Committees, and when applicable by the Biosecurity Committee, corresponding.

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

10.2 Amendments to the protocol

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

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

Amendments that substantially modify the protocol or confer an additional or different risk to the research subjects must be approved by the Committee. It is the investigator's responsibility to take action in situations that require immediate action to avoid unnecessary harm to the study participants.

The principal investigator has the responsibility to inform the Research Ethics Committee of any amendment to the protocol that could eventually affect the rights, safety or welfare of the research participants. Likewise, he must know any situation or new knowledge that shows a greater risk for the participants, the termination or premature suspension of the study, the reasons and the results obtained up to that moment. You must also inform about the conclusion of the study, when completing the research protocol.

The list of amendments, and in the necessary cases, the relation of the issuance of errata, will be referred to in the final report of the investigation.

10.3 Informed consent

10.3.1 Obtaining

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

The written consent documents will incorporate the elements of informed consent described in the Declaration of Helsinki and the ICH Guide to Good Clinical Practices and will be in compliance with all applicable laws and regulations.

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

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

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

If a subject is illiterate, the acceptance will be with their fingerprint, and in the event that the subject is not able to grant an informed written consent, a representative of the "legally authorized" subject can provide such consent. The subject in accordance with applicable laws and regulations.

The IP must also sign and date this consent.

The informed consent must be signed in duplicate by all involved, and two witnesses. One copy will be filed in the file of the subject and the other will be delivered to the participant. The PI must document the obtaining procedure, the date and time and the questions asked by the subject in which he signed the informed consent in the subject's medical history.

10.3.2 Special considerations

The auxiliary studies that will be carried out during the conduction of 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

Any change to "informed consent" constitutes an amendment to this document and must be submitted for approval to the Research Ethics Committees, and if applicable before the Competent Authorities.

The amendment will include a copy of the new version in the language or languages of the country.

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

For each subject affected by the amendment their consent must be obtained again. This new version should be obtained following the same procedure that was performed for the inclusion of the subject, at the beginning of the protocol. Therefore, the IP must document the process of obtaining the most current version of the consent in the subject's medical history.

10.4 Confidentiality

All documents and information provided to the researcher by the sponsor are strictly confidential. The researcher expressly agrees that the data on their professional and clinical experience, provided to the sponsor on paper and stored in electronic format, are only for use related to their activities with the sponsor of clinical studies, in accordance with Good Clinical Practices. The researcher accepts that he / she and the members of his team will use the information only within the framework of this study, to carry out the protocol. This agreement is mandatory as long as the confidential information has not been disclosed to the public by the sponsor. The protocol of the clinical study provided to the researcher may be used by him and by his colleagues to obtain the informed consent of the subjects for the study. The clinical trial protocol, like any information taken from it, should not be disclosed to other parties without the sponsor's written authorization.

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

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

10.5 Deviations

A deviation is any alteration in the procedures and activities described in the research protocol approved by the committees and regulatory authorities. They may be the product of modifications or omissions, and may compromise the safety of the participants or the quality of the data generated.

Major deviation / violation: is one that impacts one or more of the following aspects:

- Subject security
- Alteration of the risk-benefit balance
- Commit the integrity of the study data
- Affects the voluntariness of the subject in the participation of the study.

The list of examples cited below serves the purpose of guidance, but does not cover all possible cases, so it is not limiting:

I. **In relation to informed consent**: 1) that informed consent has been taken by an unauthorized person to do so, 2) that the subject under investigation signs a version of informed consent not approved by the committees and regulatory entity, 3) that perform a study procedure prior to signing informed consent.
II. **Regarding the inclusion / exclusion criteria:** 1) enroll subjects who do not meet all the inclusion criteria and / or meet any exclusion criteria, 2) enroll defined subjects as part of the so-called vulnerable population: children, pregnant women, prisoners, without prior approval for such group; 3) Enroll patients before the start or after the end of the study.
III. **In relation to the medication of the study:** error in the delivery or dosage of the same.
IV. **In relation to concomitant medication**: use of prohibited medication.
V. **V. In relation to the study procedures:** that those that, in the opinion of the principal investigator, compromise the safety of the research subject are not carried out.
VI. **In relation to the reporting of serious adverse events**: those that are reported outside the time stipulated by the committees.

Minor desviation: is that which does not impact on the safety of the subject, does not alter the risk-benefit balance, does not compromise the integrity of the study data or does not affect the subject's willingness to participate in the study.

The list of examples cited below serves the purpose of guidance, but does not cover all possible cases, so it is not limiting:

I. Oblivion in the taking of the study medication.
II. Lack of return of study medication by the subject.
III. Visits of the research subject carried out outside the window.

10.5.1 Management of deviations

All deviations must be reported by the IP to the sponsor and the corresponding committees.

At your discretion, and depending on the severity of the deviation, the sponsor and the corresponding committees may:

- Request more information.

- Citing the principal investigator and / or the members of his team.

- Temporarily suspend the researcher for present and / or future investigations until the situation is resolved and / or considers the explanations given by the person (s) responsible for the deviation satisfactory.

- Carry out an audit for cause.

10.6 Declaration of interests

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

10.7 Access to information

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

10.8 Auxiliary care and after the end of the study

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

10.9 Biosecurity aspects

WITHOUT BIOSECURITY IMPLICATIONS

The present protocol, with title: "Phase I clinical study, to evaluate the safety and tolerability of the ophthalmic gel PRO-167 versus Corneregel®, on the ocular surface of ophthalmological and clinically healthy subjects", and number: SOPH167-0816 / I DOES NOT HAVE BIOSECURITY IMPLICATIONS, since infectious-contagious biological material will NOT be used; pathogenic strains of bacteria or parasites; viruses of any kind; radioactive material of any kind; genetically modified animals and / or cells and / or plants; toxic, dangerous or explosive substances; any other material that endangers the health or physical integrity of the personnel of the research center or the subjects of investigation or affects the environment. It is also stated that cell, tissue or organ transplant procedures or cell therapy procedures will not be carried out in this project, nor will laboratory, farm or wildlife animals be used.

10.10 Final report and publication of results

10.10.1 Final report

Once the statistical analysis is finished, a final report will be drafted with the results obtained, in charge of the Scientific Committee of the Department of Clinical Operations of Sophia Laboratories A.S. of V.C. Said report will be prepared following the recommendations of the E3 Step 4 Guide of the ICH.

10.10.2 Communication of results

Regardless of the results in the study, Sophia Laboratories A.S. of V.C., is committed to communicate the final report of the study to the principal investigators and to the corresponding regulatory entities of the countries with participating research centers. Maintaining at all times the rights on the publication and disclosure of the information contained.

10.10.3 Publication of the results

Sophia Laboratories A.S. of V.C., pretending as a sponsor of the study, assumes full responsability for its function and retains the exclusive property rights over the results of the study, wich it can use in the way it deem convenient.

The PI undertakes not to publish or communicate data collected only in a center or in part of the centers before the publication of the full results of the study, unless prior written agreement is given by Sophia Laboratories A.S. of V.C.

Any publication and / or communication project related to the study and / or the results obtained during the study or after the completion of the study will be presented to participating medical researchers at least 30 days in the case of a publication and 15 days in the case of a summary, before the scheduled date for the communication and / or presentation of a publication. The medical researcher or doctors will comment on the project within 15 days in the case of a publication and 7 days in the case of a summary, from the date on which the project is received.

However, in the event that the sponsor is in the process of submitting a patent application on the results of the study, the sponsor may delay its publication or communication of the results of the study until the date of registration.

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12. Signature page

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External reviewer of the protocol:

Dr. Mariana Xacil Díaz Salazar

Principal investigator of the study:

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13. Annexes

13.1 Eye comfort index

Índice de Confort Ocular

Ficha de identificación

No. de estudio SOPH167-0816-I **Fecha:** / /

Iniciales del sujeto: **No. de sujeto:** 167-_____-_____

Indicaciones:

Este cuestionario fue diseñado para calificar el confort de sus ojos.

Para cada pregunta circule su respuesta

Ejemplo: En la semana pasada, ¿qué tan seguido sus ojos estuvieron rojos?

Nunca						Siempre
0	1	2	3	4	5	6

No existen respuestas correctas o incorrectas. No tome demasiado tiempo en cada pregunta.

1 En la semana pasada, ¿qué tan seguido sus ojos se sintieron *secos* ?

Nunca						Siempre
0	1	2	3	4	5	6

Cuando sus ojos se sentían *secos* , por lo general, ¿qué tan intensa era la sensación?

No lo he sentido						Severo
0	1	2	3	4	5	6

2 En la semana pasada, ¿qué tan seguido sus ojos se sintieron *arenosos* ?

Nunca						Siempre
0	1	2	3	4	5	6

Cuando sus ojos se sentían *arenosos* , por lo general, ¿qué tan intensa era la sensación?

No lo he sentido						Severo
0	1	2	3	4	5	6

3 En la semana pasada, ¿qué tan seguido sus ojos sintieron *punzadas* ?

Nunca						Siempre
0	1	2	3	4	5	6

Cuando sus ojos sentían *punzadas* , por lo general, ¿qué tan intensa era la sensación?

No lo he sentido						Severo
0	1	2	3	4	5	6

4 En la semana pasada, ¿qué tan seguido sus ojos se sintieron *cansados* ?

Nunca						Siempre
0	1	2	3	4	5	6

Cuando sus ojos se sentían *cansados* , por lo general, ¿qué tan intensa era la sensación?

No lo he sentido						Severo
0	1	2	3	4	5	6

Hoja 1 de 2

Índice de confort ocular

5 En la semana pasada, ¿qué tan seguido sus ojos se sintieron *adoloridos* ?

Nunca						**Siempre**
0	1	2	3	4	5	6

Cuando sus ojos se sentían *adoloridos* , por lo general, ¿qué tan intensa era la sensación?

No lo he sentido						**Severo**
0	1	2	3	4	5	6

6 En la semana pasada, ¿qué tan seguido sus ojos sintieron *comezón* ?

Nunca						**Siempre**
0	1	2	3	4	5	6

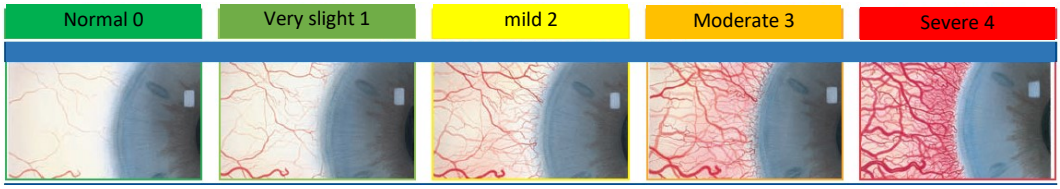
Cuando sus ojos sentían *comezón* , por lo general, ¿qué tan intensa era la sensación?

No lo he sentido						**Severo**
0	1	2	3	4	5	6

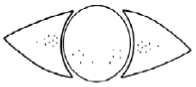
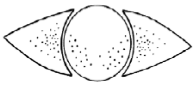
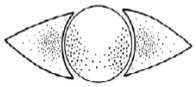
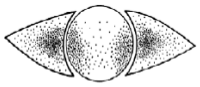
Índice de confort ocular, traducido del Ocular Comfort Index disponible en: http://iovs.arvohournals.org

Hoja 2 de 2

13.2 Efron scale for conjunctival hyperemia



13.3 Oxford Scale

PANEL	Grade	Criterion
A 	0	Equal or less than panel A
B 	I	Equal to or less than panel B, greater than A
C 	II	Equal to or less than panel C, greater than B
D 	III	Equal to or less than panel D, greater than C
E 	IV	Equal to or less than panel E, greater than D
>E	V	Greater than panel E