Creation date: July 2016

Clinical study of the efficacy of the ophthalmic emulsion PRO-145 for the management of inflammation and pain after phacoemulsification compared to prednisolone acetate 1%.

Protocol code: SOPH145-0716 / III
Protocol version: 2
Date of the version: 08/02/2018
Registration: Pending

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

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1. Summary

<table>
<tr><td colspan="3">Title of the study:
Clinical study of the efficacy of the ophthalmic emulsion PRO-145 for the management of inflammation and pain, after phacoemulsification compared to prednisolone acetate 1%.</td></tr>
<tr><td colspan="2">Protocol code: SOPH145-0716/III</td><td>Creation date: 12/07/2016</td></tr>
<tr><td colspan="2">Protocol version: 2</td><td>Date of the version: 08/02/2018</td></tr>
<tr><td colspan="3">Therapeutic indication: Anti-inflammatory.</td></tr>
<tr><td>Study period: 8 months</td><td colspan="2">Development phase: III</td></tr>
<tr><td colspan="3">Goals:
To evaluate the efficacy of the ophthalmic emulsion PRO-145 in the treatment of inflammation and pain after phacoemulsification.</td></tr>
<tr><td colspan="3">Hypothesis:
The use of the ophthalmic emulsion PRO-145 is effective in decreasing the inflammatory response evaluated by means of cellularity in the anterior chamber, after phacoemulsification.</td></tr>
<tr><td colspan="3">Methodology:
Phase III clinical trial, double-blind, controlled, parallel group, multicentre, randomized.</td></tr>
<tr><td colspan="3">Number of patients:
178 subjects divided into 2 groups (89 subjects per group), who will provide an eye for the evaluation of efficacy.</td></tr>
<tr><td colspan="3">Diagnosis and main inclusion criteria:
Diagnosis: Postoperative phacoemulsification and foldable intraocular lens placement in a bag.
Main criteria:
-Informed consent
- Age ≥ 18 years
-Both genders
- Postoperative cataract surgery by phacoemulsification
o o That they have met the criteria for phacoemulsification and a classification of the LOCS III cataract of NO ≥2 and NC ≥2</td></tr>
<tr><td colspan="3">Test product, dose and route of administration:
• PRO-145. Difluprednate 0.05%. Prepared by Sophia Laboratories, S.A. of C.V., Zapopan, Jalisco, Mexico.
- Dosage: 1 drop 4 times a day (every 4 hours) during the period of vigil in the operated eye, for 14 days. Dose reduction for 14 days at the discretion of the principal investigator.</td></tr>
</table>

- Route of administration: topical ophthalmic

Treatment duration:

28 days

Reference product, dose and route of administration:

1. Prednefrin® SF. Prednisolone Acetate 1%. Prepared by Allergan, S.A. of C.V.

- Dosage: 1 drop 4 times a day (every 4 hours) during the period of vigil in the operated eye, for 14 days. Dose reduction for 14 days at the discretion of the principal investigator.- Route of administration: topical ophthalmic

Evaluation criteria:

Effectiveness:

- Primary
  - o Cellularity in the anterior chamber
- Secondary
  - o Visual capacity (CV)
  - o Central thickness of the retina
  - or Clinical corneal edema
  - or conjunctival hyperemia
  - or Flare
  - o Symptomatology
    - Pain
    - Photophobia

Tolerability:

- Post-Stretching Ocular Symptomatology

Security:

- Visual capacity (CV)
- Adverse events (EA)
- Intraocular pressure (PIO)

Statistical methodology:

The result of the continuous quantitative variables will be presented in measures of central tendency: mean, standard deviation and ranges. The total size of the samples will consider an eye as a case for the evaluation of efficacy.

The normal distribution of the results will be obtained through the Kolmogorov-Smirnov and Shapiro-Wilks test. The statistical analysis of the continuous quantitative variables to find significant differences (p) will be in the inter-group analysis: t test for paired samples; for intra-group analysis: McNemar test. Evaluations of cellularity in the anterior chamber before the application of the intervention and in the final visit will be considered for the analysis. 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 will be carried out as follows: Difference between groups: $\chi 2$ test (Chi-square) of Pearson or Fisher's exact in expected values less than 5 ; for intra-group analysis: McNemar test

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2. Content

Index of tables, figures and illustrations

3. Index of abbreviations

NSAIDs	Nonsteroidal anti-inflammatory drugs
AV	Visual acuity
BH	Blood count
bid	twice a day
BPC	Good clinical practices
C	Cortical opacity
CCA	Cellularity in the anterior chamber
IEC	Research Ethics Committee
CI	Informed Consent
COX	Cyclooxygenase
CRF	Case Report Form (Case Report Form)
CV	Visual capacity
DFB	Difluoroprednisolone butyrate
DFBA	Difluoroprednisolone butyrate acetate
EA / EAS	Adverse event / serious adverse event
FDA	Food and Drug Administration (Food and Drug Administration)
GCR	Retinal central thickness
ICH	International Conference on Harmonization (for its acronym in English International Conference on Harmonization)
IP	Principal investigator of the clinical study
LIO	Intraocular lens
LOCS	Crystalline Opacification Classification System (Lens Opacities Classification System)
NC	Kernel color
NO	Opalescence of the nucleus
P	Posterior capsular opacity
PIO	intraocular pressure
qid	Four times a day
QS	Blood chemistry
VDF	Verification of source documents

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4. Administrative structure of the study

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

Function	Contact name	Affiliation ¥
Medical responsible for the study	Dr. Leopoldo Martín Baiza Durán leopoldo.baiza@sophia.com.mx	Medical Director and Regulatory Affairs
Director of the study	QFB. Francisco García Vélez francisco.garcia@sophia.com.mx	Clinical Operations Manager
Scientific Comittee	Dr. Oscar Olvera Montaño oscar.olvera@sophia.com.mx	Ophthalmologist Investigator
Scientific Comittee	Dr. en C. Ricardo Alonso Llamas Velázquez ricardo.llamas@sophia.com.mx	Clinical Pharmacologist
Scientific Comittee	Dra. en C. Patricia del Carmen Muñoz Villegas patricia.munoz@sophia.com.mx	Medical Editor

¥ Employees of Sophia Laboratories, S.A. of C.V Av. Paseo del Norte No.5255, Col. Guadalajara Technology Park, Carretera Guadalajara-Nogales Km13.5 C.P. 45010 Zapopan, Jalisco, Mexico Tel +52 (33) 3000 4200
Table 1. Administrative structure

Table 1. Administrtive structure

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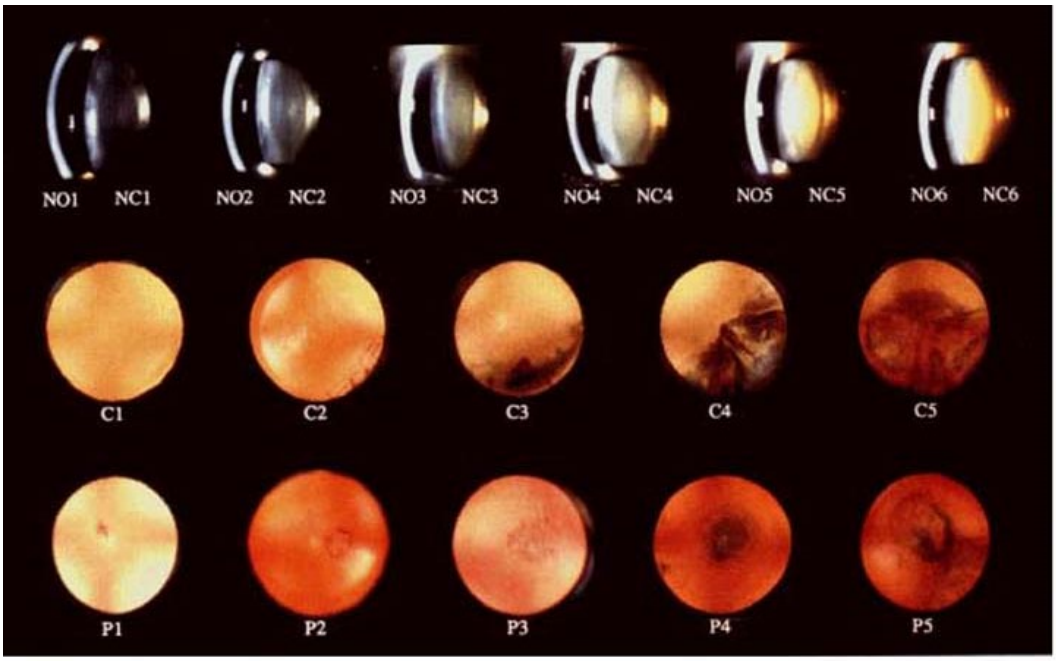
5. Introduction

5.1 Theoretical framework

A cataract is the opacity of the lens, it affects the visual function in different ways depending on its characteristics. Cataracts are of multifactorial origin, according to their pathophysiology they can be classified as senile cataracts, congenital, induced by medications, traumatic, metabolic and associated with uveitis. [1] Nevertheless, most are related to age, so they are more common in the elderly. [2] Cataracts are the leading cause of blindness in the world, responsible for 51% of global blindness, which in 2010 represented nearly 20 million people. By increasing life expectancy, the number of people with cataracts is expected to increase directly proportionally. Cataracts are also an important cause of decreased visual acuity (AV) and low vision in developed and developing countries. [3] In Mexico there are three internationally recognized studies on cataract blindness, which report that cataracts are responsible for 48 to 64% of blindness in the study population. [4] [5] [6]

The classification of cataracts based on their "maturation", degree of opacity or progression has not been sufficient for epidemiological or therapeutic studies of cataracts. The lens opacity classification system III (LOCS III, for its acronym in English of Lens Opacities Classification System III) is a standardized system used to stage and compare the type and degree of severity of cataracts. [7] It was derived from LOCS II [8], and consists of three sets of standardized photographs (See Figure 1. LOCS III). The classification evaluates four characteristics, nuclear opalescence (NO), nuclear color (NC), cortical opacity (C), and posterior subcapsular opacity (P). The use of this classification has allowed a better record of the progression of the cataract, decreases the inter-observer subjective influence and allows the creation of peri-surgical plans according to the needs of each patient. [9]

Ilustration 1. LOCS III



There is no minimum AV, nor a minimum classification of the degree of cataract, defined and globally accepted for the indication of cataract surgery; nevertheless, with the advent of new

surgical techniques, more advanced phacoemulsification machines, the introduction of femtosecond laser-assisted cataract surgery (known as FLACS, after its acronym in English femtosecond laser-assisted cataract surgery) and the evolution of Intraocular lenses (LIO), cataract surgery has been allowed to be consistently safer and with a high predictability of good visual rehabilitation, often not requiring visual correction by means of aerial lenses. This has led to the AV to indicate cataract surgery in industrialized countries from 20/30 or less. [10] [11]
In 2014 it was estimated that 2 million cataract surgeries were performed in the United States of America (USA). [12] For 2015, 3.6 million surgeries were estimated in the USA and more than 20 million worldwide. [13] In Mexico, it is estimated that the rate of cataract surgery is 1,530 surgeries per million inhabitants. [14]
Like any other type of surgery, cataract surgery induces an inflammatory response despite advances in surgical technique. Inflammation after cataract surgery continues to be a common cause of patient discomfort, delayed recovery and decreased visual outcome due to posterior synechiae, uveitis, macular edema and secondary glaucoma, among other conditions. [15] [16] [17]
The physical trauma associated with cataract surgery, including the alteration of the blood-brain barrier, induces an inflammatory response and the release of mediators of inflammation such as prostaglandins and leukotrienes (See Figure 1). Prostaglandins are released naturally from the iris and ciliary body and migrate to the retina, after cataract surgery. [18] The inflammatory response, in turn, can activate the cascade of the immune response, releasing additional neutrophils, macrophages, T lymphocytes and mediators of inflammation. [18] [19] [20]

Inflammation after cataract surgery presents with signs such as flare, cellularity in the anterior chamber, conjunctival hyperemia, edema, leukocyte migration, proliferation of fibroblasts and scarring. [21] [22] Persistent inflammation causes discomfort to the patient, increased rate of macular edema and compromises the visual result. [15] [16] [22] Potential complications of postoperative inflammation without treatment include pain, photophobia, synechiae, cellular precipitates, uveitis, increased intraocular pressure (IOP), and glaucoma. [23] Because of this, the management of postoperative inflammation is mandatory in modern cataract surgery. [17]

The development of postoperative inflammation is variable from case to case, depending on factors such as the use of drugs prior to surgery, the hardness of the lens, the technique used and the presence of concomitant diseases. [24] [25] Several studies have demonstrated the correlation between the increase in the degree of NO and NC of the LOCS III classification and the increase in the power of phacoemulsification and the effective time of ultrasound in cataract surgery, together with the increase in post-surgical inflammation. [26] [27] [9]

There are no established treatment guidelines to prevent or reduce inflammation after eye surgery. [28] [19] Therefore, the treatment includes pre and postoperative anti-inflammatory therapy with corticosteroids and / or nonsteroidal anti-inflammatory drugs (NSAIDs) see Table 2. Anti-inflammatories. Because it is impossible to predict which patients will develop clinically significant inflammation, post-surgical use of anti-inflammatory drugs is routinely performed, with corticosteroids being the most commonly used. [28] [29]

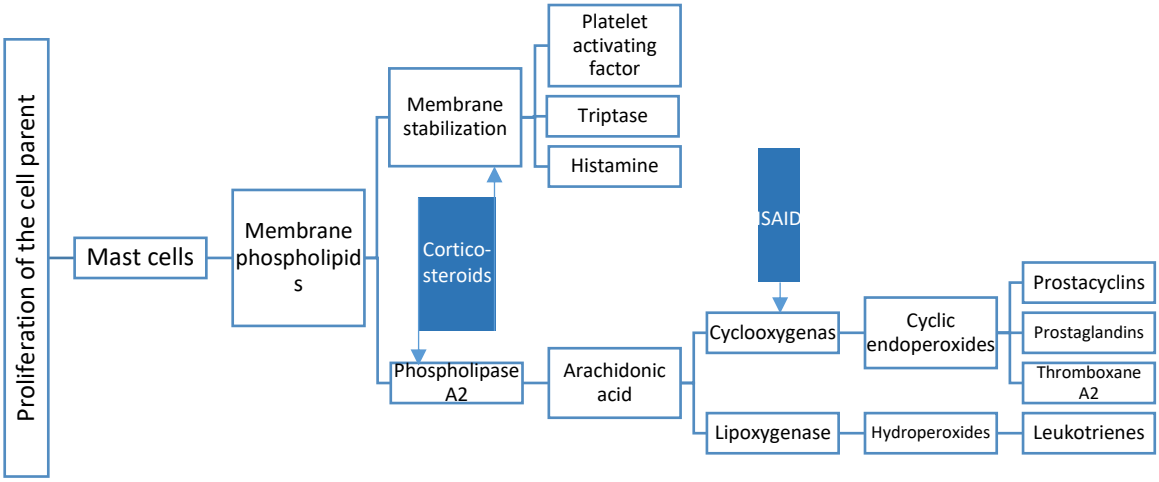


Figure 1. Cascade of inflammation

Table 2. Anti-inflammatories

Group	Mechanism of action	Effect	Effectiveness	Security
Cortico-steroids	Inhibition of phospholipase A2	It decreases the production of prostacyclines, thromboxane A2, prostaglandins and leukotrienes. Alterates the inflammatory mediators of transcription. Modulates the activity and migration of inflammatory cells.	Decreases the presence of inflammatory cells. And the postoperative pain.	Its adverse effects include: cataracts, ocular hypertension, glaucoma, decreased scarring
NSAIDs	Alters transcription and translation.	Suppression of prostaglandin production	Similar to corticosteroids. They have shown better results in decreasing the breakdown of the blood-gas barrier.	Decreased corneal sensitivity.

Corticosteroids are traditionally used to control eye inflammation in the short term and are the most used therapeutic option after cataract surgery. Compared with NSAIDs, corticosteroids have a greater range of activity in the control of inflammation, by acting at multiple points in the inflammation cascade, including both the cyclooxygenase (COX) and phospholipase A2 pathways, reducing prostaglandins. and leukotrienes. See Figure 1. [19]

5.2 Definition of the problem and fundamental reason

The inflammation after ocular surgery continues to be an undesirable consequence despite multiple advances in technology and surgical techniques. Control and prevent inflammation is of great interest to the surgeon in his eagerness to achieve optimal results.

Although it is true that currently cataract surgery does not necessarily result in significant inflammation, there is still a portion of patients who will experience some type of postoperative inflammation, which could potentially alter the visual result, not to mention the comfort of the patient.

Because it is impossible to determine who these patients will be, most surgeons use prophylactic regimens of anti-inflammatory drugs, because of their wide range of action, corticosteroids are the cornerstone of these regimens.

Difluprednate, the active ingredient of PRO-145, is a potent synthetic difluorinated corticosteroid derived from prednisolone, which in its ophthalmic formulation comes in the form of an emulsion. This gives it the advantage over other corticosteroids that are usually formulated as suspension, since it avoids flocculation, sedimentation and poor redispersibility, all of which can lead to dosing errors during administration.

5.3 Background

Approximately 8 years ago, it was approved by the United States Food and Drug Administration (FDA), 0.05% difluprednate ophthalmic emulsion (Durezol®, Alcon Laboratories, Inc. Fort Worth, TX) for use in the treatment of inflammation and pain associated with eye surgery. Since then, the favorable clinical experience of its use has been reported. [30]

5.3.1 Difluprednate

Difluprednate (difluoroprednisolone butyrate acetate, or DFBA) is a synthetic difluorinated derivative of prednisolone. Originally developed for dermatological application, the molecule owes its potency to fluorination at positions C6 and C9. [31] Its anti-inflammatory activity is further enhanced by the replacement of the 17-hydroxyl group by butyrate, while its lipophilicity, and therefore its corneal penetration, is improved by substituting the 21-hydroxyl group for acetate. [32]

5.3.1.1 Eyeball pharmacokinetics

Route of administration: Ophthalmic.

Release: immediate.

Absorption: after instillation, DFBA is rapidly deacetylated to difluoroprednisolone butyrate (DFB), an active metabolite with the same activity profile. [33] The DFB is absorbed in all structures of the anterior segment, its levels in the posterior pole and blood are undetectable after an application.

Metabolism: The acetyl group of the DFBA is rapidly hydrolyzed, nevertheless there is no hydrolysis of the DFB during the first hour.

Elimination: Based on a study with marked DFBA radio, after a single dose radioactivity was detected in the anterior and posterior segments, but not in the blood. At 24 hours postinstilation, 78.5% of the radioactivity had been excreted, and 99.5% had been eliminated after 7 days. The levels of radioactivity did not increase significantly with the increase in the number of doses. After 28 instillations applied in 7 days, concentrations in the anterior segment increased 1.5 times compared to the single application. There was little accumulation in the blood, noting the rapid metabolism of DFB to inert products. [34] [35] [36]

5.3.1.2 Preclinical studies

Studies have been done in animal models to assess safety, bioavailability and efficacy.

Sakaki et al, performed preclinical eye and systemic safety studies of DFBA. In a model in rabbits tested two emulsions of DFBA, 0.01% and 0.05%, while in another model in dogs of race beagles

tested the formulation of DFBA at 0.05% compared to betamethasone. The intervention consisted of the application 4 times a day for one month of the products under investigation. Ophthalmological evaluations, studies of blood count (BH) and blood chemistry (QS) were carried out, as well as histopathological evaluation. No toxicity was detected in any of the groups. [37]

In a study of bioavailability in a model in rabbits, carried out by Inue et al, the effect of the formulation (emulsion or suspension) and the size of the particle on the bioavailability of DFBA were evaluated. In this study it was concluded that the emulsion presents a greater bioavailability than the suspension. While the molecule sizes studied (90.3 and 129.3 nm) do not influence the bioavailability of the DFBA. [38]

To verify preclinical efficacy, a post-surgical inflammation model was created in rabbits. In this model the DFBA 0.05% against betamethasone 0.1% was compared, after a paracentesis a drop of DFBA, betamethasone or saline solution was applied. An effect of difluprednate equivalent to betamethasone was found in the decrease in flare. [39]

In another study with three models of induced uveitis, two in rats (induced by melanin and by endotoxins) and another in rabbits (induced by bovine serum albumin), it was reported that 0.05% DFBA was statistically superior in anti-inflammatory activity when compared to 0.1% betamethasone ($P < 0.01$) in all three models, decreasing signs of inflammation (cellularity and flare). [40]

In Sophia Laboratories, S.A. of C.V. safety and toxicity studies were conducted in albino rabbits New Zealand, the ophthalmic emulsion of DFBA was applied 0.05% four times a day for 90 days, compared to the vehicle; clinical signs and histopathological examination were evaluated, no statistically significant differences were found between interventions, even in the increase in PIO. [41]

Bioavailability studies were also carried out in which two formulations, a suspension and an emulsion of DFBA at 0.05% were evaluated, compared to the reference medicine Durezol® and against prednisolone acetate 1%. Between the formulation of suspension and emulsion, a greater bioavailability for the emulsion was found in all the points, consistent with that reported in the literature. When comparing the emulsion, PRO 145, against Durezol®, no statistically significant differences were found. [42] [43]

5.3.1.3 Clinical safety studies

In 1999, a phase I study was conducted to evaluate the safety of three DFBA formulations, at 0.002%, 0.01% and 0.05% in 18 healthy subjects. The intervention consisted of a single drop of the product under investigation in one eye, and in the contralateral one drop of the vehicle. Evaluation of the ocular surface and an electroretinogram were performed 24 hours after instillation. The tolerability and symptomatology was evaluated through questioning by means of a questionnaire. Adverse events (AEs) reported were mild and not necessarily related to instillation. [44]

In another phase I study, two concentrations of DFBA, 0.01% and 0.05%, were evaluated in 12 subjects. The intervention consisted in the application of two drops of the investigational drug four times a day for 7 days, in one eye, and in the contralateral vehicle. The results of this study showed that either of the two formulations was well tolerated and had little systemic effects. EAs were mild, PIO increased three times, but none of them exceeded normal limits. [44]

At Sophia Laboratories, a phase I study was conducted comparing the PRO145 emulsion against Durezol® and placebo, with an application of 1 drop qid for 10 days, continuing with a bid drop for 5 days, in both eyes. We included 27 healthy subjects, randomly divided into 3 groups corresponding to the 3 interventions. Symptoms and clinical signs, including PIO, were evaluated. In addition, laboratory tests, QS, BH and liver enzymes were performed. No statistically significant differences were found between groups. No increase in PIO was reported in any of the subjects. It was concluded that the safety profile of PRO-145 in equal circumstances is similar to that of Durezol®. [45]

5.3.1.4 Clinical efficacy studies

In a phase IIa study, the effectiveness of two formulations of DFBA, 0.002% and 0.05%, administered 4 times a day for seven days after cataract surgery was checked. In this comparative study, of parallel groups, double blind, randomized, only 6 patients were enrolled, due to strict eligibility criteria. Both formulations proved to be effective in the management of inflammation, determined by the quantification of CCA and flare. [44]

In a multicenter, parallel group study, with active control, phase IIb, the efficacy and safety of DFBA at 0.05% against betamethasone was compared in the treatment of postoperative inflammation. 24 subjects were included, the study concluded that DFBA was as effective as betamethasone and with an acceptable safety profile. The variables evaluated were CCA and flare for efficacy and EA for safety [44]

There are reports of multicentric phase 3 studies of the use of DFBA for the control of inflammation in two different models: in the management of postoperative inflammation and in the treatment of inflammation by anterior uveitis. The main characteristics of these studies are shown in Table 3.

After the commercialization of Durezol®, DFBA ophthalmic emulsion efficacy studies have continued to be reported at 0.05%, both in the management of inflammation due to endogenous anterior uveitis and secondary to intraocular surgery. Donnenfeld reported the results of a multicentre study comparing the effect of DFBA at 0.05% on corneal thickness and visual acuity, using pulse doses after cataract surgery, against prednisolone acetate at 1%. In the study, 52 patients were enrolled, who provided both eyes for the evaluation; in a randomized manner, one eye received DFBA and the contralateral one prednisolone; the dosage consisted of 7 doses during the two hours prior to surgery, 3 additional doses after surgery before being discharged, the rest of the first day a drop every 2 hours, followed by qid for a week and bid in the second week. In this study, DFBA was superior to prednisolone. [46] Dosage twice a day has also been investigated, demonstrating high effectiveness in the management of inflammation and postoperative pain. [47]

Table 3. Results of phase III studies

Author	(N)	Disease model	Intervention	Comparator	Variables	Result
Ohji [48]	182	Postsurgical	DFBA 0.05% qid for 14 days	Betamethasone 0.1% qid for 14 days	Cellularity Flare	DFBA is as effective as betamethasone

Author	(N)	Disease model	Intervention	Comparator	Variables	Result
					Overall score of inflammation Adverse events	and with a favorable safety profile.
Korenfeld [49]	438	Postsurgical	DFBA 0.05% qid or DFBA 0.05% bid	Placebo with the same scheme	Cellularity Flare Pain Discomfort Photophobia Adverse events	Both DFBA posologies were effective compared to placebo. Good security profile
Ohno [50]	136	Previous endogenous uveitis	15 days followed by dose reduction.	Betamethasone 0.15 qid for 15 days	Cellularity Flare Overall score of inflammation Adverse events Cellularity Flare Overall score of inflammation Adverse events	DFBA is as effective as betamethasone and with a favorable safety profile.
Mochizuki [51]	19	Severe refractory endogenous uveitis (did not respond to betamethasone)	DFBA 0.05% qid for 15 days	Any	Cellularity Flare Overall score of inflammation Adverse events	Significant improvement in relation to the baseline.
Sirion Therapeutics Inc [52]	90	Previous endogenous uveitis	DFBA 0.05% qid for 14 days, followed by 2 weeks of dose reduction and 2 weeks of follow-up.	Prednisolone 1% qid for 14 days, followed by 2 weeks of dose reduction and 2 weeks more follow-up	Cellularity	A greater proportion of patients in the DFBA group decreased inflammation.

In the pediatric population, the efficacy and safety of DFBA for the management of postoperative inflammation has also been evaluated, demonstrating an efficacy and safety profile similar to that of prednisolone acetate 1% when used in children aged 0-3 years. cataract surgery [53]

5.3.1.5. Safety and tolerability

It is now recognized that topical corticosteroids can lead to an increase in PIO. It is possible to present ocular hypertension in a repeated dose treatment as soon as in a week, an effect that may

be more pronounced in glaucomatous eyes. [44] Prolonged elevation of the PIO is associated with damage to the optic nerve, with subsequent alteration of the visual field and possibly AV.

Another well-documented effect of steroid use includes the formation of posterior subcapsular cataracts and the predisposition to ocular infections.

Studies previously reported have shown that DFBA causes an increase in PIO in a small number of exposed patients. This increase was resolved in all patients upon discontinuation of treatment or with the help of topical hypotensives. Compared with betamethasone and prednisolone applied with the same frequency, the incidence of PIO elevation was equal, indicating an acceptable safety profile. [44] [49] [48] [50]

5.4 Justification

Control and prevent inflammation is one of the main concerns of the ophthalmologist surgeon to achieve optimal results after surgery.

Steroids are the drugs of first choice for the control of inflammation due to its broad anti-inflammatory activity and its safety profile.

PRO-145 is a formulation of 0.05% DFBA in ophthalmic emulsion, developed by Sophia Laboratories, S.A. of C.V. which has demonstrated an acceptable safety profile in preclinical and clinical phase I studies, as well as a bioavailability in animal models similar to that reported for Durezol®. With this background, a phase III clinical study is required to verify the efficacy profile of PRO-145.

5.5 Objectives and hypothesis

5.5.1 General purpose

To evaluate the efficacy of the ophthalmic emulsion PRO-145 in the treatment of inflammation and pain after phacoemulsification.

5.5.2 Specific objectives

- Evaluate the efficacy of PRO-145 through the elimination of anterior chamber cellularity (CCA) at the final visit.
- Evaluate the efficacy of prednisolone acetate 1% by means of the elimination of CCA in the final visit

5.5.3 Secondary objectives

- Evaluate the efficacy of PRO-145 through the decrease of CCA in the ordinal scale during visits
- Evaluate the efficacy of PRO-145 by decreasing the central thickness of the retina (GCR).
- Evaluate the efficacy of PRO-145 by decreasing clinical corneal edema.
- Evaluate the efficacy of PRO-145 through the reduction of conjunctival hyperemia.
- Evaluate the efficacy of PRO-145 by means of the decrease of flare.
- Evaluate the efficacy of PRO-145 in reducing symptoms: pain and photophobia.
- To evaluate the tolerability of PRO-145 by means of the interrogation of ocular symptomatology post-stiffening.

- Evaluate the safety of PRO-145 through the CV, the PIO and the incidence of EA
- To evaluate the efficacy of prednisolone acetate 1% by means of the decrease of CCA in the ordinal scale during visits
- Evaluate the efficacy of prednisolone acetate 1% by means of the decrease in GCR.
- Evaluate the efficacy of prednisolone acetate 1% by means of the decrease of clinical corneal edema.
- Evaluate the efficacy of prednisolone acetate 1% by means of the reduction of conjunctival hyperemia.
- Evaluate the efficacy of prednisolone acetate 1% by means of the decrease in flare.
- Evaluate the efficacy of prednisolone acetate 1% in reducing symptoms: pain and photophobia.
- To assess the tolerability of prednisolone acetate 1% by means of the interrogation of ocular symptomatology postinstilation.
- Evaluate the safety of prednisolone acetate 1% by means of the CV, the PIO and the incidence of EA.

5.5.4 Hypothesis

H0: The use of the ophthalmic emulsion PRO-145 is not effective when decreasing the inflammatory response evaluated by means of cellularity in the anterior chamber, after phacoemulsification.

Ha: The use of the ophthalmic emulsion PRO-145 is effective in decreasing the inflammatory response evaluated by means of cellularity in the anterior chamber, after phacoemulsification.

5.6 Design and plan of the study.

Phase III clinical trial, parallel, controlled, randomized, double blind. Participants will be postsurgical phacoemulsification patients, who will be randomly assigned to 2 intervention groups with steroidal anti-inflammatory drugs. One group will receive the PRO-145 test formulation and the other group will be exposed to prednisolone acetate 1%.

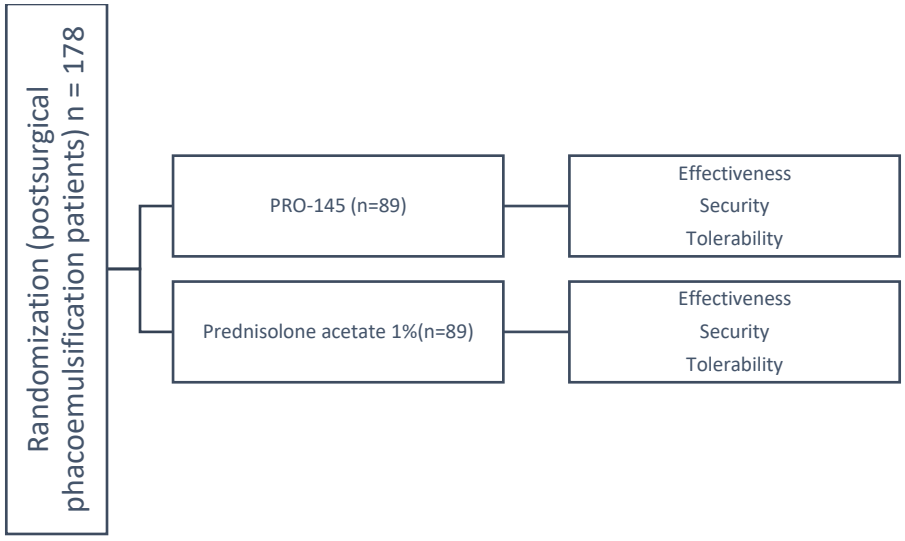


Figure 2. Study design.

5.6.1 Discussion of the study design.

In clinical research it is common to propose trials with the objective of evaluating the efficacy of a product under investigation against a reference medicine or active control, in order to compare the new product under investigation from a clinical or statistical point of view to a drug commercially available

The clinical trial is the ideal model to evaluate the effectiveness of two interventions, it allows obtaining the highest quality evidence among different types of research. The characteristics of randomization and double blind, allow to avoid biases (selection, evaluation, etc.) that can not be avoided with other models. Being controlled and parallel groups allows distinguishing the effects of interventions in isolation.

The proposed clinical trial aims to evaluate the efficacy, safety and tolerability profile of a formulation of DFBA 0.05% and compare it against the safety, tolerability and efficacy profile of commercially available steroid administration, and widely used for its efficacy profile and known security.

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.

This is a multicentre study that is intended to be carried out in Guadalajara, Mexico City and Monterrey.

6.1.1 Organization of the center.

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

The IP 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. Notwithstanding, the minimum organization of the research team requested by the sponsor requires the figure of sub-researcher, study coordinator and pharmacist.

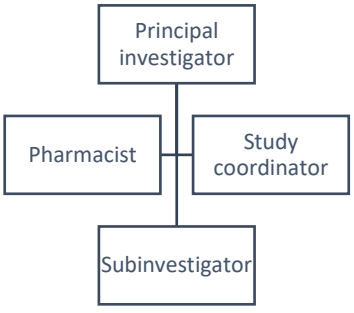


Figure 3. Minimum organization of the center.

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

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 IP must be delivered 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 sponsor's prerogative 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.
-Age ≥ 18 years.
-Both sexes.
-Postoperative cataract surgery by phacoemulsification.
- That they have met the criteria for phacoemulsification and a classification of the LOCS III cataract of NO ≥2 and NC ≥2.

6.2.2 Exclusion criteria.

6.2.2.1 General criteria.

• Pregnant women, lactating or planning to get pregnant.
• Women of reproductive age and who do not have a hormonal contraceptive method, intrauterine device or bilateral tubal obstruction.
• Participation in another clinical research study ≤ 30 days before the baseline visit.
• Have previously participated in this same study with the contralateral eye.
• That they can not comply with their attendance at appointments or with all the requirements of the protocol.

6.2.2.2 Medical and therapeutic criteria.

- Surgery in both eyes in the same surgical shift.
- Time> 24 hours after having surgery.
- LIO placement outside the bag.
- Presentation of rupture of the posterior capsule, with or without the presence of vitreous.
- Carrying out an iridectomy, or lesion of the pupillary sphincter during phacoemulsification surgery.
- Scheduled for surgical intervention in the contralateral eye during the study period.
- History of glaucoma or ocular hypertension.
- History of increased PIO with the use of steroids.
- PIO ≥24.
- History of uveitis.
- Presence of corneal abrasion or corneal ulceration in the study eye.
- Use of steroids or topical NSAIDs, 24 hours prior to surgery and until the start of instillation of investigational drugs.
- Use of anticoagulants, systemic steroids or immunomodulators in the last two weeks
- Periocular injection of any steroid in the study eye 4 weeks before the start of the instillation of the investigational drugs.
- Use of storage steroids 2 months prior to the start of instillation of investigational drugs.
- Presence or suspicion of keratitis and / or viral, bacterial or fungal conjunctivitis.
- Presence or suspicion of endophthalmitis.
- Presence or suspicion of toxic syndrome of the anterior segment.
- Severe corneal edema that does not allow assessment of the anterior chamber
- Macular diseases.

- Diabetes Mellitus with A1C ≥ 6.5% (48 mmol / mol) or fasting glucose (no caloric intake by ≥ 8 hours) of ≥ 126 mg / dL (7.0 mmol / L).
- Any disease or condition that requires the use of topical or systemic NSAIDs during the time of intervention.
- Any disease or condition that requires the use of steroids other than topical ophthalmic application.
- Subjects with a single eye.
- Any condition or disease that at the discretion of the IP does not make the subject suitable for the study.
- Known hypersensitivity to the components of the products under investigation.

6.2.3 Elimination criteria.

- Decision of the subject. The subject can decide unilaterally to withdraw from the study at any time, should inform the IP.
- Pregnancy.
- Presence of a serious adverse event (EAS).
- Investigator's decision:
  o Due to the presence of an AD that at the discretion of the IP threatens the health of the subject and requires the prescription of a medicine not authorized in the protocol
- Any deviation to the protocol that affects the safety 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 by starting with the first letter of the name, followed by the first letter of the first surname and the first of the second, obtaining maximum three letters, in case the person has two names or a compound surname will always be used the first letter of the first name or last name composed.

Example:

1. Adolfo Daniel Mercado Carrizales

to. Initials: AMC

2. Juan De la Torre Orozco

to. Initials: JDO

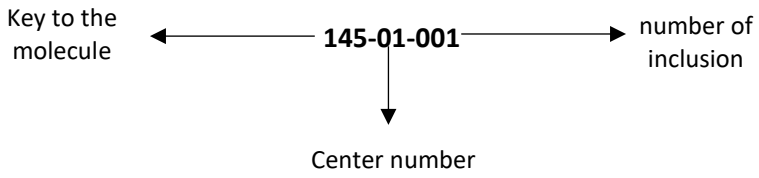
3. Luis Carlos Pérez-Gómez Ramírez

to. Initials LPR

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 composed of 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 their inclusion assigned in the research center.

Example:



6.3 Intervention .

6.3.1 Managed treatments.

The treatments will be administered four times a day, every 4 hours during the waking period, the first 14 days; later it will be completed with 14 days of application in a dose reduction scheme, this scheme will be at the discretion of the IP. The suggested schedule for applications four times a day is at 9:00 am (09:00 am), 1:00 pm (1:00 pm), 5:00 pm (5:00 pm) and 9:00 pm (9:00 pm).) for 14 days. Interventions will only be applied in the postoperative eye.

6.3.1.1 Treatment in study.

- PRO-145 .
  - Active ingredients: Difluprednate 0.05%
  - Pharmaceutical form: ophthalmic emulsion.
  - Prepared by: Sophia Laboratories, S.A. of C.V.
  - Dosage: 1 drop 4 times a day during the period of vigil in the operated eye, for 14 days. Dose reduction for 14 days at the discretion of the principal investigator.
  - Description of the emulsion: white to slightly yellow emulsion.
  - Description of container: sterile multi-dose bottle.
  - The product has certificates of sterility and stability, which are in the master folder of the study, and its characteristics are included in the researcher's manual.

Table 4. Quali-quantitative formulation of PRO-145.

Active principle	Quantity	%	Function
Difluprednate	mg / dL	0.05	Anti-inflammatory
Additives	0.50	%	Function
Castor oil	Quantity	Not shown	Not shown
Polysorbate 80	Not shown	Not shown	Not shown
Disodium edetate dihydrate	Not shown	Not shown	Not shown
Glycerin	Not shown	Not shown	Not shown
Citric acid	Not shown	Not shown	Not shown
Benzalkonium chloride	Not shown	Not shown	Not shown
Sodium hydroxide	Not shown	Not shown	Not shown
Sodium citrate dihydrate	Not shown	Not shown	Not shown
Hydrochloric acid	Not shown	Not shown	Not shown
Water for cbp injectable preparation (1)	Not shown	Not shown	Not shown

Qualitative composition of the formulation PRO-145. The agents that constitute the active substance and the additives are shown. Pharmaceutical form: emulsion. (1) How much is enough to

6.3.1.2 Reference treatment.

- Prednefrin® SF .
  - Active ingredients: prednisolone acetate 1%
  - Pharmaceutical form: Ophthalmic suspension
  - Prepared by: Allergan, S.A. of C.V.
  - Dosage: 1 drop 4 times a day during the period of vigil in the operated eye, for 14 days. Dose reduction for 14 days at the discretion of the principal investigator.
  - Description of suspension: whitish suspension.
  - Description of the container: 5ml multi-dose dropper bottle.

- The data on characterization of the reference product will be taken from the insert.

6.3.2 Strategies to improve adherence and procedure to monitor adherence.

Adherence to the intervention is essential to achieve the objectives of clinical research, adherence is defined as: "the extent to which the behavior of people (including taking medication) corresponds to the indications of the provider of services of health "[54] Effective treatments could be interpreted as ineffective due to poor adherence.

Strategies:

- At each visit, the IP reaffirms in the research subject the importance of following the indicated regimen and will ask if it has had any inconvenience in following the indications, if necessary it will retrain the subject in the application of the medications.
- In case the IP considers it necessary, the subjects that have an email, the IP or the person designated for this, will send them emails to remember the adherence to the treatment and the importance of it. The content of the emails will be previously submitted to the research ethics committee for approval.
- By means of the revision of the daily tool of the subject.

Procedure to monitor adherence:

For more than four decades, numerous investigations have been conducted on the proper way to measure and quantify adherence to medications, nevertheless none has reached consensus to establish itself as the gold standard, both in cross-sectional and longitudinal studies. [55] [56] [57] [58] [59] [60] [61] [62]

There are different procedures to measure the adherence of pharmacological interventions. The most common procedure includes self-reports, these include: patient interviews, questionnaires and self-monitoring journals. Its strengths are speed, flexibility, low cost and ease of implementation; they have a high degree of specificity for non-adherence, nevertheless the sensitivity and reliability for adherence is low. [62] [63]

The biochemical measurement of the drug, or its metabolite, is one of the methods that best confirms the use of the drug. Nevertheless, in addition to raising costs and being impractical, it is of little use in the context of ophthalmic applications, since concentrations at the peripheral level could be undetectable; and samples from other tissues imply more invasive methods that would not be advisable. [62]

Medication counting is another way to measure adherence. Classically referred to as "pills counting", in ophthalmology it is translated to the weight of the bottle. This is a simple, economical and non-invasive method. The main disadvantages of this method are: 1. The application of the medication can not be confirmed (it could have been intentionally thrown or instilled outside the eye) and 2. It depends on the subject bringing the medication back. [62] [63]

The approach with multiple procedures for measuring adhesion is recommended. Because there is no ideal adhesion measurement, it is appropriate to use more than one method when trying to achieve results that resemble reality. Selecting two or more methods allows their strengths and weaknesses to be compensated, in order to more reliably capture adherence levels. [61]

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

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

Where:

Ad = Adherence

Ar = Applications registered in the first 14 days of treatment.

Ai = Applications indicated for the intervention in the first 14 days of treatment.

At the sponsor's facilities, the bottles will be weighed at the beginning and at the end of the study. The adhesion will be calculated considering: the weight of the empty bottle, the weight of the drop, the weight of the bottle with the content, the calculation of the total of drops to be applied during the entire time of intervention and the total weight of the drops applied. The following simplified formula will be used:

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

Where:

Ad = adhesion

IP = weight of the bottle delivered to the subject at the start

Pf = weight of the bottle returned by the subject

PT = weight of the posology indicated for the intervention.

$$P_T = (P_g)G$$

Where:

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

G = number of drops indicated for the intervention

There is no standardized parameter to define an adequate adherence, it must be defined and outlined by the objectives of the research in particular. [62] The efficacy of ophthalmic steroids is based on two fundamental principles: 1) The specific type and location of the inflammation determines the appropriate route of administration and 2) The treatment should be instituted as soon as possible, and the dose should be be high enough and administration frequent enough to suppress inflammatory activity. According to the therapeutic utility curve, to establish the limits of the therapeutic window, a dosage regimen is required in which 50% of the established doses are exceeded, in order to achieve a pharmacological effect. A therapeutic regimen below this value is expected a lack of efficacy. Therefore, an adherence of over 60% according to the weight of the bottle ensures that it remains within the limits of efficacy of the therapeutic window established in the protocol. [64] [65] [66] For the efficacy analysis, only subjects with a minimum adherence of 80% by means of the subject's daily tool and a minimum of 60% by the weight of the bottle will be considered. The variation in the percentage of the measurement method has been chosen empirically to counteract the sensitivity and specificity of the same. It is estimated that with a minimum adherence of 60% the intervention can exert its expected anti-inflammatory pharmacological action. [44]

6.3.3 Treatments and concomitant interventions allowed and prohibited before and during the study.

The subjects admitted correctly to the study, who meet the eligibility criteria, may continue with the systemic treatment of the underlying diseases. If during the development of the study they require the implementation of a new permitted medication, they may do so. All concomitant medications used must be duly reported in the notes of the clinical file and in the corresponding section.

Allowed medications:

- Ophthalmic:
- All permitted medications applied via ophthalmic during the study, must wait a minimum period of 10 minutes from the last application of the treatments under study or reference. The foregoing in order to avoid the interaction of the treatments in the tear film, based on the tear flow index and the physiological tear volume. [67]
    - Tetracaine 0.5%
    - Tropicamide 0.8% / Phenylephrine 5%
    - Any antibiotic
    - Beta-blockers
    - Alpha agonists
  - Administered by a different route to ophthalmic:
    - Medications whose effect may be susceptible to modify any of the parameters of efficacy, safety or tolerability of this research protocol should notify their clinical monitor or scientific committee of the sponsor to judge the convenience of entry, continuation or elimination of the participant as appropriate.

Any medication allowed that is used, besides appearing in the clinical note, must be registered in the section of concomitant medications in the CRF.

- Prohibited medications:
- Any medication with ophthalmic application that is not on the list of allowed medications
- Systemic steroids
- Systemic NSAIDs
- Systemic immunomodulators
- Anticoagulants.

6.3.4 Treatment management.

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

6.3.4.1 Delivery and reception.

The sponsor will be responsible for delivering the study treatments at the research center according to internal procedures. The delivery will be made in closed 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 IP. 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 6.3.4.2 Storage). Subsequently verify the content (treatments) 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 IP will deliver the corresponding treatment to the inpatients. The center must register the medicine delivered.

6.3.4.2 Storage

The medication must be stored in a secure area with restricted access. Storage should be at room temperature to no more than 30 ° 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 personnel indicated by the IP in the center, their treatments in the final visit.

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 medication return form.

6.4 Outcome variables.

6.4.1 Security variables.

6.4.1.1 Primary outcome variables.

Visual ability

Adverse events

Intraocular pressure.

6.4.1.2 Tolerability variables.

Symptomatology postinstillation

6.4.2 Efficacy variables

6.4.2.1 Primary outcome variables

Cellularity in the anterior chamber

6.4.2.2 Secondary outcome variables

Visual ability

Central thickness of the retina

Clinical corneal edema

Conjunctival hyperemia

Flare

Ocular symptomatology (pain and photophobia)

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

The variables and their units of measurement are included in **Table 5 Method of measuring variables**

Variable	Unity	Symbol	Type	Method of measurement
Visual ability	Decimals	---	C. Continuous	Primer
Cellularity in the anterior chamber	Degrees	---	C. Ordinal	Direct observation (Biomicroscopy)
Clinical corneal edema	Degrees	---	C. Ordinal	Direct observation (Biomicroscopy)
Adverse events	Number of cases	N	C. Discrete	Count
Flare	Degrees	---	C. Ordinal	Direct observation (Biomicroscopy)
Central thickness of the retina	microns	µm	C. Continuous	Optical coherence tomography
Conjunctival hyperemia	Degrees	---	C. Ordinal	Direct observation (Biomicroscopy)
Intraocular pressure	Milimeters of mercury	mmHg	C. Continuous	Tonometry by Goldman applanation
Symptomatology	points	---	C. Discrete	Interrogation

Table 5 Method of measuring variables.

The following describes the methods and scales that will be used for the measurement of the variables, which are in strict alphabetical order of the procedure:

6.4.3.1 Biomicroscopy

It is the procedure by which, with the use of the slit lamp or biomicroscope, the ocular structures are evaluated thanks to the characteristics of the light source and the optical power of the instrument. A full assessment of the previous segment will be made, which will be recorded in the clinical file.

By means of biomicroscopy, **conjunctival hyperemia, clinical corneal edema, anterior chamber cellularity and flare will be evaluated**.

Conjunctival hyperemia 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

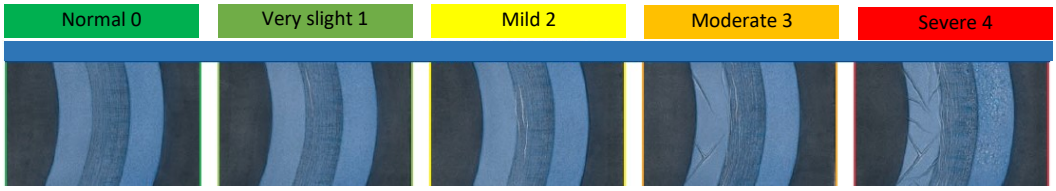
graduate using the Efron scale. [68] The number will be reported in the CRF, according to the rating granted. (**See Illustration 2**)

Illustration 2. Efron scale for conjunctival hyperemia.

Corneal edema and transparency is evaluated regularly using the biomicroscope since it offers the advantage of variable magnifications and lighting techniques, the subjective evaluation of edema is limited to the observation of signs such as microcysts, striae and folds and perhaps the comparison of opacity corneal against images of graduation scales. The transparency of the healthy cornea results from the fact that it does not absorb light and its light scattering is minimal, so that an inflamed cornea does not maintain these characteristics. [69]

Although several methods have been described in the academic literature for the clinical evaluation of inflammation and corneal transparency, there is not one that has been accepted internationally or has a widespread use in clinical practice. For the present protocol we will use the Efron scale, which is a series of pictorial sections of the cornea, including features such as grooves and folds. [68] The Efron scale has a strong correlation with variations in intensity. [69] The number will be reported in the CRF according to the rating awarded. (**See Illustration 3**)

Illustration 3. Efron scale for corneal edema



In the presence of intraocular inflammation, the increased permeability of the non-pigmented layer of the ciliary epithelium, the posterior epithelium of the iris and the vascular endothelium of the iris results in the accumulation of cells and proteins (visible to the examiner as flare) in the anterior chamber. Using a light beam of 0.2mm X 0.2mm directed obliquely to the anterior chamber with a forward inclination of the light source (slit lamp tower) the degree of flare and cellularity will be determined according to the group of work of standardization for the nomenclature of uveitis. [70] The degree of agreement to the granted rating will be reported in the CRF. (See Table 6 and Table 7)

Table 6. Scale for anterior chamber cellularity.

Grade	Number of cells
0	Any

½ +	1-5
1 +	6-15
2 +	16-25
3 +	26-60
4 +	More than 60

Visible in a field of 0.2mm x 0.2mm

Table 7. Flare scale

Grade	Number of cells
0	There is no flare
1 +	Mild
2 +	Moderate (iris and crystalline clearly visible)
3 +	Marking (iris and crsitalino slightly blurred)
4 +	More than 60 (fibrin)

6.4.3.2 Visual ability.

Visual acuity (AV) 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). [71]

The AV 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 (OD) asking the subject to keep both eyes open and using an occluder to cover the left eye (OS); the subject will read aloud the lines that the evaluator points out, the line of smaller letters that he reaches to see will be annotated by the fractional evaluator as the AV of the OD 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 visual capacity (CV), it will be recorded as a fraction in the clinical file and in the CRF, and in the CRF it will be written in decimal. By definition, the CV can not be inferior to the AV.

6.4.3.3 Evaluation of adverse events.

The evaluation of adverse events requires a questioning conducted by the IP and the appropriate exploratory techniques for its detection.

The IP will record in the corresponding section of the CRF the EAs that the subjects of the study will present.

The management of the EAs will be done according to what is described in section 9.3 Adverse events.

6.4.3.4 History of symptomatology.

The subject will be questioned directly about the presence in general (since the last visit) of the following symptoms: pain and photophobia. 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.

Symptomatology postinstilation:

The subject will be questioned if after applying the medication he felt burning, pruritus, a foreign body sensation and blurred vision.

Presence or absence: it will be marked as present (1) or absent (0) in the CRF for each of the symptoms questioned

Frequency: In all applications (4), almost in all applications (3), 50% of applications (2), almost in no application (1), in no application (0)

Duration: More than 5 minutes after the application (3), More than one minute but less than 5 (2), Less than one minute (1), Nothing (0).

The frequency and duration is for all the symptoms in general, the highest frequency and duration reported will be reported in the CRF.

6.4.3.5 Optical coherence tomography.

By means of optical coherence tomography (OCT) the GCR will be measured; Because this is a multicenter study it is not feasible to standardize the brand and model of the OCT to be used, it will allow the use of OCT Stratus (Carl Zeiss), Cirrus (Carl Zeiss), Spectralis (Heidelberg Engineering) with the minimum requirement that the baseline and final OCT are performed with the same OCT, with the same protocol and these characteristics are recorded in the clinical note and in the CRF, together with the central average.

6.4.3.6 Tonometry .

Tonometry is the objective measure of PIO, 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. [71]

The tonometry will be carried out, after instillation of the topical anesthetic, with fluorescein and the use of the cobalt blue filter (after the evaluation of the surface staining). There will be 2 shots and the average will be calculated, which will be recorded in the clinical file. The average will be registered in the CRF.

6.4.4 Measurement time.

- Measurements at the baseline visit

- Biomicroscopy
- Visual ability
- History of symptomatology
- OCT
- Tonometry
- Evaluation of adverse events
- Measurements in visit 1 and 2
- Biomicroscopy
- Visual ability
- Evaluation of adverse events
- History of symptomatology
- Tonometry
- Measurements in final visit
- Biomicroscopy
- Visual ability
- Adverse event evaluation
- History of symptomatology
- OCT
- Tonometry
- Measurements on security call
- Evaluation of adverse events

6.5 Schedule and study diagram.

The **baseline visit** will be considered on day 1 of the study and should be within the first 24 postoperative hours, the IP will indicate the subject to start the application of the investigational products that same day. If necessary, adjust the scheme so that it complies with the 4 applications of day 1; however, in the event that during the opening hours it is not feasible to adjust the 4 applications, the IP will indicate the application of at least 2 instillations, with a minimum of 2 hours between them.

Visit 1 will be performed in relation to the start of treatment on day 7 with a window period of ± 2 days.

The **visit 2 and final** will be made on days 14 and 29, respectively, with a window period of ± 2 days for visit 2 and + 3 days for the final.

The **security call** will be made on day 43, with a window period of ± 3 days.

6.5.1 Schedule

Procedure	B	1	2	Final	LL. S.
	1	7 ± 2	14 ± 2	29 + 3	43 ± 3
Eligibility criteria	X				
Informed consent signature	X				
Pregnancy test (if applicable)	X			X	
General and ophthalmological clinical history	X				
Comprehensive ophthalmologic exploration	X	X	X	X	
Assignment of subject code	X				
Assignment to treatment group	X				
Delivery of medication and start of instillation	X				
Biomicroscopy	X	X	X	X	
Visual ability	X	X	X	X	
History of symptomatology	X	X	X	X	
OCT	X[2]			X	
Tonometry	X	X	X	X	
Evaluation of concomitant medications	X	X	X	X	
Delivery of the subject's diary	X		X		

Procedure	B	1	2	Final	LL. S.
	1	7 ± 2	14 ± 2	29 + 3	43 ± 3
Evaluation of adverse events	X	X	X	X	X
Continuity evaluation		X	X	X	
Evaluation of adherence1		X	X	X	
Indication to change to dose reduction scheme			X		
Return of the medication				X	

[1] They are evaluated through the review of the subject's diary; the diary of the subject is reviewed in the three visits, but it is only collected in the second and final.

2The OCT can be done in a window period of 48 hours for this visit.

6.5.2 Procedures to be performed per visit

Below are the procedures that wiil be carried out in each visit, as well as a brief description of these.

6.5.2.1 Basal visit

- 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.
- Informed consent signature: refers to the signing of the written informed consent document. See 10.3 Consent
- Pregnancy test: 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 performed by the IP or the designated team person according to the instructions of the device delivered by the sponsor.
- 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.
- Comprehensive ophthalmological exploration: refers to the evaluation of the ophthalmic structures of the subject, eyelids and appendices, ocular surface, anterior segment and posterior segment; not considered within the outcome variables. This evaluation has the purpose of identifying alterations that may interfere with the course of the investigation or

identify adverse events. This scan will be recorded in the clinical file, in the CRF only what is considered an adverse event will be reported.

- Assignment of the subject's code: It refers to granting the number that will identify the patient throughout the study. This will be done according to section 6.2.4 Identification of the subject.
- Assignment to the treatment group: Refers to determining the treatment 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.
- Delivery of medication: Refers to the delivery of the medication to the study patient, by the research center. It will be done according to sections 6.3.1 Managed treatments and 6.3.4.1 Delivery and reception. After each medication delivery, a training or re-training of the application of the study medication will be carried out.
- Biomicroscopy: see 6.4.3.1 Biomicroscopy
- Visual capacity: see 6.4.3.2 Visual capacity
- History of symptomatology: see 6.4.3.4 History of symptomatology
- OCT: see 6.4.3.5 Optical coherence tomography. For this visit, the OCT can be done in a window period of 48 hours.
- Tonometry: see 6.4.3.6 Tonometry

- Evaluation of concomitant medications: refers to the interrogation performed by the IP of the medications the patient uses, before, during and after the study. They must be registered in the corresponding section in the CRF, including name of active substance, posology and duration. See: 6.3.3 Treatments and concomitant interventions allowed and prohibited before and during the study.
- Evaluation of adverse events: see 6.4.3.3 Evaluation of adverse events
- Subject's daily delivery: refers to the delivery by the IP, of the subject's daily instrument, to the subject.

6.5.2.2 Visit 1.

- Comprehensive ophthalmologic exploration: see 6.5.2.1 Baseline visit.
- Biomicroscopy: see 6.4.3.1 Biomicroscopy
- Visual capacity: see 6.4.3.2 Visual capacity
- History of symptomatology: see 6.4.3.4 History of symptomatology
- Tonometry: see 6.4.3.6 Tonometry
- Evaluation of concomitant medications: see 6.5.2.1 Baseline visit.
- Evaluation of adverse events: see 6.4.3.3 Evaluation of adverse events
- Continuity assessment: refers to the determination by the IP and desire of the subject to continue with their participation in the study.
- Adherence evaluation: refers to the review of the subject's diary to evaluate the drug application registry.

6.5.2.3 Visit 2.

- Comprehensive ophthalmologic exploration: see 6.5.2.1 Baseline visit.
- Biomicroscopy: see 6.4.3.1 Biomicroscopy
- Visual capacity: see 6.4.3.2 Visual capacity
- History of symptomatology: see 6.4.3.4 History of symptomatology
- Tonometry: see 6.4.3.6 Tonometry
- Evaluation of concomitant medications: see 6.5.2.1 Baseline visit.
- Evaluation of adverse events: see 6.4.3.3 Evaluation of adverse events

- Continuity assessment: see 6.5.2.2 Visit 1
- Adherence evaluation: see 6.5.2.2 Visit 1
- Delivery of the subject's diary: see 6.5.2.1 Baseline visit, this visit is made upon delivery of the diary of the subject delivered at the baseline visit.
- Indication to change to dose reduction scheme: It refers to the indication of the IP to initiate the dose reduction scheme on day 15 of the study, and to last the remaining 14 days of the intervention. The IP will determine, according to the patient's clinical condition, the scheme to follow. It will record in the clinical note and in the CRF, the outline and total number of applications indicated. Example: 1 drop 3 times a day for 5 days; followed by 1 drop 2 times a day for 5 days; finish with 1 drop a day for 4 days; and suspend (Total number of applications indicated: 29). In case visit 2 is made on day 15 that same day, the scheme must be readjusted; if the visit is made on day 16 the scheme will be adjusted from that day and for the remaining 12 days.

6.5.2.4 Final Visit.

- Pregnancy test: see 6.5.2.1 Baseline visit.
- Ophthalmological examination: see 6.5.2.1 Baseline visit.
- Biomicroscopy: see 6.4.3.1 Biomicroscopy
- Visual capacity: see 6.4.3.2 Visual capacity
- History of symptomatology: see 6.4.3.4 History of symptomatology
- OCT: see 6.4.3.5 Optical coherence tomography
- Tonometry: see 6.4.3.6 Tonometry
- Evaluation of concomitant medications: see 6.5.2.1 Baseline visit.
- Evaluation of adverse events: see 6.4.3.3 Evaluation of adverse events
- Continuity assessment: see 6.5.2.2 Visit 1
- Adherence evaluation: see 6.5.2.2 Visit 1
- Return of the medication: refers to the delivery, by the subject, of the excess medication to the research center.

6.5.2.5 Security call:

- Evaluation of adverse events: see 6.4.3.3 Evaluation of adverse events.

6.5.3 Diagram of the study

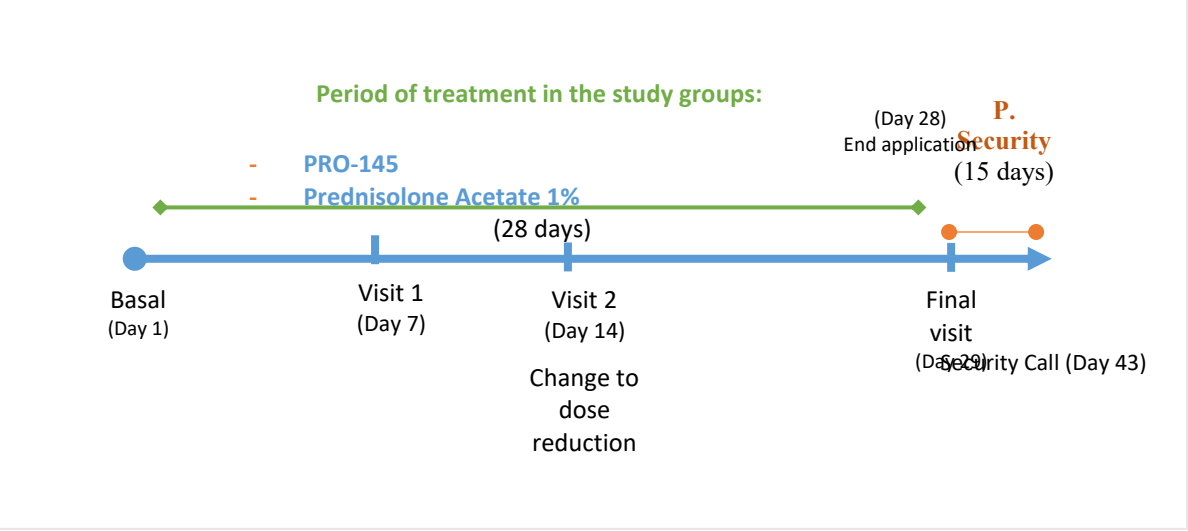


Figure 4. Diagram of the study

6.6 Sample size.

The sample size calculated for the present study is 178 subjects.

Divided into two intervention groups, each group will be comprised of 89 subjects. Each subject will provide an eye for efficacy analysis.

6.6.1 Calculation of the sample size.

The sample sample size was calculated using the formula for two proportions variables as well as the data was entered into the online calculator, software developed in: www.powerandsamplesize.com based on Chow S et al. [72]

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 to 0.84. A 78.9% efficiency ratio was considered in the reduction of the degree of cells in the anterior chamber after the application of 4 weeks of difluprednate 0.05% in 79 subjects submitted to phacoemulsification compared to an efficiency ratio of 77.5% with the use of 1% prednisolone. [53]

According to the previous calculation, the result is 74 eyes per group. The total when considering 2 intervention groups is 148 eyes, which was increased by 20% (30 eyes) for the probable losses. The total sample size required is 178 eyes. **Total n = 178 eyes.**

6.7 Recruitment

The subjects will be recruited from the outpatient IP consultation and who have met the criteria for cataract surgery by phacoemulsification. The IP may include subjects who are not operated on their own, as long as the surgeon responsible for the surgery hands over the postoperative management to the IP and its equipment.

7. Methods Assignment of the intervention

7.1 Generation of the allocation sequence.

2 strata corresponding to the intervention groups will be used, which will be balanced for each research center. The allocation will be 1: 1. The generation will be done through an electronic system validated by an external provider, previously evaluated and authorized by Sophia Laboratories S.A. of C.V. The information corresponding to this provider will be found in the master folder of the study.

7.2 Blinding mechanism

Blinding will be performed by the personnel indicated by the Clinical Operations Management of Sophia Laboratories, S.A. of C.V. The vials of both interventions will be re-labeled and the secondary packaging will be masked.

7.3 Implementation

The sequence will be generated by means of an electronic randomisation system. Said system will be hired by Sophia Laboratories, S.A. of C.V. to a third party. The information corresponding to this third party will be found in the master folder of the study.

7.4 Blinding and 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 in the case of a partial and final analysis.

The masking will be carried out using boxes in the identical primary packaging in the two groups and re-labeling the bottles of both interventions.

Blinding for the research subject and the researcher will be done by replacing the commercial labels in the case of the comparator in the bottles 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 reason of security or another reason that 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 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, trained in the ophthalmological, clinical and pharmacological area, which will be able to generate discrepancies in the event that the data do not comply with the stipulations of the research protocol or put the 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 informed in a clear way 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.
- A printed calendar will be provided with the objective of reminding 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 / her 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.), as well as the subject's diary, are considered source data.

The IP or the designated person of your team will fill out the Case Report Format (CRF) as well as all other documents provided by the sponsor (for example: documents related to the management of the treatment).

An electronic 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 research site will be done by the researcher 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 standard for freezing 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 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 results of the continuous quantitative variables will be presented in measures of central tendency: mean, standard deviation and ranges. See **Table 5 Variable measurement method**. The total size of the samples will consider an eye as a case for the evaluation of the efficacy.
The normal distribution of results will be obtained through the Kolmogorov-Smirnov and Shapiro-Wilks test, as applicable.
The statistical analysis of the continuous quantitative variables to find significant differences (p) will be the following:
. Inter-group analysis: t test for paired samples.
. Intra-group analysis: Mc Nemar test. Cellularity assessments in the anterior chamber will be considered for the analysis before the application of the intervention and in the final visit. The level of difference to consider significance will be of an alpha of 0.05 or less.
The result of nominal and ordinal qualitative variables will be presented in frequencies, proportions and percentages. See **Table 5 Method for measuring variables**

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

• Difference between groups: χ2 test (Chi-square) of Pearson or Fisher's exact in expected values less than 5.

• Intra-group analysis: Mc Nemar test.

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 will be considered. The results will be expressed in number of cases.

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

8.3.2 Additional analyzes

An internal analysis will be made to know the changes that occur between each visit. It is the sponsor's prerogative to request an additional analysis of the data, during the conduction of the study or at the end of this.

8.3.3 Population analysis and management of missing data

The effectiveness analysis will consider those cases in which the measurements of the baseline and final visit are met. Those subjects who do not comply with any of these measurements will not be integrated into the final database to evaluate the effectiveness. Nevertheless, an intention to treat analysis (ITT) will be carried out.

The safety assessment will include in the analysis all those subjects (considering one eye or both) who have been exposed at least once to any of the interventions regardless of the visit in which they were eliminated from the study.

9. Methods Monitoring

9.1 Data monitoring

Monitoring visits by a site monitor from Sophia Laboratories, S.A. of C.V. are intended to confirm that the 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 the screens completed and approved at each visit.

In accordance with the applicable regulations, Good Clinical Practices, and the procedures of Sophia Laboratories, S.A. of C.V. The monitors of Sophia Laboratories, S.A. of C.V. they will contact the site before the start of the study to review the protocol, the regulatory and ethical requirements of Laboratorios Sophia, S.A. of C. V. with the staff of the site. 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, S.A. of C.V. monitor the study to verify, among other things, that:

- The data is authentic, correct and complete.
- They are protecting the security and rights of the subjects.
- 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 completing or discontinuing the study prematurely, 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 Laboratories S.A. of C.V. procedures.

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, S.A. of C.V. 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. Nevertheless, 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, S.A. of C.V.

The researcher / institution must notify Sophia Laboratories, S.A. of C.V. of any change in file arrangements including, without limitation, the following: file in an off-site facility, ownership transfer of records in the event the investigator leaves the site.

9.2 Preliminary analysis and early termination of the study

The partial analysis 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 considers it for security alerts.
3. The Sponsor determined it for your 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, S.A. of C.V., which will have the faculty to determine the fate of the present protocol, as they deem 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. [73] [74] [75]

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 research site and / or researcher 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, the Research Committee.

The attention of the adverse events will be made according to the diagram of attention of the event (see **Figure 5. 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, S.A. of C.V., will include the report of adverse events in compliance with current national and international regulations. [73] [74]

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. If a lack of therapeutic response is detected to the investigational product and / or investigational medication, it should be reported as an adverse reaction. 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 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 to the clinical research phase in which the development of the drug is located.

It will also be necessary to record the data concerning a) batch number, b) manufacturer laboratory, c) expiration date, d) dosage, e) route of administration, f) start dates and g) term 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 in your clinical note of 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 end of the same, according to what is referred to 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:

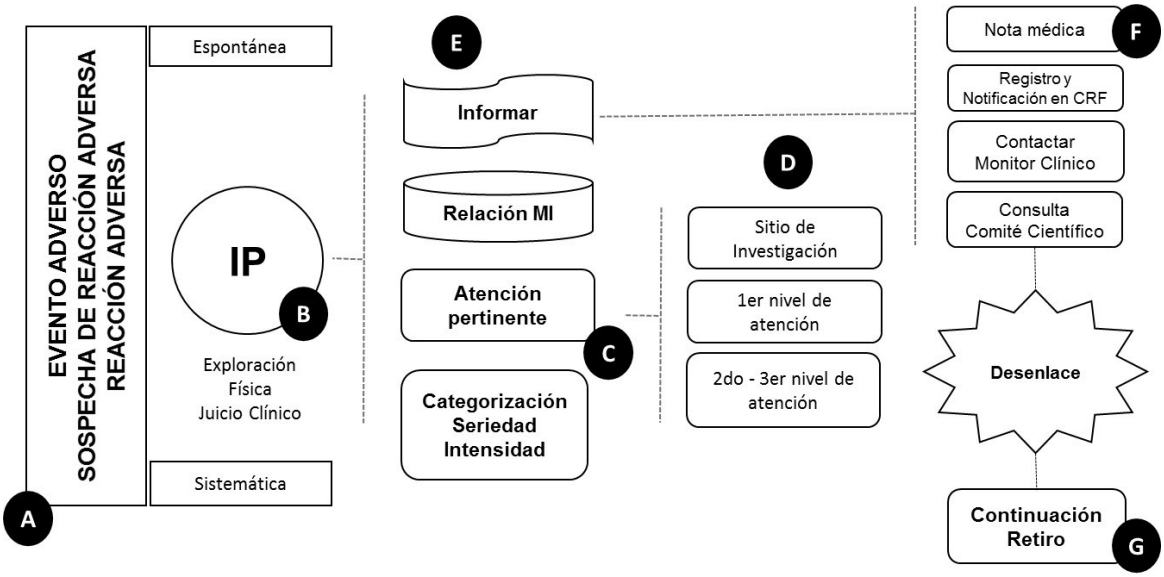


Figure 5. Attention to the adverse event

A. 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. Notwithstanding, 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, SA of 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 drug.
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 product or drug under investigation, 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 product under investigation 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, nevertheless there may be systemic alterations. Therefore, in the opinion of the researcher, the withdrawal of the participant or his / her permanence will be considered, according to the stipulations of section 6.2.3 Elimination criteria of this 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. [73] 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 to 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. [76]

Table 8. Algorithm of Karch and Lasagna modified by Naranjo

No.	Reagent	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
	Total score	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.

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. Notwithstanding, it is important that the researcher take into account the following arguments in favor of the causal relationship: the strength of association that refers to the number of cases in relation to those exposed. The consistency of the data, ie the presence of a common characteristic or pattern. The exposure-effect pattern: which determines the relationship with the site of onset,

time, dose and reversibility after suppression. The biological plausibility: that refers to the possible pharmacological or physiopathological mechanisms involved in the development or presentation of the adverse event. Experimental findings: for example the appearance of anomalous metabolites or high levels of drug or the product of its biotransformation. Analogy: experience acquired with other related drugs, adverse reactions frequently produced by the same family of pharmacological agents. Nature and characteristics of the data: objectivity, accuracy and validity of the relevant documentation. [77]

9.3.2 Responsibilities of the sponsor

The sponsor will be responsible, and will cover the expenses derived from the 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, Laboratorios Sophia S.A. of C.V. 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.

It will be conducted in accordance with the scientific and technical requirements necessary for the registration of medicines for human use of the International Conference on Harmonization (The International Council for Harmonization, ICH for its acronym in English) 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 pertinent 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 that affects driving and results, substitution of the principal investigator or identification of 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 Consent

10.3.1 Obtaining

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

This information will be 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 information of the study was clearly explained and doubts were clarified in case of existing.

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 IP must document in the patient's medical history, the date on which he signed the informed consent.

10.3.2 Special considerations

The auxiliary studies that will be conducted during the conduct of the study are not invasive and 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 having obtained the written approval of the corresponding committees and the Regulatory Entity (as applicable), with the exception of an amendment that is required to eliminate an immediate danger for the subjects of the study.

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

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 electronically or digitally, 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 written authorization of the sponsor.

The researcher will not reveal any information without the prior written consent of Sophia Laboratories, S.A. of C.V., except to the representatives of the Competent Authorities, and only by request of the same. In the latter case, the researcher undertakes to inform Sophia Laboratories S.A. of C.V. before 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, which 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
- It 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 the 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. **Regarding the study procedures**: that those who, 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 deviation: 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. I forget about taking 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
- Quote the principal investigator and / or the members of your team.
- Temporarily suspend the researcher for present and / or future investigations until the situation is resolved and / or consider the explanations given by the person (s) responsible for the deviation satisfactory.

Conduct an audit for cause.

10.6 Declaration of interests

The researchers who collaborate in the present study (principal investigator, subinvestigator) commit themselves to carry out, prior to the beginning of the study, a statement of financial interests, as well as conflict of interest.

10.7 Access to information

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

10.8 Auxiliary care and after the end of the study

The care of the EAs will be done according to section 9.3 Adverse events.

10.9 Biosecurity aspects

WITHOUT BIOSECURITY IMPLICATIONS

The present protocol, titled: "Clinical study of the efficacy of the ophthalmic emulsion PRO-145 for the management of inflammation and pain, after phacoemulsification compared to prednisolone acetate 1%". and number: SOPH145-0716 / III **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. In addition, it is 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, S.A. of C.V. Said report will be prepared following the recommendations of the E3 Step 4 Guide of the ICH.

10.10.2 Communication of results

Sponsor's plan to communicate the results of the study to researchers, participants and regulatory entities.

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

10.10.3 Publication of the results

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

Because the study is multicentric, the first publication should be made only with data collected from several centers and analyzed under the responsibility of Laboratorios Sophia S.A. of C.V. The IP 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 Laboratorios Sophia S.A. of C.V.

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. He or the medical researchers 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.

Nevertheless, in case 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

12.1 Signatures of the sponsor's representatives

First name:	
Dr. Leopoldo Martín Baiza Durán	Firm
Title:	
Medical responsible for the study	Date

First name:	
QFB. Francisco García Vélez	**Firm**
Title:	
Director of the study	**Date**

First name:	
Dr. Oscar Olvera Montaño	**Firm**
Title:	
Protocol author	**Date**

12.2 Investigator

Researcher I agree to conduct this clinical study according to the design and guidelines of this protocol, abiding by the provisions of this protocol. I agree to conduct the study in accordance with the accepted standards of Good Clinical Practices. I agree to report all information or data in accordance with the provisions of the protocol, in particular, any adverse event. Also, I agree to handle the clinical supplies, provided by the sponsor, strictly in accordance with this protocol. I understand that the information that identifies me may be used by the sponsor. Because the information contained in this protocol and the Investigator's Manual is confidential, I understand that it is prohibited to share it with any third party, who is not involved in the approval, supervision or conduct of the study. I will make sure to take the necessary precautions to protect loss information, inadvertent disclosure or access by unauthorized third parties.

First name:	
	Firm
Title:	
	Date