Excelencia en oftálmicos

Protocol:

SOPH149-0220/I

Proposed title for the study: Clinical study to evaluate the safety of the viscoelastic solution PRO-149 when used as an ophthalmic viscosurgical device during phacoemulsification surgery and intraocular lens placement in subjects diagnosed with senile cataracts, compared to Healon® EndoCoat

Information on the molecule under study
Generic name: Sodium hyaluronate 3%
Indication: Surgical medical device for use in patients undergoing anterior segment ophthalmic surgery.

Protocol information
Development phase: Pilot
Version: 2.0
Version date: 02-oct-20

This protocol has been developed in accordance with the principles of the Declaration of Helsinki and will be carried out in accordance with Good Clinical Practices and in compliance with ICH guidelines and current local legislation
Sponsor: Laboratorios Sophia, S.A de C.V

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Changelog

Changes from version 1.0 dated February 25, 2020, to version 2.0 dated October 2, 2020:

1. Cover. – Updated date and version number.
2. Change History. – The Change History sheet has been added.
3. Headers. – Updated version number and date.
4. Contents and index of tables and figures. – Updated.
5. Study Manager and Sponsor Signature Pages. – The name of the Operations Manager has been changed.
6. Summary of protocol SOPH149-0220/I. – The statistical methodology has been modified, and the protocol version number and date have been updated.
7. Illustration 1.- The name of illustration 1 is changed to figure 3.
8. Investigational Product Safety (Section 2.2.2). - A list of incidents or adverse reactions reported with sodium hyaluronate viscoelastic agents has been added.
9. Randomization and blinding (section 7.3). – It is added that the groups have the same probability of being assigned to one treatment or another and that randomization is performed by a third party using a list of random numbers.
10. Definition of variables, methods, and scales to be used for measurement (section 7.4.4). – The Student's t-test can also be used on variables that were previously evaluated with Mann-Whitney's U test.
11. Adverse events (section 7.4.4.3). – The fifth paragraph, which mentions expected adverse events, has been amended because it described adverse events expected for a topically applied product, not a viscoelastic device. The new text describes adverse events (including incidents and adverse events) reported with the use of viscoelastic medical devices.
12. Evaluation and management of adverse events and incidents (section 8). – In all texts derived from section 8, the word "drug" could be replaced with "product," "investigational product," "medical device," "device," "pharmaceutical product," or continued with the name "drug," depending on the best option. Also, in some sections of the texts where the abbreviations for "Principal Investigator," "adverse event," "adverse reactions," "suspected adverse drug reactions," or "investigational product" were used, the decision was made to remove the abbreviations to improve the wording.
13. Regulation and standards for adverse events and incidents (section 8.1). – The following text has been amended: The recording and reporting of adverse events and incidents will be carried out in accordance with the guidelines established in NOM-240-SSA1-2012, NOM-220-SSA1-2016, and the international ICH E6 guidelines.
14. Definition of adverse event, incident, adverse incident, and adverse effect (section 8.2). – The definition of incident, adverse incident, and adverse effect has been added (the previous version only included the definition of adverse event).
15. Use of adverse events as a study safety variable (section 8.3). - This section is created to explain the importance of assessing adverse events in the study.
16. Adverse event registration in the electronic case report form (section 8.5.1) – If a lack of therapeutic response to the investigational products is detected, it must be reported as a serious adverse event within the timeframe stipulated by current regulations, has been eliminated. The therapy used for the pharmacological management of the adverse event must be included among concomitant medications. The removal of the previous paragraph is because the investigational product is a medical device with no direct pharmacological effect and is for temporary use, which makes it impossible to evaluate a therapeutic response. The evaluation of the therapy used for the pharmacological management of the adverse event is included in the previous line.

Also, in this section, the texts are modified to improve their writing.

17. Procedures for a serious adverse event (section 8.5.3). – In Figure 4, the Clinical Safety Pharmacologist is removed, and the Study Director and Protocol Author are added.
18. Causality assessment (section 8.5.4). – The Karch-Lasagne algorithm modified by Naranjo is eliminated, and the causality categories described by *the Uppsala Monitoring Centre are introduced* to categorize the probability of adverse events related to concomitant and experimental treatment.

    The following 3 paragraphs are added:

    > An adverse event may or may not be related to the clinical study. A causal relationship means that the intervention caused (or is reasonably likely to have caused) the adverse event. This usually involves a relationship between the timing of the intervention and the adverse event (for example, the adverse event occurred shortly after the research subject received the intervention).
    >
    > For all adverse events, the Principal Investigator is responsible for examining and evaluating the patient to determine the association of the event with the clinical study and intervention, whether related to experimental treatment, concomitant treatment, surgical procedure, or diagnostic procedures performed during the study.
    >
    > Accepting that the adverse event is related to the clinical study requires a plausible mechanism of action, that is, a logical sequence between the event and the intervention that caused it. In some cases, it is helpful to know the opinions of other physicians directly or indirectly involved in the study, as well as whether the patient believes there is a relationship.

19. Data interpretation (section 10.1.2). – It is added that:

    If the normality of the data is observed ($p > 0.05$; for KS and SW), the statistical analysis of the continuous quantitative variables to find significant differences (p) will be as follows:

    - Intra-group analysis: will be determined using the Student's t-test for repeated measures.
    - Between-group analysis: differences between groups will be analyzed using Student's t-test for independent groups.

    For $p < 0.05$ in KS and SW, the statistical analysis of continuous quantitative variables to find significant differences (*p*) will be as follows:

    - Intra-group analysis: will be determined using the Wilcoxon rank test.
    - Between-group analysis: differences between groups will be analyzed using the Mann-Whitney U statistic.

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

20. References. – References 38 from version 1 have been removed, and 5 new references have been added.
21. Throughout the document, full stops are added to some lines where they were omitted in the paragraphs, and the section titles are standardized.

Content

Index of tables, charts and figures

Study leaders

The administrative structure of the sponsoring party, corresponding to Laboratorios Sophia, S.A. de C.V., is shown in Table 1. Study managers.

Table 1. Study leaders

Function	Name/Contact	Membership ¥
Medical director of the study	[redacted]	Medical Director
Clinical director of the study		Medical Manager
Operations Manager		Regional Clinical Research Manager
Author of the Protocol		Medical Editor
Head of Biostatistics		Biostatistics Manager

¥ Employees of Laboratorios Sophia, S.A. de C.V., Av. Paseo del Norte No. 5255, Col. Guadalajara Technology Park, Guadalajara-Nogales Highway Km 13.5 CP 45010 Zapopan, Jalisco, Mexico Tel +52(33) 3000 4200

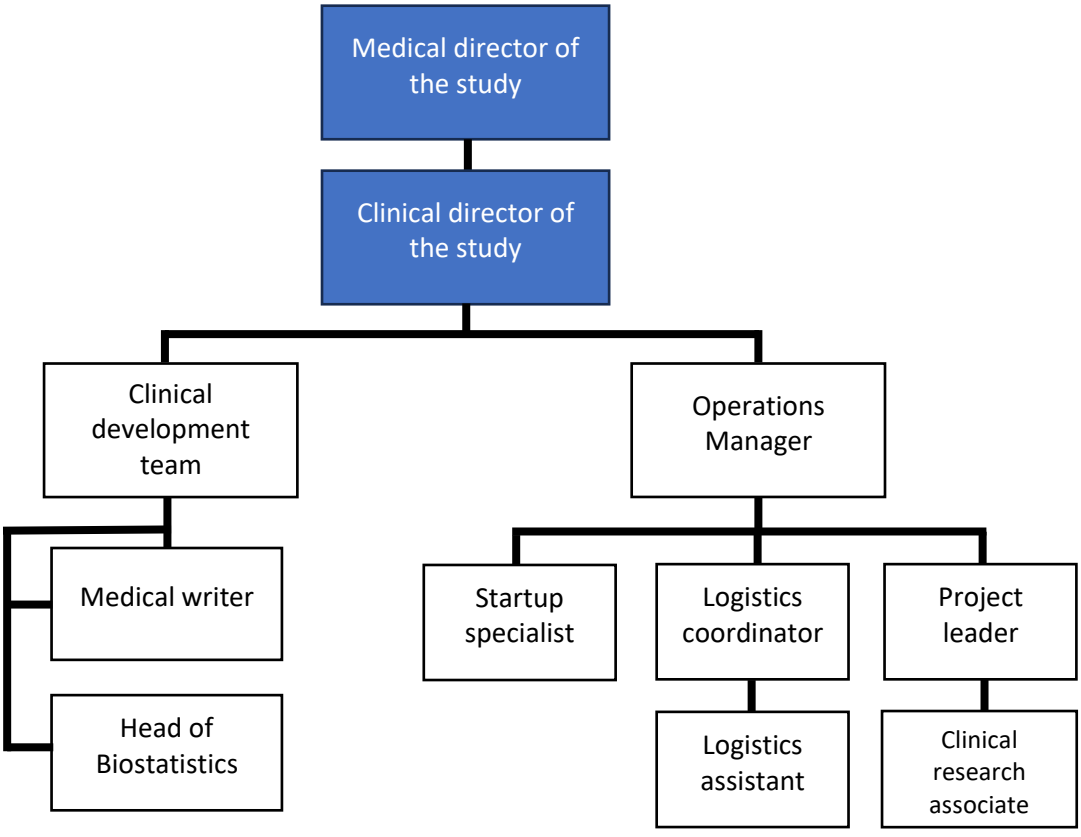


Figure 1. Administrative structure

Signature page

From the sponsor

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

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

Name: [redacted]	[redacted] **Signature**
Qualification: Operations Manager	**Date**

Name: [redacted]	[redacted] **Signature**
Qualification: Author of the Protocol	**Date**

Researcher Agreement

I agree to conduct this clinical study according to the design and guidelines of this protocol, adhering to its provisions. I declare that I will conduct the study in accordance with the standards of Good Clinical Practice and will report all information and data as indicated in the protocol, particularly any adverse events. I will also manage clinical supplies provided by the sponsor strictly in accordance with this protocol. I understand that the information that identifies me may be used by the sponsor. Because the information contained in this protocol and the Investigator's Manual is confidential, I understand that sharing it with any third party not involved in the approval, supervision, or conduct of the study is prohibited. I will ensure that necessary precautions are taken to protect the information from loss, inadvertent disclosure, or access by unauthorized third parties.

Name: *[Write the full name of the researcher]* **Qualification:** Principal Investigator **Name of the center:** *[Write name of study center]* **Geographic location (city/state/country)** *[Write the geographic data of the center]*	**Signature** **Date**

List of abbreviations

VA	Visual Acuity
BCVA	Best Corrected Visual Acuity
CBC	Complete blood count
AC	Anterior chamber
CCC	Continuous circular capsulorhexis
CEC	Corneal endothelial cells
COFEPRIS	Federal Commission for the Protection against Sanitary Risks (COFEPRIS due to its abbreviation in Spanish, Comisión Federal para la Protección contra Riesgos Sanitarios).
OVD	Ophthalmic viscosurgical device
OVDs	Ophthalmic viscosurgical devices
AE	Adverse event
AEs	Adverse events
eCRF	electronic Case Report Form
ECG	Electrocardiogram
ICF	Informed consent form
HPMC	Hydroxypropyl methylcellulose
SH	Sodium hyaluronate
I/A	Irrigation/aspiration
INR	International Normalized Ratio
PI	Principal Investigator
IWRS	Integrated web response system
IOL	Intraocular lens
IP	Investigational product
IOP	Intraocular pressure
UAP	Unanticipated problems
BC	Blood chemistry
RNEC	National Registry of Clinical Trials (RNEC due to its abbreviation in Spanish, Registro Nacional de Estudios Clínicos).
CS	Chondroitin sulfate
BSS	Balanced salt solution
PT/PTT	Prothrombin time/partial thromboplastin time
KS	Kolmogorov-Smirnov
SW	Shapiro-Wilk

1. Summary of protocol SOPH149-0220/I

1.1 Synopsis

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

Clinical study to evaluate the safety of the viscoelastic solution PRO-149 when used as an ophthalmic viscosurgical device during phacoemulsification surgery and intraocular lens placement in subjects diagnosed with senile cataracts, compared to Healon® EndoCoat</td></tr>
<tr><td>Protocol code:

SOPH149-0220/I</td><td>Creation date:

February 25, 2020</td></tr>
<tr><td>Protocol version:
2.0</td><td>Version date:
October 2, 2020</td></tr>
<tr><td>Therapeutic indication:

Ophthalmic viscosurgical device (OVD) indicated in the ophthalmic surgery of the anterior segment.</td><td>Use:

Intraocular surgery of the anterior segment, including:
• Cataract surgery with intraocular lens implantation.
• Cataract surgery without intraocular lens implantation.
• Secondary intraocular lens implantation.</td></tr>
<tr><td>Estimated duration of the study (from the first visit of the first patient to the preparation of the final report):

7 months</td><td>Development phase:

Pilot</td></tr>
<tr><td colspan="2">Aim:

To evaluate the safety of PRO-149, manufactured by Laboratorios Sophia, S.A. de C.V., when used as an OVD during phacoemulsification surgery and intraocular lens (IOL) placement in patients diagnosed with senile cataracts, compared to Healon® EndoCoat.</td></tr>
<tr><td colspan="2">Hypothesis:

H_1: PRO-149 viscoelastic solution is equivalent in safety to Healon® EndoCoat for use as an OVD in phacoemulsification surgery and IOL placement in patients with senile cataracts.

H_0: PRO-149 viscoelastic solution is not equivalent in safety to Healon® EndoCoat for use as an OVD in phacoemulsification surgery and IOL placement in patients with senile cataract.</td></tr>
<tr><td colspan="2">Study design:

Pilot, controlled, parallel-group, open-label, randomized clinical trial.</td></tr>
<tr><td>Number of subjects:

n = 36 evaluable subjects.</td><td>Main inclusion criteria:

Senile cataract.</td></tr>
</table>

18 evaluable subjects per group (one eye per subject) (2 groups).	

Selection criteria:

Inclusion criteria:

- Age equal to or greater than 49 years.
- Diagnosis of age-related cataract (senile cataract) requiring cataract phacoemulsification surgery and placement of a monofocal intraocular lens.
  Grade I to IV cataracts based on nuclear opacity (opalescence and/or color) of the lens opacity classification system (LOCS III).
- Ability to voluntarily grant informed consent.
- Be able and willing to comply with scheduled visits, treatment plan, and other study procedures.
- Desire and willingness to undergo phacoemulsification surgery and placement of a monofocal IOL.
- Have an anterior chamber depth ≥ 2.8 mm as measured by IOL Master.
- Preoperative cardiology evaluation that qualifies the patient for the surgical procedure, with supporting laboratory studies: complete blood count (CBC), three-element blood chemistry (BC), coagulation times (PT/PTT, INR), and electrocardiogram (ECG). If a prior evaluation is available, it must not be performed more than 45 days prior to signing the informed consent form (ICF).

Exclusion criteria:

- History of any systemic disease or condition that makes you ineligible for the surgical procedure under sedation and topical anesthesia.
- Diabetes mellitus with A1C ≥ 6.5% (48 mmol/mol) or fasting glucose (no caloric intake for ≥ 8 hours) of ≥ 126 mg/ dL (7.0 mmol/L)
- Uncontrolled systemic hypertension. Defined as blood pressure greater than 140/90 mmHg with the use of three antihypertensives (one of which is a diuretic) at the maximum dose.
- Have a history of eye diseases that could limit the best corrected visual acuity, or be reactivated and/or exacerbated by the surgical procedure or by the use of topical steroids (e.g. retinal detachment, macular degeneration, pathological myopia, proliferative diabetic retinopathy, diabetic macular edema, optic neuritis, uveitis or other types of ocular inflammation, glaucoma, ocular hypertension, corneal dystrophy or ectatic disorder, history of an ocular infection by herpes or varicella zoster).
- Active eye infection.
- Pseudo exfoliation syndrome in the eye to be operated on or other type of zonular involvement.
- Pharmacological mydriasis less than 6 mm.
- Any congenital ocular anomaly in the eye to be operated on.
- Any ocular abnormality that prevents obtaining a reliable Goldmann tonometry in the eye to be operated on.
- An intraocular pressure (IOP) >21 mmHg in the eye to be operated on, or a history of intraocular pressure >21 mmHg with the use of topical steroids.
- A corneal endothelial cell (CEC) density < 1500 cells/mm ^{2} in the eye to be operated on.
- History of previous corneal or intraocular surgery.

- Having multiple procedures planned during cataract surgery (i.e., trabeculectomy, relaxing keratotomies, etc.).
- History of ocular trauma in the eye to be operated on (includes surgical procedures).
- Having a one single evaluable eye.
- Having participated in another clinical research study ≤ 30 days prior to signing the ICF.
- Having previously participated in this study.
- A history of drug addiction or drug dependence, currently or within the last two years prior to signing the ICF.
- A history of ocular surgical procedures within the last 3 months prior to signing the ICF.
- Any type of surgical intervention scheduled during the study period.
- Be or have an immediate family member (e.g., spouse, parent/legal guardian, sibling, or child) who is a member of the research site or sponsor staff.

Investigational products:

Investigational product, dosage and route of administration:

- PRO-149. Sodium hyaluronate 3%. Viscoelastic solution in a pre-filled syringe. Laboratorios Sophia, S.A. de C.V.
- Posology: Enough to create the desired intraocular space and perform the required intraocular maneuvers.
- Route of administration: Intraocular, in the anterior chamber.

Comparator product, dose and route of administration:

- Healon® EndoCoat. Sodium hyaluronate 3%. Viscoelastic solution in a pre-filled syringe. Johnson & Johnson Vision Surgical.
- Posology: Enough to create the desired intraocular space and perform the required intraocular maneuvers.
- Route of administration: Intraocular, in the anterior chamber.

Duration of treatment:	**Approximate duration of the subject in the study:**
Transurgical.	45 days.

Evaluation criteria:

Primary outcome variables:

- Changes in CEC density.
- IOP.

Secondary outcome variables:

- Incidence of adverse events (AEs).
- Changes in corneal thickness.
- Cellularity in AC.
- Flare in AC.
- Best corrected visual acuity (BCVA).

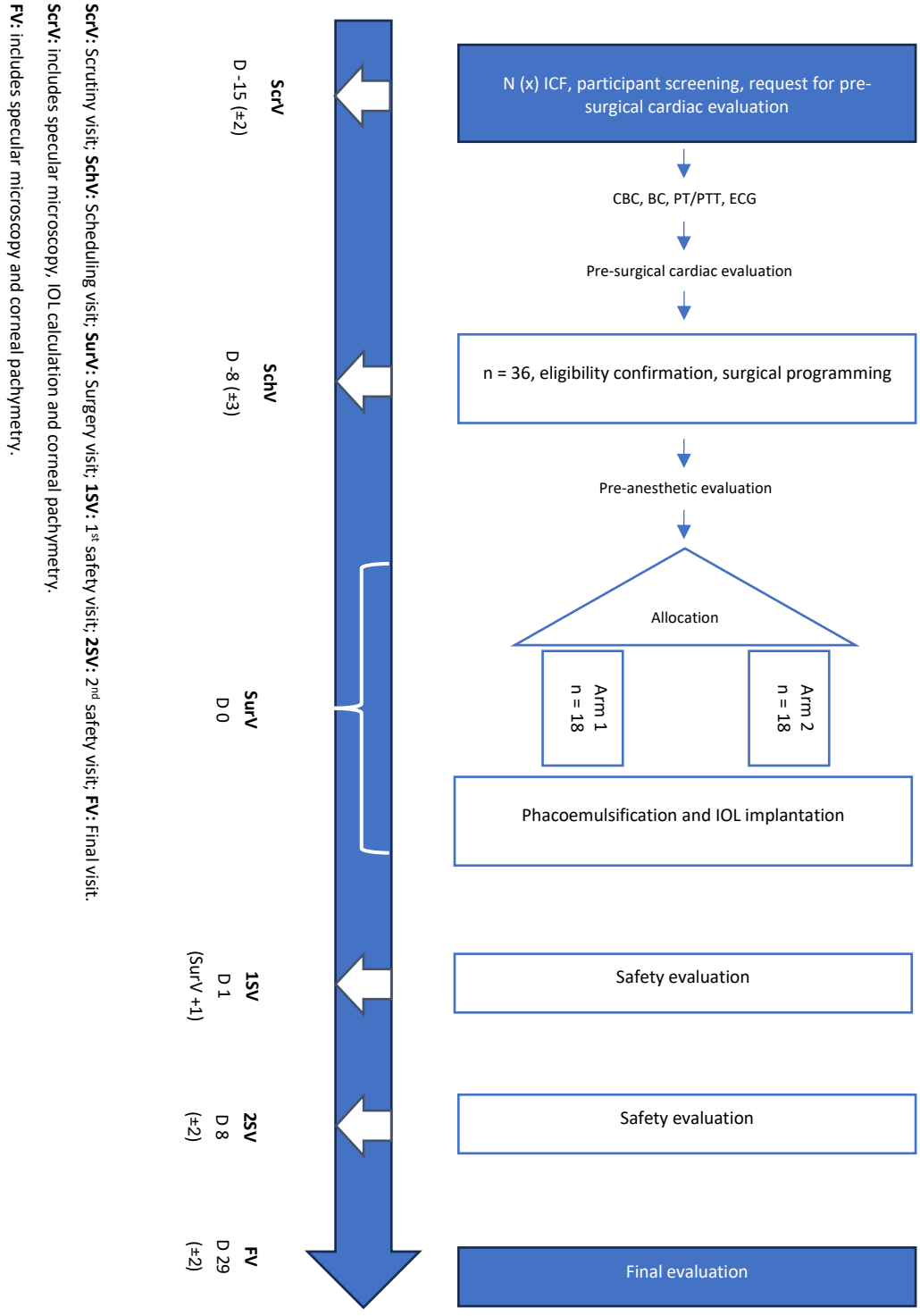
Exploratory outcome variables:

- Investigator's report of the transurgical evaluation.

Statistical methodology:

Data will be expressed with measures of central tendency: mean and standard deviation for quantitative variables, while qualitative variables will be presented as frequencies and percentages. The Kolmogorov-Smirnov (KS) and Shapiro-Wilk (SW) tests will be performed to determine whether the distribution is normal for the results obtained in each study group ($p > 0.05$). If normality is observed in the data, the Student's t-test for independent groups will be used to evaluate differences between groups on quantitative variables, while intragroup differences will be analyzed using the Student's t-test for repeated measures. If $p < 0.05$ for both KS and SW, the statistical analysis will be performed using the Mann-Whitney U test for differences between groups on quantitative variables, while intragroup differences will be analyzed using the Wilcoxon rank test. Differences between qualitative variables will be analyzed using the X^2 (chi-square) test or Fisher's exact test. An $\alpha \leq 0.05$ will be considered significant.

1.2 Study diagram



ScrV: Scrutiny visit; **SchV:** Scheduling visit; **SurV:** Surgery visit; **1SV:** 1st safety visit; **2SV:** 2nd safety visit; **FV:** Final visit.

ScrV: includes specular microscopy, IOL calculation and corneal pachymetry.

FV: includes specular microscopy and corneal pachymetry.

1.3 Study schedule

PROCEDURES	Scrutiny Visit D -15±2	Scheduling Visit D -8±3	Surgery Visit D 0	1st Safety Visit D 1	2nd Safety Visit D 8±2	Final Visit D 29 ±2
ICF Signature	X					
Medical record	X					
Somatometry	X					
Vital signs	X	X	X	X	X	X
Evaluation of Concomitant Medications	X	X	X	X	X	X
BCVA	X			X	X	X
Comprehensive ophthalmologic evaluation (cellularity, flare, posterior segment)	X			X	X	X
Ocular tonometry	X			X	X	X
Gonioscopy	X					
Assessment of pharmacological mydriasis	X					
Specular microscopy	X					X
Corneal pachymetry	X					X
Eligibility criteria	X	X				
IOL Calculation	X					
Review of anterior chamber depth by IOL Master	X					
Request for pre-surgical cardiology assessment	X					
AE Assessment	X	X	X	X	X	X
Pre-surgical cardiology assessment review		X				
Surgical scheduling		X				
Delivery of subject material		X				
Investigational product (IP) Assignment			X			
Phacoemulsification surgery and IOL placement			X			
Transurgical evaluation			X			
Continuity assessment		X	X	X	X	
Suture removal (if applicable)					X	
Return of concomitant treatment						X

SchV: Scheduling visit**; SurV:** surgery visit**; 1SV:** 1st safety visit**; 2SV:** 2nd safety visit**; FV:** final visit**.**

2. Introduction and Background

2.1 Theoretical framework

2.1.1 Ophthalmic viscosurgical devices

Ophthalmic viscosurgical devices (OVDs), also known simply as viscoelastics, have been present in ophthalmic surgery since the early 1960s, although they were initially attempted as vitreous substitutes. [1] However, it was not until the late 1970s that Balazs, Miller and Stegmann reported the successful use of OVDs in cataract surgery and intraocular lens (IOL) implantation, even introducing the term viscosurgery. [2]

Since their introduction in cataract surgery, OVDs have had a tremendous influence on the evolution of extracapsular cataract extraction techniques to phacoemulsification. [3] This is because the protection of the corneal endothelium, as well as the creation and maintenance of space, were recognized as the main advantages of viscosurgery. When an OVD is used in phacoemulsification surgery, corneal endothelial cell (CEC) loss is reduced by up to 70%, compared to when no OVD is used. [1]

Currently commercially available OVDs contain one or more of the following polymers in different concentrations: sodium hyaluronate (SH), chondroitin sulfate (CS), or hydroxypropyl methylcellulose (HPMC). These products, composed mainly of water, have practically the same density (1.0 kg/m^3). The protective, retaining, cohesive, and lubricating properties of OVDs reside in their polymeric structure, molecular weight, electrical charge, purity, and interchain molecular interactions. [4]

The physical properties commonly recognized as differentiating between OVDs are viscosity, elasticity, stiffness, pseudoplasticity, and cohesion; these properties clinically translate into tissue protection, space maintenance, and ease of injection and removal.
[1]

2.1.1.1 Rheological properties of OVDs

Viscosity (dynamic)

Viscosity is a parameter of fluids. The viscosity of pure substances varies significantly with temperature and, to a lesser extent, with pressure. The ease with which a liquid flows is a guideline for its viscosity. [5]

Viscosity is defined as the property of fluids that resists the relative motion of their molecules. For certain fluids, viscosity is constant and depends only on temperature and pressure. This group is called Newtonian fluids. Fluids that do not follow this proportional relationship are called non-Newtonian fluids; see **Figure 2.**

Dynamic viscosity is the property of fluids characterized by their resistance to flow due to the friction between their molecules. In the International System of Fluids, it is measured in Pascals per second; previously, the most commonly used unit was the centipoise (cps), equivalent to 1 mPas.

Plasticity

Plasticity refers to the property of a material that allows it to continuously deform, without breaking, when sufficient force is applied, maintaining this new shape after the force has been removed. The greater the plasticity of a material, the more the force required to deform decreases as the strain rate increases.

Pseudoplasticity

The property of becoming less viscous with increasing shear rate, when the viscosity is limited to zero shear, is called pseudoplasticity. In this sense, an OVD with a high viscosity at zero shear would be ideal for maintaining formed spaces; however, pseudoplasticity would allow its viscosity to decrease when injected through a cannula (at high shear rates), making its application easier.

Elasticity

Elasticity is defined as the tendency of a substance to return to its original shape after being deformed. By definition, viscoelastics possess this characteristic, but to varying degrees. It is desirable for OVDs to be elastic to absorb shocks caused by manipulation; however, they should not exceed their viscosity, as this would hamper fine surgical procedures.

Stiffness

Stiffness is also known as complex viscosity and refers to the perceived resistance to moving an object through a viscoelastic substance. Mathematically, stiffness is equal to the square root of the sum of the squares of the dynamic viscosity and the elasticity.

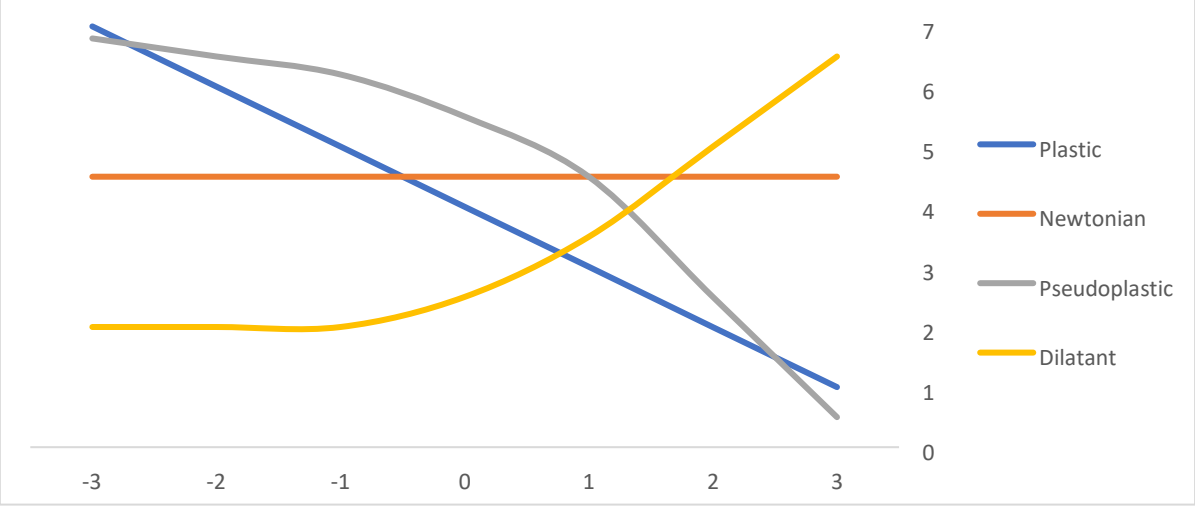
The stiffness of an OVD depends on the shear rate and vibration frequency and will be close to the viscosity or elasticity value, whichever is greater under the operating conditions of measurement. Therefore, both viscosity and elasticity will appear to predominate as the tactile quality "response" when the surgeon manipulates the OVD at a given shear rate; this translates to the surgeon's tactile perception of the OVD's behavior as viscous or elastic in a given situation.

Cohesion and dispersion

OVDs are generally divided into cohesive or dispersive behavior. In reality, this behavior is a continuum, but for study purposes, it is easier to separate them into these categories. Cohesion is the tendency of the molecules that make up a material to adhere to one another rather than disperse. A low concentration of high-molecular-mass polymers entangled in a network in solution will exhibit cohesive behavior, while a high concentration of low-molecular-mass polymers will exhibit dispersive behavior.

2.1.1.2 Rheological properties of OVDs of importance in phacoemulsification.

As surgical techniques evolve in complexity and meticulousness, the demands on OVD performance increase. Newer techniques require greater delicacy and precise manipulation to be successful. However, each step of phacoemulsification has different requirements; see **Table 2.**



X-axis = Log Cut-off Rate (sec^{-1})

Y-axis = Log Viscosity (mPas)

Figure 2. Types of fluid behavior

STEP	CUT RATE	IMPORTANT PROPERTIES
AC formation	1000	High pseudoplasticity
Capsulorhexis	0	High viscosity, elasticity
Core emulsification	Varies with the position of the AC	High retention
Cortical I/A	Varies with the position of the AC	High retention
Formation of capsular bag	1000	High pseudoplasticity
Keep bag open	0	High viscosity, elasticity
IOL insertion	2-5	High pseudoplasticity
Removal	Varies with the position of the AC	High cohesion, displacement

Table 2. Desirable properties of OVDs during phacoemulsification [1]

2.1.2 Cataracts

A cataract is an opacity of the lens; it affects visual function in different ways depending on its characteristics. Cataracts are multifactorial in origin; according to their pathophysiology, they can be classified as senile, congenital, drug-induced, traumatic, metabolic, and uveitis-associated cataracts. [6] However, most are age-related, so they are more common in the elderly. [7] Cataracts are the leading cause of blindness worldwide, responsible for 51% of global blindness, which in 2010 represented about 20 million people. As life expectancy increases, the number of people with cataracts is expected to increase in direct proportion. Cataracts are also an important cause of decreased visual acuity (VA) and low vision in both developed and developing countries. [8] 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. [9, 10, 11]

Cataract classification based on the degree of opacity or progression has not been sufficient for epidemiological or therapeutic studies of cataracts. The Lens Opacities Classification System III (LOCS *III) Classification System III*) is a standardized system used to stage and compare the type and severity of cataracts. [12] It was derived from LOCS II [13], and consists of three sets of standardized photographs (See **Figure 3**). The classification evaluates four features, nuclear opalescence (NO), nuclear color (NC), cortical opacity (C), and posterior subcapsular opacity (P). The use of this classification has allowed better recording of cataract progression, decreased interobserver subjective influence, and allowed the creation of perisurgical plans according to the needs of each patient. [14]

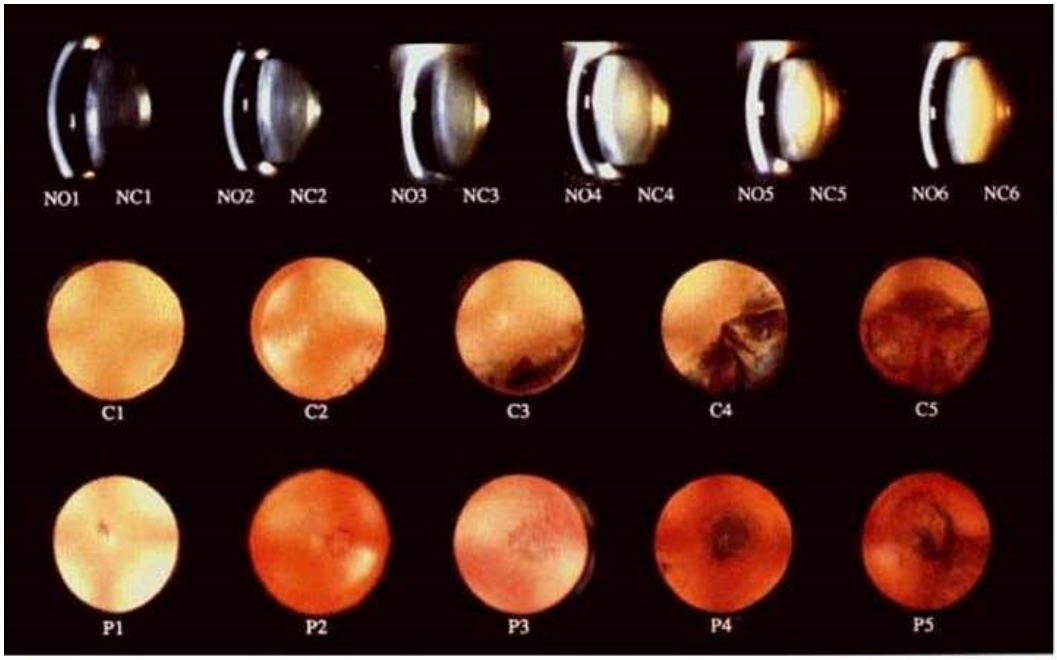


Figure 3. Lens Opacity Classification System III (LOCS III)

There is no universally defined and accepted minimum visual acuity (VA) or minimum cataract grade classification for cataract surgery; however, with the advent of new surgical techniques, more advanced phacoemulsification machines, the introduction of femtosecond laser-assisted cataract surgery (FLACS), and the evolution of intraocular lenses (IOLs), cataract surgery has become consistently safer and more predictable in terms of good visual rehabilitation, often not requiring corrective lenses. This has led to VA levels of 20/30 or better being considered for cataract surgery in industrialized countries. [15] [16]VI

In 2014, an estimated 2 million cataract surgeries were performed in the United States of America (USA). [17] By 2015, an estimated 3.6 million surgeries were performed in the USA and more than 20 million worldwide. [18] In Mexico, the cataract surgery rate is estimated to be 1,530 surgeries per million inhabitants. [19]

As previously mentioned, OVDs are currently an essential part of cataract surgery, both for space formation and for protecting structures, primarily the ECCs.

2.2 Background information on the investigational product

SH is a glycosaminoglycan with viscoelastic rheology. It is composed of repeating units of N-acetyl-D-glucosamine and sodium-D-glucuronate. [20] It has a high molecular weight (2.5–4 million daltons) and low protein content. Its half-life is 1 day in aqueous humor and 3 days in vitreous humor. [3] SH is naturally found in various tissues of the body, mainly found in high concentrations in vitreous humor, synovial fluid, and umbilical cord.

SH is used in various concentrations in many of the currently available OVDs and can be extracted and purified from different sources, such as rooster combs or by bacterial cell-assisted fermentation. Depending on the extraction source, the molecular weight may vary, but the structure remains the same. The SH used in PRO-149, like that in Healon® EndoCoat, is a highly purified extract obtained by bacterial fermentation, well tolerated by the eye, non-antigenic, and non-pyrogenic.

2.2.1 Efficacy of the investigational product

The efficacy of various SH-containing OVDs has been established in several clinical studies. A multicenter, double-blind, randomized clinical study was conducted with the Healon® EndoCoat OVD, which contains the same concentration of SH as PRO-149, in 400 patients undergoing phacoemulsification and IOL implantation.

Two hundred patients were assigned to the Healon® EndoCoat group and 200 to the control group, corresponding to Viscoat®. Efficacy was measured by CEC protection. Healon® EndoCoat demonstrated non-inferiority when compared to Viscoat® in the CEC count from pre-surgery to 3 months post-surgery ($p < 0.0001$, 1-tailed t-test, $\delta = 5\%$). The mean percentage changes observed were -4.7% for Healon® EndoCoat and -7.0% for Viscoat® with a percentage point difference of 2.3 (90% confidence interval: [0.23, 4.33]). [21]

2.2.2 Safety of the investigational product

In the same clinical study described above, safety was evaluated by the cumulative rate of intraocular pressure (IOP) peaks ≥30 mmHg and the presence of adverse events (AEs).

The results demonstrated that the percentage of subjects with IOP spikes in the Healon® EndoCoat group was not higher than that in the Viscoat® group (cumulative percentage of subjects with IOP ≥ 30mmHg during the study ($p = 0.0003$, $\delta = 0.13$, 90% confidence interval [-1.74, 7.72]).

Surgical complications reported were 3% (6/200) in the Healon® EndoCoat group and 8% (16/200) in the Viscoat® group.

Regarding AEs, 39 subjects reported an AE during the study. None of these were considered unexpected. Ninety-two percent of the AEs were IOP ≥30 mmHg; the incidence of this AE was 10.5% in the Healon® EndoCoat group and 7.5% in the Viscoat® group. The three AEs that did not correspond to an increase in IOP included: one subject in the Healon® EndoCoat group who developed cystoid macular edema (requiring treatment) and two subjects in the Viscoat® group : one subject who required IOL exchange for haptic damage and one who underwent removal of an ocular surface foreign body. None of the above AEs were considered related to OVD use. [21]

List of incidents or adverse reactions reported with a 3% sodium hyaluronate viscoelastic or with the use of intraocular sodium hyaluronate: [21] [22]

- Eye inflammation (iritis, hypopyon, endophthalmitis)
- Increased intraocular pressure
- Corneal edema
- Secondary glaucoma
- Corneal decompensation

All of the described incidents or adverse reactions may potentially occur with the use of PRO-149 or Healon® EndoCoat. [21] [22]

2.2.3 Summary of the pharmaceutical development of the investigational product

The development of PRO-149 included physicochemical and rheological characterization tests, as well as stability tests. In addition, preclinical studies were conducted in New Zealand albino rabbits using two models: an aqueous exchange model and an aqueous humor replacement model with subsequent AC washout. [23]

Twenty eyes of 20 research subjects (rabbits) were studied and divided into two groups of 10, group 1 underwent aqueous humor exchange (anterior chamber exchange, via paracentesis, 0.05 mL of aqueous humor for 0.05 mL of OVD) and group 2 underwent AC lavage (exchange of the total volume of aqueous humor in AC for the OVD, which was lavaged and replaced with balanced saline solution by manual I/A). In turn, both groups were subdivided into A and B, with 5 subjects per group, for the PRO-149 and Healon® EndoCoat groups.

The primary safety variables were IOP, corneal opacity, AC cellularity and flare, presence of fibrin, iris congestion, conjunctival hyperemia, discharge, conjunctival edema, and incidence of AEs. Toxicity variables included abnormalities in histopathological examinations of the tissues studied.

In both models, no statistically significant differences were observed in the safety variables between both DVOs. [23]

2.3 Background on the research

2.3.1 From the research question

There is no prior data on PRO-149 in clinical trials. However, the efficacy and tolerability of SH-containing OVDs have been previously tested.

2.4 Risk benefit assessment

2.4.1 Known potential risks

OVDs are safe formulations whose use during phacoemulsification surgery and IOL placement has been recognized as beneficial in increasing the safety of the procedure. Since SH is a polysaccharide naturally present in many body tissues, it is very well tolerated by the human eye. However, transient postoperative inflammation and increased IOP have been reported in clinical studies with these OVDs.

Cataract surgery, currently performed by phacoemulsification, is the most frequently performed surgery worldwide by ophthalmic surgeons [18]. Like any medical procedure, it is not exempt from complications; however, the risk-benefit balance is favorable to the procedure.

2.4.2 Known potential benefits

The benefits are described in three orders. First, for the study subjects, it restores vision lost directly due to lens opacity. Second, for phacoemulsification surgery, the use of an OVD protects structures such as the CECs and facilitates surgical maneuvers. Third, for the investigational product, it documents the safety profile of PRO-149.

2.5 Problem statement

A few decades ago, cataract surgery was performed with the aid of an air bubble to maintain the AC formation. This technique provided poor protection to the structures and was minimally effective in maintaining the AC formation. With the advent of OVDs, this changed, allowing cataract surgery to evolve toward a safer process.

However, there is no ideal OVD; each case or even each surgical step may require specific OVD characteristics. For this reason, various OVDs have been developed, ranging across the spectrum from dispersivity to cohesiveness.

PRO-149 has rheological characteristics that could make it a safe and efficient dispersive OVD.

2.6 Justification

Unlike pharmaceutical compounds, in which the active ingredient maintains its pharmacokinetic and pharmacodynamic properties between formulations, provided the concentrations and compatibility with excipients are respected, OVDs cannot be properly designated as generics.

The chain length, pH, osmolarity, presence of other solutes, polymer conformation, and electrical charge can vary between these apparently identical formulations, which would directly affect their rheological properties and, consequently, their clinical behavior.

This study is necessary to test the safety of PRO-149 by comparing it with the safety found in a product already on the market (Healon® EndoCoat) and to understand its behavior during phacoemulsification surgery.

3. Objectives and hypotheses

3.1 Primary objectives

To evaluate the safety of PRO-149, manufactured by Laboratorios Sophia, S.A. de C.V., when used as an OVD during phacoemulsification surgery and intraocular lens (IOL) placement in patients diagnosed with senile cataracts, compared to Healon® EndoCoat.

3.2 Specific objectives

- To compare the safety of OVD PRO-149 versus Healon® EndoCoat in cataract phacoemulsification surgery and intraocular lens implantation, through changes in pre and postoperative CEC density.
- To compare the safety of OVD PRO-149 versus Healon® EndoCoat in cataract phacoemulsification surgery and intraocular lens implantation, through changes in IOP.

3.3 Secondary objectives

- To compare the safety of OVD PRO-149 versus Healon® EndoCoat in cataract phacoemulsification surgery and intraocular lens implantation, with the incidence of AEs.
- To compare the safety of OVD PRO-149 versus Healon® EndoCoat in cataract phacoemulsification surgery and intraocular lens implantation, through changes in central corneal thickness.
- To compare the safety of OVD PRO-149 versus Healon® EndoCoat in cataract phacoemulsification surgery and intraocular lens implantation, with the presence of cellularity in postoperative AC.
- To compare the safety of OVD PRO-149 versus Healon® EndoCoat in cataract phacoemulsification surgery and intraocular lens implantation, with the presence of postoperative AC flare.
- To compare the best-corrected visual acuity obtained after cataract phacoemulsification surgery and intraocular lens implantation between PRO-149 and Healon® EndoCoat.

3.4 Exploratory objectives

- To compare the intraoperative performance of PRO-149 versus Healon® EndoCoat in cataract phacoemulsification surgery and intraocular lens implantation, as assessed by the surgeon.

3.5 Hypothesis

H_1: PRO-149 viscoelastic solution is equivalent in safety to Healon® EndoCoat for use as an OVD in phacoemulsification surgery and IOL placement in patients with senile cataracts.

H_0: PRO-149 viscoelastic solution is not equivalent in safety to Healon® EndoCoat for use as an OVD in phacoemulsification surgery and IOL placement in patients with senile cataract.

4. Study design

4.1 Design Overview

Pilot, controlled, parallel-group, open-label, randomized clinical trial.

4.2 Justification of the study design

The study design (clinical trial) is considered the highest standard of data quality when exploring the effect of an intervention. The development, or pilot, phase for a device corresponds to the study objective, which is to evaluate safety, so the intervention time is short and the required sample size is smaller than that of a pivotal clinical trial. The presence of parallel groups allows for comparisons between the intervention groups on outcome variables. Primary blinding was not considered for this study due to the characteristics of both investigational products; however, the statistical analysis will be blinded.

4.3 Expected duration

The total duration of the study, from the first patient's first visit to the preparation of the final report, is estimated to be 7 months.

The planned recruitment period is 4 months. Considering the proposed sample size of 36 subjects, the average total recruitment rate during the study should be no less than 1 subject enrolled every 4 days.

The approximate duration of each subject in the study is 45 days.

5. Study population

5.1 Eligibility criteria

5.1.1 Inclusion criteria

- Age equal to or greater than 49 years.
- Diagnosis of age-related cataract (senile cataract) requiring cataract phacoemulsification surgery and placement of a monofocal intraocular lens.
  Grade I to IV cataracts based on nuclear opacity (opalescence and/or color) of the lens opacity classification system (LOCS III).
- Ability to voluntarily grant informed consent.
- Be able and willing to comply with scheduled visits, treatment plan, and other study procedures.
- Desire and willingness to undergo phacoemulsification surgery and placement of a monofocal IOL.
- Have an anterior chamber depth ≥ 2.8 mm as measured by IOL Master.
- Preoperative cardiology evaluation that qualifies the patient for the surgical procedure, with supporting laboratory studies: complete blood count (CBC), three-element blood chemistry (BC), coagulation times (PT/PTT, INR), and electrocardiogram (ECG). If a prior evaluation is available, it must not be performed more than 45 days prior to signing the informed consent form (ICF).

5.1.2 Exclusion criteria

- History of any systemic disease or condition that makes you ineligible for the surgical procedure under sedation and topical anesthesia.
- Diabetes mellitus with A1C ≥ 6.5% (48 mmol/mol) or fasting glucose (no caloric intake for ≥ 8 hours) of ≥ 126 mg/ dL (7.0 mmol/L)
- Uncontrolled systemic hypertension. Defined as blood pressure greater than 140/90 mmHg with the use of three antihypertensives (one of which is a diuretic) at the maximum dose.
- Have a history of eye diseases that could limit the best corrected visual acuity, or be reactivated and/or exacerbated by the surgical procedure or by the use of topical steroids (e.g. retinal detachment, macular degeneration, pathological myopia, proliferative diabetic retinopathy, diabetic macular edema, optic neuritis, uveitis or other types of ocular inflammation, glaucoma, ocular hypertension, corneal dystrophy or ectatic disorder, history of an ocular infection by herpes or varicella zoster).
- Active eye infection.
- Pseudo exfoliation syndrome in the eye to be operated on or other type of zonular involvement.
- Pharmacological mydriasis less than 6 mm.
- Any congenital ocular anomaly in the eye to be operated on.
- Any ocular abnormality that prevents obtaining a reliable Goldmann tonometry in the eye to be operated on.
- An intraocular pressure (IOP) >21 mmHg in the eye to be operated on, or a history of intraocular pressure >21 mmHg with the use of topical steroids.
- A corneal endothelial cell (CEC) density < 1500 cells/mm ^{2} in the eye to be operated on.
- History of previous corneal or intraocular surgery.
- Having multiple procedures planned during cataract surgery (i.e., trabeculectomy, relaxing keratotomies, etc.).
- History of ocular trauma in the eye to be operated on (includes surgical procedures).
- Having a one single evaluable eye.
- Having participated in another clinical research study ≤ 30 days prior to signing the ICF.
- Having previously participated in this study.

- A history of drug addiction or drug dependence, currently or within the last two years prior to signing the ICF.
- A history of ocular surgical procedures within the last 3 months prior to signing the ICF.
- Any type of surgical intervention scheduled during the study period.
- Be or have an immediate family member (e.g., spouse, parent/legal guardian, sibling, or child) who is a member of the research site or sponsor staff.5.2 Criteria for elimination and/or substitution of subjects

5.2.1 Elimination criteria

- Withdrawal of informed consent.
- Major deviation from the protocol that could impact the integrity of the results.
- Presentation of an adverse event, whether or not related to the investigational product, which, in the opinion of the PI and/or the sponsor, could affect the subject's ability to safely continue the study procedures.
- Non-tolerability or hypersensitivity to any of the compounds used during the tests (fluorescein, lissamine green, tetracaine).
- Non-tolerability or hypersensitivity to any of the investigational drugs.

5.2.2 Subject substitution

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

5.3 Scrutiny failures

A screening failure is defined as a participant who agrees to participate in the study, giving their consent, but who is not assigned to a treatment group; that is, they do not enter the study. The following information regarding screening failures must be reported, at a minimum:

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

The above is necessary to comply with the CONSORT guidelines (*Consolidated Standards of Reporting Trials)* for the publication of results or to respond to potential questions from regulatory authorities.

Subjects who do not meet the eligibility criteria for participation in the study due to a specific modifiable factor may be re-screened. Subjects in this situation must use the same initial screening number.

5.4 Recruitment and retention strategies

This is a pilot study and the minimum expected recruitment rate is 1 subject every 4 days.

The duration of the subject's participation in the study is approximately 45 days, during which they will be required to attend six visits in total, which correspond to standard screening and surgery scheduling visits, as well as cataract surgery follow-up visits. Strategies to improve subject retention include, but are not limited to:

- Clearly communicate the importance of the study and the benefits the population will gain from its results.
- Make calls or send text messages to remind yourself of appointments or activities to do.

- Provide a printed calendar and ID card to remind you of upcoming appointments and activities, as well as their estimated duration.
- Offer flexible business hours.
- Systematic organization of the study procedures, so that the subject does not stay longer than necessary during his visit.
- Minimize subject wait times.

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

5.5 Procedure in case of early discontinuation

For this protocol, early discontinuation is defined as those subjects who were randomized, and who at some point were active subjects in the study, but their final evaluation could not be completed.

If the subject does not complete their participation due to withdrawal of consent or a major deviation, the last visit at which their withdrawal was determined will be considered their final visit. Subjects withdrawn due to the presence of AEs will continue the follow-up as determined until their AE is resolved.

In cases where the participating subject does not attend their appointment, the research site will call to determine the reason and will attempt to schedule a new appointment within the established window or an unscheduled appointment. If an appointment cannot be scheduled, the subject will be considered lost to follow-up, and the presence of adverse events and the reason for discontinuing the study will be asked as minimum data.

5.6 Subject identification

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

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

Example:

Name: Ariel Daniel Mercado Carrizalez. **Initials:** AMC.

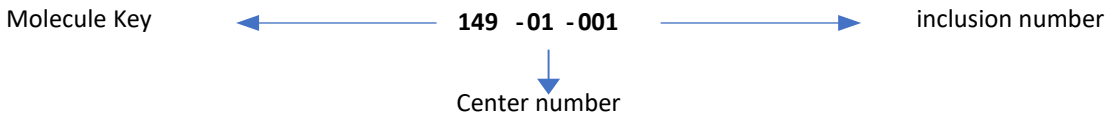
Name: Juan De la Torre Orozco. **Initials:** JDO.

During the counting stage, you will be assigned a participant number consecutively, using 3 consecutive digits.

Once the subject has been selected, they will be assigned a randomization number, which will be used to identify them throughout the study. This code will consist of eight numbers in the following order from left to right:

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

Example of randomization number:


Molecule Key
149 -01 -001
inclusion number
Center number

6. Investigational product

6.1 Managed Products

6.1.1 Investigational product

- Generic name: Sodium Hyaluronate.
- Distinctive name: PRO-149.
- Active ingredients: Sodium Hyaluronate 3%.
- [redacted]
- Pharmaceutical form: Viscoelastic solution.
- Presentation: prefilled syringe, 1 cc.
- Prepared by: Laboratorios Sophia, S.A. de C.V.
- Solution description: Clear solution, free of visible particles.

6.1.2 Reference product

- Generic name: Sodium Hyaluronate.
- Distinctive name: Healon® EndoCoat.
- Active ingredients: Sodium Hyaluronate 3%.
- Excipients: sodium chloride, potassium chloride, calcium chloride, magnesium chloride, sodium acetate, sodium citrate, dibasic sodium phosphate, monobasic sodium phosphate, water for the manufacture of injectables.
- Pharmaceutical form: Viscoelastic solution.
- Presentation: 0.85 cc prefilled syringe.
- Prepared by: Johnson & Johnson Vision Surgical, Santa Ana, CA, USA.
- Solution description: Clear solution, free of visible particles.

6.1.2.1 Justification of the reference product

Healon® EndoCoat is a commercially available OVD with a previously described safety and efficacy profile.

6.1.3 Dosage of investigational products

As much as is necessary for the formation of spaces and the performance of surgical maneuvers.

6.1.3.1 Justification of the dose

There is no standardized dose for OVDs; each case is customized according to the anatomical characteristics and surgical needs.

6.1.4 Concomitant treatment

Both groups will be treated with:

- Generic name: Ciprofloxacin 0.3%/Dexamethasone 0.1%
- Distinctive name: Sophixin DX
- Active ingredients: Ciprofloxacin 0.3%, Dexamethasone 0.1%.
- Pharmaceutical form: Ophthalmic solution.
- Presentation: 5 mL dropper bottle.
- Prepared by: Laboratorios Sophia, S.A. de C.V.
- Solution description: Clear solution, free of visible particles.

- Dosage: 1 drop every 4 hours for 10 days in the operated eye.

6.2 Storage and handling of investigational products at the study center

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

Reception will be carried out by the assigned research team staff. They must verify the condition of the primary packaging (box). If it shows alterations or defects in its integrity that, in their judgment, could have damaged the contents, they must report this to the sponsor. If the package shows no significant defects, they will proceed to open it.

Inside the shipment, you must locate the receipt and temperature *data logger.* You must verify that the recorded temperature meets the specifications for its transport and storage. You will verify the contents (PI) with what is reported on the document. If the document matches the contents, you will sign the receipt and send it to the sponsor. If not, you will notify the sponsor.

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

Storage temperature should be 2° to 30°C.

Upon receipt at the center and until the IP is out of stock, the research center is required to review the IP's storage conditions daily and manually record, in the designated format, the temperature recorded by the *data logger* (current, minimum, and maximum temperatures). *These data will be reviewed by the clinical monitor during monitoring visits according to the records stored in the data logger*'s memory.

In the event of material loss, this must be documented in the input and output log along with a clear description of the mechanism by which the loss occurred.

Upon completion of the protocol, all study materials will be retrieved by the sponsor as part of the final visit. The final return of materials will be made by the principal investigator or the person designated by the principal investigator to return materials at the end of the study.

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

6.3 Concomitant treatments and medications (permitted and prohibited)

Any medication used, in addition to appearing in the clinical note, must be recorded in the concomitant medications section of the electronic Case Report Form (eCRF).

<u>Permitted medications:</u>

- Ophthalmic:

All permitted ophthalmic medications administered during the study must be after the last application of the study or reference treatments, waiting a minimum of 10 minutes. This is to avoid treatment interactions with the tear film, based on the physiological tear flow rate and volume. [24]

  - Tetracaine 0.5%
  - Tropicamide 0.8% / Phenylephrine 5%
  - Any antibiotic
  - β -blocker*

- α -agonist*
- Any topical steroid
- Any topical nonsteroidal anti-inflammatory drug

*Topical antihypertensives are permitted after the 1st safety visit; they cannot be used prophylactically.

- Administered by a route other than ophthalmic:
  - The use of medications for the treatment of chronic diseases that do not appear as an exclusion criterion (e.g., medications for the treatment of systemic arterial hypertension) will be permitted.
  - Medications with ocular hypotensive action, such as acetazolamide or mannitol, are prohibited as prophylactic agents; their use may be permitted after 1st safety visit.
  - Any medication whose effect may be susceptible to modifying any of the efficacy, safety or tolerability parameters of this research protocol must be notified to the clinical monitor or the sponsor's clinical team to determine the appropriateness of the participant's admission, continuation or elimination as appropriate.

Prohibited medications:

- Any medication with ophthalmic application that is not on the list of permitted medications
- Systemic immunomodulators
- Anticoagulants
- Medications with non-ophthalmic applications and with hypotensive action at the ocular level

6.4 Procedure for monitoring and measuring adherence

For over four decades, numerous investigations have been conducted on the appropriate way to measure and quantify medication adherence, however, none has reached a consensus to establish itself as the gold standard, both in cross-sectional and longitudinal studies. [25, 26, 27, 28, 29, 30, 31, 32]

Due to the characteristics of the study, which evaluates the use of a device during a surgical procedure, the IP's adherence is directly dependent on the principal investigator's (PI) application during surgery. This rules out adherence errors such as applications outside the eye or forgetting to apply them (the surgical procedure cannot be performed without the use of OVDs). There is no predetermined dosage, so the quantity (volume of the syringe applied) to be used will be customized for each surgical event at the PI's discretion. Adherence will be measured by the clinical monitor during monitoring visits by counting the syringes used.

However, adherence to concomitant treatment (Ciprofloxacin 0.3%/Dexamethasone 0.1% ophthalmic solution) will be measured, as adherence is critical for managing postoperative inflammation; such inflammation could be a confounding factor in the evaluation of study variables.

There are different procedures for measuring adherence to pharmacological interventions. The most common procedure involves self-reports, which include patient interviews, questionnaires, and self-monitoring diaries. Their strengths are speed, flexibility, low cost, and ease of implementation; they have a high degree of specificity for non-adherence; however, their sensitivity and reliability for adherence are low. [32, 33]

Biochemical measurement of the drug, or its metabolite, is one of the methods that best confirms drug use. However, in addition to being costly and impractical, it is of little use in ophthalmic applications, as

peripheral concentrations may be undetectable; and samples from other tissues require more invasive methods that would not be advisable. [32]

Medication counting is another way to measure adherence. Classically referred to as "pill counting," in ophthalmology it is translated as the weight of the bottle. This is a simple, inexpensive, and noninvasive method. The main disadvantages of this method are: 1. It cannot confirm the application of the medication (it could have been intentionally dropped or instilled outside the eye), and 2. It depends on the subject bringing the medication back. [32, 33]

Adhesion assessment will be based on the bottle's weight and will be performed taking into account the following information: drop weight, initial container weight, final container weight, and the total number of applications. The following simplified formula will be used:

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

Where:
Ad = adhesion
P_i = weight of the container delivered to the subject at the beginning
P_f = weight of the container returned by the subject
P_T = weight of the dosage indicated for the investigational products

$$P_T = (P_g)G$$

Where:
P_g = weight of one drop of the medicine, determined by the research and development department
G = number of applications indicated for the investigational products

Containers that are not physically intact will not be considered for adherence calculations. Subjects who do not return the concomitant treatment container at the final visit will be considered non-adherent.

There is no standardized parameter to define adequate adherence; this must be defined and outlined by the objectives of the particular research. [32]

For this study, a minimum adherence of 60% will be considered necessary to meet the research objectives. Therefore, subjects with less than 60% adherence will be included in the intention-to-treat population.

6.5 Strategies to improve adherence

1. The PI will educate the subject on the importance of correctly administering concomitant treatment to achieve the study objectives.
2. Direct questioning by the PI regarding the application of concomitant treatment.
3. Delivery of a printed calendar specifying the date of the visit and its activities.

If deemed necessary, text messages may be sent as reminders. The content of these messages must be approved in advance by the IEC.

7. Methods and procedures of the study

7.1 Research center

This study will be conducted at one or more research centers previously evaluated by the sponsor. The center will be an institution or facility that conducts health research and complies with current regulations.

The research center will be responsible for forming a multidisciplinary research team to execute the clinical study according to the protocol. It is its prerogative to design the organization and select the personnel who will perform these functions. However, the sponsor requires that the PI and sub-investigator be physicians specializing in ophthalmology.

Any person assigned, under the PI's responsibility, to a part of the study monitoring (sub-investigator, nurse, etc.) or a specific role in the study (pharmacist, administrative assistant, study coordinator, etc.) must be listed in the "Delegation of Responsibilities."

The competency and training of all individuals directly involved in study activities must be verified prior to the conduct of any protocol-related activities. This must be recorded, and documents constituting evidence of this competency and/or training must be retained in the study master file. The competency and training of personnel involved in the study, both at the central level and at the study sites, is the responsibility of the sponsor.

The sponsor must ensure that all study site personnel participating in the study are adequately trained in the study (research protocol, investigator's manual, amendments, standard operating procedures, etc.) and in ICH Good Clinical Practices prior to the start of their participation in the study. Training must be documented in writing and filed in the study master file.

7.2 Clinical study registration

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

7.3 Randomization and blinding

Treatment allocation/randomization will be performed centrally using an integrated web-based response system (IWRS). There are two treatment groups. Participants will be randomly assigned 1:1 to treatment with PRO-149 or Healon® EndoCoat, with equal probability of being assigned to either treatment.

After signing the ICF, the subject will receive a patient number under which all information will be coded pseudo-anonymously during collection and completely anonymized during analysis.

The generation will be carried out by a third party, authorized by Laboratorios Sophia, S.A. de C.V., through its electronic system, using a list of random numbers (SAS Institute Inc, Cary, NC, USA). Information corresponding to this third party will be found on file.

This is an open-label study, meaning there is no blinding, except for the statistical analysis. The investigational products will be identified by labels that comply with current and applicable regulations. These labels must contain, at a minimum, the following:

- Name, address and telephone number of the sponsor.

- Pharmaceutical form and route of administration.
- Number of doses.
- Batch number.
- Legend “Exclusively for clinical studies”
- Expiration date.

7.4 Outcome variables

7.4.1 Primary outcome variables

- Changes in CEC density.
- IOP.

7.4.2 Secondary outcome variables

- Incidence of adverse events.
- Changes in corneal thickness.
- Cellularity in AC.
- Flare in AC.
- Best corrected visual acuity

7.4.3 Exploratory outcome variable

- Transurgical evaluation investigator's report.

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

Variable	Guy	Unit (symbol)	Measurement method	Normal value	Evaluation time	Statistical test
Of outcome primary						
Endothelial cell count (cornea)	Continuous quantitative	Cells / ^{mm2}	Microscopy speculate	1500-3500	VE and VF	Student t - test Mann-Whitney U Wilcoxon ranks *
Intraocular Pressure	Continuous quantitative	mmHg	Goldmann tonometry	10-21	VE, V1, V2 and VF	Student t test Mann-Whitney U Wilcoxon ranks *
Of outcome secondary						
Events adverse	Discreet	Number of cases (n)	Counting	0	VE, VP, VC, V1, V2 and VF	Student t test Mann-Whitney U*

Events adverse (Bis)	Nominal categorical	Present / Absent	Observation	Absent	VE, VP, VC, V1, V2 and VF	χ^2 or Fisher's exact test McNemar test **
Changes in corneal thickness	Continuous quantitative	µm	Corneal pachymetry	545 ± 40	VE and VF	Student t test Mann-Whitney U Wilcoxon ranks *
Cellularity of the anterior chamber	Qualitative ordinal	Degrees	Biomicroscopy	0= None	VE, V1, V2 and VF	χ^2 or Fisher's exact test McNemar test **
Flare in the anterior chamber	Qualitative ordinal	Degrees	Biomicroscopy	0= No flare	VE, V1, V2 and VF	χ^2 or Fisher's exact test McNemar test **
AVMC	Discreet	Fraction (-)	Snellen chart	0.6-2.0	VE, V1, V2 and VF	Student t test Mann-Whitney U Wilcoxon ranks *
Of outcome exploratory						
Transurgical evaluation	Qualitative ordinal	Bad (0) / Very good (5)	Observation	…	VC	χ^2 or Fisher's exact test McNemar test **

BCVA, best-corrected visual acuity; ScrV, scrutiny visit; SurV, surgery visit; SchV, scheduling visit; V1-2, 1st / 2nd safety visits; VF, final visit; χ^2, Chi-square; *For KS/SW, $p < 0.05$; **When applied

Table 3. Operational definition of variables

The variables, method, and scales used to measure them are described in detail below. They are listed in order according to **Table 3.**

7.4.4.1 Corneal endothelial cell density

Specular microscopy allows a clear view of live endothelial cells without altering their function or morphology. In turn, a surface area count can be performed to determine if there is an alteration in the shape or size of the endothelial cells, parameters that must be taken into account to determine the functional capacity of the corneal endothelium. CEC density decreases over time, due to diseases and intraocular surgical procedures. Analysis of CEC density will be performed using a specular microscope

(the make and model of the equipment must be specified). The density in cells/mm^2 will be recorded in the eCRF. The area and strategy used in the scrutiny visit must be the same as the final visit.

Management as AE: This value, by itself, will not be considered an AE regardless of the changes; the AE will correspond in each case to a clinical corneal decompensation when so judged by the PI.

7.4.4.2 Intraocular pressure

Tonometry is the objective measure of IOP, based primarily on the force required to flatten the cornea, or the degree of corneal depression produced by a fixed force. Goldman tonometry is based on the Imbert-Fick principle. [34]

Tonometry will be performed after instillation of topical anesthetic with fluorescein and the use of a cobalt blue filter (after assessing surface staining). Two readings will be taken, and the average will be recorded in the clinical record. The average will be recorded in the eCRF.

Management as AE: IOP peaks ≥30mmHg should be reported as AE.

7.4.4.3 Adverse events

As described in section **8.2,** an adverse event is defined as Any adverse medical occurrence in a subject to whom an investigational product is administered, regardless of causal attribution.

The management of adverse events will be carried out in accordance with the provisions of Section 8. Evaluation and management of adverse events and incidents.

Any adverse events that study subjects experience will be reported by the PI in the corresponding section of the eCRF and also in the clinical record.

For an adequate assessment of adverse events, in addition to the targeted questioning, a Comprehensive Ophthalmologic Evaluation must be performed at each visit. This evaluation consists of: ophthalmologic examination of the eyelids and adnexa; anterior and posterior segments, which are performed during a routine ophthalmologic examination, procedures not specifically included in the study variables. The posterior pole evaluation may be performed with direct or indirect ophthalmoscopy, with or without pharmacological mydriasis, at the discretion of the PI. The fundus will be assessed for abnormalities that could alter the study results. IOP will be measured during this evaluation, using the PI's chosen instrument, and should be measured after the stain evaluation. The results of the evaluation will be recorded in the clinical record. Only those findings that the Principal Investigator considers to be adverse events will be reported in the eCRF.

Adverse events (including incidents, adverse events) that may occur with the use of PRO-149 or Healon® EndoCoat medical devices are: ocular inflammation (iritis, hypopyon, endophthalmitis), increased intraocular pressure, corneal edema, secondary glaucoma, corneal decompensation, cystoid macular edema, blurred vision, burning, ocular pain, ocular irritation, breakage of intraocular lens haptics, foreign body on ocular surface.

7.4.4.4 Changes in corneal thickness

Pachymetry, the measurement of central corneal thickness, will be performed simultaneously with the CEC density measurement using a specular microscope (the brand and model of the equipment used must be specified). It will be recorded in the eCRF.

Management as AE: This value, by itself, will not be considered an AE regardless of the changes; the AE will correspond, in each case, to clinical corneal decompensation when so judged by the PI.

7.4.4.5 Cellularity and flare in the anterior chamber

In the presence of intraocular inflammation, increased permeability of the non-pigmented layer of the ciliary epithelium, the posterior iris epithelium, and the iris vascular endothelium results in the accumulation of cells and proteins (visible to the examiner as flare) in the anterior chamber. Using a 0.2mm X 0.2mm light beam directed obliquely into the anterior chamber with a forward tilt of the light source (slit lamp tower), the degree of flare and cellularity will be determined according to the Uveitis Nomenclature Standardization Working Group. [35] The degree of agreement will be reported in the eCRF according to the given grade (See **Table 4** and **Table 5)**.

Table 4. Scale for anterior chamber cellularity

Degree	Number of cells
0	None
½ +	1-5
1 +	6-15
2 +	16-25
3 +	26-60
4 +	More than 60

Visible in a 0.2mm x 0.2mm field

Table 5. Flare scale

Degree	Number of cells
0	There is no flare
1 +	Mild
2 +	Moderate (iris and lens clearly visible)
3 +	Marked (iris and lens slightly blurred)
4 +	More than 60 (fibrin)

Management as AE: Reported values ≥3 for cellularity or flare should be reported as AE.

7.4.4.6 Best Corrected Visual Acuity

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

Snellen notation is described as the distance at which the test is performed divided by the distance at which the letter is vertically equivalent to 5 minutes of arc. Thus, at 6 meters a letter 6/6 (20/20) is equivalent to 5 minutes of arc, a letter 6/12 (20/40) is equivalent to 10 minutes, and a letter 6/60 (20/200) is equivalent to 50 minutes. The Snellen fraction can also be expressed as a decimal (i.e., 20/20 = 1 and 20/40 = 0.5).[34]

VA will be assessed at baseline, without refractive correction, using the Snellen chart. This chart will be placed in a location with adequate natural or artificial lighting and at a distance of 3 m from the subject being assessed. Visual acuity will be measured in the study eye, asking the subject to keep both eyes open and using an occluder to cover the contralateral eye. The subject will read aloud the lines indicated by the

evaluator. The line with the smallest letters visible will be recorded by the evaluator as a fraction of the OD VA in the clinical record.

The subject's best refractive correction will then be performed, and the examination will be repeated using the obtained refraction. This result will be reported as best-corrected visual acuity, recorded as a fraction and decimal in both the clinical record and the eCRF.

Management as AE: This value, by itself, will not be considered an AE regardless of the changes; the AE will correspond, in each case, to clinical corneal decompensation when so judged by the PI.

7.4.4.7 Transurgical evaluation

During the surgical procedure, the surgeon will assess the clinical behavior of the PI. Immediately after completing the procedure, he or she will answer the questionnaire "Evaluation of OVD performance", appendix **15.1.** The ability of the OVD to maintain the AC formed during continuous circular capsulorhexis (CCC) and IOL implantation, retention during phacoemulsification, ease of use (including blister removal, syringe assembly, ease of injection), ergonomics, facilitation of CCC performance, transparency during surgery, and ease of removal will be evaluated. They will be graded on a 5-point scale: 0 = very poor; 1 = poor; 2 = acceptable; 3 = good; 4 = very good. The results will be recorded in the eCRF.

Management as AE: Not applicable. The results of this questionnaire should not be considered AE.

7.5 Program of visits and activities of the study

7.5.1 Description of activities per visit

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

7.5.1.1 Scrutiny Visit

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

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

Somatometry: refers to the measurement of the research subject's weight and height, expressed in kg and cm, respectively. It will be performed with calibrated instruments of the center's choice.

Concomitant Medication Assessment: Refers to the PI questioning the subject about medication use.

Vital signs: refers to taking heart rate, respiratory rate, systemic blood pressure and temperature.

AVMC: See 7.4.4.6

Ophthalmological evaluation: See 7.4.4.3

Ocular tonometry: See 7.4.4.2*

Gonioscopy: Refers to the evaluation of the AC angle. After applying a drop of 0.5% tetracaine ophthalmic solution, the 60° lateral mirror of the goniolens is used to evaluate the iridocorneal angle, which is graded according to the Shaffer classification.

Assessment of pharmacological mydriasis: After checking the AC angle, apply one drop of 5% Phenylephrine/0.8% Tropicamide every 5 minutes, on three occasions. Five minutes after the last application, the pupillary diameter will be measured using a slit lamp. This measurement will be recorded in the eCRF.

Specular microscopy: See 7.4.4.1

Corneal pachymetry: See 7.4.4.4

Eligibility criteria: Refers to the PI's review, which verifies that the subject can be included in the study if they meet all the inclusion criteria and do not meet the exclusion criteria. See 5.1

IOL calculation and anterior chamber measurement: Once the relevant eligibility criteria have been met, the IOL calculation will be performed. This involves biometric measurements (keratometry, anterior chamber depth, and axial length) and their integration into the PI selection formula to determine the power, expressed in diopters, of the IOL to be implanted. This will be performed using the Zeiss IOL Master device (the model must be specified).

Preoperative cardiology evaluation request: This refers to the delivery to the research subject of the requests for laboratory tests (blood pressure, serum calcium and PT/TPT, INR), ECG, and subsequent preoperative cardiology evaluation. The subject must arrive at the scheduled time and date for the tests and evaluation.

AE Assessment: See 7.4.4.3

7.5.1.2 Scheduling Visit

Vital signs: See 7.5.1.1

Evaluation of concomitant medications: See 7.5.1.1

Preoperative cardiology assessment review: Refers to the review, by the PI or designated staff member, of the preoperative cardiology evaluation. This assessment must be performed by a physician specializing in cardiology or internal medicine, who must confirm that the patient is suitable for the indicated surgical procedure.

Eligibility criteria: Subject selection criteria are completed by reviewing the pre-surgical cardiology assessment.

Surgical scheduling: This refers to the scheduling of a date for the surgical procedure and the request for pre-anesthesia evaluation. An anesthesiologist must perform this evaluation.

Subject Material Delivery: Once your participation has been confirmed, your subject's calendar and ID card will be delivered.

AE Assessment: See 7.4.4.3

7.5.1.3 Surgery Visit

Vital signs: See 7.5.1.1

Evaluation of concomitant medications: See 7.5.1.1

PI Assignment: Refers to the randomization and assignment of the OVD to be used during surgery using the IWRS system.

Phacoemulsification surgery: refers to the surgical procedure, which will be performed with topical anesthesia, 0.5% tetracaine ophthalmic solution, and sedation. A drop of 5% povidone-iodine solution will be used as prophylaxis in the conjunctival fornix. After asepsis and antisepsis, sterile drapes with complete eyelash coverage and a blepharostat will be placed, the following steps will be performed:

- 1mm limbal incision, with a 15º knife.

Capsular staining with 0.6% trypan blue, at the surgeon's discretion, air bubbles may or may not be used and washing with BSS.

Application of the OVD to form the anterior chamber, quantity at the surgeon's discretion.

2.2mm limbal incision with double-bevel knife, with self-sealing wound architecture.

Continuous circular capsulorhexis, assisted by the surgeon's preferred instrument.

Hydrodissection and hydrodelineation with BSS.

Phacoemulsification with the surgeon's preferred technique for the case.

Cortical aspiration with coaxial I/A.

Capsular bag formation with OVD.

Insertion of enVista® IOL (Bausch & Lomb)

Removal of the OVD with coaxial I/A piece.

If necessary, close the 2.2mm wound with 10-0 Nylon.

> The procedures and order mentioned here are for informational purposes only; the surgeon's judgment should prevail over the order, modification, or waiver of any procedure. The OVD may be used at another time during surgery at the surgeon's discretion.

AE Assessment: See 7.4.4.3

Transurgical evaluation: See 7.4.4.7

Continuity assessment: refers to the PI's assessment to ensure that there are no reasons for the subject to withdraw from the study.

7.5.1.4 1st Safety Visit

Vital signs: See 7.5.1.1

Evaluation of concomitant medications: See 7.5.1.1

AVMC: See 7.4.4.6

Ophthalmological evaluation: See 7.4.4.3

Ocular tonometry: See 7.4.4.2

AE Assessment: See 7.4.4.3

Delivery of concomitant treatment: refers to the delivery, by the research center to the subject, of the concomitant treatment (Sophixin DX® Ofteno) and the indication of the dosage to follow.

Continuity assessment: See 7.5.1.3

7.5.1.5 2nd Safety Visit

Vital signs: See 7.5.1.1

Evaluation of concomitant medications: See 7.5.1.1

AVMC: See 7.4.4.6

Ophthalmological evaluation: See 7.4.4.3

Ocular tonometry: See 7.4.4.2

AE Assessment: See 7.4.4.3

If a stitch has been placed in the main port, remove it.

Continuity assessment: See 7.5.1.3

7.5.1.6 Final Visit

Vital signs: See 7.5.1.1

Evaluation of concomitant medications: See 7.5.1.1

AVMC: See 7.4.4.6

Ophthalmological evaluation: See 7.4.4.3

Ocular tonometry: See 7.4.4.2

Specular microscopy: See 7.4.4.1

Corneal pachymetry: See 7.4.4.4

AE Assessment: See 7.4.4.3

Return of concomitant treatment: refers to the return of the Sophixin DX® Ofteno bottle by the subject to the research center.

7.5.2 Unscheduled follow-up visits

At the request of the subject or study personnel, unscheduled follow-up visits may be conducted to report adverse events or any other situation that warrants it. During these visits, all relevant data on reported adverse events must be collected, and an appropriate management plan must be established, if applicable.

7.6 Data collection

7.6.1 Source documents

Source documents are all written or printed records derived from automated processes (e.g., printouts of laboratory results issued by automated analytical equipment) where information is first recorded and which become part of the subject's permanent medical record. Examples of source documents include medical records, clinical progress notes, laboratory reports, office study reports, nursing notes, follow-up notes, surgical records, etc.

The PI is obligated to accept monitoring of study-related information, audits, review by ethics and research committees, and inspections by the health authority. This obligation implies direct access to source documents.

7.6.2 Electronic forms of data collection

All protocol-related data will be captured via an electronic case report form (eCRF) by research team staff. Protocol-related data should NOT be captured directly into the eCRF, but rather transcribed from the corresponding source document. This procedure allows for monitoring to verify the information captured in the eCRF. It is the researcher's responsibility to ensure that the information is transcribed into the eCRF correctly, completely, and in a timely manner. It is understood that all data captured and submitted via the eCRF for data analysis have been approved by the researcher.

7.6.3 Archive

The data collected in this database are anonymous (only the subject number is stored along with other relevant information). The software used for data capture and storage meets the traceability requirements necessary for conducting clinical studies. The collected data will be stored by the sponsor or designated clinical research organization for a period of 10 years. Records of subject number assignment will remain at the participating institutions under the care of the PI or their team and must be maintained for at least 5 years.

8. Evaluation and management of adverse events and incidents

8.1 Regulation and standards on adverse events and incidents

The registration and reporting of adverse events and incidents will be carried out in accordance with the guidelines established in NOM-240-SSA1-2012, NOM-220-SSA1-2016 and the international ICH E6 guidelines. [36, 37, 38, 39, 40]

8.2 Definition of adverse event, incident, adverse incident and adverse effect

According to the International Conference on Harmonization (ICH), an adverse event (AE) is any unfavorable medical occurrence in a clinical research subject administered a pharmaceutical product, regardless of causal attribution. [38, 39, 40]

Therefore, an AE may be any of the following: any unfavorable, unintended disease, symptom, or sign (including an abnormal laboratory finding) that is temporally related to the use of a medical product, whether or not considered to be related to that product; any new disease or exacerbation of an existing disease (worsening of the nature, frequency, or severity of a known condition); relapse of an intermittent medical condition (e.g., headache) not present at baseline; any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is related to the symptoms or that results in a change in study or concomitant treatment or discontinuation of study drug. [38, 39, 40]

As defined in the previous paragraph, an adverse event is defined as any event that occurs during treatment with a drug or device. However, the definition can also apply to any undesirable event that occurs during a clinical trial, including behavioral disturbances. [40]

According to NOM-240-SSA1-2012, an incident is any event related to the use of a medical device; while an adverse incident is any proven event related to the use of a medical device that has conclusive evidence of the causal relationship between the incident and the medical device, and that could be caused by a malfunction or alteration of the characteristics of the medical device and that could cause death or serious deterioration of the health of the user. An adverse incident will not be considered an incident derived from abnormal use or a use different from that recommended by the holder of the sanitary registration of the medical device or its legal representative in Mexico. [37]

According to NOM-012-SSA3-2012, an adverse effect is the set of uncalculated and unexpected signs and symptoms that occur in a research subject, as a consequence of the application of experimental maneuvers planned in a protocol or research project for health in human beings and that potentially represent a risk to their health. [41]

8.3 Use of adverse events as a study safety variable

Measuring the safety of PRO-149 use is paramount to the study, therefore, it is considered important to report any undesirable manifestation or illness that occurs during the course of the study, regardless of whether the manifestation is considered related to the investigational treatment or not. [40]

Reporting all adverse events occurring during the investigation will allow us to subsequently determine their causality to the investigational treatment (medical devices) and determine whether they are incidents or adverse events; or determine their causality to concomitant medical treatment or other procedures. [36, 37, 38, 39, 40, 41]

8.4 Definitions relevant to the classification of adverse events

Severity (serious/non-serious), also called seriousness (serious/non-serious). A serious event is defined as any event that: results in death, threatens life, requires hospitalization or prolongs hospitalization, causes permanent or significant disability or incapacity, causes abnormalities or malformations in the newborn, or other medically significant conditions.

Severity (mild, moderate, or severe). Mild symptoms are those that present with minimal symptoms and do not require treatment or discontinuation of the medication; moderate symptoms interfere with normal activities without threatening the subject's life, require treatment, and may or may not require discontinuation of the medication; severe symptoms interfere with normal activities and require pharmacological treatment and discontinuation of the medication. [36, 38, 39]

Causality. It is the relationship assigned between the pharmaceutical product and the adverse event: certainly caused by the pharmaceutical product, there is clear evidence of causality, i.e. the adverse event reappears with the administration of the pharmaceutical product; probably caused by the pharmaceutical product, there is a high suspicion of causality but direct evidence is lacking or it is considered unnecessary or dangerous, i.e. the reaction disappears upon discontinuation of the pharmaceutical product; possibly caused by the pharmaceutical product, there is additional information suggesting that the cause may be due to another pharmaceutical product or disease; unlikely to be caused by the pharmaceutical product, there is a clear explanation for the origin due to the underlying disease or the use of another pharmaceutical product; conditional, there is a lack of data to issue a clear causality; unclassifiable, those for which once all possible information on the adverse event has been obtained, it remains unclassifiable. [36, 38, 39, 40]

8.5 Researcher Responsibilities

It is the investigator's responsibility to verify AEs and incidents through questioning, a relevant physical examination, assessment of progress, and appropriate medical and pharmacological management; as well as to follow up until the AE or incident is resolved or resolved and finally discharged, following the definitions established in national and international regulations. [36, 38, 39]

In the event of an AE or any event that puts the health and well-being of the subjects at risk, appropriate medical care will be provided, either at the research center or by referring the subject to the highest-resolution hospital with which the research center has a medical care agreement. The PI will notify the sponsor's clinical monitor, in accordance with the timeframes established in national and international regulations. In the case of serious adverse events, the PI will notify the sponsor and record the corresponding information in the eCRF, and in turn, will inform the IEC and the IC.

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

The final report that will be drafted by the Clinical Team of the Clinical Operations Department of Laboratorios Sophia, S.A. de C.V., will include the report of adverse events in compliance with current national and international regulations. [36] [38]

If the research subject develops a chronic adverse event during their participation in the study, such as diabetes or arterial hypertension, they will be referred to a healthcare professional for chronic treatment. Follow-up and termination of participation will be in accordance with ICH guidelines.

8.5.1 Recording of adverse events in the electronic case report form

The adverse event registry considers:

- Subject identification information such as: subject number, age, sex, and if applicable, specify the eye.
- Information about the causality of the adverse event, its relationship to the investigational products, or to another study-related drug, as appropriate.
- Information on important dates:
  - Date on which the adverse event occurs.
  - Date on which the Principal Investigator is informed of the same.
  - Date of resolution or outcome, as applicable.
- Information on diagnosis and clinical management.
- Establish the outcome or resolution of the event:
  - Recovered/resolved without sequelae
  - Recovered/resolved with sequelae
  - Not recovered/Not resolved
  - Subject who died due to the adverse event
  - Subject who presented death and it is judged that the investigational product may have contributed
  - Subject who died and this was not related to the product under investigation,
  - A stranger
- Information about the investigational product or the product associated with the adverse event, incident, adverse event, ADR, or SRAM must be recorded. The essential information to be recorded is the generic name, distinctive name, or code of the investigational product or the product associated with the undesirable clinical manifestation. It will also be necessary to record data concerning the lot number, manufacturing laboratory, expiration date, dose, route of administration, start and end dates of administration and/or consumption, and reason for the prescription, depending on whether it is an investigational product or medication (a protocol in which the subject is currently participating) or a medication that the research subject is taking for the treatment of underlying concomitant diseases or for the management of any transient signs or symptoms that do not correspond to the natural history of the pathology that motivated their entry into the research protocol.
- Indicate whether the adverse event disappears upon withdrawal of the suspected product (which caused the event). Also indicate whether a dose adjustment is made, whether the event changes in intensity or severity, and whether the reaction persists. It is important to indicate whether the AE reappears in subjects who are re-exposed to the product after having been previously discontinued.
- Information regarding concomitant pharmacotherapy. Indicate the generic name, dose, route of administration, start and end dates, and the reason for the prescription, regardless of whether it is in accordance with the prescribing information or the data sheet or if it is used outside of the regulations or as authorized by the local, national, or international regulatory body.
- Information on relevant clinical history. The analysis of the AE considers the information previously described. However, the clinical context in which the adverse event occurs in the participants in the clinical research protocol is of particular interest. Therefore, information about previous conditions, hypersensitivity or allergy symptoms, previous surgical procedures,

laboratory tests or imaging examinations the participant has undergone, etc., that the researcher deems appropriate may be mentioned.

8.5.2 Monitoring of adverse events

The Principal Investigator will provide care and follow-up of the adverse event presented by the participant until its outcome, in accordance with the provisions of the following section.

8.5.3 Procedures for a serious adverse event

The adverse event handling process considers the following stages:

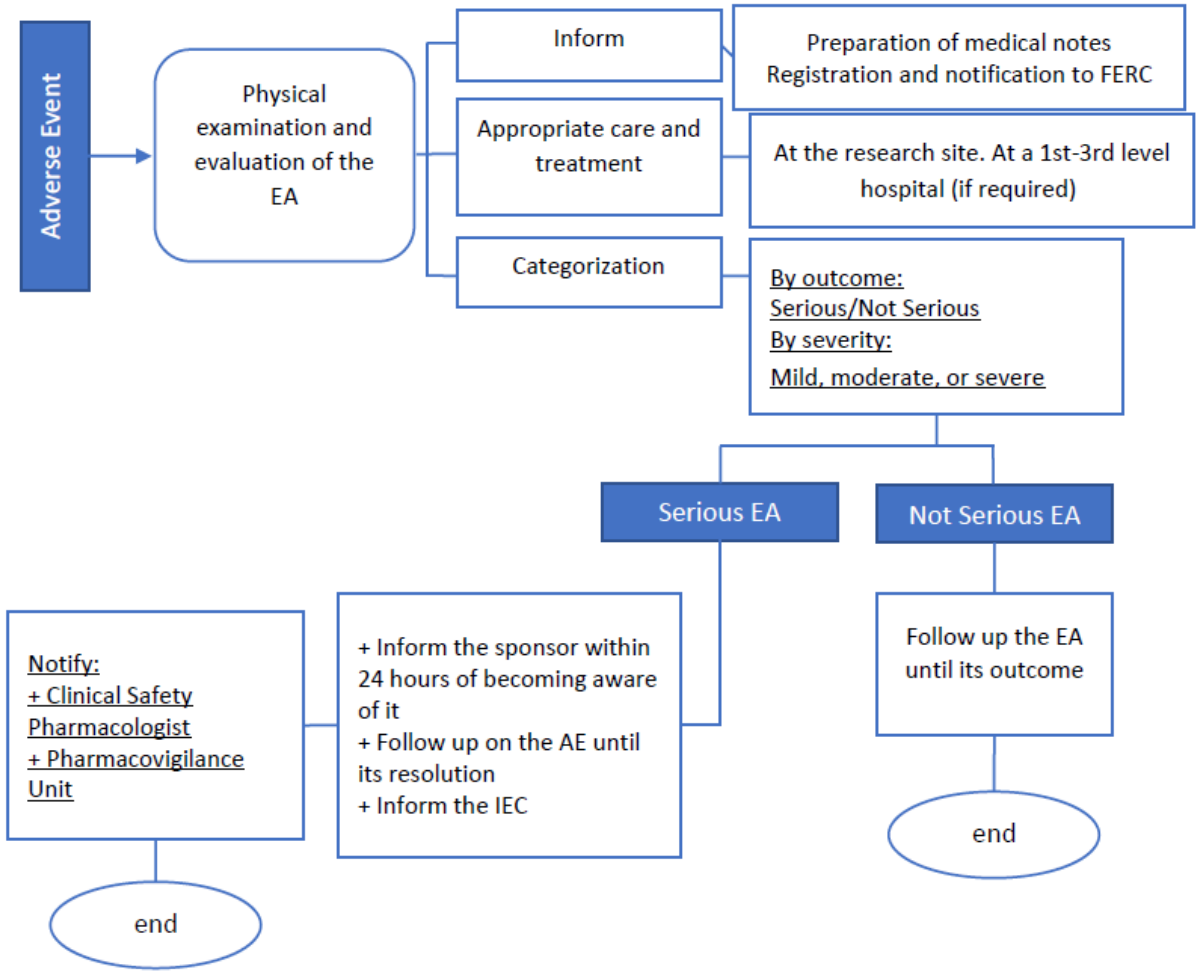


Figure 4. Adverse event care

During the development and conduct of this study, undesirable harmful events or adverse reactions/incidents with medical implications may occur in the research subject, which are not necessarily causally related to the investigational products. These harmful phenomena may occur during the use of investigational pharmaceutical products at doses authorized for human use by a local, national, or international regulatory body. However, it may be suspected that the investigational product may cause some unwanted clinical manifestation. AEs, Incidents, Adverse Incidents, ADRs, or SRAMs related to one or more pharmaceutical products may occur during the systematic evaluation of participants (on the days on which the clinical review is scheduled, according to the schedule of activities) or suddenly, in such a way that:

1. The investigator should be the first person to whom the subject notifies that he or she has developed or experienced any clinically harmful phenomena during his or her participation in this study.
2. Based on their clinical judgment, the principal investigator will determine the appropriate treatment for the adverse event/reaction based on the relevant physical examination, history, etc., as well as the analysis of information available in the medical literature and the information contained in the investigator's manual, Prescribing Information, or the comparator drug's data sheet.
3. This care may be provided at the research center or at the hospital with the highest capacity for treatment. Thus, if the subject is referred by the PI to a hospital, they will be provided care through a referral system. The referral may be through a card identifying the subject as a study participant and linking them to the pre-established agreement with the institution, or through a referral medical note issued by the Principal Investigator. Laboratorios Sophia, S.A. de C.V., will pay the costs for the participating subject's medical care when the adverse event is associated with or related to the investigational product.
4. Taking into account the clinical information collected, either during the care provided at the research center or provided by the treating physician(s) at the hospital, the PI will record the AE in his/her clinical note, stating the seriousness, intensity (mild, moderate, or severe), and relationship to the investigational product.
5. The PI must migrate the relevant data to the eCRF and its respective adverse event section. Serious adverse events must be reported to the study's clinical monitor within 24 hours of becoming aware of them, so that they can then inform the Clinical Team and the UTFLS, and subsequently notify the IEC/CI. Non-serious adverse events will be recorded and appropriately addressed, and the corresponding regulatory body will be informed about the safety profile of the PI or investigational drug in the final clinical trial report.

Recording the outcome of the AE depends substantially on the Principal Investigator's follow-up of the subject, as most adverse events (see the safety profile section in section 2.2.2 and the investigator's manual) are expected to be ophthalmic in nature; however, systemic alterations may occur. Therefore, at the investigator's discretion, the participant's withdrawal or continuation will be considered.

8.5.4 Assessment of causality

Causality assessment is the methodology used to estimate the probability of attributing an observed adverse event to a pharmaceutical product. It considers probabilistic categories according to the available evidence and the quality of the information, based on national pharmacovigilance and technovigilance regulations. [36] [42]

An adverse event may or may not be related to the clinical trial. A causal relationship means that the intervention caused (or is reasonably likely to have caused) the adverse event. This usually involves a relationship between the timing of the intervention and the adverse event (e.g., the adverse event occurred shortly after the research subject received the intervention). [40]

For all adverse events, the Principal Investigator is responsible for examining and evaluating the patient to determine the association of the event with the clinical study and intervention, whether related to experimental treatment, concomitant treatment, surgical procedure, or diagnostic procedures performed during the study. [40]

Accepting that the adverse event is related to the clinical study requires a plausible mechanism of action—that is, a logical sequence between the event and the intervention that caused it. In some cases, it is

helpful to know the opinions of other physicians directly or indirectly involved in the study, as well as whether the patient believes there is a relationship. [40]

There are no guidelines or algorithms available to help determine the causality of an adverse event in the case of the use of a medical device. This means that the relationship is established by the opinion of the researcher and the reasoning on how the adverse event occurred. However, the Pharmacovigilance and Technovigilance Unit of Sophia Laboratories (UFTLS) may use the causality categories described by *the Uppsala Monitoring Centre,* to categorize the probability of the adverse event to concomitant or experimental treatment (medical devices for convenience may be evaluated as drugs within the categories): [36] [42]

- Definite (certain): A clinical event, including laboratory test abnormalities, which occurs in a plausible time sequence related to drug administration and that cannot be explained by concurrent disease or by other drugs or substances. The response to drug withdrawal must be clinically plausible. The event must be definitive from a pharmacological or phenomenological point of view, using, if necessary, a conclusive rechallenge procedure. [36] [42]
- Probable: A clinical event, including laboratory test abnormalities, which occurs in a reasonable time sequence related to drug administration, is unlikely to be attributed to the concurrent disease or to other drugs or substances, and to which withdrawal of the drug produces a clinically reasonable response. Rechallenge information is not required for this definition. [36] [42]
- Possible: A clinical event, including laboratory test abnormalities, which occurs in a reasonable time sequence related to drug administration, but that may also be explained by concurrent disease, or by other drugs or substances. Information regarding drug withdrawal may be missing or unclear. [36] [42]
- Unlikely: A clinical event, including laboratory test abnormalities, which occurs in a time sequence that is unlikely to occur in relation to the administration of the drug and that can be more plausibly explained by concurrent disease, or by other drugs or substances. [36] [42]
- Conditional/Unclassified: A clinical event, including laboratory test abnormalities, reported as an adverse reaction, for which further data are essential for proper evaluation, or additional data are under review. [36] [42]
- Not evaluable/Unclassifiable: A report that suggests an adverse reaction, but which cannot be judged due to insufficient or contradictory information, and which cannot be verified or completed in its data. [36] [42]

Thus, the degree of certainty to establish the investigational product as the causal agent of the harmful phenomenon that occurs in the subject of the clinical study can be indicated directly by the Principal Investigator based on his or her clinical experience or through the application of the causality categories described by *the Uppsala Monitoring Centre*. It is important that the researcher and the UFTLS consider the following arguments in favor of the causal relationship:

a) Strength of association, which refers to the number of cases in relation to those exposed.
b) The consistency of the data, that is, the presence of a common characteristic or pattern.
c) The exposure-effect pattern, which determines the relationship with the site of onset, time, dose and reversibility after suppression.
d) Biological plausibility, which refers to the possible pharmacological or pathophysiological mechanisms involved in the development or presentation of the adverse event.
e) Experimental findings, for example, the appearance of anomalous metabolites or high levels of drug or its biotransformation product.

f) Analogy, which refers to the experience acquired with other related drugs, adverse reactions frequently produced by the same family of pharmacological agents.
g) Nature and characteristics of the data, i.e., objectivity, accuracy and validity of the relevant documentation. [43]

8.6 Unanticipated problems

Unanticipated problems (ANP) are considered situations that pose risks to the participating subjects, generally any incident, experience or result that meets all of the following criteria:

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

8.6.1 UAPs Report

The PI will be responsible for reporting UAPs to the sponsor, the IC, and the IEC. The report should contain the following information:

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

UAPs that are EAS must be reported to the IEC/ CI and the sponsor within the first 24 hours of the PI becoming aware of it.

Any other UAP will be reported to the IEC/CI and the sponsor within the first 5 business days after the PI becomes aware of it.

9. Study monitoring

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

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

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

9.1 Monitoring of study centers

The research centers participating in the study will be monitored. At least one initial visit and one closing visit must be conducted for each center, although one or more follow-up visits may be required between these two mandatory visits.

The initial visit must be conducted before the first participant is enrolled at that center. During this visit, the monitor will verify that the materials to be used during the study have been received and that the personnel involved in study activities have been trained in the study. The monitor will also verify compliance with applicable regulatory requirements and standard operating procedures.

At the follow-up visit(s), the monitor will review the study documents to confirm that the research protocol and applicable standard operating procedures are being followed, that data entry is complete and timely, and that adverse event reporting is being conducted appropriately. At each visit, the monitor will discuss the findings with the investigator and determine the appropriate actions to be taken.

The closing visit will take place at the end of the study, once the last participant at the site has been discharged from follow-up. During this visit, the monitor will verify that the site has all necessary documentation for archiving, that all biological samples have been analyzed, that all PI (used and unused) has been returned to the sponsor, and that all unused materials have been recovered.

Details of monitoring are set out in the relevant plan.

9.2 Audit and quality control

To ensure compliance with GCPs and all applicable regulatory requirements, Laboratorios Sophia, S.A. de C.V. may conduct quality assurance audits. Regulatory agencies may also conduct a regulatory inspection of this study.

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

9.2.1 Pre-study audit

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

9.2.2 Audit during the conduct of the study

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

10. Statistical analysis

10.1 Data analysis

10.1.1 Statistical analysis

Statistical analysis will be performed by staff of Laboratorios Sophia, S.A. de C.V. The statistical software SPSS version 19.0 for Windows (IBM Corporation, Armonk, NY, USA) will be used.

Although the study design is open-label, to avoid potential interpretation bias, the staff assigned to the statistical data management will be blinded to the intervention groups. Coding will be performed using consecutive numbers for each intervention group.

The data will be collected and organized in an Excel spreadsheet (Microsoft® Office). The data will then be exported to the SPSS software platform. Variables will be categorized according to their nature; see **Table 3.**

10.1.2 Data interpretation

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

KS and SW tests will be performed, as applicable, to determine whether the distribution presents normality in the results obtained in each study group. [44]

If normality of the data is observed ($p > 0.05$; for KS and SW), the statistical analysis of the continuous quantitative variables to find significant differences (*p)* will be as follows:

- Intra-group analysis: will be determined using the Student's t-test for repeated measures.
- Between-group analysis: differences between groups will be analyzed using Student's t-test for independent groups.

For $p < 0.05$ in KS and SW, the statistical analysis of continuous quantitative variables to find significant differences (*p)* will be as follows:

- Intra-group analysis: will be determined using the Wilcoxon rank test. [45]
- Between-group analysis: differences between groups will be analyzed using the Mann-Whitney U statistic.

The level of difference to consider significance will be an α of 0.05 or less [46].

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

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

- Intra-group differences: will be determined by the McNemar test [47], which is applied to 2×2 contingency tables with a dichotomous trait and pairs of matched subjects to determine whether the marginal frequencies of row and column are equal (marginal homogeneity).
- Difference between groups: Differences between groups will be analyzed using Pearson's X^2 test or Fisher's exact test when expected values are less than 5.

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

For the reporting of adverse events, participants who were randomly assigned to an intervention group after application of the investigational product will be considered.

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

The investigational product will be considered safe when there are no clinical and statistical differences in all primary outcome variables, with respect to its comparator (Healon EndoCoat®).

10.1.3 Procedure for handling missing data

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

10.1.4 Deviations from the statistical analysis plan

According to the sample size calculation to meet the study objective, 28 evaluable subjects (14 cases per arm) are required. If this number is not met due to a loss of subjects exceeding the 20% threshold established in this protocol (loss to follow-up or withdrawal from ICF), the sponsor may substitute these subjects to balance the treatment groups.

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

10.1.5 Subjects included in the analysis

Those subjects who complete all their visits will be included in the statistical analysis to meet the study objective (PP; per-protocol population).

The variables, method and scales for their measurement are described in detail below.

10.2 Sample size calculation

10.2.1 Number of subjects calculated

36 evaluable subjects were estimated (18 subjects per arm, one eye per subject).

10.2.2 Justification of the sample calculation

Although there are no references on sample size calculation for pilot studies, it was considered appropriate to perform the calculation based on the clinical study by Storr-Paulsen et al [48], who compared the influence of three OVDs of 1%, 2% and 3% SH on corneal endothelial cell count during cataract surgery up to three months postoperatively. All three OVDs showed a decrease in postoperative cell count, for SH-1% it was 18.46%, for SH-2% it was 18.03% and for SH-3% it was 6.97%. [48]

The percentage decrease in dispersive OVD at 3% SH was considered. The sample size was calculated using the equation for an equivalence ratio [49], which is useful when we want to test whether a ratio *p,* is different from a standard reference value, p_0. In this case, we want to test that PRO-149 is equivalent to its comparator (Healon® EndoCoat). Here the test falls on PRO-149; that is, equivalence is represented by the alternative hypothesis (H_1), rather than the null hypothesis (H_0).

Working hypothesis for calculating the sample size:

$$H_0: |P - P_0| \geq \delta$$
$$H_1: |P - P_0| < \delta$$

Considering an α = 0.05 corresponding to the type I error (95% confidence level), a power (β) = 0.20 corresponding to the type II error (80% power) and a test margin (δ) of 5%. The calculation to estimate the sample size was performed using an online tool (*Sample size calculators, http://powerandsamplesize.com)*, following the following equations:

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

$$1 - \beta = 2[\Phi(z - z_{1-\alpha}) + \Phi(-z - z_{1-\alpha})] - 1, z = \frac{|p - p0| - \delta}{\sqrt{\frac{p(1-p)}{n}}}$$

Where:

n: sample size,

p_0: comparison value,

Φ: function of the standard normal distribution

Φ^{-1}: normal standard quantile function

α: Type I error

β: Type II error (1-β is the power)

δ: test margin.

According to the previous calculation, the result was 14 cases (eyes) per arm; this calculation was increased by 20% to account for potential losses. The total sample size required is 18 cases (eyes) per treatment arm, a total of 36 cases. This calculation is consistent with the sample size used in similar clinical studies where OVDs were employed. [50, 51, 52]

11. Ethical considerations

11.1 Approval of committees

This study will be conducted in accordance with the standards of the Declaration of Helsinki, World Medical Association 2013. Nuremberg Code; Nuremberg Judgment by the International Tribunal at Nuremberg, 1947. Belmont Report, National Commission for the Protection of Subjects of Biomedical and Conduct Research, 1979. It will be conducted in accordance with the scientific and technical requirements necessary for the registration of medicines for human use of the International Conference on Harmonization (The International Council for Harmonisation (ICH) Guideline for Good Clinical Practice. International Ethical Guidelines for Biomedical Research Involving Human Subjects of the Council for International Organizations of Medical Sciences of Medical Sciences, CIOMS, 2002). International Ethical Guidelines for Epidemiological Studies of the Council for International Organizations of Medical Sciences of Medical Sciences, CIOMS, 2008). The Research Ethics Committee and the Research Committee will evaluate the protocol before conducting the study and will issue their approval or any possible modifications for its implementation. These Committees must be notified of any significant changes to the protocol. In addition to the above, the current regulations of the regulatory authority must also be complied with.

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

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

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

The study is considered to be research with greater than minimum risk, in accordance with the Regulations of the General Health Law on Health Research, Title Two, Chapter I, Article 17, Section III, published in the Official Gazette on January 6, 1987.

11.2 Amendments to the protocol

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

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

Amendments that substantially modify the protocol or impose additional or different risks to research subjects must be approved by the aforementioned Committees. It is the investigator's responsibility to

take measures in situations requiring immediate action to prevent unnecessary harm to study participants.

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

11.3 Early termination of the study

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

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

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

In the event of suspension, the study may be resumed once the situations that led to the suspension have been resolved, provided this justification is sufficient for the sponsor, IC, IEC, and regulatory authorities.

11.4 Informed consent

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

The ICF will be considered a source document and will be filed as such. The site's principal investigator is responsible for ensuring that all new versions of the informed consent form undergo the appropriate approvals (the same ones that the original informed consent form underwent) and that the most current approved version is presented to the study subjects.

11.4.1 Obtaining

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

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

The PI, or the study staff delegated by him or her, will provide the potential participant with all information regarding the characteristics of the study, its potential benefits, risks, objectives, and procedures.

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

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

In the event that a subject is illiterate, acceptance will be specified with his or her fingerprint, and in the event that the subject is not capable of providing adequate written informed consent, a “legally authorized” representative of the subject may provide such consent for the subject in accordance with applicable laws and regulations.

Likewise, the PI, or the study staff delegated by him, must sign and date this consent.

The ICF must be signed in duplicate by all involved; one copy will be filed in the researcher's folder and the other will be given to the participant. The PI or designated staff member must document the process of obtaining Informed Consent through a detailed, accurate, and contemporaneous medical note, specifying the signed version, the date the document was signed, and how the process was carried out.

11.4.2 Special considerations

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

11.4.3 Modifications to informed consent

Any change to the ICF constitutes an amendment to this document and must be submitted for approval to the Research Ethics Committees and COFEPRIS.

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

A re-consent process must be conducted for each subject affected by the amendment under the same conditions as those described above, in order to promptly communicate the new information contained in the document. The subject will be given an original signed amendment, and the researcher will retain the second original amendment.

11.5 Confidentiality

All documents and information provided to the research center by the sponsor are strictly confidential. The PI expressly agrees that the data regarding his or her professional and clinical experience, provided to the sponsor in paper form and stored electronically, are solely for use in connection with his or her activities with the clinical study sponsor, in accordance with Good Clinical Practice.

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

The clinical study protocol provided to the PI may be used by the PI and his or her team to obtain informed consent from the subjects for the study. The clinical study protocol, as well as any information derived from it, must not be disclosed to other parties without the sponsor's written authorization.

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

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

In the eCRF and all communications related to study subjects, they will be identified only by their study subject identification number, either the screening number or the randomization number. The information collected in this study will be exchanged between the sponsor and the research site and must be treated confidentially. The Health Authority, the IRB, the IC, the sponsor, the monitors/auditors, and third-party auditors will be the only bodies authorized to review the study documentation. If publications arise from this research project, under no circumstances will they contain information about the identification of the study subjects. If the study results are published, no personal information about the study subjects will be disclosed.

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

11.6 Conflict of interest

The independence of the study's conduct and results from any actual or perceived external influences is critical. Therefore, any current conflict of interest of any person playing a role in the design, conduct, analysis, publication, or any other aspect of this study will be declared. Furthermore, those with a perceived conflict of interest will be asked to manage it in a manner appropriate to their participation in the study.

11.6.1 Declaration of interests

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

11.7 Access to information

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

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

11.8 Auxiliary and post-study care

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

12. Biosecurity aspects

NO BIOSECURITY IMPLICATIONS

This protocol, titled: “Clinical study to evaluate the safety of the PRO-149 viscoelastic solution when used as an ophthalmic viscosurgical device during phacoemulsification surgery and intraocular lens placement in subjects diagnosed with senile cataracts, compared to Healon® EndoCoat.”, and number: SOPH149-0220 / I HAS NO BIOSECURITY IMPLICATIONS, since infectious biological material will NOT be used; pathogenic strains of bacteria or parasites; viruses of any type; radioactive material of any type; genetically modified animals and / or cells and / or plants; toxic, hazardous or explosive substances; any other material that puts the health or physical integrity of the research center personnel or the research subjects at risk or affects the environment. It is also declared that this project will not involve cell, tissue, or organ transplantation procedures, or cell therapy, nor will it involve the use of laboratory, farm, or wildlife animals.

13. Publication Policy

13.1 Final report

Once the statistical analysis is completed, the final report will be written with the results obtained, by the Medical Management Department Team of Laboratorios Sophia, S.A. de C.V. This report will be prepared following the recommendations of the ICH E3 *Step 4 Guide.*

13.2 Communication of results

Regardless of the results of the study, Laboratorios Sophia, S.A. de C.V., is committed to communicating the final study report to the principal investigators and COFEPRIS. These results will also be shared with the research committee and the IEC. The PI will be responsible for communicating the results to the research subjects.

Laboratorios Sophia, S.A. de C.V. will retain at all times the rights to the publication and dissemination of the information contained herein.

13.3 Publication of results

Laboratorios Sophia, S.A. de C.V., acting as the sponsor of the study, assumes full responsibility for its role and retains exclusive ownership rights to the study results, which it may use as it sees fit.

The PI agrees not to publish or communicate data collected from the study, unless prior written agreement is obtained from Laboratorios Sophia, S.A. de C.V. Any manuscript derived from the data obtained with this protocol must be reviewed by the sponsor before any attempt to submit it for publication in any journal or scientific conference.

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

Authorship assignments for publications are the sponsor's responsibility. However, express authorization from those invited to participate as authors is required. Authors have the right to review the manuscript prior to publication, as well as to provide comments and suggestions. Such comments must be submitted within the first 15 calendar days of receipt of the project.

14. Financing and insurance

14.1 Compensation to study participants

Subjects participating in the study will not receive financial compensation for their participation.

14.2 Insurance for study participants

Subjects participating in the study will sign the informed consent form, which specifies that Laboratorios Sophia, S.A. de C.V. agrees to pay for immediate treatment resulting from injuries or illnesses caused by the investigational products until resolved, in accordance with medical judgment.

All study participants will be covered by a liability insurance policy contracted by Laboratorios Sophia, S.A. de C.V. Information on the policy will be made available to the research centers. In the event of a medical emergency, the research center must have the personnel, materials, equipment, and procedures in place for immediate management.

15. Annexes

15.1 OVD performance evaluation

OVD performance evaluation

Identification card

Study No. SOPH149-0220-I **Date:** //

Subject's initials:_____ **Subject No.:** 149-_____-_____

Directions:

This questionnaire must be answered by the surgeon immediately after completing the surgical procedure.
For each question, circle your answer.
Where:

0=very bad; 1=bad; 2=acceptable; 3=good; 4=very good

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1 How do you consider the ability of the OVD to form and maintain the AC during CCC and IOL implantation?

0 1 2 3 4

2 How do you rate the ability of the OVD to be retained during phacoemulsification?

0 1 2 3 4

3 How do you consider the overall ease of use of the OVD?

0 1 2 3 4

4 How do you rate the ergonomics of the OVD?

0 1 2 3 4

5 How do you consider the transparency of the OVD during surgery?

0 1 2 3 4

6 How do you consider the ease of withdrawing the OVD from the AC?

0 1 2 3 4

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