Creation date: August 1, 2018

Phase I clinical study, to evaluate the safety and tolerability of the ophthalmic solution PRO-179 compared with Travatan®, on the ocular surface of clinically healthy subjects.

Protocol Code: SOPH179-0818/I

Protocol version: 1

Date of the version : 01/08/2018

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

1.1 Summary

1.2 Synopsis

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

Phase I clinical study, to evaluate the safety and tolerability of the ophthalmic solution PRO-179 compared with Travatan®, on the ocular surface of clinically healthy subjects.</td></tr>
<tr><td>Protocol code:

SOPH179-0818/I</td><td>Creation date:

August 1, 2018</td></tr>
<tr><td>Protocol version:
1</td><td>Date of the version:
August 1,2018.</td></tr>
<tr><td>Therapeutic indication:

Ocular hypotensor</td><td>Use:

Primary open-angle glaucoma</td></tr>
<tr><td>Estimated duration of the study (from the first visit of the first patient to the preparation of the final report):

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

I</td></tr>
<tr><td colspan="2">Goals:

To evaluate the safety and tolerability of the formulation PRO-179 manufactured by Laboratorios Sophia S.A. of C.V. on the ocular surface of clinically healthy subjects.</td></tr>
<tr><td colspan="2">Hypothesis:

The ophthalmic solution PRO-179 presents a profile of safety and tolerability similar to Travatan® in healthy subjects.</td></tr>
<tr><td colspan="2">Methodology:

Clinical trial Phase I, controlled, of parallel groups, double blind, with randomization.</td></tr>
<tr><td>Number of patients:

n= 24

12 subjects per group (both eyes).</td><td>Main inclusion criteria:

Clinically healthy subjects.</td></tr>
<tr><td colspan="2">Main selection criteria:

<u>Inclusion criteria:</u>

- Be clinically healthy.
- Have the ability to give their signed informed consent and show willingness to comply with the study procedures
- Have an age between 18 to 45 years.
- Indistinct sex.
- Women should ensure the continued use of a hormonal contraceptive method or intrauterine device (IUD) during the study period.
- Present blood tests: within normal parameters or with a range of ± 20% as long as the subject is clinically healthy.</td></tr>
</table>

- Blood count (BH): Hemoglobin, erythrocytes, hematocrit, total leukocytes, platelets, mean corpuscular volume and mean corpuscular hemoglobin.
- Blood chemistry of three elements (QS): Glucose, urea and creatinine.
- Liver function tests (PFH): TGO, TGP, total bilirubin, direct and indirect.

- Present visual ability 20/30 or better in both eyes.
- Present vital signs within normal parameters.
- Present intraocular pressure ≥10 and ≤ 21 mmHg.

Exclusion criteria:

- Be a user of topical ophthalmic products of any kind.
- Be a user of medicines, or herbal products, by any other route of administration, with the exception of hormonal contraceptives in the case of women.
- In case of being a woman, being pregnant or breastfeeding.
- Have participated in clinical research studies 90 days prior to inclusion in the present study.
- Have previously participated in this same study.
- Be a user of contact lenses and can not suspend their use during the study.
- That they can not follow the lifestyle considerations described in section 6.2.2
- Having started the use of hormonal contraceptives or IUD, 30 days prior to inclusion in the present study.
- Having a history of any chronic-degenerative disease.
- Present inflammatory or infectious disease, active at the time of admission to the study.
- Present injuries or unresolved traumas at the time of entering the study.
- Having the antecedent of any type of eye surgery.
- Having undergone surgical procedures, not ophthalmological, in the last 3 months.

Test product, dose and route of administration:

- PRO-179. Travoprost 0.004%. Ophthalmic solution. Sophia Laboratories, S.A. of C.V.
- Dosage: 1 drop at night.
- Route of administration: Ophthalmic.

Reference product, dose and route of administration:

- Travatan®. Travoprost 0.004%. Ophthalmic solution. Alcon Laboratories, Inc.
- Dosage: 1 drop at night. Both eyes.
- Route of administration: Ophthalmic.

Treatment duration:	**Duration of subject in the study:**
10 days.	15 to 22 days.

Evaluation criteria:

Primary outcome variables:

- Incidence of adverse events (AD) (Evaluation Time: day 5, 11 and 14).
- Ocular Comfort Index Score (ICO) (TE: day 11).

Secondary outcome variables:

- Changes in visual ability (TE: day 5 and 11).
- Changes in corneal and conjunctival staining with lysine green (TE: day 5 and 11).

- Changes in corneal and conjunctival staining with fluorescein (TE: day 5 and 11).
- Changes or conjunctival hyperemia (TE: day 5 and 11).
- Incidence of chemosis (TE: day 5 and 11).
- Incidence of alterations in the results of laboratory tests (TE: day 11).
- Incidence of alterations in heart rate (HR) (TE: day 5 and 11).
- Incidence of alterations in the respiratory frequency (RR) (TE: day 5 and 11).
- Incidence of alterations in systemic blood pressure (SBP) (TE: day 5 and 11)).

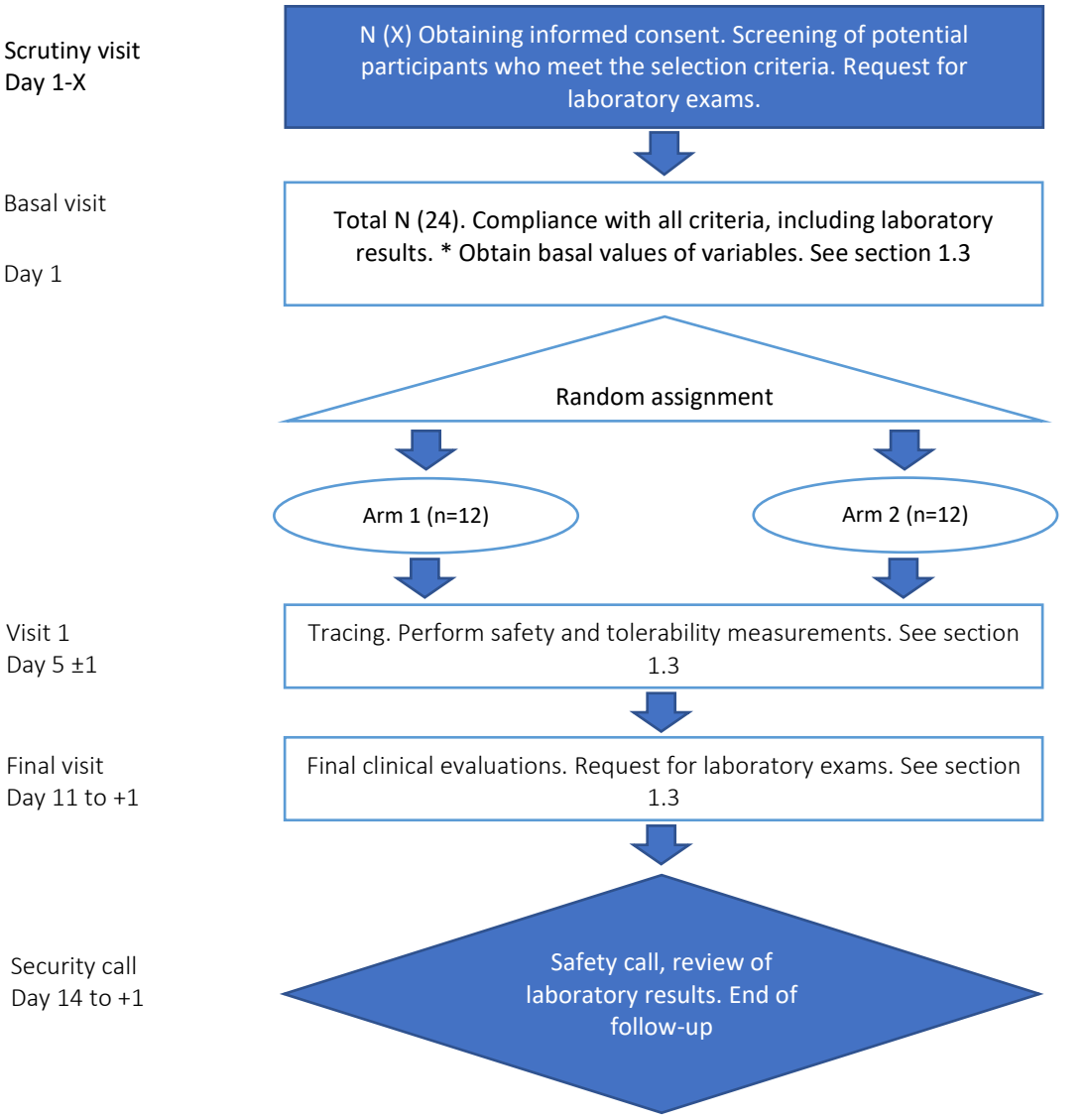
Exploratory outcome variables:

- Changes in intraocular pressure (TE: day 5 and 11).

Statistical methodology:

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

1.2 Diagram of the study.



* Baseline measurements can be taken from those made during the screening visit. It is the investigator's prerogative to perform them again at the baseline visit.

1.3 Schedule of the study .

Procedures	Scrutiny D 1 - X[a]	VB D 1	V1 D 5 ± 1	VF D 11 a + 1	LlS D 14 ± 1
CI Signature	X				
Clinic history	X				
Concomitant Medication Evaluation	X	X	X	X	
Urine pregnancy test	X			X	
Vital signs	X	X[1]	X	X	
CV	X	X[1]	X	X	
Integrity of the ocular surface	X	X[1]	X	X	
PIO	X	X[1]	X	X	
Comprehensive ophthalmological evaluation	X	X[1,2]	X	X[2]	
Eligibility criteria	X	X[b]			
Blood sampling	X			X	
EA evaluation	X	X	X	X	X
Review of laboratory results		X			X
Assignment of Research Product (PI)		X			
Ocular Comfort Index		X		X	
Delivery of the IP and start of intervention		X			
Adherence evaluation			X	X	
Daily delivery of the subject		X	X		
Continuity evaluation of the subject			X		
Return / Evaluation of the subject's Journal			X	X	
Return of IP				X	

a. The counting visit may be up to 7 days before the baseline, if it exceeds these the subject can not enter.
b. These criteria will be completed with the results of the laboratory tests and those obtained during the screening visit. 1 They can be taken from the scrutiny visit, it is the prerogative of the PI to measure them again at the baseline visit. 2 Includes subsequent segment valuation.

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2 Content

3 Index of abbreviations.

AA	Alpha-adrenergic agonists
BB	Beta-blockers
BH	Blood count
CONSORT	Consolidated Standards of Reporting Trials
CRF	Tumbler report format
CV	Visual ability
EA	Adverse events
EAS	Serious adverse events
FC	Heart rate
FR	Breathing frequency
GPAA	Primary open-angle glaucoma
HTO	Ocular hypertension
IAC	Carbonic anhydrase inhibitors
ICO	Eye comfort index
PI	Principal investigator
LLS	Security call
OD	Right eye
OS	Left eye
PFH	Liver function tests
PG	Prostaglandins
PGA	Prostaglandin analogues
IP	Product under investigation
PIO	Intraocular pressure
PM	Monitoring plan
PNA	Unanticipated problems
QS	Blood chemistry
TAS	Systemic blood pressure
TE	Evaluation time
TGO	Oxalacetic glutamic transaminase
TGP	Pyruvic glutamic transaminase

V1	Visit 1
VB	Basal visit
VF	Final visit

4 Administrative structure of the study.

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

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

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

Table 1. Administrative structure.

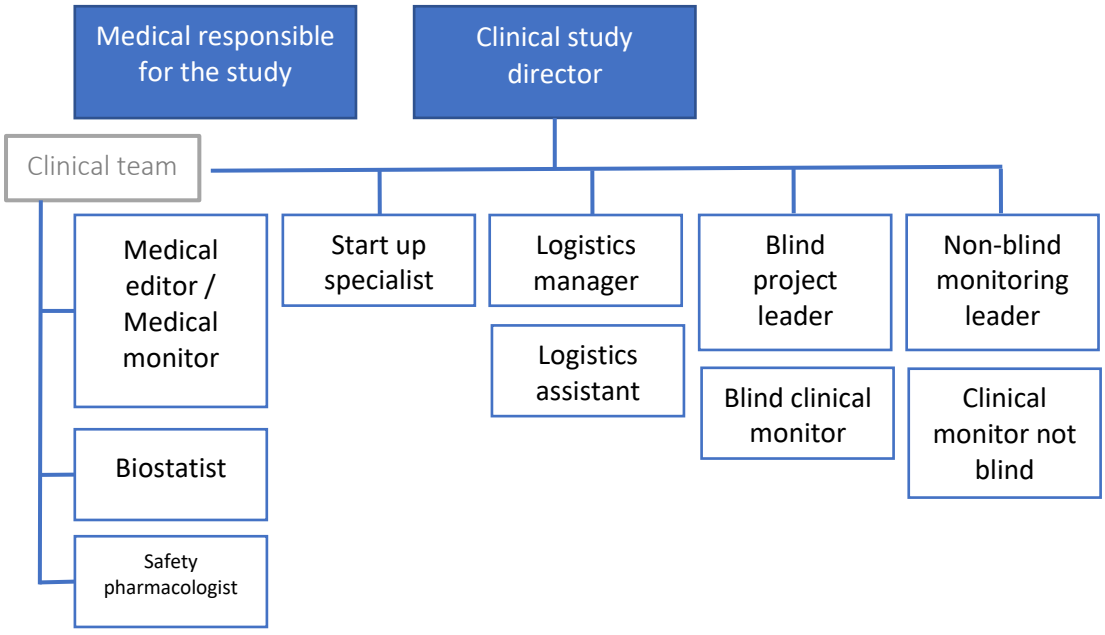

Figure 1. Administrative structure.

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5 Introduction

5.1Theoretical framework.

Glaucoma is a progressive optic neuropathy characterized by the loss of ganglion cells of the retina and their respective axons, resulting in the distinctive appearance of the optic disc and concomitant loss of visual function. [1] It is the second cause of blindness worldwide and it is estimated that by 2020, 79.6 million people will have glaucoma, with 74% of these corresponding to primary open-angle glaucoma (POAG). [2]

The mechanism by which glaucoma damages the optic nerve is probably multifactorial, nevertheless, elevated intraocular pressure (IOP) is the main risk factor and the only one that can be modified at present to prevent the progression of glaucoma damage, including Normo-tense glaucoma. [3, 4, 5, 6, 7]. It has also been shown that the reduction in IOP decreases the rate of conversion of ocular hypertension (OHT) to glaucoma. [5] The Early Manifest Glaucoma Trial, showed that in patients in the early stages of the disease, the risk of progression decreased by 10% per mmHg reduction compared to baseline. [8] Other authors, such as Chauhan et al, have reported that for each mmHg of increase in IOP, the risk of glaucoma progression increases 19%. [3]

Despite the great advances in surgical filtering treatments, implants and laser procedures that improve trabecular drainage, [9] pharmacological therapy continues to be the initial therapy for the majority of patients with OHT and glaucoma; this treatment typically includes the topical application of antihypertensive agents. [10]

Currently the pharmacological options for the reduction of IOP, with topical application, include prostaglandin analogues (PGA), beta blockers (BB), alpha adrenergic agonists (AA), carbonic anhydrase inhibitors (CAI) and parasympathomimetics. Commonly, pharmacotherapy begins with the application of a single hypotensive agent, usually of the so-called first-line agents (prostaglandin analogs and beta-blockers).[11]

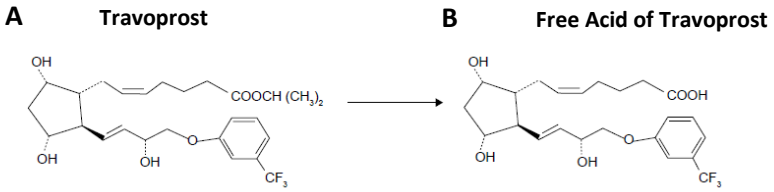
PGAs are a family of ocular hypotensors whose effect is through the prostaglandin (PG) F receptors, located in the ciliary muscle and the trabecular meshwork. [12, 13] Due to its hypotensive efficacy, once a day posology and a low rate of systemic and topical adverse reactions, PGAs have become first-line drugs for the treatment of glaucoma. [14]

5.2 Background.

5.2.1 Pharmacology of travoprost.

The travoprost is a synthetic derivative of the natural PG F2α (PGF2α). The natural PG, especially the F series, are relatively polar and hydrophilic, having a poor penetration of cell membranes. [15] Synthetic esterification in carbon-1 gives travoprost lipophilic properties, increasing its penetration through lipid membranes, such as the corneal epithelium. [16, 17] During passage through the cornea, the isopropyl ester in carbon-1 of travoprost is hydrolyzed, which generates an active free acid. [12, 13, 18] The free acid of travoprost is a potent agonist of the PGF receptors, approximately 10 times more potent than latanoprost. [13, 18]

Illustration 1. Chemical structure of travoprost.



Taken from Quaranta et al. [14]

5.2.1.1 Pharmacokinetics .

In animal models, a high concentration has been found in the anterior segment of the eye (aqueous humor and ciliary body) after its topical application, while in the posterior segment (vitreous, retina, choroid) it is found in low concentrations. [19] In a study in rabbits, their maximum concentration, 20 ng / g, was found between 1 and 2 hours after topical administration. The free acid was found at its maximum concentration in plasma, 25ng / L, at 10-30 minutes of the application, rapidly declining below the limit of detection at 1 hour. [18, 20]

A drop of travoprost 0.004% contains 1.2µg of the travoprost prodrug. After bilateral administration, travoprost-free acid reaches a maximum plasma level of 10-10 M. [21] The plasma half-life is approximately 45 minutes and less than 2% of the ophthalmic dose is excreted in the urine within the first 4 hours.

Metabolism is the main route of elimination for travoprost and its free acid. The metabolic pathways are the same as those for the endogenous prostaglandin F2α.[18, 20]

5.2.1.2 Pharmacodynamics .

Like other PGs, travoprost exerts its hypotensive effect mainly by increasing the uveoscleral flow, however, it also has some effect on the trabecular meshwork. [22] Increase in uveoscleral flow has been demonstrated in preclinical and clinical studies. [23, 24] No effects on the production of aqueous humor have been described.

The remodeling of the extracellular matrix in the ciliary body is the most studied mechanism of action of the PGA. The travoprost stimulates the secretion and activation of the matrix metalloproteinase (MMP) 2 in the cells of the ciliary muscle, by extracellular signaling and protein kinase C, regulated by the protein kinase 1 and 2 dependent pathways. [25] MMP2, together with MMP1 and MMP3, induce the dissolution of collagen type I and III of the extracellular matrix. [26]

5.2.2 Efficiency of travoprost.

There are many studies in the literature that demonstrate the efficacy of topical administration of travoprost 0.004% to reduce IOP in patients with OHT and POAG. [15, 27] In a review study it was calculated that travoprost produced, on average, a 28.7% decrease in IOP of patients with POAG. [28] Similarly, the meta-analysis of van de Valk estimated that travoprost was able to induce a decrease in IOP between 29% and 31%. [29]

The main studies that have shown the effectiveness of travoprost have compared it against timolol, previously considered the first line therapy in the treatment of glaucoma; in these studies, a superiority in the decrease in IOP in favor of travoprost has been demonstrated. [30, 31, 32, 33]

In clinical studies in which travoprost has been compared against other PGAs, no significant differences have been demonstrated in its efficacy in decreasing IOP. [32, 34, 35, 36]

The travoprost has also been used in fixed combinations, associated with timolol.

5.2.3 Safety of travoprost.

Conjunctival hyperemia is a common adverse reaction of PGAs, mainly due to vasodilation in sclera and conjunctiva. [37] Several studies place the occurrence of conjunctival hyperemia between 27% and 49%. [32, 38, 39]

Other reactions commonly attributed to PGAs are the growth and darkening of the eyelashes and the darkening of the iris. [40, 41, 42]

There have been some reports of cases of potential risk of cystoid macular edema in pseudophakic patients using PGAs. [43, 44] Nevertheless, this relationship has not been confirmed with appropriate scientific literature. [37]

Cases of anterior uveitis related to the use of travoprost have been reported, which remit when the travoprost is discontinued and with the administration of topical steroids. [45]

5.2.4 Risk benefit evaluation.

5.2.4.1 Known potential risks.

The frame of reference of travoprost places it as a safe molecule, with a known safety and tolerability profile. PRO-179 shares the same active principle, in the same concentration as Travatan®. The main adverse effects, such as conjunctival hyperemia and alterations in eyelashes and eyelids are reversible. The effects on changes in iris coloring appear in the first 6 to 8 months of treatment.

Pre-clinical studies of PRO-179 compared to Travatan® have been conducted, where a safety and toxicity profile has been demonstrated, as well as similar bioavailability in a model of albino rabbits New Zealand. [46, 47]

5.2.4.2 Known potential benefits.

The effectiveness of travoprost has been previously documented in the literature. Generic drugs help reduce the costs of treatments by generating direct competition with the innovator.

The present study does not represent a direct benefit for patients; nevertheless, neither a potential risk in the medium or long term; due to the antecedents that place travoprost as safe. In the same way, the procedures proposed to be carried out during the study do not represent an additional risk to the subject.

5.3 Statement of the problem.

Chronic diseases, such as glaucoma, pose a significant economic burden to the patient and society. Due to this the health authorities support the development of generic medicines, once the patent of the innovator has expired. The above would mean obtaining the drugs at a lower cost.

In systemic medications, bioequivalence studies are required to demonstrate the interchangeability of the generic by the innovator; Generally, these consist of the determination of the plasma concentration of the drug. Nevertheless, this is not possible for drugs in ophthalmic formulations, due to the low concentrations available in plasma after topical application.

In Mexico, and other countries, generic ophthalmic drugs can obtain their registration fulfilling certain specifications in their formulation and characterization, not requiring clinical studies.

In general, published scientific data supporting the equivalence of a generic ophthalmic and the innovative are scarce.

5.4 Justification.

Travatan® developed by Alcon Laboratories, Inc. was the first 0.004% travoprost formulation commercially available in Mexico and other countries in the world. Since 2001, Travatan® has registered with COFEPRIS. Currently there are generic options in Mexico, which do not have their own clinical studies, supported only by the information and publications of the innovator.

PRO-179 is a formulation of travoprost 0.004%, elaborated by Sophia Laboratories, S.A. of C.V., which is not yet commercially available but has registration with COFEPRIS under the distinctive name of Bristrio®. Although it is a generic product, which does not differ in the concentration of the active principle in relation to the innovative Travatan®, it is desired to document its safety and tolerability profile in a phase I study.

5.5 Objectives and hypothesis.

5.5.1 General objective.

- To evaluate the safety and tolerability of the ophthalmic solution PRO-179 on the ocular surface.

5.5.1.1 Specific objectives.

- Compare the safety of the ophthalmic solution PRO-179 with Travatan® by means of the incidence of adverse events during the study.
- To compare the tolerability of the ophthalmic solution PRO-179 with Travatan® by means of the ICO score.

5.5.2 Secondary objectives.

- Compare the safety of PRO-179 with Travatan® through changes in visual ability during visits.
- Compare the safety of PRO-179 with Travatan® through changes in corneal and conjunctival stains with lysine green during visits.
- Compare the safety of PRO-179 with Travatan® through changes in corneal and conjunctival stains with fluorescein during visits.
- Compare the safety of PRO-179 with Travatan® through changes in conjunctival hyperemia during visits.
- Compare the safety of PRO-179 with Travatan® by the incidence of chemosis during visits.
- Compare the safety of PRO-179 with Travatan® by means of the incidence of alterations in the results of the laboratory tests on day 11.

- Compare the safety of PRO-179 with Travatan® through the incidence of changes in HR during visits.
- Compare the safety of PRO-179 with Travatan® by means of the incidence of RF alterations during visits.
- Compare the safety of PRO-179 with Travatan® by the incidence of changes in SAD during visits.

5.5.3 Exploratory objectives.

- Compare changes in intraocular pressure during visits.

5.5.4 Hypothesis.

H0 The ophthalmic solution PRO-179 presents a profile of safety and tolerability similar to Travatan® in healthy subjects.

Ha The ophthalmic solution PRO-179 presents a different safety and tolerability profile Travatan® in healthy subjects.

5.6 Design and plan of the study.

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

5.6.1 Discussion of the study design.

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

The comparator, Travatan®, has a known safety profile and shares the same active principles in the same concentrations as PRO-179, which is why it was chosen as the best option to compare.

5.6.2 Justification of the posology.

The chosen dosage is one drop every 24 hours at night, this is the indicated and approved dosage for the reference medicine. Clinical studies demonstrate the sufficiency of 1 drop every 24 hours; likewise, they have shown that the administration at night presents less IOP fluctuations during 24 hours, unlike the morning application. [38]

For this phase I study, we do not consider it necessary to expose the research subjects to dosage rates higher than those recommended, since it is not justifiable.

6 Material and methods. Participants, interventions and variables.

6.1 Study center.

The present study will be carried out in a research center previously evaluated by the sponsor. This center will be an institution or establishment where health research is carried out that complies with current regulations.

6.1.1 Organization of the center.

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

The PI will also be responsible for forming a multidisciplinary research team to carry out the clinical study according to protocol, under its scientific guidance. It is the prerogative of the PI the design of the organization of its center and the selection of the personnel that will perform the functions. Notwithstanding, the minimum organization of the research team requested by the sponsor requires the figure of sub-researcher, study coordinator and pharmacist or non-blinded staff. (See **Figure 2 Minimum organization of the center**).

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

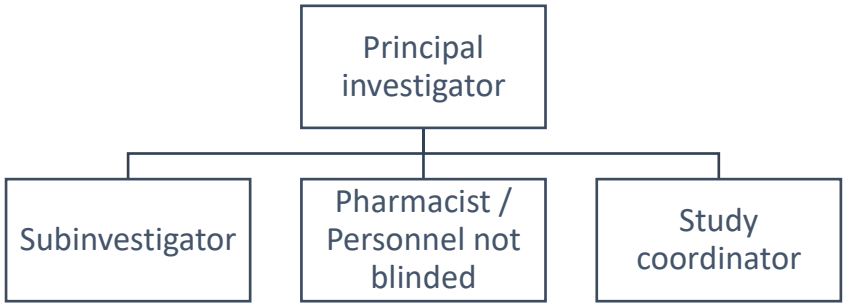


Figure 2 Minimum organization of the center.

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

6.1.2 Documentation to be delivered to the sponsor.

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

- Curriculum vitae updated, in Spanish, dated and signed (maximum 10 pages), of the PI and the personnel that make up the organizational chart of the center.

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

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

- Copy of operation notice.

- Certificate of Good Clinical Practices in force. In case the certificate does not specify the validity time in the certificate, the date of issue of the certificate must not exceed one year.

6.1.3 Closure of the center.

The closing of the center will be carried out once the last visit of the last included subject previously agreed between the sponsor and the PI has been made. The closing process will be according to the normal procedures of the sponsor's internal operations and must have the disposition and participation of the PI and whoever he designates.

It is the sponsor's prerogative to prematurely close a study center, it must inform the PI the reasons for the closure. These can be, but do not exclude:

a) Lower recruitment to the projected.
b) Deviations greater than the protocol, which at the sponsor's discretion merit closing the center.
c) Recidivism of deviations to the protocol, which at the sponsor's discretion merit closing the center.
d) Early termination of the study.

6.2 Study population.

6.2.1Selection criteria.

6.2.1.1 Inclusion criteria.

- Be clinically healthy.
- Have the ability to give their signed informed consent and show willingness to comply with the study procedures
- Have an age between 18 to 45 years.
- Indistinct sex.
- Women should ensure the continued use of a hormonal contraceptive method or intrauterine device (IUD) during the study period.
- Present blood tests: within normal parameters or with a range of ± 20% as long as the subject is clinically healthy.
    - Blood count (BH): Hemoglobin, erythrocytes, hematocrit, total leukocytes, platelets, mean corpuscular volume and mean corpuscular hemoglobin.
    - Blood chemistry of three elements (QS): Glucose, urea and creatinine.
    - Liver function tests (PFH): TGO, TGP, total bilirubin, direct and indirect.
- Present visual ability 20/30 or better in both eyes.
- Present vital signs within normal parameters.
- Present intraocular pressure ≥10 and ≤ 21 mmHg.

6.2.1.2 Exclusion criteria.

6.2.1.2.1 General criteria.

– Be a user of ophthalmic topical products of any kind.
– Be a user of medicines, or herbal products, by any other route of administration, with the exception of hormonal contraceptives in the case of women.
– In case of being a woman, being pregnant or breastfeeding.

- Have participated in clinical research studies 90 days prior to inclusion in the present study.
- Have previously participated in this same study.
- Be a user of contact lenses and can not suspend their use during the study.
- That they can not follow the lifestyle considerations described in numeral 6.2.2

6.2.1.2.2. Medical and therapeutic criteria.

- Have started the use of hormonal contraceptives or IUD, 30 days prior to inclusion in the present study.
- Having a history of any chronic-degenerative disease.
- Present inflammatory or infectious disease, active at the time of study entry.
- Present unresolved injuries or traumas at the time of study entry.
- Having a history of any type of eye surgery.
- Have undergone surgical procedures, not ophtalmological, in the las 3 months.

6.2.1.3 Elimination criteria.

- Withdrawal of the consent letter under information.
- Presentation of a serious adverse event related or not to the investigational product, which has criteria of the PI and / or the sponsor could affect the ability of the patient to continue with the study procedures safely.
- No tolerability or hypersensitivity to any of the compounds used during the tests (fluorescein, green lysine, tetracaine)
- No tolerability or hypersensitivity to any of the investigational drugs.

6.2.2 Lifestyle considerations.

For the study it is necessary that the participants modify the following activities of their lifestyle:

- Abstain from alcohol consumption, from entering the study to taking laboratory tests of the final visit.
- Refrain from tobacco use.
- Refrain from the use of electronic vaporizers.
- Avoid submerging in water without eye protection (goggles-protective glasses).
- Avoid direct exposure to fans (including air conditioning vents) during activities that involve sight. 24 hours before your review visits.
- Do not modify your sleep-wake cycle with which you enter the study.

6.2.3 Scrutiny failures.

A failure to scrutinize is defined as those participants who agree to participate in the study, granting their consent, but who are not assigned to any intervention, that is, they do not enter the study. It is necessary that the following information of the inclusion faults be reported minimally:

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

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

Subjects who do not meet the eligibility criteria to participate in the study (inclusion failure) due to a specific modifiable factor, could re-participate in the scrutiny. Subjects in this case must use the same initial screening number.

6.2.4 Recruitment and retention strategies.

This is a phase I study, which will be conducted in a center. The selected center will be responsible for the recruitment of healthy subjects. The minimum recruitment index is 0.53 patients per day, because it must recruit 24 subjects in 45 days.

The duration of the participation of the subject in the study is short, so no retention problems are anticipated. However, the subjects will be creditors of a travel allowance support and fulfill their visits. Other strategies to improve the retention of subjects include, but are not limited to:

- Clearly inform the importance of the study and the benefits that the population will obtain from the results of the study.
- Make calls or send text messages to remember appointments or activities to perform.
- Provide a printed calendar and an identification card with the purpose of remembering appointments and activities that will be carried out, in addition to the estimated duration of the same.
- In case the participant does not attend his / her appointment, the research center must make a call to know the reason and try to arrange a new appointment within the established window period or an unscheduled appointment. In case it is not possible to make an appointment, it will be asked about the presence of adverse events and the reason for leaving the study, as minimum data.

All materials to be delivered to the subject will be submitted for approval by the corresponding committees.

6.2.5 Identification of the subject.

The study patients 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 maximum three letters, in case the person has two names or last name always composed the first letter will be used.

Example:

A. Arieh Daniel Mercado Carrizalez
   a. Initials: AMC

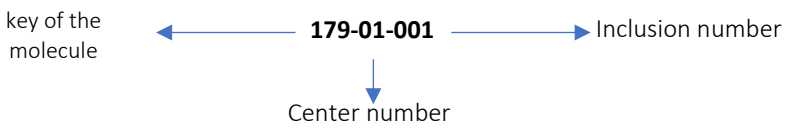
B. Juan De la Torre Orozco
   b. Initials: JDO

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

- three digits of the molecule under study according to the denomination by the sponsor.
- two digits corresponding to the research center number.

- three digits of the number consecutive to its inclusion assigned to the research center.

Example:



6.3 Intervention.

The subjects will be divided into two equal groups, to which they will be assigned randomly and blinded to one of the products in research (PI) PRO-179 or Travatan®.

Dosage: 1 drop every 24 hours, at night, in both eyes.

Instructions for administration: instillate a drop in the conjunctival sac, it is recommended to exert gentle traction on the lower eyelid, with the index finger, to expose the cul-de-sac and instillation. Avoid blinking energetically for the next few minutes or closing your eyes in a forced way.

Duration of the intervention: 10 days.

6.3.1 Medications administered.

6.3.1.1 Drug under study.

- Generic name: Travoprost
- Distinctive denomination: Bristrio® (PRO-179)
- Active principles: Travoprost 0.004%.
- Pharmaceutical form: Ophthalmic solution
- Presentation: multi-dose dropper bottle, 2.5 ml.
- Prepared by: Sophia Laboratories, S.A. of C.V.
- Description of the solution: transparent solution, free of visible particles.
- Description of container: White bottle with 5mL capacity, made of low density polyethylene.

Agent	Quantity mg / mL	Function
Travoprost	0.040	Active principle
Hydroxypropylbetacyclodextrins	Not showing	Stabilizer
Mannitol	Not showing	Toning
Boric acid	Not showing	Buffer Agent
Sodium Borate Dehydrated	Not showing	Buffer Agent
Disodium edetate Dihydrate	Not showing	Chelating Agent
Benzalkonium Chloride (1)	Not showing	Conservative
Water for the preparation of Injectables c.b.p.	1.000 mL	Vehicle

Quali-quantitative formulation of IP PRO-179. The concentration of the active principles is shown, as well as the substances that act as additives. 1 50% solution c.b.p. How much is enough to.

Table 2. Quali-quantitative formulation of PRO-179.

6.3.1.1 Reference medicine.

- Generic name: Travoprost
- Distinctive denomination: Travatan®
- Active ingredients: Travoprost 0.004%
- Pharmaceutical form: Ophthalmic solution.
- Presentation: multi-dose dropper bottle, 2.5 ml.
- Prepared by: Alcon Laboratories Inc.
- Description of the solution: transparent solution, free of visible particles.
- Consult information to prescribe.

6.3.2 Strategies to improve adherence and procedure to monitor adherence.

1. 1. Direct questioning by the PI about the application of the IP.
2. 2. Delivery of a printed calendar specifying the date of the visit and its activities.
3. 3. Journal of the subject.

6.3.2.1 Procedure to monitor adherence.

For more than four decades, there have been numerous investigations on the proper way to measure and quantify adherence to medications, however none has reached consensus to establish itself as the gold standard, both in cross-sectional and longitudinal studies. [48, 49, 50, 51, 52, 53, 54, 55]

There are different procedures to measure the adherence of pharmacological interventions. The most common procedure includes self-reports, these include: patient interviews, questionnaires and self-monitoring journals. Its strengths are speed, flexibility, low cost and ease of implementation; they have a high degree of specificity for non-adherence, nevertheless, the sensitivity and reliability for adherence is low. [55, 56]

The biochemical measurement of the drug, or its metabolite, is one of the methods that best confirms the use of the drug. Nevertheless, in addition to raising costs and being impractical, it is of little use in the context of ophthalmic applications, since concentrations at the peripheral level could be undetectable; and samples from other tissues imply more invasive methods that would not be advisable. [55]

Medication counting is another way to measure adherence. Classically referred to as "pill counting", in ophthalmology it is translated to the weight of the bottle. This is a simple, economical and non-invasive method. The main disadvantages of this method are: 1. The application of the medication can not be confirmed (it could have been intentionally thrown or instilled out of the eye) and 2. It depends on the subject bringing back the medication. [55, 56]

For the purposes of this study, the evaluation of the adherence will be favored by means of the diary of the subject, and will be carried out in the following way:

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

$Ad = Adherence$

$Ar = Registered\ applications$

$Ai = Applications\ indicated\ for\ the\ IP$

The final adhesion will be determined by the average of the adherence of each one of the visits. Overall adherence (all subjects) will be determined by the average final adherence of each of the subjects.

6.3.3 6.3.3 Treatments and concomitant medications allowed and prohibited during the study.

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

Nor is the use of herbal or naturist products, whose purpose is to modify some physiological function of the subject.

6.3.4 Treatment management.

The IPs will be provided by Sophia Laboratories, S.A. of C.V. It will be the responsibility of the sponsor to select and ensure the logistic methods for the distribution of the medication. They will be labeled and reconciled. The handling of the treatment will be under the responsibility of the researcher or a designated member of his team.

6.3.4.1 Delivery and reception.

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

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

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

6.3.4.2 Storage.

Storage and safekeeping is the responsibility of the sponsor and the research center. The medication must be stored in a secure area with restricted access.

The storage temperature should be 2 ° C to 25 ° C.

The research center has the obligation to record, in the designated format, the temperature recorded in the data logger, every day while the protocol is in force and has IPs.

These data will be reviewed by the clinical monitor according to the registration in the data logger.

6.3.4.3 Return.

The return will be made by the research center when the sponsor indicates it. Prior to the return, the research center must make a count of the assigned medication and the remaining medication, with the aim of creating an inventory which serves for the final filling of the medication return form.

6.4 Delay variables.

6.4.1 Security variables.

6.4.1.1 Primary outcome variables.

- Incidence of adverse events.

6.4.1.2 Variables of primary outcome of tolerability.

- ICO score.

6.4.1.3 Secondary outcome variables.

- Changes in visual ability.
- Changes in corneal and conjunctival staining with lysine green.
- Changes in corneal and conjunctival staining with fluorescein.
- Changes conjunctival hyperemia.
- Incidence of chemosis.
- Incidence of alterations in the results of laboratory tests.
- Incidence of alterations in the FC.
- Incidence of alterations in the RF.
- Incidence of alterations in the TAS.

6.4.2 Exploratory variables.

- - Changes in IOP.

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

Variable	Kind	Unit (Symbol)	Method of measurement	Normal value	Evaluation time	Statistical test
Primary						
Adverse events	Discreet Categorical rating	Number of cases (n) Present/ absent	Count Observation	0 Absent	VB, V1, VF y LLS	Mann-Whitney U χ^2 o Fisher's exact
ICO score	Discreet	Points	Questionnaire	NA	VB, VF	Mann-Whitney U
Secondary						
Visual ability	Discreet	Fraction	Snellen Primer	1	VB, V1 y VF	Mann-Whitney U
Corneal and conjunctival staining with fluorescein	Ordinal	Degrees	Direct observation with slit lamp and cobalt blue filter, Oxford scale graduation	0	VB, V1 y VF	χ2 or Fisher's exact

Variable	Kind	Unit (Symbol)	Method of measurement	Normal value	Evaluation time	Statistical test
Corneal and conjunctival staining with lysamine green	Ordinal	degrees	Direct observation with slit lamp, Oxford scale graduation	0	VB, V1 y VF	χ2 or Fisher's exact
Conjunctival hyperemia	Ordinal	Normal / Very Light / Mild / Moderate / Severe	Direct observation. Classification of Efron.	Normal	VB, V1 y VF	χ2 or Fisher's exact
Chemosis	Categorical rating	Present / absent		Absent	VB, V1 y VF	χ2 or Fisher's exact
FC	Discreet	eats per minute (l / m)	Auscultation with stethoscope	60 to 100	VB, V1 y VF	Mann-Whitney U
FR	Discreet	Breaths per minute (r / m)	Auscultation with stethoscope	12 to 24	VB, V1 y VF	Mann-Whitney U
TAS	Discreet	Millimeters of mercury (mmHg)	Measurement with sphygmomanometer	90-120/ 60-80	VB, V1 y VF	Mann-Whitney U
Erythrocytes	Continuous	Thousands per microliter (Mil / dL)	Laboratory analysis	4.0- 6.3	VB y VF	Mann-Whitney U
Hemoglobin	Continuous	Grams over deciliter (g / dL)	Laboratory analysis	11.0-16.0	VB y VF	Mann-Whitney U
Hematocrit	Continuous	Percentaje (%)	Laboratory analysis	36-51	VB y VF	Mann-Whitney U
VGM	Continuous	Femto liters (fL)	Laboratory analysis	80-97	VB y VF	Mann-Whitney U
HCM	Continuous	Picograms (pg)	Laboratory analysis	25-32	VB y VF	Mann-Whitney U
Leukocytes	Continuous	Thousands per liter units (Mil / uL)	Laboratory analysis	4.0-11.0	VB y VF	Mann-Whitney U
Platelets	Continuous	Thousands per liter units (Mil / uL)	Laboratory analysis	150-400	VB y VF	Mann-Whitney U
Glucose	Continuous	Milligrams over deciliter (mg / dL)	Laboratory analysis	70-100	VB y VF	Mann-Whitney U
Urea	Continue	Milligrams over deciliter (mg / dL)	Laboratory analysis	10-50	VB y VF	Mann-Whitney U

Variable	Kind	Unit (Symbol)	Method of measurement	Normal value	Evaluation time	Statistical test
Creatinine	Continuous	Milligrams over deciliter (mg / dL)	Laboratory analysis	0.6-1.1	VB y VF	Mann-Whitney U
Glutamic pyruvic transaminase	Continuous	Units over liter (U / L)	Laboratory analysis	0-31	VB y VF	Mann-Whitney U
Oxalacetic glutamic transaminase	Continuous	Units over liter (U / L)	Laboratory analysis	0-32	VB y VF	Mann-Whitney U
Total bilirubin	Continuous	Milligrams over deciliter (mg / dL)	Laboratory analysis	0-1.1	VB y VF	Mann-Whitney U
Direct bilirubin	Continuous	Milligrams over deciliter (mg / dL)	Laboratory analysis	0.0-0.3	VB y VF	Mann-Whitney U
Indirect Bilirubin	Continuous	Milligrams over deciliter (mg / dL)	Laboratory analysis	0.0-0.8	VB y VF	Mann-Whitney U
Exploratoria						
Presión intraocular	Continuous	Millimeters of mercury (mmHg)	Goldmann Tonometry	10 to 21	VB, V1 y VF	Mann-Whitney U

Table 3. Table of operational definitions of variables.

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

6.4.3.1 Visual capacity.

Visual acuity (VA) is a test of visual function. Spatial visual acuity is the ability to distinguish separate elements of an object and identify them as a whole. It is quantified as the minimum separation angle (located at the nodal point of the eye) between two objects that allows perceiving them as separate objects.
The 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 arc minutes. Thus, at 6 meters a letter 6/6 (20/20) equals 5 minutes of arc, a letter 6/12 (20/40) equals 10 minutes, and a letter 6/60 (20/200) equals 50 minutes The Snellen fraction can also be expressed as a decimal (ie 20/20 = 1 and 20/40 = 0.5). [57]

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

will be annotated by the fractional evaluator as the DO of the DO in the clinical file. Proceed to the OS with the same method.

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

6.4.3.2 Comprehensive ophthalmologic evaluation.

It refers to the ophthalmological exploration of eyelids and appendages, anterior segment and posterior segment that is performed in a routine ophthalmologic review, whose procedures are not specifically included in the study variables. This evaluation has the purpose of identifying unexpected events. The evaluation of the posterior segment will be carried out under drug mydriasis (Tropicamide 0.8% / Phenylephrine 5%), in the slit lamp with an aerial loupe (at the choice of the IP). An integral assessment of the fundus (including optic disc, posterior pole and periphery) will be performed in search of abnormalities that alter the result of the study. The result of the assessment will be recorded in the clinical file. In the CRF it will be registered as normal, abnormal or abnormality that does not affect.

6.4.3.3 Eye comfort index.

It is a questionnaire designed to measure the irritation of the ocular surface with Rasch analysis to produce estimates on a linear scale of intervals (ratings: 0-100). Similar to the index for ocular surface diseases, the ocular comfort index (ICO) evaluates symptoms. The ICO contains items that focus on the discomfort associated with alterations of the ocular surface. Each of these questions has two parts, which inquire separately the frequency and severity of the symptoms. [58] See annex Eye comfort index.

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

6.4.3.4 Integrity of ocular surface:

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

The variables that will be registered in this protocol are:

- *Conjunctival hyperemia.*
  It is defined as the simplest reaction of the conjunctiva to a stimulus, a red appearance secondary to the vasodilation of the conjunctival vessels of variable intensity. He will graduate using the Efron scale. [59] See annex Efron's scale for conjunctival hyperemia.
- *Chemosis*.
  It is defined as conjunctival edema, the result of an inflammatory reaction. It is qualified as present or absent. The assessor will use a narrow beam of light at 60 ° and will measure if the conjunctiva separates from the sclera by ≥ 1/3 of the total palpebral opening or if it exceeds the gray line. [60]

6.4.3.4.1 Stains.

- *Staining with lysine green.*

  A drop of topical anesthetic will be instilled in the conjunctival cul-de-sac, then a drop of saline solution will be applied to the tip of the green lysine strip and it will be allowed to slide

towards the bottom of the sac. It is essential to quickly evaluate the staining, in sequence, first in the OD and then the OS, so that the observed patterns are equally bright. [61] See annex Scale of Oxford.

- *Fluorescein staining.*

A drop of topical anesthetic will be instilled in the conjunctival cul-de-sac, then a second drop will be applied to the tip of the fluorescein strip and it will be allowed to slide towards the bottom of the sac. It is essential to quickly evaluate the staining, in sequence, first in the OD and then the OS, so that the observed patterns are equally bright. This valuation will be done with the cobalt blue filter. [61] See annex Scale of Oxford.

6.4.3.5 Presence of adverse events.

The management of the EAs will be done according to what is described in the Adverse Events section.
The PI will register in the corresponding section of the CRF the EAs that come to present the subjects of the study in addition to referring it in the clinical file.

6.4.3.6 Intraocular pressure.

Tonometry is the objective measure of IOP, based primarily on the force required to flatten the cornea or the degree of corneal indentation produced by a fixed force. Goldman's tonometry is based on the Imbert-Fick principle. [57] The tonometry will be performed, after instillation of a drop of topical anesthetic (tetracaine 0.5%), with fluorescein and the use of the cobalt blue filter (after evaluation of the corneal surface staining). There will be 3 shots, which will be recorded in the clinical file and the average will be registered in the CRF.

6.4.3.7 Vital signs.

The vital signs to be evaluated (FC, FR and TAS) can be measured by an assistant duly indicated in the organization of the center and the delegation of responsibilities, the technique to be used for the FC and FR will be with the count of repetitions in one minute by direct auscultation with stethoscope.
The SBP should be measured with 5 minutes of previous rest, in the left arm. The instrument can be manual or automatic according to the PI. It is necessary that all measurements are equal in circumstances. The PI will register in the note and the CRF.

6.4.3.8 Laboratory tests.

The designated personnel will perform the extraction of the blood sample, through venipuncture. The vein will be chosen at the discretion of the personnel in charge and will perform asepsis of the skin of the area to be punctured prior to the procedure. It will generate the order of the studies of BH, QS and PFH, to be carried out by the clinical laboratory designated by the sponsor. The clinical laboratory will deliver to the the results for its assessment and registration. The normal parameters to be considered will be the ranges established by the laboratory, with a lower and superior margin of 20% in a clinically healthy subject, at the discretion of the PI.

6.4.4 Measurement time.

The measurements of the variables of primary and secondary outcome, as well as the activities contemplated in the protocol, will be carried out and evaluated for each visit, according to the following:

Basal Visit / Day 1.

Some of these measurements will be taken at the screening visit to complete the eligibility criteria, at the discretion of the PI, they may be taken to complete the baseline visit data.

1. 1. Eye comfort index.
2. 2. Visual ability
3. 3. Vital signs
4. 4. Evaluation of ocular surface.
5. to. It includes stains.
6. 5. Intraocular pressure.
7. 6. Comprehensive ophthalmological evaluation.
8. 7. Evaluation of adverse events.
9. 8. Evaluation of results of laboratory tests.

Visit 1 / Day 5.

1. It can be done in a period ± 1 days in relation to the 4th day of application.
2. 1. Visual ability
3. 2. Intraocular pressure.
4. 3. Evaluation of ocular surface.
5. to. It includes stains.
6. 4. Comprehensive ophthalmological evaluation.
7. 5. Vital signs
8. 6. Evaluation of adverse events.

Final Visit / Day 11.

1. It can be done in a period + 1 day in relation to day 11, not before day 11 since the 10 days of application would not be fulfilled.
2. 1. Visual ability
3. 2. Intraocular pressure.
4. 3. Eye comfort index.
5. 4. Evaluation of ocular surface.
6. to. It includes stains.
7. 5. Comprehensive ophthalmological evaluation.
8. 6. Vital signs
9. 7. Evaluation of adverse events.

Security call / Day 14.

1. It can be done in a period ± 1 day in relation to the 14th day of the start of application.
2. 1. Ask about the presence of an adverse event.
3. 2. Evaluation of results of laboratory tests.

6.5 Timeline and study diagram.

Procedures	Scrutiny	VB	V1	VF	LIS
	D 1 - X[a]	D 1	D 5 ± 1	D 11 a + 1	D 14 ± 1
CI Signature	X				
Clinic history	X				
Concomitant Medication Evaluation	X	X	X	X	
Urine pregnancy test	X			X	
Vital signs	X	X[1]	X	X	
CV	X	X[1]	X	X	
Comprehensive ophthalmological evaluation	X	X[1]	X	X	
Integrity of the ocular surface	X	X[1]	X	X	
PIO	X	X[1,2]	X	X[2]	
Eligibility criteria	X	X[b]			
Blood sampling	X			X	
EA evaluation	X	X	X	X	X
Review of laboratory results		X			X
Assignment of Research Product (PI)		X			
Ocular Comfort Index		X		X	
Delivery of the PI and start of intervention		X			
Adherence evaluation			X	X	
Daily delivery of the subject		X	X		
Continuity evaluation of the subject			X		
Return / Evaluation of the subject's Journal			X	X	
Return of PI				X	

a The counting visit may be up to 7 days before the baseline, if it exceeds these the subject can not enter.

b These criteria will be completed with the results of the laboratory tests and those obtained during the screening visit. 1 They can be taken from the scrutiny visit, it is the prerogative of the PI to measure them again at the baseline visit. 2 Includes subsequent segment valuation.

Table 4. Activities schedule.

6.5.1 Procedures to be carried out per visit.

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

6.5.1.1 Scrutiny visit.

- Signature of informed consent: refers to the signing of the informed consent document in writing. Without obtaining informed consent it is not possible to perform any of the study procedures. See 10.4.1 Obtaining.
- General and ophthalmological clinical history: refers to the technical, clinical and legal document in which the patient's health conditions, medical acts and other procedures performed on the patient are recorded chronologically. It includes anthropometric measurements, the anamnesis, comprehensive ophthalmological exploration that allows to discern the patient's eligibility, that is to say, evaluation of both eyes of ocular adnexa, exploration with slit lamp of the ocular surface and the anterior segment and funduscopy. If the patient is taken from the established population base of the study center, he / she will be able to use the existing clinical history, and should only perform an update.
- Evaluation of concomitant medications: refers to the interrogation by the PI to the subject, inquiring about the use of medications.
- Urine pregnancy test: Refers to the performance of a rapid pregnancy test in all women of childbearing age who wish to enter the study. By fertile age we understand women who have presented their menarche and have not presented their menopause. Menopause is defined as 12 months from the last menstruation in women over 40 years of age; or those who underwent bilateral hysterectomy or oophorectomy. Women of childbearing age with contraceptive methods including bilateral tubal obstruction should be tested for pregnancy. This test will be done by the PI or the designated team person according to the instructions of the device delivered by the sponsor.
- Vital signs: see 6.4.3.7 Vital signs.
- Visual capacity: see 6.4.3.1 Visual capacity.
- Comprehensive ophthalmological evaluation: see 6.4.3.2 Comprehensive ophthalmological evaluation.
- Integrity of the ocular surface: see 6.4.3.4 Integrity of ocular surface:
- Intraocular pressure: see 6.4.3.6 Intraocular pressure.
- Eligibility criteria: refers to the review by the PI, where it states that the subject can be included in the study by meeting the inclusion criteria and not meeting the exclusion criteria. See 6.2.1 Selection criteria.
- Sampling of laboratory samples: see 6.4.3.8 Laboratory tests.
- Adverse events: see 6.4.3.5 Presence of adverse events.

6.5.1.2 Basal visit.

- Review of laboratory tests: refers to the review and analysis by the PI of the results of the BH, QS and PFH.
- Eligibility criteria: with the results of the laboratory the profile of the subject will end for its inclusion or not.
- Evaluation of variables: The data of the evaluation of the variables listed below can be taken from the scrutiny visit. It is the prerogative of the PI to decide whether to use the information from the screening visit or to repeat the evaluations in this visit.
    - Intraocular pressure
    - Visual capacity
    - Integrity of the ocular surface

  - Comprehensive ophthalmologic evaluation
  - vital signs
- Eye comfort index: see 6.4.3.3 Eye comfort index.
- Assignment of IP: Refers to determine the intervention that the patient will follow during the study. It will be done according to the Methods section. Assignment of the intervention. This assignment will be made at the baseline visit (day 1) and will go along with the indication to start the treatment period at night.
- Delivery of IP: Refers to the delivery of the product under investigation to the patient of the study, by the research center. It will be done according to section 6.3.4.1 Delivery and reception.
- Delivery of the subject's diary: It refers to the delivery by the PI to the subject of the instrument: the subject's diary. The assigned personnel will perform a training on the subject, on the filling of the instrument.
- Adverse events: see 6.4.3.5 Presence of adverse events.
- Evaluation of concomitant medications: Ver **¡Error! No se encuentra el origen de la referencia.**

6.5.1.3 Visit 1.

- Return / evaluation of the subject's diary: refers to the submission of the subject's diary to the PI by the subject. The PI will review the journal to assess its correct filling, and the registration of the applications.
- Adherence evaluation: refers to the assessment performed by the PI according to the section Procedure to monitor adherence.
- Delivery of the subject's diary: see Basal visit.
- Adverse events: see 6.4.3.5 Presence of adverse events.
- Vital signs: see 6.4.3.7 Vital signs.
- Visual capacity: see 6.4.3.1 Visual capacity.
- Integrity of the ocular surface: see 6.4.3.4 Integrity of ocular surface:
- Intraocular pressure: see 6.4.3.6 Intraocular pressure.
- Evaluation of concomitant medications: See 6.5.1.1
- Continuity assessment of the subject: refers to the determination by the PI and desire of the subject to continue with their participation in the study.

6.5.1.4 Final visit.

- Return of the IP: refers to the return of the IP by the subject to the non-blind staff of the center.
- Return / evaluation of the subject's diary: see Visit 1.
- Adherence evaluation: refers to the assessment made by the PI according to section 6.3.2.1 Procedure to monitor adherence.
- Adverse events: see 6.4.3.5 Presence of adverse events.
- Urine pregnancy test: see Screening visit.
- Vital signs: see 6.4.3.7 Vital signs.
- Visual capacity: see 6.4.3.1 Visual capacity.
- Comprehensive ophthalmological evaluation: see 6.4.3.2 Comprehensive ophthalmological evaluation.
- Integrity of the ocular surface: see 6.4.3.4 Integrity of ocular surface:
- Intraocular pressure: see 6.4.3.6 Intraocular pressure.
- Sampling of laboratory samples: see 6.4.3.8 Laboratory tests.
- Eye comfort index: see 6.4.3.3 Eye comfort index.

- Evaluation of concomitant medications: See **¡Error! No se encuentra el origen de la referencia.**

6.5.1.5 Security call.

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

6.5.1.6 Early termination visit.

If the research subject's participation ends earlier than scheduled, due to an adverse event or any other situation, an unscheduled visit will be made, which will serve as the final visit. In case the subject refuses to attend, the last visit made will be taken as final. Subsequently, the security call will be made in the normal time established.

6.5.2 Diagram of the study.

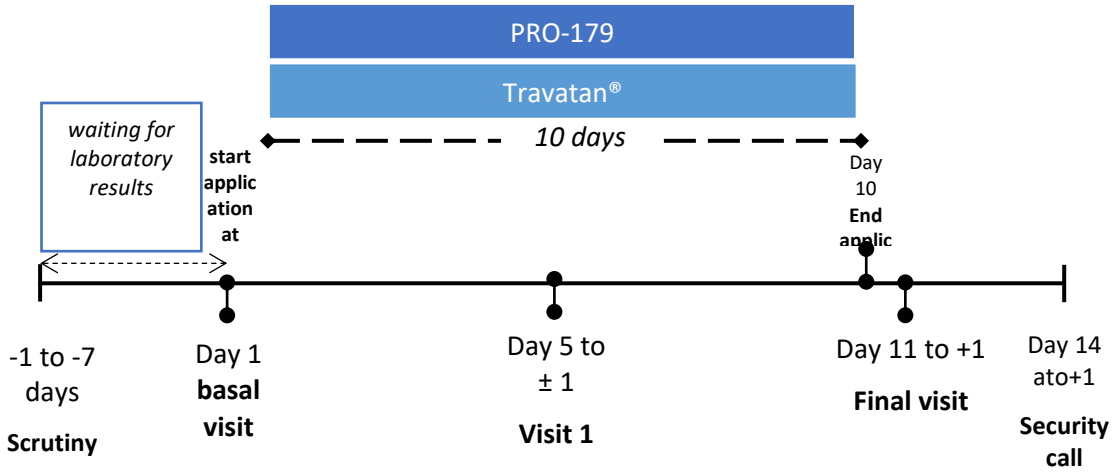
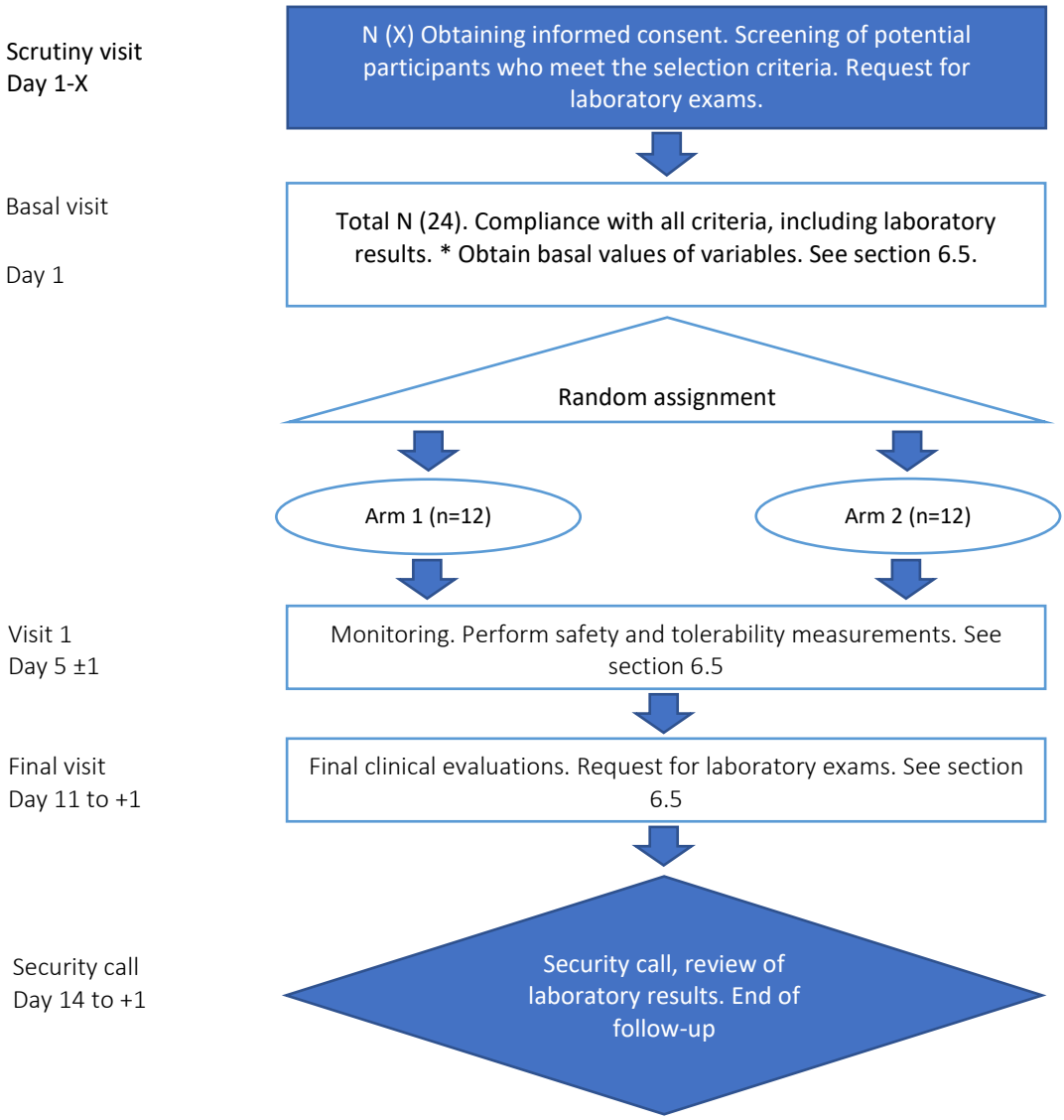


Figure 3. Horizontal diagram of the study.



* Baseline measurements can be taken from those made during the screening visit. It is the investigator's prerogative to perform them again at the baseline visit.

Figure 4. Vertical diagram of the study.

6.6 Sample size.

A total size of 24 subjects is estimated, divided into 2 intervention groups (12 subjects per group). A 45-day enrollment time is expected for the total sample.

6.6.1 Calculation of the sample size.

Although there are no references on the calculation of sample size in phase I studies, the incidence of ocular adverse events was considered, basing the calculation on the presence of conjunctival hyperemia.

Based on the following work hypothesis:

$$H_0 = p_A - p_B \leq \delta$$
$$H_1 = p_A - p_B > \delta$$

The formula for proportions was used (Chow et al., 2008) [62]:

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

The study by Mishra et al, whose objective was to compare the efficacy and safety of latanoprost, bimatoprost, travoprost and timolol in the reduction of intraocular pressure (IOP) and the incidence of adverse events in patients with primary angle glaucoma, was used as a reference open (GPAA). [63] This was a prospective, unicentric study in 140 patients with recent diagnosis of POAG who were assigned to some intervention (n = 35 per arm / both eyes). Follow-up at 2, 6 and 12 weeks. The main safety variable was the presence of adverse events (AD). OAEs were observed in 41.9% (13/31) of patients treated with travoprost with an incidence of conjunctival hyperemia of 12.9%. The EA reported were: conjunctival hyperemia, dry eye, discomfort and keratitis.

Calculation: the percentage of AD presented in the group treated with travoprost was considered. Expecting a similar proportion of conjunctival hyperemia due to PGA and healthy subjects. Considering a power of 80%, a significance level of 0.05 (α) and a non-inferiority margin of 5% (δ).

Calculated sample: 20, increasing the calculation by 20% considering possible losses, 25 subjects.

Suggested sample: 12 subjects (24 eyes) per treatment arm.

6.7 Recruitment.

It is essential that, if necessary during the development of this research protocol, the principal investigator requests the approval of the Research Ethics Committee and the Research Committee, as well as the authorization of COFEPRIS, to publish or disseminate in mass media, the invitation to participate in the study to those people who meet the selection criteria.

It is possible to discuss with other health professionals the opportunity for healthy subjects to be evaluated by an ophthalmologist at no cost, as well as cabinet exams that will allow the more accurate determination of their ocular clinical status by participating in a sponsored clinical research protocol by Sophia Laboratories, SA of C.V.

7 Methods. Assignment of the intervention.

7.1 Generation of the allocation sequence.

Two strata corresponding to the intervention groups will be used, which will be balanced for a research center. The allocation will be 1: 1. The generation will be carried out by a third party, authorized by Sophia Laboratories, S.A. of C.V., through its electronic system. The information corresponding to this third party will be found in the file.

7.2 Blinding mechanism.

Blinding will be done by the Department of Clinical Operations of Sophia Laboratories, S.A. of C.V. Which will consist of the elimination of the primary label (commercial) in the case of Travatan® and the placement of a label identical to the other IP. Because the bottle in which Travatan® is packaged differs in color and shape to that used for PRO-179, a masking will be made in the primary packaging which will be identical for the interventions. The subject will have determinedly prohibited to comment with another person that is not the pharmacist aspects related to the primary container (bottle).

7.3 Implementation.

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

7.4 Blinding (Masking).

Blinding will correspond to the principal investigator and subinvestigator. In addition, the statistical analysis will be carried out in a blinded manner for the final analysis. Blinding can not be guaranteed in the subject.

The masking will be done through the secondary container. The primary packaging will not be masked by the morphological difference between them. The sponsor and the research center will have two teams blinded / not blinded.

They will be identified by means of identical labels. Which, in accordance with current and applicable regulations, must contain at least:

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

7.4.1 Opening of blinding.

Blinding may be opened in the following cases:

1. Presence of a serious adverse event.
2. Safety alarm due to the use of the drugs under study.
3. In case the sponsor determines it for any security reason or other reason that it considers pertinent.
4. In the event that the regulatory authority or ethics committee so rightly requests so as to deem it necessary.

8 Methods. Collection, administration and data analysis.

8.1 Data collection methods.

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

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

Once all discrepancies generated by the team of clinical monitors and clinical staff have been resolved, the data will be downloaded into an electronic database (Excel Sheet) by personnel designated by the sponsor. A new revision of the data will be carried out to corroborate the fidelity of the same and new discrepancies may be generated in case it is considered as such.

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

8.1.1 Strategies to complete the follow-up.

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

8.2 Data management.

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

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

An electronic CRF was designed to record the data that are required in the protocol and that the researcher collects in each of the visits. This design is made by a third party, authorized by Sophia Laboratories, S.A. of C.V., through its electronic system.

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

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

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

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

The monitor should ensure that all data has been filled in the CRF. After comparing the data against the source documents, the monitor will ask the researcher to make the correction / clarification using clarifications, so that they are answered and closed as quickly as possible. Once the verification by the monitor is finished, the data will be blocked to avoid modifications.

The Clinical Team of Sophia Laboratories, S.A. of C.V. will give the last medical-scientific review and, if necessary, will unblock data if necessary (request for clarification, opening questions, etc ...) and confirm the freezing of data at the end of the study.

8.3 Statistical methodology.

8.3.1 Analysis of primary and secondary outcome variables.

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

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

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

The results of the continuous quantitative variables will be presented in measures of central tendency: mean, standard deviation and ranges, see table 3 (section 6.4.3).

The Kolmogorov-Smirnov test will be performed to know if the distribution presents normality in the results obtained in each study group [64].

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

- Intra-group analysis: will be determined by the Wilcoxon rank test, for quantitative variables [65]
- Inter-group analysis: will be determined by the Mann-Whitney U test Kruskal-Wallis. This non-parametric test will be used to test whether a group of data comes from the same

population. Intuitively, it is identical to the ANOVA with the data replaced by categories using the student's t statistic.

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

The result of nominal and ordinal qualitative variables will be presented in frequencies, proportions and percentages, see table 3 (section 6.4.3).

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

- Intra-group difference: McNemar test [66]. Which is applied to 2 × 2 contingency tables with a dichotomous trait, with pairs of matched subjects, to determine if the marginal frequencies of row and column are equal (marginal homogeneity).
- Inter-group difference: Pearson's χ2 test (or Fisher's exact).

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

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

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

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

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

8.3.2 Additional analyzes.

No additional analyzes are contemplated to those previously described. Nevertheless, these may be performed if during the conduction of the study it is required to analyze specific safety aspects of any intervention, maintaining the blinding until the end of the study.

8.3.3 Population analysis and management of missing data.

An intention-to-treat analysis will be carried out, where the data of the participants who have completed the Visit 1 will be included.

9 9 Methods. Monitoring.

9.1 Data monitoring.

Monitoring visits by a monitor from Sophia Laboratories, S.A. of C.V. are intended to confirm that the studies sponsored by Sophia Laboratories, S.A. of C.V. they are conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practices and with the applicable regulatory requirements.

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

Sophia Laboratories, S.A. of C.V. will monitor the study to verify, among other things, that:

- The data is authentic, correct and complete.
- They are protecting the security and rights of the subjects.
- The study is being carried out in accordance with the currently approved protocol, any other study agreement, Good Clinical Practices and all applicable regulatory requirements.

The details of the monitoring are documented in the Monitoring Plan (PM). The PM describes: the frequency and level of detail with which the monitoring will be performed, the activities to be carried out during the study according to its role (blind / non-blinded), the description of deviations from the protocol and its management.

9.2 Adverse events.

9.2.1 Responsibilities of the researcher.

Perform the verification of adverse events through questioning, review of the information recorded in the journal of the subject, relevant physical examination, assessment of evolution, as well as the appropriate medical and pharmacological management, resolution or outcome and final discharge following the definitions determined in the national and international regulations. [67] [68] [69]

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

The attention of the adverse events will be made according to the diagram of attention of the event (see Figure 5. Attention of the adverse event).

In the final report that will be drafted by the Clinical Team of the Department of Clinical Operations of Sophia Laboratories, S.A. of C.V., will include the report of adverse events in compliance with current national and international regulations. [68] [67]

If the research subject debuted during his participation in the study with an adverse event of a chronic course, such as diabetes or systemic arterial hypertension, he / she will be referred to the competent health professional for chronic treatment and we will adhere to the stipulations of the ICH for follow-up and completion of your participation.

9.2.1.1 Record of adverse events in the Case Report Form.

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

Information about the type of event that is adverse to the IP or to the study medication, as appropriate. The date on which the adverse event occurs is reported, as well as in which the Investigator is aware of it, date of resolution or outcome, as applicable. The clinical diagnosis is indicated. If a lack of therapeutic response is detected to the IP and / or investigational medication, it must be reported as a serious adverse event within the period stipulated by the current regulations. The therapy used for the pharmacological management of the adverse event should be included in concomitant medications. Record the outcome or resolution of the event: patient recovered without sequelae, with sequelae, not recovered. Patient who presented death due to the adverse event, patient who presented death and it is judged that the drug could have contributed, patient who presented death and this is not related to the investigational product or medication, or indicate that it is not known which is the consequence of the event.

Consign information about the product or drug under investigation or the drug associated with the adverse event, adverse reaction or suspected adverse reaction. As applicable, the information concerning generic name, distinctive denomination or code of the IP and / or investigational drug should be recorded, as appropriate according to the methodological design of the study, this is relevant in the case of blinded studies or those where placebo is used as comparators, since there are circumstances that justify the opening of the blind person to determine if the adverse event may be attributable to the active agent, the combination of active agents, or the pharmacologically inert substance (s), such as vehicles or additives, as appropriate to the clinical research phase in which the drug development is located. It will also be necessary to record the data concerning the batch number, manufacturer laboratory, expiration date, dosage, route of administration, start and end dates of administration and / or consumption, reason for the prescription; according to whether it is a product or drug under investigation (protocol in which the patient currently participates) or is a medicine that the subject in question consumes for the treatment of basic concomitant diseases or used for the management of any sign or transient symptom that does not correspond to the Natural History of the pathology that motivated its entry into the research protocol.

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

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

Concerning the relevant clinical antecedents. The analysis of the adverse event considers the information previously reported, notwithstanding the clinical context in which this harmful phenomenon occurs in the participants of the clinical research protocol, it is of special interest, so that information about the previous conditions, phenomena of hypersensitivity or allergy, previous surgical procedures, laboratory analysis or cabinet examinations that have been practiced on the participant, etc., that the investigator deems fit to mention may do so. In case to have enough space in the case report format, you can complete the information in your clinical note in the clinical file.

9.2.1.2 Monitoring of adverse events.

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

9.2.1.3 Procedures for a serious adverse event.

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

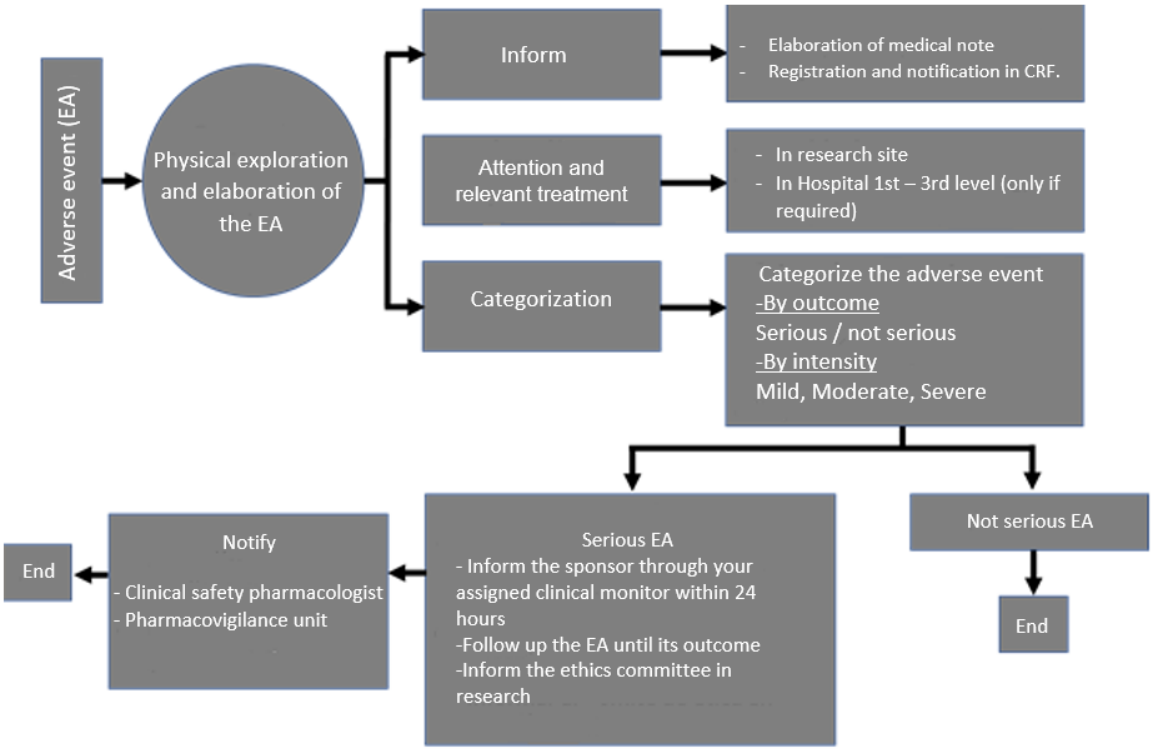


Figure 5. Attention to the adverse event.

1. During the development and conduct of the present clinical investigation, undesirable damaging events or adverse reactions, of medical involvement, which do not necessarily have a causal relationship with the IP or investigational medication, may occur in the participant patient. These harmful phenomena can occur during the use of investigational drugs, unintentionally, at doses authorized for use in humans; by a local, national or international regulatory entity, whether for prophylaxis, diagnosis, treatment or for the modification of some physiological process. However, it can be

suspected that the IP or the investigational drug or the placebo cause some unwanted clinical manifestation. Adverse events, adverse reactions or suspected adverse reactions to one or several medications can occur during the systematic evaluation of the participants (on the days when the clinical review is scheduled, according to the schedule of activities) or suddenly, as such way that;

2. The researcher must be the first person to whom the patient reports that they have developed or presented a harmful clinical phenomenon during their participation in this research protocol.
3. According to your clinical judgment; on the basis of the pertinent physical examination, questioning, etc., as well as the analysis of the information available in the medical literature and of what is referred to in the researcher's manual, information to prescribe or technical record of the comparator drug, the principal investigator determines the relevant attention of the event / harmful reaction; either,
4. at the research site or at the hospital with the greatest resolving power (1st, 2nd or 3rd level of medical attention). In such a way that, in case the patient is sent by the Investigator to a hospital, he / she attends by means of a reference system, it can be with an identification card that the patient belongs to the present investigation and there is an official number or folio, which pertains to the emergency care agreement with the health institution with the greatest resolving power, or a medical reference note issued by the principal investigator, so that appropriate attention is given to the participating patient. It should be noted that the Study Sponsor, Sophia Laboratories, S.A. of C.V., will pay the expenses for the medical attention of the participant patient, only if the adverse event is associated or is in relation to the IP or investigational medication.
5. Taking the clinical information collected, either during the care provided in the research site or provided by the attending physician (s) in the hospital, the principal investigator records the adverse event in his / her clinical note. of the clinical record stating the seriousness, intensity (mild, moderate or severe), relationship with the product or drug under investigation, as well as,
6. The migration of the relevant data to the case report format and to its respective adverse event section; noting the pertinent information, already referred to in section 9.3.1.1., in virtue of the fact that in cases of serious adverse events, which must be notified in less than 24 hours after the moment in which the principal investigator has knowledge of the same, the clinical monitor of the study is informed, so that in turn it informs the Clinical Team and the Pharmacovigilance Department of the sponsor and later it is informed to the Committee of Ethics in Research. With respect to non-serious adverse events, these will be recorded and adequately addressed and the corresponding regulatory entity will be informed about the safety profile of the IP or investigational medication in the final report of the clinical trial.

The record of the outcome of the adverse event depends substantially on the follow-up that the principal investigator makes to the participant, since it is expected that the majority of harmful phenomena, consult section of the safety profile in number 5.3 and in the researcher's manual, are of a nature ophthalmic, however, there may be systemic alterations. Therefore, in the opinion of the researcher, the withdrawal of the participant or his / her permanence will be considered, according to what is stipulated in section 6.2.1.2 Exclusion criteria of the present research protocol.

9.2.1.4 Causality evaluation.

The assessment of causality, the methodology used to estimate the probability of attributing a drug, investigational drug or IP to the observed adverse event, considers probabilistic categories, according to the available evidence and the quality of the information, based on the national pharmacovigilance regulations. [67] As a tool to facilitate the probabilistic categorization of causality, the department of pharmacovigilance and tegno-vigilance of Sophia Laboratories (UFTLS) can use the algorithm of Karch and Lasagna modified by Naranjo referred by Aramendi I, 2011 in which different items are qualified which allow assign a value to the cause-effect relationship between the administration of the drug and the adverse reaction. [70] **See Table 5. Algorithm of Karch and Lasagna modified by Naranjo**.

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

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

Table 5. Algorithm of Karch and Lasagna modified by Naranjo.

In such a way that the degree of certainty to establish the IP or investigational medication (as appropriate) as the causal agent of the harmful phenomenon that happens to the participating patient, can be indicated directly by the principal investigator based on his clinical experience or through the voluntary application of the tool mentioned previously. However, it is important that

the researcher and the UFTLS take into account the following arguments in favor of the causal relationship:

B. Strength of association that refers to the number of cases in relation to those exposed.
C. The consistency of the data, ie the presence of a common characteristic or pattern.
D. The exposure-effect pattern: which determines the relationship with the site of onset, time, dose and reversibility after suppression.
E. The biological plausibility: that refers to the possible pharmacological or physiopathological mechanisms involved in the development or presentation of the adverse event.
F. Experimental findings: for example, the appearance of abnormal metabolites or high levels of drug or the product of its biotransformation.
G. Analogy: experience acquired with other related drugs, adverse reactions frequently produced by the same family of pharmacological agents.
H. Nature and characteristics of the data: objectivity, accuracy and validity of the relevant documentation. [71]

9.2.2 Responsibilities of the sponsor.

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

9.3 Unanticipated problems.

The unanticipated problems (NAP) consider those situations that pose risks for the participating subjects, in general, any incident, experience or result that meets all the following criteria:

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

9.3.1 Report of PNAs.

The PI will be responsible for reporting PNAs to the sponsor, to the CI, to the CEI. The report must contain the following information:

- Identification of the study: protocol title and number, name of the PI and, where appropriate, the center.
- Detailed description of the event, incident, experience or result.
- Explanation, justification of the reasons why the incident represents an NAP.
- Description of changes to the protocol or corrective actions taken or proposed in response to the NAP.

The PNAs that are EAS must be reported to the CEI and the sponsor within the first 24 hours that the PI has knowledge of this.

Any other NAP will be reported to the CEI and the sponsor within the first 5 business days, after the PI has knowledge of this.

9.4 Audit.

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

9.4.1 Pre-study audit.

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

9.4.2 Audit / Inspection during the conduction of the study.

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

10 Ethical considerations.

10.1 Approval of the committees.

The present study will be conducted according to the standards of the Declaration of Helsinki, World Medical Association 2013. Nuremberg Code; Nuremberg Trial by the International Tribunal of Nuremberg, 1947. Belmont Report, National Commission for the Protection of Subjects of Biomedical Research and Conduct, 1979. Will be conducted in accordance with scientific and technical requirements for the registration of medicines for use of the International Conference on Harmonization (The International Council for Harmonization, ICH) Guide to Good Clinical Practices. International Ethical Guidelines for Biomedical Research in Human Beings of the Council for International Organizations of Medical Sciences (Council for International Organizations of Medical Sciences, CIOMS, 2002). International Ethical Guidelines for epidemiological studies of the Council for International Organizations of Medical Sciences (Council for International Organizations of Medical Sciences, CIOMS, 2008). The Research Ethics Committee and the Research Committee will evaluate the protocol before conducting the study and will issue their approval or possible modifications for its realization, these Committees should be notified of any significant changes to the protocol. In addition to the above, the current regulations issued by the Ministry of Health will also be complied with. General Health Law, NOM 012 Official Mexican Standard NOM-012-SSA3-2012, Which establishes the criteria for the execution of research projects for human health. The study is considered as an investigation with a risk greater than the minimum according to the Regulation of the General Health Law on Health Research, Title Two, Chapter I, Article 17, Category III, published in the Official Gazette on 6 January 1987.

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

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

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

10.2 Amendments to the protocol.

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

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

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

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

10.3 Early termitation of the study.

The study may be temporarily suspended or terminated prematurely if there is a sufficiently reasonable cause. The written notice, which documents the reason for the suspension or early termination, must be delivered by the executing party of the suspension. The PI must inform the study participants, the CI and the CEI as soon as possible, providing the reasons.

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

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

In case of suspension, the study can be resumed once the situations that led to suspension have been remedied; as long as this justification is sufficient for the sponsor, CI, CEI and regulatory authorities.

10.4 Consent

10.4.1 Obtaining

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

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

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

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

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

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

The PI must also sign and date this consent.

The informed consent must be signed in duplicate by all involved, and two witnesses, one copy will be filed in the researcher's folder and the other will be delivered to the participant. The PI or delegated personnel, must document the process of obtaining the Informed Consent by means of a detailed medical note, where the signed version is specified, the date on which the document was signed and how the process was carried out.

10.4.2 Special considerations

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

10.4.3 Modification to informed consent

Any change to "informed consent" constitutes an amendment to this document and must be presented for approval before the Ethics in Research Committees, and if applicable before the Competent Authorities.
The amendment will include a copy of the new version in the language or languages of the country. Such amendments may be implemented only after obtaining the written approval of the Research Ethics Committee and the Regulatory Entity (as applicable), with the exception of an amendment that is required to eliminate an immediate danger to the subjects of the study.

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

In the event that new information may arise that may be relevant to the subject's decision to continue participating in the study, this information should be communicated in a timely manner to the latter. This information will be provided through an amendment to the informed consent, which must be completed, dated and signed in duplicate through a process of re-consent.

10.5 Confidentiality

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

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

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

10.6 Conflict of interests

The independence of the conduction of the study and its results, of any current or perceived external influence is critical. For this reason, any current conflict of interest of any person who exercises a role in the design, conduct, analysis, publication or any aspect of this study will be declared. Moreover, those people who have a perceived conflict of interest will be asked to handle it in a way appropriate to their participation in the study.

10.6.1 Declaration of interests

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

10.7 Access to information

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

10.8 Auxiliary care and after the end of the study.

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

10.9 Biosecurity aspects.

WITHOUT BIOSECURITY IMPLICATIONS.

The present protocol, with the title: "Phase I clinical study, to evaluate the safety and tolerability of the ophthalmic solution PRO-179 compared with Travatan®, on the ocular surface of clinically healthy subjects", and number: SOPH179-0818 / I NO HAVE BIOSECURITY IMPLICATIONS, since infectious-contagious biological material will NOT be used; pathogenic strains of bacteria or parasites; viruses of any kind; radioactive material of any kind; animals and / or cells and / or genetically modified plants; toxic, dangerous or explosive substances; Any other material that endangers the health or physical integrity of the research center's personnel or the research subjects or affects the environment. It is also stated that cell, tissue or organ transplant procedures or cell therapy procedures will not be carried out in this project, nor will laboratory, farm or wildlife animals be used.

10.10 Final report and publication of results.

10.10.1 Final report.

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

10.10.2 Communication of results.

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

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

10.10.3 Publication of results.

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

The PI undertakes not to publish or communicate data collected from the study, unless prior written agreement is given by Sophia Laboratories, S.A. of C.V.

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

researcher or doctors will comment on the project within 15 days in the case of a publication and 7 days in the case of a summary, from the date on which the project is received.

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

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12 Signature page.

12.1 Signatures of the sponsor's representatives.

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

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

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

12.2 Investigator.

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

Name: **Title:**	**Signature** **Date**

13 Annexes.

13.1 Eye comfort index.

Identification file.

Study number SOPH122-0518-I **Date:** ____/____/____

Initials of the subject:_____ **Subject number**_____

Indications:
This questionnaire was designed to qualify the comfort of your eyes.
Circle your answer for each question.

Example: The last week, how often your eyes were red?

Never						Always
0	1	2	3	4	5	6

There are no correct or incorrect answers. Do not take too much time in each question.

1 The last week, how often your eyes felt dry?

Never						Always
0	1	2	3	4	5	6

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

I have not felt it						Severe
0	1	2	3	4	5	6

2 The last week, how often your eyes felt sandy?

Never						Always
0	1	2	3	4	5	6

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

I have not felt it						Severe
0	1	2	3	4	5	6

3 The last week, how often your eyes felt throbbing?

Never						Always
0	1	2	3	4	5	6

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

I have not felt it						Severe
0	1	2	3	4	5	6

4 The last week, how often your eyes felt tired?

Never						Always
0	1	2	3	4	5	6

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

I have not felt it						Severe
0	1	2	3	4	5	6

5 The last week, how often your eyes felt sore?

Never						Always
0	1	2	3	4	5	6

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

I have not felt it						Severe
0	1	2	3	4	5	6

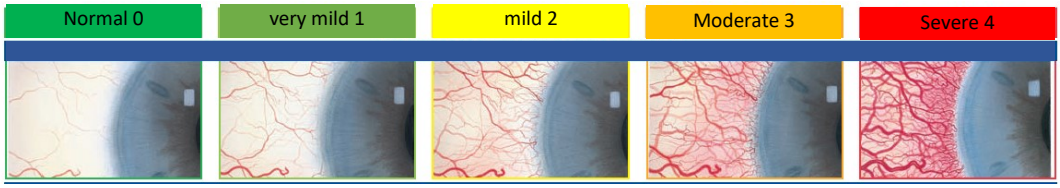
6 The last week, how often your eyes felt itchy?

Never						Always
0	1	2	3	4	5	6

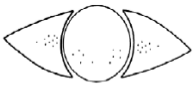
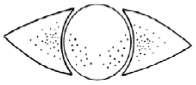
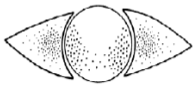
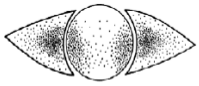
When your eyes felt itchy, usually, how intense was the sensation?

I have not felt it						Severe
0	1	2	3	4	5	6

13.2 Efron scale for conjunctival hyperemia.



13.3 Oxford Scale.

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