Creation date: August 2016

Phase I clinical study, to evaluate the safety and tolerability of the ophthalmic solution PRO-174 versus Sophixín Ofteno®, elaborated by Sophia Laboratories, S.A. of C.V. on the ocular surface of ophthalmologically and clinically healthy subjects

Protocol code: SOPH174-0816/I

Protocol version: 1.1

Date of the version: 18/04/2017

Registry: 173301410A0149/2017

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

1. Summary

<table>
<tr><td colspan="3">Title of the study:
Phase I clinical study, to evaluate the safety and tolerability of the ophthalmic solution PRO-174 versus Sophixín Ofteno®, elaborated by Sophia Laboratories, S.A. of C.V. on the ocular surface of ophthalmologically and clinically healthy subjects.</td></tr>
<tr><td colspan="2">Protocol code:
SOPH174-0816/I</td><td>Creation date:
22/08/2016</td></tr>
<tr><td colspan="2">Protocol version:
1.1</td><td>Date of the version:
18/04/2017</td></tr>
<tr><td colspan="3">Therapeutic indication:
Eye antibiotic</td></tr>
<tr><td>Study period:
3 to 4 months</td><td colspan="2">Development phase: I</td></tr>
<tr><td colspan="3">Goals:
To evaluate the safety and tolerability of the formulation PRO-174 manufactured by Sophia Laboratories, S.A. of C.V. on the ocular surface of clinically healthy subjects.</td></tr>
<tr><td colspan="3">Hypothesis:
The ophthalmic solution PRO-174 presents a safety and tolerability profile similar to the comparator in healthy subjects.</td></tr>
<tr><td colspan="3">Methodology:
Phase I clinical trial, controlled, of parallel groups, double blind, randomized, exploratory.</td></tr>
<tr><td colspan="3">Number of patients:
30 subjects, divided into 2 groups [15 subjects (30 eyes) exposed per group]</td></tr>
<tr><td colspan="3">Diagnosis and main inclusion criteria:
- Signed informed consent.
- Systemically and ophthalmologically healthy subjects
- Age between 18 to 45 years.
-Both genders.
- Blood tests [complete blood count (BHc), three element blood chemistry (QS) and liver function tests (PFH)] within normal parameters specified by the reference laboratory with a lower and upper margin of 10%.
- Visual capacity 20/30 or better, in both eyes.-
-Intraocular pressure ≥11 and ≤ 21 mmHg.</td></tr>
</table>

Test product, dose and route of administration, lot number:

- **PRO-174.** Levofloxacin 0.5% ophthalmic solution. Prepared by Sophia Laboratories, S.A. of C.V, Zapopan, Jalisco, Mexico.
- Dosage: 1 drop every 2 hours during the waking period (8 daily applications), on day 1 and 2; continuing with 1 drop every 4 hours during the waking period (4 daily applications) from day 3 to 7. Both eyes.
- Route of administration: ophthalmic

Duration of treatment: 7 days

Reference product, dose and route of administration, lot:

- Sophixin Ofteno. Ciprofloxacin 0.3% ophthalmic solution. Prepared by Laboratories Sophia, S.A. of C.V., Zapopan, Jalisco, Mexico.
- Dosage: 1 drop every 2 hours during the waking period (8 daily applications), on day 1 and 2; continuing with 1 drop every 4 hours during the waking period (4 daily applications) from day 3 to 7. Both eyes.
- Route of administration: ophthalmic

Evaluation criteria:

Primary security outcome variables:

- Presence of adverse events.
- Intraocular pressure.
- Visual ability
- Laboratory tests: BHc, QS and PFH.
- Ocular surface staining with fluorescein and lissamine green using Oxford scale
- Ophthalmological signs: conjunctival hyperemia, chemosis.

Primary outcome variables of tolerability:

- Burning

- Foreign body sensation

- Itching

- Eye comfort index

Primary outcome variables of tolerability:

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

Statistical methodology:

The data will be expressed with measures of central tendency: mean and standard desviation for the quantitative variables. The qualitative variables will be presented in frequencies and percentages. The statistical analysis will be carried out through the Mann-Whitney U test for quantitative variables for the difference between the groups. The intra-group difference will be made with the Wilcoxon rank test. The difference between the qualitative variables will be analyzed by means of X2 (Chi2). An alpha ≤ 0.05 will be considered significant.

2. Content

Index of tables, figures and illustrations

3. Index of abbreviations

ALT	Alanino transferase
AST	Aspartate transferase
BD	Bilirrubin direct
BI	Bilirrubin indirect
BHc	Complete blood count
BPC	Good clinical practice
BT	Total Bilirubin
CV	Visual capacity
CCI	informed consent letter
CEI	Research Ethics Committee
CI	Informed Consent
CRF	Case Report Form (Case Report Form)
EA /EAS	Adverse event / serious adverse event
FDA	Food and Drug Administration (Food and Drug Administration)
FC	Heart rate
FR	Respiratory frequency
ICH	International Conference on Harmonization (for its acronym in English International Conference on Harmonization)
ICO	Eye comfort index
IP	Principal investigator of the clinical study
PFH	Liver function tests
PIO	intraocular pressure
TAS	Systemic blood pressure
TF	Fluorescein staining
TVL	Green lysine stain
QS	Blood chemistry

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4. Administrative structure of the study

The administrative structure of the sponsoring party, corresponding to Sophia Laboratories, 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	Dr. Aldo Arturo Oregón Miranda aldo.oregon@sophia.com.mx	Clinical Operations Manager
Scientific Comittee	Dr. Oscar Olvera Montaño oscar.olvera@sophia.com.mx	Ophthalmologist Investigator
Scientific Comittee	Dr. en C. Arieh Roldán Mercado Sesma arieh.mercado@sophia.com.mx	Medical Editor
Coordinator of regulatory procedures	LN. Ana Isabel Alcaraz Ledón ana.alcaraz@sophia.com.mx	Specialist in the beginning of clinical studies
Monitoring coordinator	QFB Virginia Manuela Villa Félix virgina.villa@sophia.com.mx	Monitor coordinator
Monitor	QFB Jessica Lizette Mejía Gutiérrez jessica.mejia@sophia.com.mx	Senior Monitor
Monitor	LP María Angela González Ávila maria.gonzalez@sophia.com.mx	Junior Monitor
Monitor	QFB Lizeth de Jesús Pérez Lerma lizeth.perez@sophia.com.mx	Junior Monitor
Monitor	LN Pilar Carolina Castro Mata pilar.castro@sophia.com.mx	Junior Monitor
Administrative Assistant	LAET Maira Alejandra Ramírez Velazco alejandra.ramirez@sophia.com.mx	Clinical Operations Assistant

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

Table 1. Administrative structure

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5. Introduction

5.1 Theoretical framework

The human being is constantly exposed to a wide variety of microorganisms, including bacteria, viruses and fungi. In the majority of the occasions, these microorganisms do not produce infections, because the skin and the superficial membranes provide an effective barrier before the invasion of these. Nevertheless, some microorganisms can directly invade these barriers, and others, take the opportunity to enter the human body through injuries, whether they are surgical or traumatic. Normally, if microorganisms manage to penetrate external barriers, the immune system deals with them effectively. Notwithstanding, some of it have special properties that allow them to overcome the immune system; in some cases the person's immune system is not functioning optimally, allowing microorganisms, which in normal situations would not represent a greater threat, cause an infection. [1]

Throughout history, different types of compounds have been used to help the immune system fight these microorganisms. Each of the main categories of microorganisms that produce infections (bacteria, viruses and fungi) has a characteristic structure and metabolism. The differences are so significant that compounds that are toxic to an organism in one category usually do not have activity against members of the other two categories. Therefore, the compounds against these microorganisms are classified as antibacterial, antiviral and antifungal. [2]

Besides, a single compound has no activity against all species of microorganisms within a category. The species against which a drug demonstrates intrinsic activity is known as the spectrum of action. A narrow spectrum is when the drug only has action against a few species, while a broad spectrum, has activity against a variety of species. [1]

Fluoroquinolones are drugs that inhibit the synthesis of bacterial DNA, which leads to cell death. Its primary targets are topoisomerase II and topoisomerase IV, which are involved in the maintenance of the superhelical structure of DNA during synthesis. Human cells do not contain these enzymes, so they are not affected by fluoroquinolones. [3]

Traditionally, fluoroquinolones have been classified into generations; Nevertheless, this classification has not been standardized and lacks formality. Nevertheless, it finds clinical utility in classifying them based on their spectrum of action and indications. [1] [3]

Currently there are formulations available in ophthalmic solutions, fluoroquinolones second (ciprofloxacin, norfloxacin, ofloxacin), third (levofloxacin) and fourth generation (gatifloxacin, besifloxacin, moxifloxacin). These drugs have a broad spectrum and effectiveness against gram-positive and gram-negative bacteria. Due to the increase in the resistance index, especially of gram-positive bacteria, the clinical usefulness and effectiveness of the second generation fluoroquinolones has decreased. [1] [3]

Infectious conjunctivitis is a common condition; It is estimated that close to 1% of medical consultations in the first level of care are related to this, affecting about 6 million people a year in the United States of America. [2] [4] [5]

Although only about a third of patients diagnosed with conjunctivitis, in the first level, the diagnosis of bacterial conjunctivitis is confirmed, 80% receive antibiotic treatment. [6] The bacterial etiology is varied, and depends on geographical and age factors, but the most common includes species of: Staphylococcus, Streptococcus, Haemophilus, Pseudomonas, Corynebaterium and Moraxella. [2]

Some cases of bacterial conjunctivitis can be self-limiting, although they find use in the use of topical antibiotics, since they accelerate recovery and avoid complications that can range from mild superficial corneal erosion to permanent damage to the cornea that results in visual disturbances. [2] [7] Bacterial conjunctivitis is responsible for an annual cost of approximately $ 377 to $ 875 million in the United States of America. [8]

5.2 Definition of the problem and fundamental reason

Bacterial conjunctivitis and other ocular surface infections are a common condition throughout the world. It has been estimated that infectious conjunctivitis is suspected in 3% of patients treated by a general practitioner, and of these, the final diagnosis is made in two thirds. [7] In the United States of America, the incidence of bacterial conjunctivitis is 135 cases per 10,000 inhabitants per year. [8]

The bacterial conjunctivitis is due to infections by several bacteria, among which are: Haemophilus Influenzae, Streptococcus pneumoniae or Staphylococcus aureus. It is considered self-limiting, nevertheless, the proper use of antibiotics accelerates recovery, reduces recurrences and prevents complications such as orbital cellulitis, keratitis and panophthalmitis. [9] [7]

Currently in Mexico and other countries of the American continent where Sophia Laboratories, S.A. of C.V has presence, the use of levofloxacin 0.5% ophthalmic solution is not approved. So PRO-174 could be a safe and effective option in the treatment of bacterial conjunctivitis and other ocular surface infections.

5.3 Background

The ophthalmic solution of levofloxacin 0.5% is an antibiotic formulation, marketed and approved under the name of Cravit® (Santen Pharmaceutical, Co., Ltd., Osaka, Japan), for use in bacterial conjunctivitis and ocular surface infections in Japan; in the United States of America and Europe it is approved for the treatment of bacterial conjunctivitis under the names of Quixin® and Oftaquix®, respectively. The active ingredient is a synthetic antimicrobial agent of the fluoroquinolone family. [10] [11]

Fluoroquinolones exert their antimicrobial activity by inhibiting topoisomerases II and IV, enzymes involved in the synthesis of bacterial DNA. Fluoroquinolones have been widely used in the treatment of bacterial infections due to their potent activity and broad spectrum of action against gram-positive and gram-negative bacteria. In addition, its use in ophthalmic formulations is common, due to its known safety and efficacy profile in the treatment of ocular surface infections. [12]

5.3.1 Levofloxacin

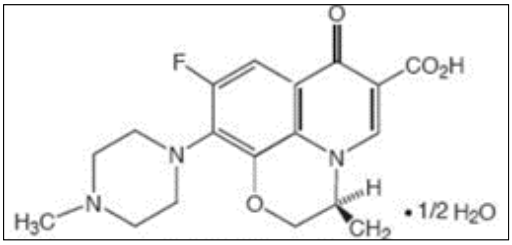
Levofloxacin is the L-enantiomer of ofloxacin, it has twice as much antimicrobial activity as this one; in neutral pH it has greater solubility in water than this, which allows the preparation of formulations with high concentrations.

Chemical Name: (-) - (S) -9-Fluoro-2,3-dihydro-3-methyl-10- (4-methyl-1-piperazinyl) -7-oxo-7H-pyrido [1,2,3 -of] -1,4 benzoxazin-6-carboxylic acid hemihydrate.

Chemical formula $C_{18}H_{20}FN_3O_4 \bullet ½\ H_2O$

Molecular weight: 370.38

Illustration 1. Structural formula of levofloxacin



5.3.1.1 Pharmacodynamic properties

Levofloxacin acts, like the rest of the drugs of the fluoroquinolone family, by inhibiting the topoisomerase II (DNA gyrase) and topoisomerase IV enzymes, essential for the synthesis of bacterial DNA. Topoisomerase II is involved in the supercoiling of DNA, and in the replication and transcription of bacterial DNA; topoisomerase IV helps separate the DNA formed from the one used as a template for replication. [13]

5.3.1.1.1 Antibacterial activity

Levofloxacin has demonstrated activity, in vitro, against a wide range of gram positive and negative eye isolates. Demonstrated activity against methicillin-susceptible S. aureus, methicillin-susceptible coagulase-negative staphylococci, α-hemolytic group streptococci, S. pneumoniae (including susceptible, intermediate and penicillin-resistant strains), Enterococcus spp., Moraxella catarrhalis, H. influenzae, H aegyptius, Enterobacter spp., Proteus spp., Serratia spp., Klebsiella spp., Acinetobacter spp., Pseudomonas spp. and P acnes. **See Table 2**

Table 2. Levofloxacin antibacterial activity against eye isolates in Japan

Species (number of isolated)[a]	MIC_{90} (μg/mL)						
	LVX	MXF	GAT	TFLX	OFX	NOR	LOM
Gram-positive bacteria							
S. aureus (56)	3.13	0.78	1.56	0.78			
MSSA (299)	0.25-05	0.12	0.25	0.12	0.5-1	2-4	2
MRSA (223)	64-128	8	16	>16	>128	>128	>128
MS CNS (100)	0.5-2				1-4	4-8	4-32
MR CNS (100)	4				8	32	64
S. epidermidis (447)	3.13-8	0.78-2	1.56-2	3.13-16			
S. α-hemolítico (43)	1.56	0.2	0.39	0.39			
S. pneumoniae (30)	2	0.25	0.5	0.25			
S. pneumoniae (PS) (100)	1				2	8	8
S. pneumoniae (PI) (50)	1				2	8	8
S. pneumoniae (PR) (30)	1				2	4-8	8
Enterococcus spp. (30)	2				4	8	8
Enterococcus faecalis (32)	1.56-2	0.2-0.5	0.39-1	0.2-0.5			

Corynebacterium spp. (366)	>128	128	64	>16	>128	64	128
Corynebacterium macginleyi (136)	>128	64	32	>16			
Gram-negative bacteria							
Moraxella catarrhalis (60)	≤0.06				0.12	0.25	0.25
H. influenzae (133)	≤0.06	0.06	0.03	0.03	≤0.06	≤0.06	0.12
H. aegyptius (10)	≤0.06				≤0.06	≤0.06	≤0.06
Enterobacter spp. (20)	0.25				0.5	0.25	1
Proteus spp. (20)	2				4	8	8
Serratia spp (71)	0.25	0.5	0.5	0.25	0.5	0.25-0.5	0.5
Klebsiella spp. (20)	0.12				0.25	0.25	0.5
Acinetobacter spp. (30)	0.25				0.5	8	1
Pseudomonas spp. (39)	0.78-1	1.56	0.78	0.2	2	4	4
P. aeruginosa (100)	2-8				4-16	2-8	4-16
Gram-positive anaerobes							
Propionibacterium acnes (738)	0.5-1	0.25	0.25	1	1-2	8	4-8

[a] All isolates were tested against LVX. In two studies they were tested against OFX, NOR and LOM, and in two studies they were tested against MXF, GAT and TFLX

GAT = gatifloxacin; LOM = lomefloxacin; MR CNS = coagulase negative staphylococcus resistant to methicillin; MRSA = S. aureus resistant to methicillin; MS CNS = coagulase-negative staphylococcus susceptible to methicillin; MSSA = S. aureus susceptible to methicillin; MXF = moxifloxacin; NOR = norfloxacin; OFX = ofloxacin; PI = intermediate susceptibility to penicillin; PR = resistant to penicillin; PS = susceptible to penicillin; TFLX = tosufloxacin

Adapted from Keating GM, et al. [14]

Levofloxacin has also shown bactericidal activity dependent on concentration and post-antibiotic effect of 2 -4.5 hours, depending on the pathogen. [15]

5.3.1.2 Pharmacokinetics in ophthalmic application

Route of administration: Ophthalmic.

Release: immediate.
Distribution: after instillation, in the bottom of a sac, of a drop of the ophthalmic solution of levofloxacin 0.5%, in healthy subjects, a Cmax of 221.06 µg / mL was obtained in tears in 15 minutes, detecting up to 1.37 µg / mL, 24 hours after instillation. [16] The concentrations, after the application of a drop of levofloxacin 0.5%, in conjunctiva, cornea and aqueous humor are 2.34 (20min), 0.37 µg / mL (31 min) and 18.26 µg / mL (36 min) respectively. [17] [18] In one study, in 11 subjects who underwent vitrectomy, the concentration in vitreous and aqueous humor was measured, after the application of 2 drops three times a day, the day before surgery, and every 20 minutes in the 2 hours before surgery; the concentrations were 0.77 µg / mL and 0.02 µg / mL, for aqueous and vitreous humor respectively. [19] Plasma concentrations of levofloxacin were

evaluated in 15 healthy subjects, who applied the ophthalmic solution of levofloxacin 0.5% for 15 days; the highest measured mean concentration was 2.25 ng / mL, on day 4. [10]

5.3.1.3 Clinical efficacy

In Keating's review article, on the use of levofloxacin in the treatment of eye infections, the efficacy that has been demonstrated in various clinical studies in Japan, the United States of America and Poland is summarized. These were multicentre, masked, randomized studies.

Table 3. Clinical efficacy of levofloxacin in the treatment of bacterial conjunctivitis.

Author	Treatment	Evaluation Point	Response rates (% of patients) [number of evaluable patients]		
			Clinical efficacy	Microbial eradication	Clinical cure
Hwang et al [20]	LVX 0.5%[b]	Final visit		92***[59]	78*[59]
	PL[b]	Final visit		53 [55]	61[56]
	LVX 0.5%[b]	Final point		90*** [60]	77*[60]
	PL[b]	Final point		53 [57]	60[57]
Kitano et al [21]	LVX 0.5%[c]		93[d] [112]	79 [112]	
	TFLX 0.3%[c]		94[d,e][109]	80 [110]	
Schwab et al [22]	LVX 0.5%[b]	Final visit		89*[d] [103]	
	OFX 0.3%[b]	Final visit		80[d] [92]	
	LVX 0.5%[b]	Final point		90*[d] [109]	76[d]
	OFX 0.3%[b]	Final point		81[d] [99]	76[d]
Shimomura et al [23]	LVX 0.5%[c]		98[d][125]	85[f]	
	MXF 0.5%[c]		94[d,e][139]	95**[f]	
Szaflik et al [24]	LVX 0.5% tid[g]	Final visit		93 [40]	85[d] [40]
	LVX 0.5% q2h→q4h[b]	Final visit		96 [37]	92[d] [37]

[a] a The final visit was on days 6-10 [20] [22] or on day 7 [24]. The end point was defined as the last observation carried out (last observation carried forward).
[b] b One to two drops every 2 hours, in the waking period, on days 1 and 2. Followed every 4 hours, in the waking period, on days 3-5.
[c] c One drop three times a day for 14 days.
[d] d Primary endpoint.
[e] e MXF [23] and TFLX [21] were not inferior to LVX at the lower limit of 95% of the confidence interval (CI) since the intergroup difference exceeded -10%: 95% CI -8.1, 1.4 [23] and 95% CI -5.9.7.3 [21].
[f] f Microbial eradication index accumulated on day 15.
[g] g One to two drops three times a day during the wake period for 5 days.MXF = moxifloxacino; OFX= ofloxacino; PL= placebo; qxh= every x hours; TFLX= tosufloxacino; *p<0.05, ** p<0.01, ***p<0.001 against comparator.

Adapted from Keating GM, et al. [14]

5.3.1.4 security

The safety of levofloxacin was evaluated in the previously mentioned clinical studies, and in a phase IV study. The population included in the safety analysis of these studies was 244 [20], 413 [22], 331 [23], 340 [21] and 6,686 [25]

In general, 0.5% levofloxacin ophthalmic solution has been well tolerated, most of the adverse events related to treatment reported in the studies were of a mild to moderate intensity. In the phase IV study, 42 patients (0.63%) were reported with an adverse reaction, none of which was classified as serious. The reactions that were reported most frequently were: blepharitis, eye irritation, punctate keratitis, keratitis and pruritus; there was only one non-ocular reaction report (contact dermatitis, urticaria and oral numbness).

In the controlled studies, there was no statistical difference between the events reported in the levofloxacin group and control.

The most frequent adverse reactions in the entire study population were: transient decrease in visual acuity, fever, foreign body sensation, headache, transient burning, pain or ocular discomfort, pharyngitis and photophobia. These occurred in approximately 1-3% of patients. Other reported reactions, which occurred in less than 1% of patients, included allergic reactions, eyelid edema, dry eyes and pruritus. [10]

5.4 Justification

Although eye infections can be considered minor infections, they can threaten eyesight. Topical antibiotics are widely prescribed for the treatment of eye infections or as peri-surgical prophylaxis. An antibiotic drug must have a selective toxicity; it must be more toxic to the microorganism than to the patient. Ideally an antibiotic should kill the microorganism and cause minimal or no adverse effect on the user.

Levofloxacin, active ingredient of PRO-174, is a third-generation fluoroquinolone that has been formulated as an ophthalmic solution and approved in countries with high pharmacological surveillance, for use in the treatment of eye infections caused by susceptible strains. In Japan it is approved for the treatment of bacterial conjunctivitis, other ocular surface infections and in surgical prophylaxis. In the United States of America, it has been approved for the treatment of bacterial conjunctivitis since August 2000. Currently, Mexico does not have approval for its use.

Within the development of PRO-174, by Sophia Laboratories, S.A. of C.V, it is required the elaboration of clinical studies that evaluate the safety and tolerability of its ophthalmic use, which are the foundation of future clinical studies that prove effectiveness. Although there is sufficient bibliographic reference of the active principle of PRO-174, the current commitment of Sophia Laboratories, S.A. of C.V is to generate proprietary information for their products that serves for the relevant regulatory procedures, and as a scientific basis for their commercialization.

5.5 Objectives and hypotheses

5.5.1 General purpose

To evaluate the safety and tolerability of the ophthalmic solution PRO-174 manufactured by Sophia Laboratories, S.A. of C.V on the ocular surface.

5.5.2 Specific objectives

- Describe the safety of the PRO-174 ophthalmic solution through the presentation of adverse events.

- Describe the safety of the PRO-174 ophthalmic solution through changes in intraocular pressure.
- Describe the safety of the ophthalmic solution PRO-174 by means of changes in visual capacity.
- Describe the safety of the PRO-174 ophthalmic solution through changes in laboratory tests.
- Describe the safety of the ophthalmic solution PRO-174 through changes in ocular surface stains.
- Describe the safety of the ophthalmic solution PRO-174 through changes in ophthalmological signs (conjunctival hyperemia and chemosis).
- Describe the safety of the ophthalmic solution PRO-174 by means of changes in the time of tear rupture.
- Describe the safety of the PRO-174 ophthalmic solution through changes in vital signs.
- Describe the safety of the ophthalmic solution PRO-174 by means of changes in the posterior segment.
- Describe the tolerability of the ophthalmic solution PRO-174 through the presence of ocular symptoms (burning, foreign body sensation and pruritus).
- Describe the tolerability of the ophthalmic solution PRO-174 through changes in the ocular comfort index.
- Describe the safety of the Sophixín Ofteno® ophthalmic solution through the presentation of adverse events.
- Describe the safety of the Sophixin Ofteno® ophthalmic solution through changes in intraocular pressure.
- Describe the safety of the Sophixín Ofteno® ophthalmic solution through changes in visual ability.
- Describe the safety of the Sophixin Ofteno® ophthalmic solution through changes in laboratory tests.
- Describe the safety of the Sophixin Ofteno® ophthalmic solution through changes in ocular surface stains.
- Describe the safety of the Sophixín Ofteno® ophthalmic solution through changes in ophthalmological signs (conjunctival hyperemia and chemosis).
- Describe the safety of the Sophixin Ofteno® ophthalmic solution by means of changes in the tear rupture time.
- Describe the safety of the Sophixín Ofteno® ophthalmic solution through changes in vital signs.
- Describe the safety of the Sophixín Ofteno® ophthalmic solution through changes in the posterior segment.
- Describe the tolerability of the ophthalmic solution Sophixín Ofteno® by means of the presence of ocular symptoms (burning, sensation of foreign body and pruritus)
- Describe the tolerability of the ophthalmic solution Sophixín Ofteno® by means of changes in the ocular comfort index.

5.5.3 Hypothesis

Ha The ophthalmic solution PRO-174 presents a safety and tolerability profile similar to the comparator in healthy subjects.

Ho The ophthalmic solution PRO-174 presents a safety and tolerability profile different from the comparator in healthy subjects.

5.6 Design and plan of the study

Phase I clinical trial, controlled, of parallel groups, double blind with randomization, exploratory.

5.6.1 Discussion of the study design

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

6. Material and methods. Participants, interventions and variables

6.1 Study Center

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

6.1.1 Organization of the center

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

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

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

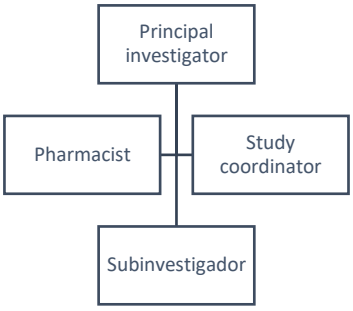


Figure 1 Minimum organization of the center

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

6.1.2 Documentation to be delivered to the sponsor

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

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

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

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

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

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

6.1.3 Closure of the center

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

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

6.2 Eligibility criteria

6.2.1 Inclusion criteria

- Signed informed consent.
- Systemically and ophthalmologically healthy subjects evaluated during the clinical history.
- Age between 18 to 45 years.
- Both genders.
- Blood tests [complete blood count (BHc), three element blood chemistry (QS) and liver function tests (PFH)] within normal parameters specified by the reference laboratory with a lower and upper margin of 10%.

- Vital signs within normal parameters. (Vital signs at rest: blood pressure ≤ 139/89 mmHg, heart rate 60 -100 beats per minute and respiratory rate of 12-24 breaths per minute).
- - Visual capacity 20/30 or better, in both eyes.
- - Intraocular pressure ≥11 and ≤ 21 mmHg.

6.2.2 Exclusion criteria

6.2.2.1 General criteria

- Subjects with a history of hypersensitivity to any of the components of the research products.
- Subject users of topical ophthalmic medications of any pharmacological group.
- Subject users of medication by any other route of administration.
- Pregnant or lactating women.
- Women of childbearing age, who do not ensure a hormonal contraceptive method or intrauterine device during the study period or without a history of bilateral tubal obstruction, oophorectomy or hysterectomy; as fertile age we understand women who have not had their menopause, defined as 12 months since the last menstruation in women over 40 years.
- Subjects with participation in clinical research studies 90 days prior to inclusion in the present study.
- Diagnosis of liver disease or elevation to three times the normal upper value of any of the following liver enzymes: aspartate transferase (AST), alanine transferase (ALT) or bilirubin.
- Inability to attend or answer the evaluations made in each of the visits.
- Positive smoking (specified as cigarette consumption regardless of amount and frequency)
- Positive alcoholism (specified as the consumption of alcoholic beverages, regardless of quantity and frequency, during the study intervention period).
- Contact lens users.
- Occlusible iridocorneal angle, defined as a trabecular mesh visible in less than 90 ° of the angular circumference to gonioscopy.

6.2.3 Elimination criteria

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

6.2.4 Identification of the subject

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

The initials of the study subject will be obtained starting with the first letter of the name, followed by the first letter of the first surname and the first letter of the second surname, obtaining maximum

three letters, in case the person has two names or a compound surname the first letter will always be used.

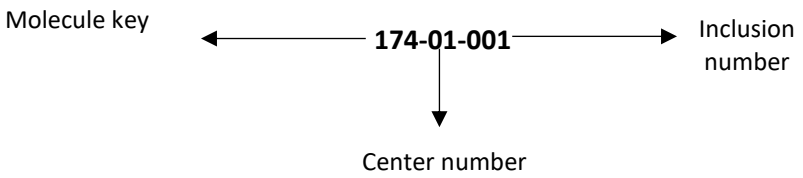
Example:

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

In the counting stage, the participant number will be assigned consecutively, using 3 consecutive digits. Once the subject has been selected, he will be assigned a number with which he will be identified throughout the study. Said code will be 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 in the research center.

Example:



6.3 Intervention

6.3.1 Managed treatments

6.3.1.1 Treatment under study

The characterization and stability tests of the treatment under study are issued by Sophia Laboratories , S.A. of C.V and will be found in the certificates contained within the master folder of the study.

More detailed information can be found in the researcher's manual.

- **PRO-174**
    - Active substance: Levofloxacin 0.5%
    - Pharmaceutical form: ophthalmic solution
    - Prepared by: Sophia Laboratories, S.A. of C.V
    - Dosage: 1 drop in both eyes, 8 times a day during the waking period
    - Description of the solution: transparent solution, free of visible particles.
    - Description of container: sterile multi-dose bottle

Table 4. Quali-quantitative formulation of PRO-174

Type of agent	Amount mg/mL	Function
Levofloxacin hemihydrate [(1)]	5.0	Active principle
Sodium Citrate Dihydrate	Without showing	Additive
Citric acid monohydrate	Without showing	Additive
Disodium Edetate Dihydrate	Without showing	Additive
Sodium chloride	Without showing	Additive
Benzalkonium Chloride [(2)]	0.1	Additive
Fumante Hydrochloric Acid [(3)]	Without showing	Additive
Sodium Hydroxide [(4)]	Without showing	Additive
Water for preparation of injectables c.b.p.[(5)]	1.0 ml	Vehicle

Quali-quantitative formulation of the product under investigation PRO-174. The concentration of the active ingredients is shown, as well as the substances that act as an additive.
OBSERVATIONS:
(1) Equivalent to Levofloxacin (adjustment made by power).
(2) 50% solution.
(3) 4N hydrochloric acid solution.
(4) 4N sodium hydroxide solution.
(5) c.b.p. (how much is enough for).

6.3.1.2 Reference treatment

As the reference treatment, a commercially available medication, your batch number and IPP will be kept as proof of the characterization of said product.

- **Sophixín Ofteno®**
  -
  - Active substance: Ciprofloxacin 0.3%
  - Pharmaceutical form: Ophthalmic solution
  - Prepared by: Sophia Laboratories, S.A. of C.V
  - Dosage: 1 drop in both eyes, 8 times a day during the waking period
  - Description of the solution: transparent solution, free of visible particles.
  - Description of container: sterile multi-dose bottle

Table 5. Sophixin Ofteno quali-quantitative formulation

Type of agent	Amount mg/mL	Function
Ciprofloxacin(1)	3.0	Active principle
Boric acid	Without showing	additive
Benzalkonium Chloride (2)	0.22	additive
Sodium chloride	Without showing	additive
Disodium edetate dihydrate	Without showing	additive
Water for injection preparation c.b.p.(3)	1.0 ml	vehicle

Quali-quantitative formulation of Sophixín Ofteno®. The concentration of the active ingredients is shown, as well as the substances that act as an additive.
OBSERVATIONS:
(1) It is added as Ciprofloxacin Monohydrate.
(2) 50% solution.
(3) How much is enough for.
(4) 4N sodium hydroxide solution.
(5) c.b.p. (how much is enough for).

6.3.2 Strategies to improve adherence and procedure to monitor adherence

1. 1. Direct questioning by the PI about the application of the intervention.
2. 2. Depending on the IP, messages can be sent or reminder calls can be made.
3. 3. Delivery of a printed chronogram specifying the date of the visit and its activities
4. 4. Review on each visit of the subject's diary.

6.3.2.1 Procedure to monitor adherence

Adherence monitoring will be done in the research center through the diary of the subject, will be done as follows:

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

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

This result will allow the PI to determine if the subject continues in the study according to the stipulations of the elimination criteria.

6.3.2.2 Procedure to determine adherence

The final adhesion will be determined by the sponsor by means of the weight of the bottle.

Before delivering the medication to the research center, the weighing of the bottles to be delivered must be carried out. After the return of the medication by the center will be weighing. The weighing will be carried out according to the procedures regulated by the sponsor.

The adhesion will be calculated considering: the weight of the empty bottle, the weight of the drop, the weight of the bottle with the content, the calculation of the total of drops to be applied during the entire time of intervention and the total weight of the drops applied. The following simplified formula will be used:

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

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

$$P_T = (P_g)G$$

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

6.3.3 Treatments and concomitant interventions allowed and prohibited during the study

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

6.3.4 Treatment management

The interventions will be provided by Sophia Laboratories, S.A. of C.V, for each research center. They will be labeled, reconciled and weighed previously. 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 in closed cardboard boxes by means of a courier service or directly by the sponsor's staff to the address of the research center according to the study plan.

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

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

In the study center, the personnel assigned by the IP will deliver to the inpatients the corresponding treatment, sufficient to complete the indicated applications. The center must register the medicine delivered.

6.3.4.2 Storage

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

It should be stored at room temperature at <30º Celsius.

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

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

6.3.4.3 Return

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

6.3.5 Overdose

Overdosage with PRO-174 or Sophixin Ofteno® is not likely to cause effects that threaten function, the organ or less, life. The above, because increasing the number of drops instilled in an application will not increase the exposure to the drug, since the lacrimal lake does not have the capacity to contain a volume greater than one drop, spilling the rest. In case of increasing the frequency of instillations, an increase in the incidence of adverse reactions could be seen (eg, foreign body sensation, headache, photophobia, etc).

For purposes of this protocol we understand as overdosage the increase in 25% of the indicated instillations. That is, 10 or more applications per day on days 1 and 2, or 5 or more applications on days 3 to 7.

1. The report of the overdose will be made in the following tenor:
2. How a deviation to the protocol. The regime instructed in the protocol was not followed.
3. How an EA. Only if it is associated with signs and symptoms.
4. How an EAS. If you meet the criteria to be classified as an EAS.

6.4 Outcome variables

6.4.1 Security variables

6.4.1.1 Primary outcome variables

- Presence of adverse events.
- Intraocular pressure.
- Visual ability
- Laboratory tests: BHc, QS and PFH.
- Ocular surface staining with fluorescein and lissamine green using the Oxford scale.
- Ophthalmological signs: conjunctival hyperemia, chemosis.

6.4.1.2 Primary outcome variables of tolerability Ardor

- Foreign body sensation
- Itching
- Eye comfort index.

6.4.1.3 Secondary outcome variables

- Rupture time of the tear film
- Life signs: FC, FR, TAS.
- Posterior segment

6.4.2 Efficacy variables.

6.4.2.1 Primary outcome variables

It does not apply because it is a phase I study.

6.4.2.2 Secondary outcome variables

It does not apply because it is a phase I study.

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

Variable	Unity	Symbol	Type	Measuring method	Normal value
Age	Years	--	Continuous	Calculation from the date of birth	NA
Gender	Female/ Male	F / M	Nominal	Direct questioning	NA
Adverse events	Number of cases	n	Discreet	Count	NA
Intraocular pressure	Milimeters of mercury	mmHg	Continuous	Goldman´s applanation tonometry	11 - 21
Visual ability	Fraction	Snellen	Nominal	Primer	
Tear rupture time	Seconds	s	Continuous	Direct count	> 10
Eye comfort index	points	--	Discreet	Questionnaire	
	Present / Absent	--	Nominal	Comprehensive valuation	Absent
Vital signs					
Heart rate	Beats per minute	lpm	Discreet	Auscultation	60 – 100
Breathing frequency	Breaths per minute	rpm	Discreet	Auscultation	12 – 24
Systemic blood pressure	Milimeters of mercury	mmHg	Continuous	Non-invasive auscultatory measurement	< 120 / 80
Previous segment					
Ocular surface staining	Degrees	--	Discreet	Direct observation with fluorescein and green lysamin stain	Oxford Scale
Ophthalmologic signs and symptoms					

Variable	Unity	Symbol	Type	Measuring method	Normal value
Conjunctival hyperemia	Normal / Very Light / Mild / Moderate / Severe	--	Ordinal	Direct observation. Classification of Efron.	Normal
Chemosis	Present / Away	--	Nominal	Direct observation	Absent
Burning	Severity: Absent, very mild, mild, moderate and severe	--	Nominal	Direct questioning	Absent
Foreign body sensation	Severity: Absent, very mild, mild, moderate and severe	--	Nominal	Direct questioning	Absent
Pruritus	Frequency: At all times, almost at all times, 50% of the time, almost in no time, at any time	--	Nominal	Direct questioning	Absent
Posterior segment					
Macula	Normal / Abnormal	--	Nominal	Direct observation	Normal
Optical disk integrity	Normal / Abnormal	--	Nominal	Direct observation	Normal
Blood count					
Erythrocytes		M/uL	Continuous		
Hemoglobin	Grams over deciliter	g/dL	Continuous		
Hematocrit	Percentage	%	Continuous		
VGM	Femto liters	fL	Continuous		

Variable	Unity	Symbol	Type	Measuring method	Normal value
HCM	picograms	pg	Continuous		
CMHbG	Grams over deciliter	g/dL	Continuous		
Leukocytes	Thousands per liter units	Mil/uL	Continuous		
Platelets	Thousands per liter units	Mil/uL	Continuous		
Myelocytes	Percentage	%	Discreet		
Metamyelocytes	Percentage	%	Discreet		
Bands	Percentage	%	Discreet		
Segmented	Percentage	%	Discreet		
Lymphocytes	Percentage	%	Discreet		
Monocytes	Percentage	%	Discreet		
Eosinophils	Percentage	%	Discreet		
Basophils	Percentage	%	Discreet		
Blastos	Percentage	%	Discreet		
Blood chemistry					
Glucose	Milligrams on deciliter	mg/dL	Continuous		
Urea	Milligrams on deciliter	mg/dL	Continuous		
Creatinine	Milligrams on deciliter	mg/dL	Continuous		
Liver function tests					
Alanine transferase	Units on liter	U/L	Continuous		
Aspartate transferase	Units on liter	U/L	Continuous		
Total bilirubin	Milligrams on deciliter	mg/dL	Continuous		
Direct bilirubin	Milligrams on deciliter	mg/dL	Continuous		
Indirect Bilirubin	Milligrams on deciliter	mg/dL	Continuous		

Table 6. Scales to be used

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

6.4.3.1 Visual ability

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

Snellen's notation is described as the distance at which the test is performed, divided by the distance at which the letter is vertically equivalent to 5 arc minutes. Thus, at 6 meters a letter 6/6 (20/20) equals 5 minutes of arc, a letter 6/12 (20/40) equals 10 minutes, and a letter 6/60 (20/200) equals 50 minutes The Snellen fraction can also be expressed as a decimal (ie 20/20 = 1 and 20/40 = 0.5). [26]

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

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

6.4.3.2 Eye comfort index

It is a questionnaire designed to measure the irritation of the ocular surface with Rasch analysis to produce estimates on a linear scale of intervals (ratings: 0-100). Similar to the index for ocular surface diseases, the ocular comfort index (ICO) evaluates symptoms. The ICO contains 8 items (one positive and eight negative) that focus on the discomfort associated with alterations of the ocular surface. Each of these questions has two parts, which inquire separately the frequency and severity of the symptoms. [27] See annex 13.1 Index of ocular comfort

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.

6.4.3.3 Eye surface integrity:

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

The variables that will be registered in the CRF in this protocol, and correspond with the variables, 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. [28] See annex 13.2 Efron scale for conjunctival hyperemia
- Chemosis.
It is defined as conjunctival edema, the result of an inflammatory reaction. It is qualified as present or absent. The evaluator will use a narrow beam of light at 60 ° and will measure if

the conjunctiva separates from the sclera at ≥ 1/3 of the total palpebral opening or if it exceeds the gray line. [29]

6.4.3.3.1 Stains

• Staining with green lysine.

A drop of topical anesthetic will be instilled in the conjunctival cul-de-sac, then a second drop will be applied to the tip of the strip of green lysine and it will be allowed to slip towards the bottom of the sac. It is essential to quickly evaluate the staining, in sequence, first in the DO and then the OS, so that the observed patterns are equally bright. [30] See Annex 13.3 Oxford Scale

• Fluorescein staining.

A drop of topical anesthetic will be instilled into 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 slip to the bottom of the sac. It is essential to quickly evaluate the staining, in sequence, first in the DO and then the OS, so that the observed patterns are equally bright. This valuation will be made with the cobalt blue filter. [30] See Annex 13.3 Oxford Scale

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

6.4.3.4 Presence of adverse events

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

The PI will register in the corresponding section of the CRF the EAs that come to present the subjects of the study in addition to referring it in its essential document.

6.4.3.5 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. [26] Tonometry will be performed, after instillation of a drop of topical anesthetic (tetracaine 0.5%), with fluorescein and the use of cobalt blue filter (after evaluation of 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.

6.4.3.6 posterior segment

The evaluation of the posterior segment will be carried out under medication mydriasis (tropicamide 0.8% / phenylephrine 5%), in the slit lamp with an aerial loupe (at the choice of the PI). An integral assessment of the fundus (including optic disk, posterior pole and periphery) will be performed in search of abnormalities that alter the study result. Prior to mydriasis medicamentosa, the evaluation of the iridocorneal angle should be counted, in order to rule out an occludable angle, which is defined as a posterior trabecular mesh visible in less than 90 ° of the angular circumference. [31] [32] The result of the assessment will be recorded in the clinical file. The CRF will record the assessment of the macula and optic nerve as normal, abnormal or abnormality that does not affect.

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 IP. It is necessary that all measurements are equal in circumstances. 3 measurements will be made, with a minimum interval of 5 minutes between them. The IP will record the average in the note and the CRF.

6.4.3.8 Ocular symptomatology

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

Severity: Absent (0), very mild (1), mild (2), moderate (3) and severe (4)

Frequency: At all times (4), almost at all times (3), 50% of the time (2), almost at no time (1), at any time (0).

The number corresponding to each symptom will be registered in the CRF.

6.4.3.9 Breaking time of the tear film

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

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

6.4.3.10 Pregnancy test

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

6.4.3.11 Lab tests.

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

6.4.4 Measurement time

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

Visit scrutiny / Day 0 – X

This visit, by definition, must precede the baseline visit. There is no minimum period to be observed between the scrutiny visit and the baseline, it will depend on having the results of the laboratory tests; notwithstanding, the period between these visits should not exceed 10 days.

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

1. Laboratory sample taking.
2. Visual ability

3. Intraocular pressure.Índice de confort ocular
   4. Evaluation of ocular signs and symptoms
   5. Integrity of ocular surface
   to. Epithelial defects (TF and TVL)
   6. TRL
   7. Subsequent segment evaluation.
   8. Vital signs
   9. Evaluation of adverse events

Basal Visit / Day 0.

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

1. Visual ability
2. Intraocular pressure.
3. Eye comfort index
4. Evaluation of ocular signs and symptoms
5. Integrity of ocular surface
   a. Includes stains
6. TRL
7. Subsequent segment evaluation.
8. Vital signs
9. Evaluation of results of laboratory tests
10. Evaluation of adverse events

Visit 1 / Day 3.

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

1. Visual ability
2. Intraocular pressure.
3. Evaluation of ocular signs and symptoms
4. Integrity of ocular surface
   a.Includes stains
5. TRL
6. Vital signs.
7. Evaluation of adverse events.

Final visit/ Day 8.

If the visit can not be made on the 8th, it can be done within a period of up to two days, that is, on the 9th or 10th day. Not before, since the application of the medication will not be completed as dictated the protocol.

1. Visual ability
2. Intraocular pressure.
3. Eye comfort index
4. Evaluation of ocular signs and symptoms
5. Integrity of ocular surface
   a. Includes stains

6. TRL
7. Subsequent segment evaluation.
8. Vital signs.
9. 9. Evaluation of adverse events.

Security call / Day 12.

It can be done in a period ± 1 day in relation to day 12 of the start of application.

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

6.4 Timeline and study diagram

Procedures	*Scrutiny* Day 0 -X	Basal Visit Day 0	Visit 1 Day 3 ± 1	Final Visit Day 8 a +2	Call Security Day 12 ± 1
CI Signature	X				
Clinic history	X				
Ophthalmological clinical history	X				
Laboratory sample taking	X			X	
Laboratory tests review		X			X
Pregnancy test	X			X	
Eligibility criteria	X	X[a]			
Assignment		X			
Delivery of intervention and indication of starting the application the next day day 1.		X			
Return of intervention				X	
Adherence evaluation			X	X	
Adverse events	X	X	X	X	X
Intraocular pressure	X	X[1]	X	X	
Visual ability	X	X[1]	X	X	
TRL	X	X[1]	X	X	
Eye surface integrity	X	X[1]	X	X	
Eye symptoms	X	X[1]	X	X	
posterior segment	X	X[1]		X	
Vital signs	X	X[1]	X	X	
Ocular Comfort Index		X		X	
Daily delivery of the subject		X	X		
Return / Evaluation of the subject's Journal			X	X	
Continuity evaluation of the subject			X		

[a] Eligibility criteria will be completed with the review of laboratory tests
1 These measurements may be taken from the result of the scrutiny visit, if it does not exceed 10 days previous. It is the prerogative of the IP to decide whether to repeat the measurements at the baseline visit.

6.5.1 Procedures to be performed per visit

6.5.1.1 Scrutiny visit

- Signature of informed consent: refers to the signing of the written informed consent document. See 10.3 Consent.

- General and ophthalmological clinical history: refers to the technical, clinical and legal document in which the patient's health conditions, medical acts and other procedures performed on the patient are recorded chronologically. It includes the anamnesis and comprehensive ophthalmological exploration that allows to discern the patient's eligibility. If the patient is taken from the established consultation of the study center, he / she will be able to use the existing clinical history, only having to perform an update.
- Taking laboratory samples: see 6.4.3.11 Laboratory tests.
- Pregnancy test: see 6.4.3.11 6.4.3.10 Pregnancy test.
- Eligibility criteria: refers to the review by the IP, where it states that the subject can be included in the study by meeting the inclusion criteria and not meeting the exclusion criteria. See 6.2 Eligibility criteria
- Intraocular pressure: see 6.4.3.5 Intraocular pressure
- Visual ability: see 6.4.3.1 Visual capacity
- TRL: see 6.4.3.9 Rupture time of the tear film
- Integrity of ocular surface: see 6.4.3.3 Integrity of ocular surface:
- Eye symptoms: 6.4.3.8 Ocular symptomatology
- Subsequent segment: see 6.4.3.6 Subsequent segment
- Vital signs: see 6.4.3.7 Vital signs
- Adverse events: see 6.4.3.4 Presence of adverse events6.5.1.2 Visita basal
- Review of laboratory tests: refers to the review and analysis by the IP of the results of the BH, QS and PFH. See 6.4.3.11 Laboratory tests.
- Eligibility criteria: with the laboratory results, the subject's profile will be finalized for inclusion or not.
- Assignment: It refers to determining the intervention that the patient will follow during the study. It will be done according to section 7. Methods. Assignment of the intervention. This assignment will be made at the baseline visit (day 0) and will go along with the indication to start the treatment period the next day (day 1).
- Delivery of intervention: Refers to the delivery of the product under investigation to the patient of the study, by the research center. It will be done according to sections 6.3.1 Managed treatments and 6.3.4.1 Delivery and reception.
- Evaluation of variables: The data of the evaluation of the variables listed below can be taken from the scrutiny visit, as long as it does not exceed 7 days prior to this visit. It is the IP's prerogative to decide whether to use the information from the screening visit or to repeat the evaluations on this visit.
    - Intraocular pressure
    - Visual capacity
    - TRL
    - Integrity of ocular surface
    - Eye symptoms
    - Subsequent segment
    - vital sign
- Eye comfort index: see 6.4.3.2 Eye comfort index
- Delivery of the subject's diary: It refers to the delivery by the IP to the subject, the subject's daily instrument.
- Adverse events: see 6.4.3.4 Presence of adverse events

6.5.1.3 Visita 1

- Evaluation of adherence: refers to the assessment made by the IP according to section 6.3.2.1 Procedure to monitor adherence
- Adverse events: see 6.4.3.4 Presence of adverse events
- Intraocular pressure: see 6.4.3.5 Intraocular pressure
- Visual ability: see 6.4.3.1 Visual capacity
- TRL: see 6.4.3.9 Rupture time of the tear film
- Integrity of ocular surface: see 6.4.3.3 Integrity of ocular surface:
- Eye symptoms: 6.4.3.8 Ocular symptomatology
- Vital signs: see 6.4.3.7 Vital signs
- Submission of the subject's diary: see 6.5.1.2 Baseline visit
- Return / daily evaluation of the subject: refers to the delivery of the subject's diary to the IP by the subject. The PI will review the diary to assess its correct filler, evaluate postinstilation symptoms and record applications.
- Continuity assessment of the subject: refers to the determination by the IP and desire of the subject to continue with their participation in the study.

6.5.1.4 Final Visit

- Laboratory sample taking: ver6.4.3.11 Laboratory tests
- Pregnancy test: see 6.4.3.10 Pregnancy test
- Return of intervention: see 6.5.1.3 Visit 1.
- Evaluation of adherence: refers to the assessment made by the IP according to section 6.3.2.1 Procedure to monitor adherence
- Adverse events: see 6.4.3.4 Presence of adverse events
- Intraocular pressure: see 6.4.3.5 Intraocular pressure
- Visual ability: see 6.4.3.1 Visual capacity
- TRL: see 6.4.3.9 Rupture time of the tear film
- Integrity of ocular surface: see 6.4.3.3 Integrity of ocular surface:
- Eye symptoms: 6.4.3.8 Ocular symptomatology
- Subsequent segment; see 6.4.3.6 Subsequent segment
- Vital signs: see 6.4.3.7 Vital signs
- Eye comfort index: see 6.4.3.2 Eye comfort index
- Return / daily evaluation of the subject: see 6.5.1.3 Visit 1.

6.5.1.5 Security call

- Adverse events: see 6.4.3.4 Presence of adverse events
- Review of laboratory tests: see 6.5.1.2 Baseline visit

6.5.2 Diagram of the study

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

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

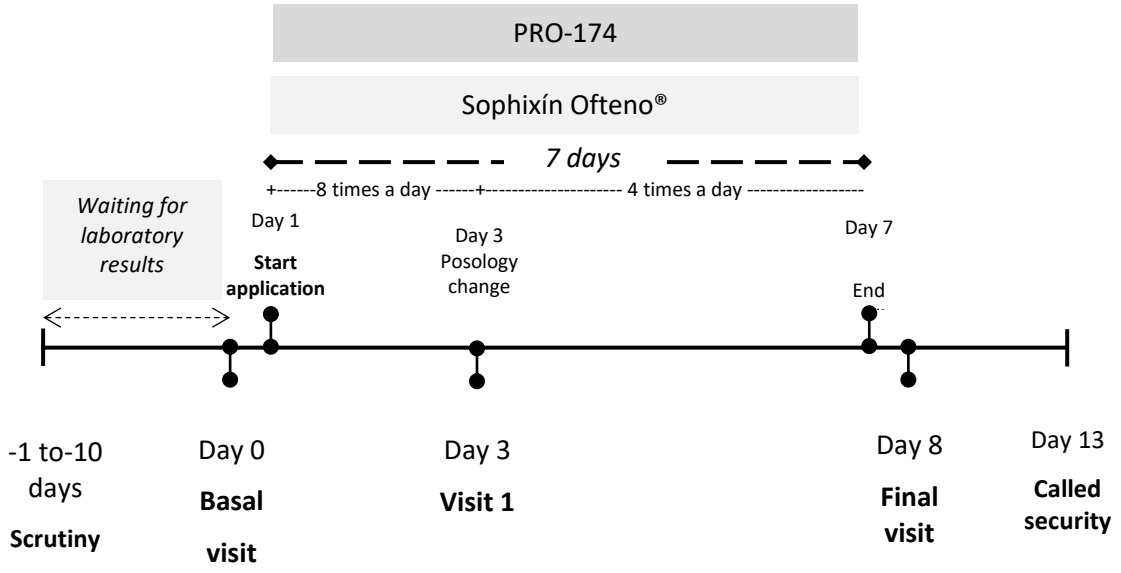


Figure 2. Study diagram

6.6 Sample size

A total size of 30 subjects is estimated, distributed in intervention groups [15 subjects (30 eyes) per group]

6.6.1 Calculation of the sample size

Although there are no references on the calculation of sample size in phase I studies, it was considered pertinent to perform it according to the presentation of adverse events reported by Schwab IR, et al, in a case-control study in 423 subjects with ophthalmic solutions of levofloxacin 0.5 % and ofloxacin 0.3% for 5 days. [22]

The percentage of adverse events that occurred with the preservative-free HS solution was 7.3%, which is why we consider that at least more than 60% of the exposed subjects will not present this rate of adverse events.

The sample size was calculated using the formula for proportions

$$n = \left[(p1)(p2) + (p1)(p2)\left(\frac{Z_{1-\alpha}}{2} + Z_{1-\beta}\right)^2\right]/(p1 - p2)^2$$

With a statistical confidence of 95% corresponding to the type I error, equal to 1.96, with a power of 80%, corresponding to the type II error, equal 0.84.

According to the previous calculation, the result is 12.5 subjects (13) per group. The total when considering 2 intervention groups is 26 subjects, which was increased by 20% for the probable losses. The total sample size required is 30 subjects. Therefore, each group will consist of 15 subjects, who will provide both eyes for the analysis, so that the total sample to be analyzed will be composed of 60 eyes.

6.7 Recruitment

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

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

7. Methods Assignment of the intervention

7.1 Generation of the allocation sequence

The random numbers will be generated through the online tool:
www.randomization.com
Two strata corresponding to the intervention groups will be used, which will be balanced for a research center. The allocation will be 1: 1.

7.2 Blinding mechanism

Blinding will be performed by personnel assigned by the Clinical Operations Management of Laboratorios Sophia, S.A de C.V. Which will consist in the elimination of the primary label (commercial) in the case of Sophixín Ofteno® and the placement of a label identical to the other intervention. There will be a masking in the secondary packaging which will be identical for the interventions.

7.3 Implementation

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

7.4 Blinding (Masking)

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

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

7.4.1 Opening of blinding

Blinding may be opened in the following cases:

1. Presence of a serious adverse event.
2. Safety alarm due to the use of the drugs under study.

3. In case the sponsor determines it for any security reason or other reason that it considers pertinent.

8. Methods Collection, administration and data analysis

8.1 Methods of data collection

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

The data registered in the CRF will be reviewed by personnel of Sophia Laboratories, S.A. of C.V trained in the ophthalmological, clinical and pharmacological area, which will have the power to generate discrepancies in the event that the data do not adhere to the stipulations of the research protocol or endanger the participants.

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

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

8.1.1 Strategies to complete the follow-up

- You will be clearly informed of the importance of the study and the benefits that the population will obtain from the results of the study.
- Transportation assistance will be provided in order for the participant to attend their visits.
- In case the IP deems it convenient, it can make calls or send text messages or via email to the research subject. The content of these must be previously approved by the ethics committee.
- A printed calendar will be provided with the objective of reminding the participant of their appointments and the activities that will be carried out, in addition to the estimated duration of the same.
- In case the participant does not attend his / her appointment, the research center must make a call to know the reason and try to arrange a new appointment within the established window period or an unscheduled appointment.
- • In case it is not possible to make an appointment, it will be asked about the presence of adverse events and the reason for leaving the study, 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 IP or the designated person of your team will fill out the Case Report Format (CRF) as well as all other documents provided by the sponsor (for example, documents related to the handling of the treatment).

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

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

The data capture in the investigator's site will be done by the investigator or the designated person of his team after performing the Medical File. The researcher or a designated person of your team will be trained in 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 must ensure that all the data has been filled in the CRF. After comparing the data against the source documents, in case a correction or clarification is necessary, the monitor will request it from the researcher; which must be answered and closed as soon as possible.

The Scientific Committee of Laboratories Sophia, S.A. of C.V. will give the latest medical-scientific review, and will set the standard for freezing the database.

8.3 Statistical methodology

8.3.1 Analysis of primary and secondary outcome variables.

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

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

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

The result of the continuous quantitative variables will be presented in measures of central tendency: media, standard deviation and ranges. **See Table 6.** Scales to be used

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

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

• Intra-group analysis: Wilcoxon rank test.

• Inter-group analysis: Mann-Whitney U test.

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

The result of nominal and ordinal qualitative variables will be presented in frequencies, proportions and percentages. See table 1 (section 6.4.3).

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

• Intra-group difference: McNemar test.

• Difference between groups: test χ2 (Chi-square) of Pearson.

The level of difference to consider significance will be of 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. It was considered that from the minimum dose necessary to obtain a pharmacological effect and the presence of adverse events (exposure) is sufficient to fulfill the general objective of the design, according to the pharmacological characteristics of the product under investigation.

8.3.2 Additional analyzes

No additional analyzes are contemplated to those previously described. Nevertheless, these may be performed in the event that 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 final visit will be included.

9. Methods Monitoring

9.1 Data monitoring

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

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

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

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

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

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

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

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

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

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

After the study is closed, the researcher must keep all study records on the site in a safe place. Records should be maintained to allow easy and timely recovery, when necessary (for example, in an audit or inspection). Sophia Laboratories, S.A. of C.V. will inform the investigator / institution the period of time they will have to retain these records, in order to comply with all applicable regulatory requirements. Nevertheless, the investigator / institution must seek the written approval of the sponsor before proceeding to the elimination of these records. The minimum retention time will satisfy the most stringent standard applicable to that site for the study, in accordance with the provisions of the PCBs, any institutional requirements or the applicable laws or regulations, or the standards / procedures of Sophia Laboratories, S.A. of C.V

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

9.2 Preliminary analysis and early termination of the study.

The partial analysis described in section 6.5 and 8.3.2 will allow the sponsor to make a decision about the early termination of the study in the event that the safety of the participants is compromised.

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

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

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

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

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

9.3 Adverse events

9.3.1 Investigator's responsibilities

Perform the verification of adverse events through questioning, relevant physical examination, assessment of evolution, as well as adequate medical and pharmacological management, resolution or outcome and final discharge following the definitions determined in national and international regulations. [33] [34] [35]

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

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

In the final report to be drafted by the Scientific Committee of the Department of Clinical Operations of Sophia Laboratories, S.A. of C.V, will include the report of adverse events in compliance with current national and international regulations. [34] [33]

9.3.1.1 Record of adverse events in the Case Report Form

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

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

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

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

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

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

so. If you have enough space in the case report format, you can complement the information of your clinical note in the clinical file.

9.3.1.2 Follow up of adverse events

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

9.3.1.3 Procedures for a serious adverse event.

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

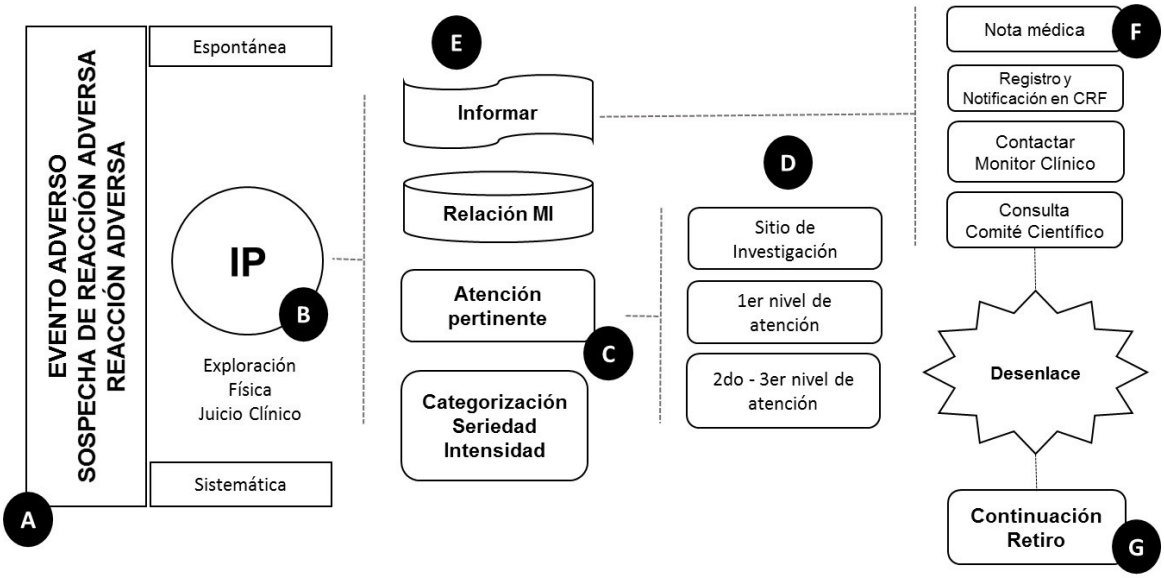


Figure 3. Attention to the adverse event.

A. During the development and conduct of the present clinical research, undesirable damaging events or adverse reactions, of medical implication, which do not necessarily have a causal relationship with the investigational product or investigational medication, may occur in the participant patient. These harmful phenomena can occur during the use of investigational drugs, unintentionally, at doses authorized for use in humans; by a local, national or international regulatory entity, whether for prophylaxis, diagnosis, treatment or for the modification of some physiological process. Nevertheless, it can be suspected that the investigational product or the investigational drug or the placebo cause some unwanted clinical manifestation. Adverse events, adverse reactions or suspected adverse reactions to one or several medications can occur during the systematic evaluation of the participants (on the days when the clinical review is scheduled, according to the schedule of activities) or suddenly, as such way that,
B. The investigator must be the first person to whom the patient reports that they have developed or presented a harmful clinical phenomenon during their participation in this research protocol.
C. According to your clinical judgment; on the basis of the pertinent physical examination, interrogation, etc., as well as the analysis of the information available in the medical literature and that referred to in the investigator's manual, information to prescribe or

technical data sheet of the comparator drug, the principal investigator determines the relevant attention of the event / harmful reaction; either.

D. in the research site or in the hospital with the greatest resolving power (1st, 2nd or 3rd level of medical attention). In such a way that, in case the patient is sent by the Investigator to a hospital, he / she attends by means of a reference system, it can be with an identification card that the patient belongs to the present investigation and there is an official number or folio, which pertains to the emergency care agreement with the health institution with the greatest resolving power, or a medical reference note issued by the principal investigator, so that appropriate care is given to the participating patient. It should be noted that the Study Sponsor, Sophia Laboratories, S.A. C.V., will pay the expenses for the medical care of the participating patient, only if the adverse event, adverse reaction or suspected adverse reaction to medication is associated or found in relation to the investigational product or investigational drug.
E. Taking the clinical information collected, either during the care provided at the research site or provided by the treating physician (s) in the hospital, the principal investigator records the adverse event, suspected reaction adverse or adverse reaction to medication in your clinical note of the clinical record, indicating the seriousness, intensity (mild, moderate or severe), relationship with the product or drug under investigation, as well as:
F. The migration of the relevant data to the case report format and to its respective adverse event section; noting the pertinent information, already referred to in section 9.3.1.1., this in virtue of the fact that in cases of serious adverse events, which must be notified in less than 24 hours after the moment in which the principal investigator has knowledge of the same, the clinical monitor of the study is informed, so that in turn he / she informs the Scientific Committee and the Pharmacovigilance Department of the sponsor and later he / she informs the Research Ethics Committee. Regarding non-serious adverse events, these will be recorded and adequately addressed and the corresponding regulatory entity will be informed about the safety profile of the product under investigation or investigational medication in the final report of the clinical trial.

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

9.3.1.4 Causality evaluation.

The assessment of the causality, the methodology used to estimate the probability of attributing to a drug, investigational drug or investigational product the adverse reaction, the suspicion of the same or the observed adverse event, considers probabilistic categories, according to the evidence available and the quality of information, based on national pharmacovigilance regulations. [33] As a tool to facilitate the probabilistic categorization of causality, the principal investigator can use the algorithm of Karch and Lasagna modified by Naranjo referred to by Aramendi I, 2011 in which different items are qualified which allow assigning a value to the relationship cause-effect between

the administration of the drug and the adverse reaction. [36] **See Table 7. Algorithm of Karch and Lasagna modified by Naranjo**.

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

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

Table 7. Algorithm of Karch and Lasagna modified by Naranjo.

In such a way that the degree of certainty to establish the investigational product or investigational medication (as appropriate) as the causal agent of the harmful phenomenon that befalls the participating patient, can be directly indicated by the principal investigator based on his or her

clinical experience or well through the voluntary application of the tool mentioned previously. Nevertheless, it is important that the investigator take into account the following arguments in favor of the causal relationship:

3. a) Force of association: refers to the number of cases in relation to those exposed.
4. b) The consistency of the data: that is, the presence of a common characteristic or pattern.
5. c) The exposure-effect pattern: which determines the relationship with the site of onset, time, dose and reversibility after suppression.
6. d) The biological plausibility: which refers to the possible pharmacological or physiopathological mechanisms involved in the development or presentation of the adverse event.
7. e) Experimental findings: for example the appearance of anomalous metabolites or high levels of drug or the product of its biotransformation.
8. f) Analogy: experience acquired with other related drugs, adverse reactions frequently produced by the same family of pharmacological agents.
9. g) Nature and characteristics of the data: objectivity, accuracy and validity of the relevant documentation. [37].

9.3.2 Responsibilities of the sponsor.

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

9.4 Audit

To guarantee compliance with the PCBs and with all applicable regulatory requirements, Sophia Laboratories, S.A. of C.V, the COFEPRIS and / or the CEI could carry out a compliance audit to the research center.

9.4.1 Pre-study audit

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

9.4.2 Audit / Inspection during the conduction of the study

They may take place at any time before, during or after the conclusion of the study. If an audit or inspection is performed, the investigator and the institution should agree to allow the auditor / inspector direct access to all relevant documents, and will allocate their time and that of their staff to the auditor / inspector to discuss the findings and any relevant problems.

10. Ethical considerations

10.1 Approval of the committees

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

of Subjects of Biomedical and Behavioral Research, 1979". It will be conducted in accordance with the scientific and technical requirements necessary for the registration of medicines for human use according to the "Guide to Good Clinical Practices of the International Conference on Harmonization" (The International Council for Harmonization, ICH). "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 to carry it out. These Committees must be notified of any significant changes to the protocol. In addition to the above, the current regulations issued by the Ministry of Health 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, study coordinators or personnel authorized by the sponsor will be evaluated by the Research Ethics Committees, Research Committees, and when applicable, the Biosecurity Committee; the essential documentation of the research project: research protocol, informed consent letter, 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 to the methodological structure, substitution of the principal investigator or when identifying risks in the research subjects.
The documents susceptible of amendment will be: protocol, letter of informed consent, researcher's manual, documents for the patient, scales of measurement and schedule of activities.

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

Amendments that substantially modify the protocol or confer an additional or different risk to the research subjects, must be approved by the corresponding 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 shows a greater risk for the participants, the termination or premature suspension of the study, the reasons and the results obtained up to that moment. You must also inform about the conclusion of the study, when completing the research protocol.

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

10.3 Consent

10.3.1 Obtaining

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

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

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

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

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

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

The IP must also sign and date this consent.

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

10.3.2 Special considerations.

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

10.3.3 Modification to informed consent.

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

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

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

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

10.4 Confidentiality

All documents and information provided to the researcher by the sponsor are strictly confidential. The researcher expressly agrees that the data on their professional and clinical experience, provided to the sponsor on paper and stored 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 reveal any information without the prior written consent of Sophia Laboratories, S.A. of C.V, except to the representatives of the Competent Authorities, and only by request of the same. In the latter case, the researcher undertakes to inform Sophia Laboratories, S.A. of C.V before revealing the information to these authorities.
The researcher will fill out and maintain a record of the subjects' selection, as well as the identification and enrollment list of each of the subjects participating in the study. The researcher agrees to give on-site access to the auditor and / or the representatives of the Competent Authorities. The information will be treated in compliance with professional secrecy.

10.5 Deviations

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

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

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

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

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

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

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

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

10.5.1 Management of deviations

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

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

- Request more information.
- Citing the principal investigator and / or the members of his team.
- - Temporarily suspend the researcher for present and / or future investigations until the situation is resolved and / or considers the explanations given by the person (s) responsible for the deviation satisfactory.
- - Conduct an audit for cause.

10.6 Declaration of interests

The PI is committed to making 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 IP will not have access to it, unless it has prior written authorization from the sponsor.

10.8 Auxiliary care and after the end of the study

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

10.9 Biosecurity aspects

WITHOUT BIOSECURITY IMPLICATIONS

The present protocol, with the title: "Phase I clinical study, to evaluate the safety and tolerability of the ophthalmic solution PRO-174 versus Sophixín Ofteno®, prepared by Sophia Laboratories, S.A. of C.V on the ocular surface of ophthalmologically and clinically healthy subjects ", and number: SOPH174-0816 / I DOES NOT HAVE BIOSECURITY IMPLICATIONS, since infectious-contagious biological material will NOT be used; pathogenic strains of bacteria or parasites; viruses of any kind; radioactive material of any kind; genetically modified animals and / or cells and / or plants; toxic, dangerous or explosive substances; any other material that endangers the health or physical integrity of the personnel of the research center or the subjects of investigation or affects the environment. In addition, it is stated that cell, tissue or organ transplant procedures or cell therapy procedures will not be carried out in this project, nor will laboratory, farm or wildlife animals be used.

10.10 Final report and publication of results

10.10.1 Final report

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

10.10.2 Communication of results

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

10.10.3 Publication of the results

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

The PI undertakes not to publish or communicate data collected only in a center or in part of the centers before the publication of the full results of the study, unless prior written authorization is obtained from 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 the communication and / or presentation of a publication. The medical researcher or doctors will comment on the project within 15 days in the case of a publication and 7 days in the case of a summary, from the date on which the project is received.

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

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12. Signature page

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Internal reviewer of the protocol:

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External reviewer of the protocol:

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Principal investigator of the study:

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13. Annexes

13.1 Eye comfort index

Índice de Confort Ocular

Ficha de identificación

No. de estudio SOPH174-0816-I **Fecha:** / /

Iniciales del sujeto: **No. de sujeto:** 174-_____-_____

Indicaciones:

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

Para cada pregunta circule su respuesta

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

Nunca						Siempre
0	1	2	3	4	5	6

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

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

Nunca						Siempre
0	1	2	3	4	5	6

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

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

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

Nunca						Siempre
0	1	2	3	4	5	6

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

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

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

Nunca						Siempre
0	1	2	3	4	5	6

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

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

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

Nunca						Siempre
0	1	2	3	4	5	6

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

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

Hoja 1 de 2

Índice de confort ocular

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

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

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

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

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

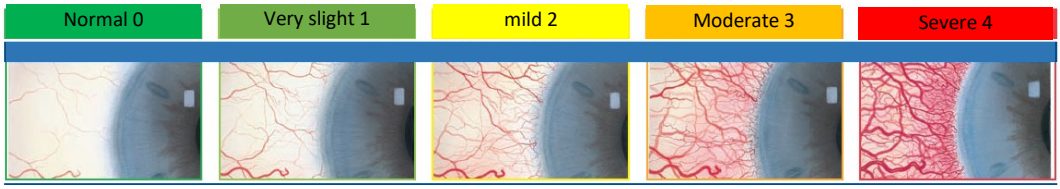
Nunca						**Siempre**
0	1	2	3	4	5	6

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

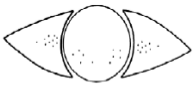
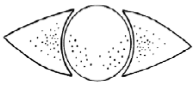
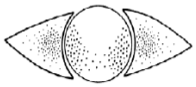
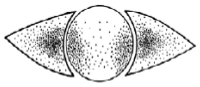
No lo he sentido						**Severo**
0	1	2	3	4	5	6

Índice de confort ocular, traducido del Ocular Comfort Index disponible en: http://iovs.arvohournals.org
Hoja 2 de 2

13.2 Efron scale for conjunctival hyperemia



13.3 Oxford Scale

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