Title of the document	Clinical Research Protocol
Title of the study	Phase II, multi-center, randomized, double-masked clinical study to evaluate the safety and efficacy of the PRO-157 ophthalmic solution in three different posologies versus Moxifloxacin and versus Gatifloxacin in patients with bacterial conjunctivitis.
Study drug	Pazufloxacin
Indication	Antibiotic for the treatment of bacterial conjunctivitis
Development phase	Phase II
Protocol Code	SOPH157 - 0114 / II
Sponsor	Sophia Laboratories, S.A. of C.V.
Version 4	April 2016

1.- SUMMARY STUDY

Sponsor's name: Laboratorios Sophia, S.A. of C.V.
Finished Product Name: NA
Active Ingredient Name: Pazufloxacin
Title of the study: Phase II clinical study, multicenter, randomized, double masked to evaluate the safety and efficacy of the ophthalmic solution PRO-157 in three different posologies versus Moxifloxacin and versus Gatifloxacin in patients with bacterial conjunctivitis.
Study centers: To be defined

Study period: 7 days	**Phase of development of the study:** Phase II

Objectives:

General purpose:

To evaluate the safety and efficacy of the ophthalmic solution PRO-157 in three different posologies versus Moxifloxacin and versus Gatifloxacin in patients with bacterial conjunctivitis.

Specific objectives:

To determine the safety of the PRO-157 solution in three different posologies versus Moxifloxacin and versus Gatifloxacin in patients with bacterial conjunctivitis by the incidence of adverse events.

To evaluate the efficacy of the ophthalmic solution PRO-157 in three different posologies versus Moxifloxacin versus Gatifloxacin in patients with bacterial conjunctivitis through the evaluation of ocular signs and symptoms such as: burning, lacrimation, foreign body sensation, pruritus, photophobia, hyperemia conjunctival, chemosis, secretion, membranes and / or pseudomembranes, scales and palpebral edema, epitheliopathy.

Work hypothesis

The ophthalmic solution PRO-157 is so safe and effective in any of its different posologies when demonstrating non-inferiority when compared against Moxifloxacin and Gatifloxacin in the treatment of bacterial conjunctivitis.
Ho: The ophthalmic solution PRO-157 is not as safe and effective in any of its different dosages when demonstrating non-inferiority when compared against Moxifloxacin and Gatifloxacin in the treatment of conjunctivitis
Ha: The ophthalmic solution PRO-157 is so safe and effective in some of its different posologies when demonstrating non-inferiority when compared against Moxifloxacin and Gatifloxacin in the treatment of conjunctivitis

Sponsor's name: Laboratorios Sophia, S.A. of C.V.
Finished Product Name: NA
Active Ingredient Name: Pazufloxacin
Methodology Multicentric double randomized study masked.
Number of participants: 300 eyes, 60 eyes per treatment group
Diagnosis and main criteria for inclusion Patients with bacterial conjunctivitis (signs and / or symptoms and / or culture) Subjects aged 0 years to 99 years.
Study medication: **Pazufloxacin**
- **Treatment duration:** - **- Recruitment period: 4 months** - **- Period of treatment: 7 days** - **- Period of follow-up: 15 days**
Criteria for evaluation: **<u>Efficacy measurements:</u>** **Main efficacy criterion** It will be determined as effective if there is a reduction in the number or species of bacterial flora comparing the basal culture against the final between the five different groups of patients and / or if there is a reduction or absence of the infection with the clinical evaluation through signs and symptoms such as: burning, tearing, foreign body sensation, pruritus, photophobia, conjunctival hyperemia, chemosis, secretion, palpebral edema, membranes and / or pseudomembranes, palpebral scales and epitheliopathy **Security measurements:** **Visual ability** **Adverse events**

INDICE

List of Paintings

List of figures

List of appendices

2. GLOSSARY AND DEFINITIONS

EA	Adverse Event
AV	Visual acuity
CV	Visual Capacity
FRC	Case Report Form
BPC	Good Clinical Practices
ICH	International Harmonization Conference
CI	Informed Consent
MY	Researcher's Manual
CIE	Independent Ethics Committee
CCI	Informed Consent Letter
CRI	Institutional Review Committee
ITT	Population Evaluable for Intent to Treat
IOP	Intraocular Pressure
PP	Estimatable Population by Proper Protocol
EAS	Serious Adverse Event
AMI	File Master of the Investigator
AME	Master Studio File
CP	Rear Camera
ME	Study Medication

3 ADMINISTRATIVE STRUCTURE OF THE STUDY

3.1 Non-sponsoring parties

A central microbiological laboratory will be responsible for collecting and processing conjunctival sac fundus samples.

3.2 Sponsoring parties

Table 1. - Department of Clinical Research / Laboratories Sophia S.A. of C.V.
Address:
Sophia S.A. Laboratories de C.V., Paseo del Norte Av. No.5255, Guadalajara Technology Park, Carretera Guadalajara-Nogales Km13.5 C.P45010 Zapopan, Jalisco, Mexico Tel +52 (33) 3000 4200

Function	Name / email	Telephone number
Clinical Operations Manager	MBA Marco Antonio Cid López CCRP marco.cid@sophia.com.mx	+33 3001 4200 Ext. 1074
scientific Comittee	Dr. Aldo Arturo Oregon Miranda aldo.oregon@sophia.com.mx	+33 3001 4200 Ext. 1125
Senior Monitor	Q.F.B Jessica Mejía Gutiérrez jessica.mejia@sophia.com.mx	+33 3001 4200 Ext. 1192
Junior Monitor	Q.F.B Sandra Carolina Gómez Méndez sandra.gomez@sophia.com.mx	+33 3001 4200 Ext.1191
Junior Monitor	LN. Ana Isabel Alcaraz Ledón ana.alcaraz@sophia.com.mx	+33 3001 4200 Ext. 1193

4 INFORMATION ABOUT BACKGROUND
4.1 INTRODUCTION

Conjunctivitis (partial or total inflammation of the conjunctiva) caused by an external pathogen can be divided into bacterial and viral, however we must not forget that if we take into account its etiology we can name by fungal, allergic, autoimmune and by physical means (heat burns, friction, chemical).

In the following document, we will concentrate on exposing the epidemiological and clinical panorama of conjunctivitis caused by pathogens (bacteria and viruses) and the suffering related to the mass.

Currently about 6 million cases are registered per year in the general consultation (1% of the total annual consultations), this does not mean that all cases will be sent to the ophthalmologist, however as a reason for consultation 70% of the subjects come first with a family doctor and 35% refer to ophthalmologists because it is a case that does not remit with symptomatic or because the severity warrants it.

The cost of treating conjunctivitis according to data collected in the American union represents more than 377 million dollars a year.

Viral conjunctivitis:

Viral conjunctivitis represents an average of 80% of reported cases, it is estimated that 50% of these will be misdiagnosed as bacterial, this when compared to positive cultures.

65-90% of cases are caused by adenoviruses found in any of its two pathogenic entities, either in the form of epidemic keratoconjunctivitis or pharyngo-conjunctival fever. Clinically both are characterized by local inflammatory reactions, hyaline secretion, chemosis, photophobia, hyperemia, corneal deposits and lymphadenopathy.

The adenovirus is highly contagious and an estimated 10 to 50% chance of spread. 46% of the cultures in the hands of patients diagnosed with keratoconjunctivitis are positive, so their spread is verified mainly by contact and fomites.

Its incubation period ranges from 5 to 12 days and its transmission period of 10-14 days.

Its treatment consists of treating the symptoms with eye lubricants, NSAIDs, eye antihistamines, cold compresses, etc. Prophylaxis with antibiotics is not indicated since its benefit has not been proven, more if complications and delay in diagnosis of other entities are reported.

Bacterial conjunctivitis:

Its incidence is estimated at 135 per 10,000 inhabitants. The main routes of infection are by contact, although the proliferation of normal flora can occur as sole etiology or concomitantly.

The pathogenesis usually involves the disruption of the ocular surface defense mechanisms, due to trauma, tear film dysfunction or palpebral abnormalities, etc.

Usually its installation occurs 1 to 2 days after contact, characterized by rapid appearance of clinical signs such as palpebral edema, hyperemia, mucopurulent secretion, membranes and / or pseudomembranes.

The main infectious agents in adults are H. influenzae, staphylococci and streptococci. H. influenzae, S pneumoniae, and Moraxella catarrhalis are the most frequent agents in children. The course of the clinical picture is 7 to 10 days long.

Due to its clinical presentation, it is convenient to divide them according to their installation time, in acute, acute or chronic hyperinflation, and can guide diagnostic tests and empirical treatment according to the time of presentation.

Common pathogens according to the time of evolution

Acute	***Híper Acute***	***Chronic***
Staphilococcus Aureus.	Neisseria Gonorreae.	Moraxella catarrallis.
Streptococcus pneumoniae.	Neisseria meningitidis.	Moraxella Lacunata.
Haemophilus influenzae.		Enterobacterias.

Special conditions:

In sexually active subjects who do not give up the clinical picture with empirical treatment (ceftriaxone 1gr b.i.d), we should investigate Chlamydia Trachomatis and add the relevant treatment.

In the case of infants or minors (less than 2 years old), we should consider granting systemic treatment because 50% of them concur with infections in other systems.

In oculo-vaginal infections we must investigate on strains compatible with trachoma (A-C); since we must remember that it affects more than 40 million subjects in areas of poor hygiene and continues to be a leading cause in non-reversible blindness.

4.1 JUSTIFICATION

Conjunctivitis and bacterial keratitis are the pathologies of the ocular surface most commonly found in our environment. In general, they resolve spontaneously, however if they are not treated properly they can have irreversible consequences for visual health

(corneal ulcers, endophthalmitis, etc.), especially in patients who will be operated on ophthalmic surgery and / or senile, children, contact lens wearers, among others.

These pathologies do not respect age, gender or social status. They are transmitted through contact with flush when talking to an infected person or through touch - hand - eye. Hence, it is quite common. The acute form of the infection is usually caused by Haemophilus species, S. pneumoniae, S. aureus or epidermidis, some of them normal habitual residents of the human conjunctiva.

Its management, sometimes represents a diagnostic and therapeutic challenge for both the general practitioner and the ophthalmologist. The etiology of it is a very useful guidance to improve the patient's prognosis. Much of the morbidity produced by this pathology can be lessened with adequate therapy by reducing treatment time and comfort. Hence the importance of knowing the ocular pathogens commonly associated with our environment, isolating them in an accurate manner and correlating them with the specific characteristics of the patient.

There are innumerable reports in the literature in this regard, however we have no knowledge of a specific one in our geographical area. The prevalence of Staphylococcus aureus 80 (23.7%), Staphylococcus albus 65 (19.2%), Pseudomonas aeruginosa 34 (10.1%), Streptococcus pneumoniae 29 (8.6%), Haemophilus influenzae 26 (7.7%), Streptococcus pyogenes 20 has been recently published. (6.2%), Klebsiella pneumoniae 18 (6.2%) Escherichia coli 15 (4.4%), Neisseria gonorrhoeae 13 (3.9%), Streptococcus viridans 11 (3.5%), Moraxella catarrhalis 10 (3.0%), among others, found that The most frequent isolations were made from the conjunctiva (66.7%) in contrast to the cornea (20.1%). These data correspond to the majority of what is published, however the socioeconomic and environmental conditions of the place where they were carried out are not the same to our region.

In other regions, such as India (with characteristics probably similar to our environment) it is observed that S. Aureus frequently causes infections of the eyelids and conjunctiva, S. pneumoniae is responsible for those inherent to the lacrimal apparatus and S. coagulase negative corresponds to infections intraocular.
In 10-year reviews in developed countries (eastern US) 1997- 2008, a tendency is observed in turn to the prevalence of Staphylococcus Aureus as the main ocular pathogen.

The effectiveness of 4th generation quinolones in the treatment of bacterial conjunctivitis since 1 year of age with a posology that varies from 2 to 4 times a day has been demonstrated in recent evidence, which corresponds to the preclinical studies and phase I of the drug. viii

We can also state the following points that support its use in infants and children under 18 years.

Due to the satisfactory results of the phase I study of the medication carried out in the adult population, in a phase II its implementation is justified in the child population since the evidence collected in said study allows inferring that its use is safe and effective to use it in the model of proposed disease, bacterial conjunctivitis. Ix

Also the incidence of adverse events of musculoskeletal toxicity in children with chronic use of quinolones of 4th generation is reported as not significant at 5-year follow-up, so it was concluded that its use is adequate in this population. viii, ix

Currently, up to 26% resistance to the 4th generation quinolones (moxifloxacin, gatifloxacin and levofloxacin) is reported in strains of methicillin-resistant Staphilococcus epidemidis, so pazufloxacin represents a treatment option in such cases. ix, x

Sophia S.A de C.V. has developed a new ocular topical formulation belonging to the group of the fourth-generation quinolones, called Pazufloxacin mesylate, which has shown through in vivo and in vitro studies to have greater antimicrobial activity against methicillin-resistant S. aureus, Haemophilus influenzae ampicillin resistant, as well as E. coli, Proteus mirabilis, Serratia marcecens and P. aeruginosa. It should be noted that this formulation is free of preservatives.

Initially indicated for all those patients with bacterial conjunctivitis to susceptible organisms.

Pazufloxacin has been clinically shown to be equally effective in the prophylaxis and control of ocular infections when compared to gatifloxacin, moxifloxacin, and levofloxacin in models of Staphylococcus aeurusix infections. This is the reason why we are interested in determining the consistency of these results with the Pro-157 formulation developed by Laboratorios Sophia SA de CV.

4.2 NON-CLINICAL PHARMACOLOGY

Distribution of pazufloxacin in vivo iv
Sophia Laboratories were tested with three independent experiments in rabbits, which were separated into 6 groups, and slaughtered at times 15, 30, 60, 90, 120, 180 minutes to which they were applied exactly and only once 30 µL of the formulation under study (pazufloxacin 0.3%). The cornea and the aqueous humor were extracted and stored at -20 ° C until the determination of pazufloxacin by HPLC.

Distribution of pazufloxacin in cornea
Table 1 shows the average concentration of pazufloxacin found per mg of cornea.

Table 1. Average concentration of pazufloxacin found per mg of cornea

Minutes	ng Pazufloxacin / mg cornea
15	3.9
30	3.2
60	2.4
90	2.0
120	1.4

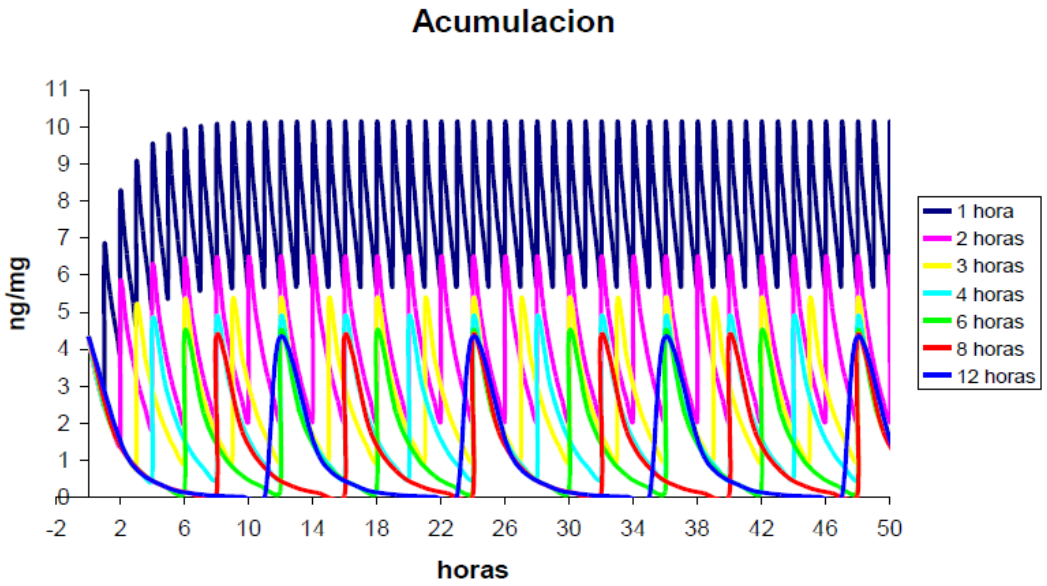
Calculation of pharmacokinetic parameters
An entry is assumed as if it were intravenously and a first-order model of corneal removal. It also considers a volume of distribution in cornea of 0.08mL. It is considered that 30 mL of a solution of 3mg / 1000µL was added, which corresponds to a total amount of 90,000 ng of pazufloxacin, Table 1.

With regard to the concentrations in multiple dosing regimen, it can theoretically be said that the max and min concentrations of the drug follow different administration intervals (Table 3), based on pharmacokinetic parameters obtained from a single administration (Table 2, graphs 1 and 2).)

Table 2. Pharmacokinetic parameters for pazufloxacin in cornea, calculated from the results of table 1.

Parameter	**Value**
(kep) Constante de permeabilidad de la barrera epitelial	0.00083 $cm \cdot hr^{-1}$
(k) Constante de eliminación	0.0094648 min^{-1} 0.567889 hr^{-1}
($t_{1/2}$) Vida media	73.2 minutos
(F) Fracción absorbida	0.00388 0.388%.
AUC Área bajo la curva	459.4 ng/mg min

Graph 1. Representation of the behavior of the kinetics of pazufloxacin in the cornea following a first order reaction, simulating different dosage intervals.



Graph 2. Simulation of levels of pazufloxacin in cornea in vivo, dosing on the first day from 8 a.m. at 10 p.m. and resuming treatment at 6 a.m. of the next day.

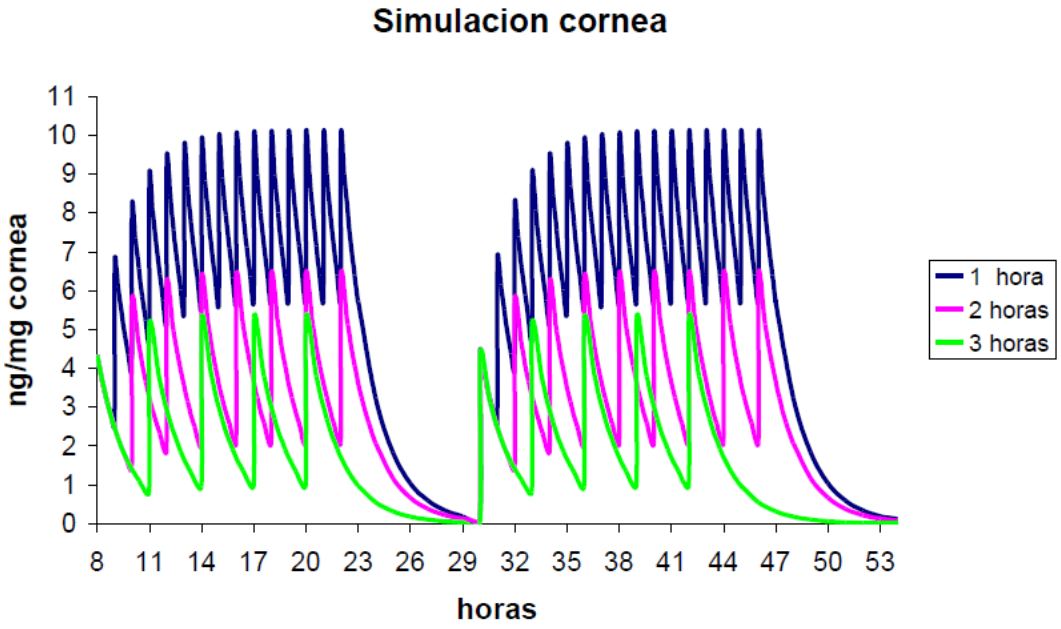


Table 3. Maximum and minimum concentration in cornea in vivo (theoretical) reached in equilibrium, considering different dosage intervals.

Hora	Cmax (ug Pazu/mg córnea)	Cmin (ug Pazu/mg córnea)
1	10.070	5.707
2	6.428	2.064
3	5.334	0.971
4	4.865	0.502
5	4.634	0.271
6	4.513	0.150
7	4.447	0.083
8	4.410	0.047
9	4.390	0.026
10	4.378	0.015
11	4.372	0.008
12	4.368	0.005

Distribution of pazufloxacin in aqueous humor
For the calculation of pharmacokinetic parameters, a compartment model with first order absorption and elimination was followed. The volume of distribution for the aqueous humor of 0.25 mL, administration of 30 µL of a solution of 3mg / 1000µL is considered, a total amount of 90,000 ng is obtained, Table 4 shows the average concentration found of pazufloxacin per mL of aqueous humor (Table 5).

Table 4. Average found concentration of pazufloxacin per mL of aqueous humor.

Minutos	ng Pazufloxacino/mL Humor acuoso
15	211
30	295
60	499
90	590
120	472
180	365

Table 5.- Pharmacokinetic parameters for pazufloxacin in aqueous humor, calculated from table 4.

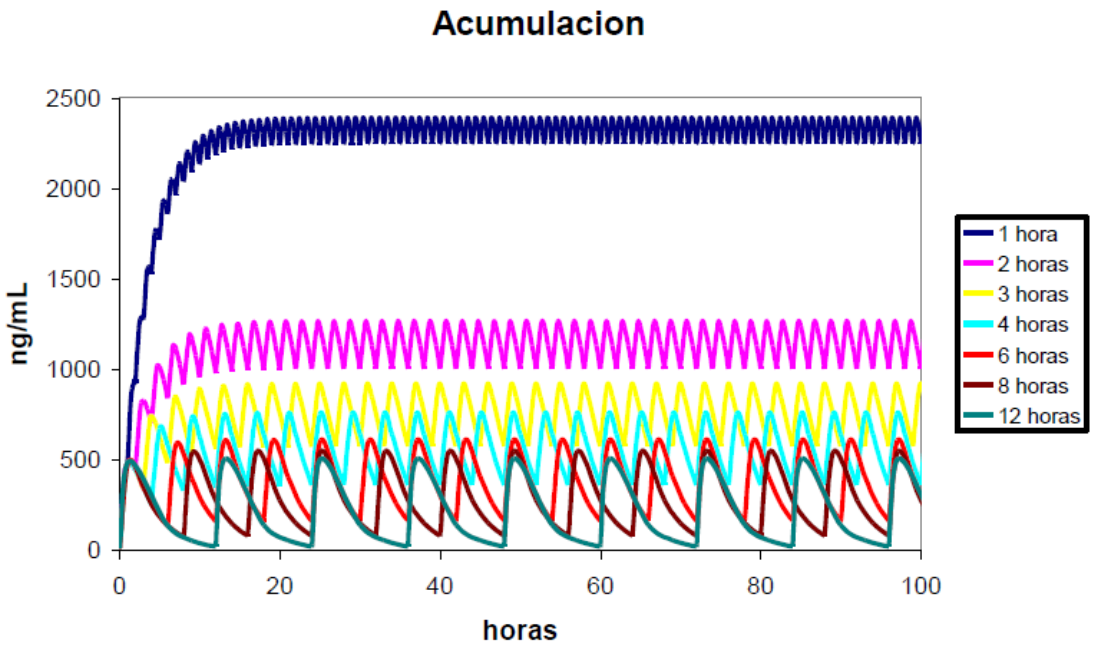
Parámetro	Valor
(k) Constante de eliminación	0.005129 min^{-1} 0.3078 hr^{-1}.
(ka) Constante de absorción	0.02835 min^{-1} 1.70008 hr^{-1}
(t_{max})	73.6 min
($t_{1/2}$) Vida media	135 min
(F) Fracción absorbida	0.002 0.2%
AUC Area bajo la curva	136275 ng/mL min

The max and min concentration of the drug can theoretically be predicted by following different administration intervals (Table 6), based on pharmacokinetic parameters obtained from a single administration (table 5, graph 3 and 4).

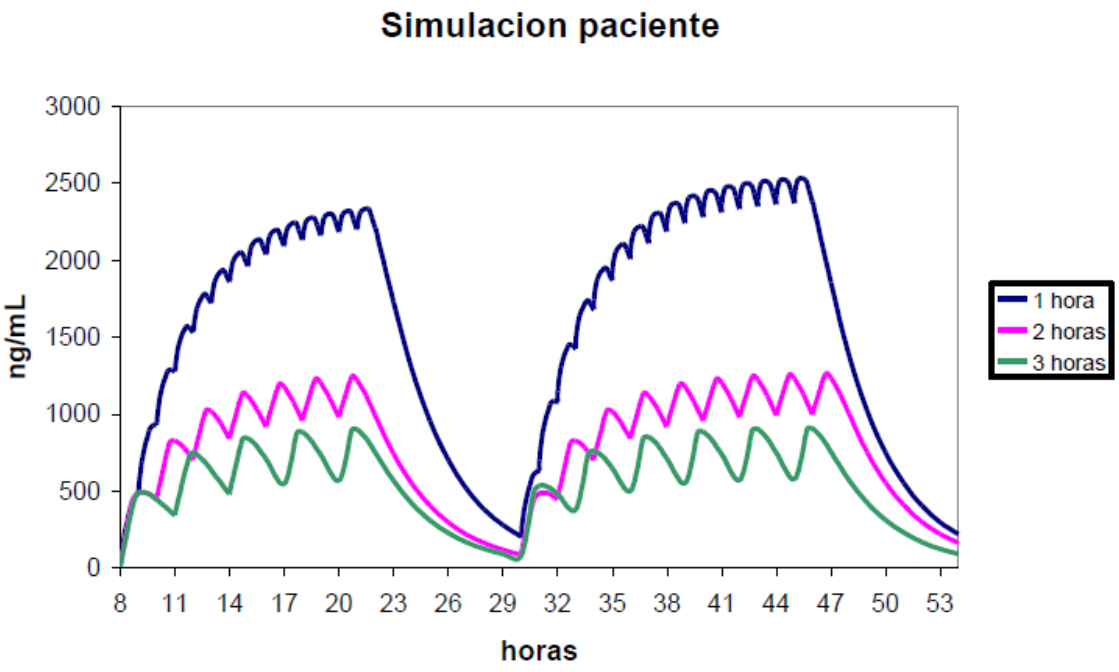
Table 6 Maximum and minimum concentration in aqueous humor reached at equilibrium considering different dosage intervals

horas	t max eq(hrs)	Cmax ng/mL	Cmin ng/mL
1	0.42	2389	2246
2	0.69	1265	1033
3	0.87	914	579
4	0.98	752	362
5	1.05	663	240
6	1.10	609	165
7	1.14	574	115
8	1.16	550	82
9	1.18	534	59
10	1.19	523	42
11	1.20	515	31
12	1.21	509	22

Graph 3. State of equilibrium in aqueous humor in different dosing times



Graph 4.- Continuous administration during the day of 8 a.m. at 10 p.m. resuming treatment at 6 a.m. of the next day.



We also performed a preclinical study (PRO-0157-PZ), comparative randomized, unicentric, prospective, longitudinal and blinded in 30 rabbits (60 eyes) albino males New Zealand, whose objective was to compare and evaluate, safety as the toxicity of the topical ophthalmic solution of pazufloxacin vs Moxifloxacin hydrochloride and Gatifloxacin in the ocular surface in a clinical and histological manner.

The allocation to the treatment group was randomly 1: 1, 10 rabbits were assigned for each treatment group, for purposes of the analysis both eyes were evaluated so the total number of eyes analyzed per treatment group was 20. The variables evaluated were:

Conjunctival hyperemia, corneal surface, fluorescein staining, lysamine green stain and tonometry, presence of adverse events, red eye, lacrimation, findings in the revision of the periocular area and the anterior segment, findings in fundoscopy. In the histopathological study, histological changes were evaluated, as well as the toxicity in cornea, conjunctiva, ciliary body and retina.

The results obtained showed that in the different visits very few cases were found with the presence of sign in the rabbits, also, when making the intergroup comparisons, only statistically significant differences were found ($p = 0.036$) for the variable chemosis in the evaluation corresponding to the day 30, where there were 4 (20%) reported cases in an area smaller than 25% of the total, 4 (20%) cases between 1 and 3, in the Moxifloxacin group a total of 11 (55%) cases were reported in an area smaller than 25% of the total, 4 (20%) cases between 1 and 3, while in the Gatifloxacin group there were 4 (20%) and 2 (10%) cases respectively.

It should be noted that in the rest of the variables evaluated the differences found were not statistically significant (p <0.05)

5 CLINICAL STUDIES
A phase I clinical study was conducted to evaluate the safety and tolerability of the PRO157 ophthalmic solution in healthy volunteers. The tolerability was determined by the presence of: burning, hyperemia, chemosis, foreign body sensation and lacrimation. Safety by assessing visual acuity and / or visual capacity, fluorescein staining, green lysine and intraocular pressure and the frequency of adverse events. A total of 5 visits were made.

• Visit 0: Basal, day 0 (selection period).
• Visit 1: Follow-up, day 2 (treatment period).
• Visit 2: Follow-up, day 4 (treatment period).
• Visit 3:. Follow-up, day 7 (treatment period).
• Visit 4: Final day 11 (final visit).

During which time the drop was applied 4 times a day in both eyes, the results that were obtained determined that the variables that reflect tolerability of the product, such as ocular burning, red eye, conjunctival hyperemia and lacrimation, remained predominantly in a low intensity (mild). There was no presence of chemosis or secretion. More than 88% of the eyes studied showed no sensation of a foreign body in the eye and more than 70% of the eyes did not present pruritus in the different evaluations.
Variables that reflect the safety of the product, such as visual capacity and intraocular pressure, were always within normal parameters. No findings were reported during the revision of the anterior segment or the posterior segment, none of the eyes studied showed any degree of fluorescein or green lysine uptake in the corneal surface, there were no reports of adverse events. Vi

6 HYPOTHESES AND OBJECTIVES OF THE STUDY

6.1 Working hypothesis

The ophthalmic solution PRO-157 is so safe and effective in any of its different posologies when demonstrating non-inferiority when compared against Moxifloxacin and Gatifloxacin in the treatment of bacterial conjunctivitis.

Ho: The ophthalmic solution PRO-157 is not as safe and effective in any of its different dosages when it shows no inferiority when compared to Moxifloxacin and Gatifloxacin in the treatment of conjunctivitis.

Ha: The ophthalmic solution PRO-157 is so safe and effective in some of its different posologies when demonstrating non-inferiority when compared against Moxifloxacin and Gatifloxacin in the treatment of conjunctivitis.

6.2 Objectives

General purpose:

To evaluate the safety and efficacy of the ophthalmic solution PRO-157 in three different posologies versus Moxifloxacin and versus Gatifloxacin in patients with bacterial conjunctivitis.

Specific objectives:

To determine the safety of the PRO-157 solution in three different posologies versus Moxifloxacin and versus Gatifloxacin in patients with bacterial conjunctivitis by the incidence of adverse events and visual capacity.
To evaluate the efficacy of the ophthalmic solution PRO-157 in three different posologies versus Moxifloxacin and versus Gatifloxacin in patients with bacterial conjunctivitis through conjunctival cul-de-sac culture and the clinical evaluation of some ocular signs and symptoms such as: burning, lacrimation, Foreign body sensation, pruritus, photophobia, conjunctival hyperemia, chemosis, secretion, palpebral edema, membranes and / or pseudomembranes, scales and epitheliopathy.

7 STUDY DESIGN

7.1 Point or limit points

Criteria for the evaluation.

Efficacy measurements:

Main efficacy criterion

Efficacy will be determined by taking cultures of the lower conjunctival cul-de-sac background quantifying (colony-forming units) and identifying genus and basal and final microbial species.
It will be determined as effective if there is a reduction in the number or species of bacterial flora comparing the basal culture against the end between the five different groups of patients and / or if there is a reduction or absence of the following specific signs and symptoms: burning, tearing, Foreign body sensation, pruritus, photophobia, conjunctival hyperemia, chemosis, palpebral edema and secretion, membranes and / or pseudomembranes when comparing the study medication versus Moxifloxacin and versus Gatifloxacin from baseline to final visit.

Efficiency parameters

• The effectiveness of the drug will be evaluated by means of:

1. Clinical referral

2. Microbiological remission

Clinical remission will be evaluated by means of the signs and symptoms that the patient presents at the beginning and at the end of the study.

Variable	Operationalization	Measurement scale	Value
Secretion	Dependent Qualitative ordinal	Absent Present	Must be recorded as absent in 95% of the subjects evaluated
Conjunctival hyperemia	Dependent Qualitative ordinal	Absent Mild Moderate Severe	You must comply with the following: • Absent ≥ 95.0% • Mild ≤ 5.0% • Moderate ≤ 2.5% Severe ≤ 1.0%
Chemosis	Dependent Qualitative ordinal	Absent Present	Must be recorded as absent in 95% of the subjects evaluated
Eyelid edema	Dependent Qualitative ordinal	Absent Present	Must be recorded as absent in 95% of the subjects evaluated
Corneal epithelial defects	Dependent Qualitative ordinal	Affected area, percentage	Percentage of affected area less than 95%

The microbiological remission will be evaluated by means of the culture taken from the conjunctival sac fundus.

Variable	Operationalization	Measurement scale	Value
Culture	Dependent Discrete quantitative	UFC * / ml Eradication Reduction Proliferation	Must be recorded as absent in 95% of the subjects evaluated

* Colony forming units

The drugs under study will be considered effective if the patient has any of the following:

1. Clinical remission + Microbiological remission.
2. Clinical referral.
3. Microbiological remission.

Security measurements:

Adverse events and visual capacity.

Evaluation parameters

• The safety of the use of PRO-157 will be evaluated in the visits indicated in the schedule, through the following parameters:

1. Visual capacity
2. Eye surface
3. Exploration of the previous segment
4. Exploration of the posterior segment
5. Burning
6. Foreign body sensation
7. Lachrymation
8. Conjunctival hyperemia
9. Itching
10. Photophobia
11. Chemosis
12. Tear discharge
13. Eyelid edema
14. Membranes / pseudomembranes
15. Scales
16. Corneal epithelial defects
17. Adverse events

It will be considered that the drug under evaluation is safe for use in humans if there are no changes in the parameters indicated in more than 5% of the subjects, in both eyes, if the

patient goes to all the visits of the study and complies with adherence to treatment ≥ 80% during the time of evaluation of the study.

Variable	Operationalization	Measurement scale	Value
Visual ability	independent Discrete quantitative	Points logMAR 0-1 0 = Snellen 20/20	Do not present change in 1 line in the Snellen letter or in 1 logarithmic point (log MAR)
Ocular surface	Dependent Qualitative ordinal	Absent Present	Abnormalities in any area of the ocular Surface
Exploration of the previous segment	Dependent Qualitative ordinal	Normal Abnormal	Abnormalities in any of the structures included: cornea, iris, pupil, irido-corneal and crystalline angle.
Exploration of the posterior segment	Dependent Qualitative ordinal	Normal Abnormal	Abnormalities in any of the structures included: vitreous, retina, macula and the optic nerve
burning	Dependent Qualitative ordinal	Absent Present	Must be recorded as absent in 95% of the subjects evaluated
strange body sensation	Dependent Qualitative ordinal	Absent Present	Must be recorded as absent in 95% of the subjects evaluated
tearing	Dependent Qualitative ordinal	Absent Present	Must be recorded as absent in 95% of the subjects evaluated

Secretion	Dependent Qualitative ordinal	Absent Present	Must be recorded as absent in 95% of the subjects evaluated
Conjunctival hyperemia	Dependent Qualitative ordinal	Absent Mild Moderate Severe	You must comply with the following: Absent ≥ 95.0% Mild ≤ 5.0% Moderate ≤ 2.5% Severe ≤ 1.0%
Photophobia	Dependent Qualitative ordinal	Absent Mild Moderate Severe	You must comply with the following: Absent ≥ 95.0% Mild ≤ 5.0% Moderate ≤ 2.5% Severe ≤ 1.0%
Chemosis	Dependent Qualitative ordinal	Absent Present	Must be recorded as absent in 95% of the subjects evaluated
Eyelid edema	Dependent Qualitative ordinal	Absent Present	Must be recorded as absent in 95% of the subjects evaluated
Memranas Pseudomembranes	Dependent Qualitative ordinal	Absent Present	Must be recorded as absent in 95% of the subjects evaluated
Scales	Dependent Qualitative ordinal	Absent Present	Must be recorded as absent in 95% of the subjects evaluated

Epithelial defects corneal	Dependent Qualitative ordinal	Affected area, percentage	Percentage of the affected area 95%
Adverse events	Dependent Qualitative ordinal	serious Not Serious	Must be recorded as absent in 95% of the subjects evaluated

8 STUDY PLAN

This is a phase II, randomized, double masked, multicentre, national study.

This study will be carried out with 60 eyes with diagnosis of bacterial conjunctivitis, by treatment group, of patients of the ophthalmological consultation.

Patients diagnosed with bacterial conjunctivitis (signs and / or symptoms and / or culture) recruited will be treated for 7 days with any of the three posologies of PRO157, Moxifloxacin, or Gatifloxacin. The randomization of any of the medications will be coordinated by a member of the research team previously designated who will not be masked and will be responsible for indicating to the patients how to apply the drops, emphasizing the patients of by no means mentioning the evaluating physician with the frequency who applies the study medication.

No patient may use the aforementioned treatment more than the prescribed time. For purposes of the protocol, the infected eye (s) will be taken into account at baseline but the study medication and procedures will be applied and will always be done in both eyes to protect the healthy eye and the possibility of infection if Do not be infected from the beginning.

The study is divided into the following periods:

There will be a total of 3 visits which are divided into 1 baseline visit (day 1) 1 treatment visits (day 3), 1 final visit (day 8). A telephone call will finally be made to evaluate adverse events after 15 days of the last application of medication (day 23)

At each visit from the baseline a clinical photograph of the eyes will be made, each of them must be identified by patient and visit number and delivered once the 30 patients are completed on a CD or USB.

1. Period of treatment of 7 days (from day 1 to 7) where any of the following posologies are applied according to randomization:

PRO157 1 drop 2 times a day in both eyes.
PRO157 1 drop 3 times a day in both eyes.
PRO157 1 drop 4 times a day in both eyes.
Moxifloxacin 1 drop 3 times a day in both eyes
Gatifloxacin1 drop 3 times a day in both eyes

The study medications will be delivered by a coordinator (not blinded) or a person previously designated by the principal investigator, who will indicate how to apply the study medication according to the randomization and will place special emphasis on not mentioning the principal investigator or designee. perform the evaluations as the drop or any characteristic of the jars is applied.

An artificial lagrima without conservative Lagricel Ofteno® will also be applied one drop 4 times a day to all patients who enter the study during the 7 days of treatment with the study medication.

The valuation days indicated in Figure 1 of the Study Plan must be carefully observed. A variation of ± 1 days can be accepted in relation to the inclusion visit (from day 1 to 8). In the case of the inclusion of subjects from 0 years to less 18 years minus 1 day, they will be included progressively as follow:

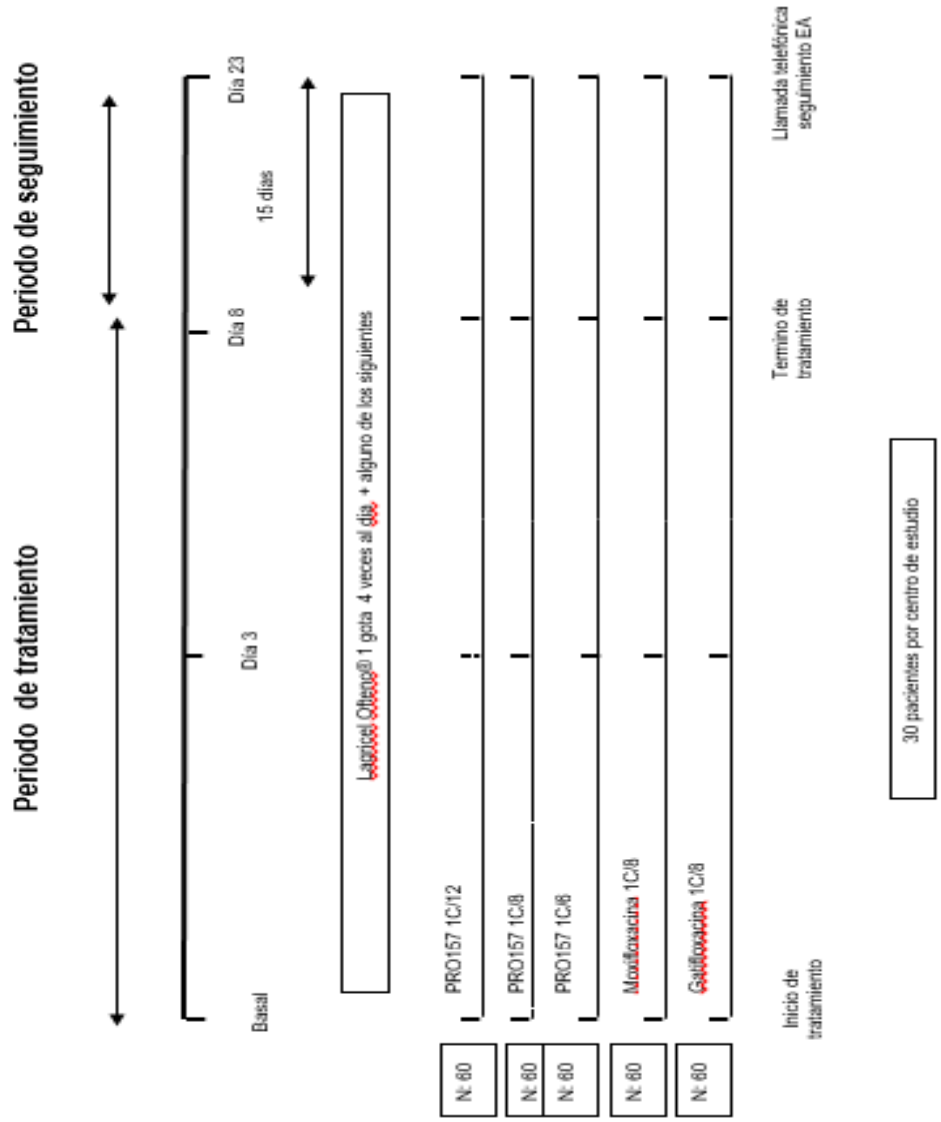
• Age group of 12 to 18 years.
• Age group from 2 to 12 years old.
• Age group from 0 to 12 years old.

This with the intention of integrating patients once the dosage parameters have been established as safe and recommended for the younger age groups.
The indications of the inclusion periods will be made as the results are gathered in the groups of minors.

Blinding

The double-blind study is a procedure in which the patient and the attending physician do not know which of the intervention groups was assigned by the study patient.
The blinding codes are protected by a person outside the study.

Figure 1 - Plan of the Study



30 patients per study center

Table 2: Timeline

Procedimiento	Visita Basal	Visita 1	Visita Final	Seguimiento Telefónico EA	Visita no programada / Descontinuación
	Día 1	Día 3	Día 8	Día 23	
Criterios de Elegibilidad	X				
Firma de consentimiento informado	X				
Datos demográficos	X				
Prueba de embarazo en orina (si aplica)	X		X		
Historia Clínica General y Oftalmológica	X				
Padecimiento actual					X
Toma de muestra para cultivo	X		X		
Fotografía clínica de los ojos	X	X	X		
Asignación de número al paciente	X				
Entrega de medicamento	X				
Inicio de aplicación de medicamento	X				
Aplicación de medicamento	X	X	X		
Devolución de medicamento por parte del paciente			X		
Sintomatología Ocular (A,B,C,D)	X	X	X		X
Agudeza y/o Capacidad Visual	X	X	X		X
Biomicroscopia anterior (F,G,H,I,J,K)	X	X	X		X
Tinciones de fluoresceína/verde de lisamina	X	X	X		
Revisión del segmento posterior (L,M,N,O)	X	X	X		X
Evaluación de eventos adversos	X	X	X	X	X
Evaluación de medicamentos concomitantes	X	X	X		X

A) Burning B) Lachrymation C) Foreign body sensation D) Pruritus E) Photophobia DF) Conjunctival hyperemia G) Chemosis H) Secretion I) Eyelid edema J) Membranes and / or pseudo-membranes K) Epitheliopathy L) Vitreous M) Retina N) macula O) optic nerve.

9 MEASURES TO REDUCE DEVIATIONS TO MINIMUM

On the other hand, adherence to treatment will be evaluated as follows:

- With the study medication accounting returned.

- Patients will have a "diary of the subject" where time of application of the drop and any incident or mishap at the time of the application of the drop, for example forgetfulness in the application of the drop, application of extra drops etc. will be noted.

- The adherence to treatment must be greater than 80%.

Example:

Favor de anotar con pluma negra y letra de molde los siguiente:
Fecha: _____ Hora: _____
dd/mm/aaaa hh:mm

A)	SI	NO	COMENTARIOS
1.-Aplico la gota oftalmica:	☐	☐	sí, NO pase a sección B
2.-Cuantas gotas aplico:	1☐	2☐	
- Sí fue 2 ó mas explicar:	_____		

B)	SI	NO	COMENTARIOS
3.-Olvido la aplicación:	☐	☐	
4.-Intento aplicar la gota nuevamente:	☐	☐	
- En caso de sí, anotar la hora:			_____
5.-Cuantas gotas aplico:	1☐	2☐	_____
- Sí fue mas de 2 explicar:	_____		

A meeting of researchers will be organized for the physicians involved in the study before beginning with the inclusion of subjects. And your attendance will be mandatory.

At the end of the study the patients will answer a questionnaire of satisfaction of the subject in the local language and the researcher will explain to the subject how to answer it. It is not authorized for the researcher to report / correct the qualification of the subject in the self-qualification questionnaires.

10 ADMINISTERED PRODUCTS

Table 3. Description of study drugs

Ophthalmic drops PRO157

- Chemical name:

Pazufloxacin mesylate [S - (-) - 10- (1-aminocicloprοpyl) -9-fluoro-3-methyl-7-oxo-2,3-dihydro-7H-pyrido (1, 2,3-de) (1, 4) -benzoxazine-6-carboxylic acid monomethanosulfate.

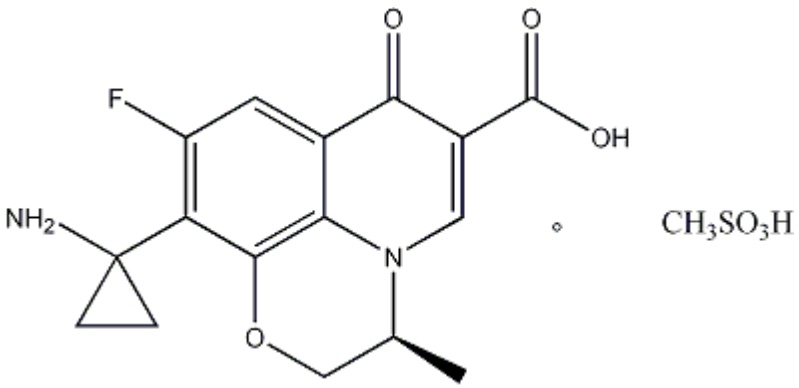
- Molecular weight:

414.41g / mol

-Molecular formula:

C16H15FN2O4 • CH3SO3H

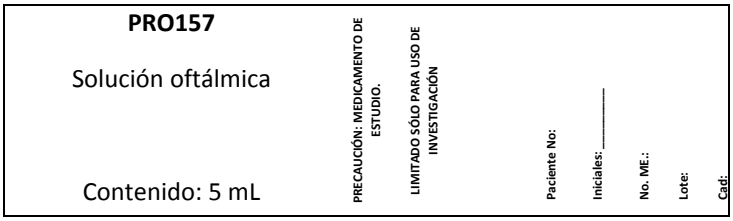
- Chemical structure:



11 DESCRIPTION OF THE PACKAGING

Multi-dose bottle

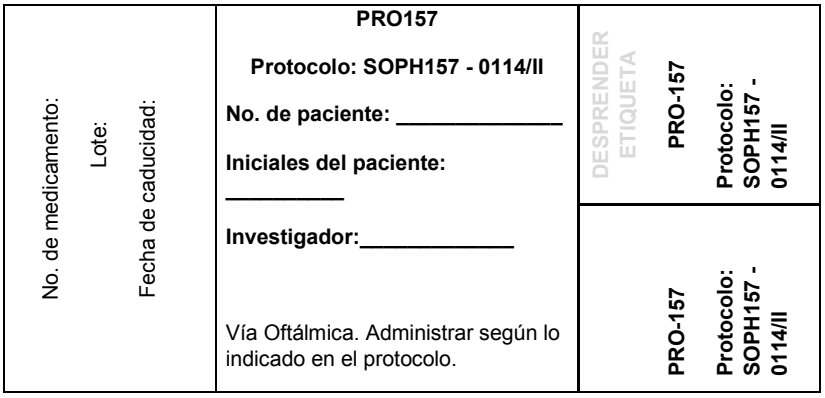
Primary packaging



Secondary package

The primary packaging will be contained in a secondary packaging in which the patient's initials and the researcher's name will have to be noted; It will also contain information on drug management as shown in the example.

Example



12 MANAGEMENT OF THE STUDY MEDICINE

The medications will be supplied from the manufacturing site (Sophia SA Laboratories of C.V.) previously weighed.
The management of the study medication will be under the responsibility of the researcher and / or pharmacist of the health care establishment (when applicable), including:

- The reception and storage of the study medication (ME). The receipt of the study medication will be charged by signing and returning the medication delivery form. The study medication must be stored in a secure area with restricted access. Some special storage conditions are requested
• The PRO-157 ophthalmic solution should be stored at room temperature to no more than 30 ° C,
• The bottle must be kept tightly closed.

The investigating doctor or the person previously designated in the delegation of responsibility format is obliged to keep a documented record of humidity and minimum and maximum daily temperatures on one occasion a day, for the realization of these measurements, Sophia Laboratories will provide a thermo hygrometer which will be returned at the end of the clinical study.

- The discharge of the thermo hygrometer data will be done by the clinical monitor during the monitoring visits.

- The expiration date will appear on each box and label of the investigational medication.
- The delivery of the study medication will be in accordance with the study plan and following the delivery methods described in the section. The researcher and / or pharmacist of the health care establishment should use the treatment delivered only for the patients participating in the study.
- The study medication count.

The investigating physician and / or a previously designated responsible person of your study team must fill out in real time all the documents that the sponsor provides for the management of the study medication (acknowledgment of receipt in the shipping formats, tracking form of study medication).

The study monitor will periodically check the management and counting of the medication under study.

At the end of the study, the researcher and the study monitor will perform the final count of the medication, and it will be recorded in the corresponding format.
The study monitor will collect and send to Laboratorios Sophia S.A. of C.V. the remaining study drugs, for storage and subsequent destruction, after quantification thereof.

All defects or deterioration of medications or their packaging must be reported to the study monitor. The investigator will notify the monitor of all complaints received from a patient.

In case of early return of the treatments to the sponsor (withdrawal of the lot), the sponsor will prepare an informative letter addressed to the researcher and / or pharmacist of the health care establishment. This letter will be sent by the people locally responsible for the study. Upon receipt of the letter, the investigator and / or pharmacist will identify the patients who have the treatment in their possession at the time the incident is known, using the tracking form of the study medication, and will contact them immediately. . The monitor will organize the return of the study medication to proceed with its destruction.

13 CENTER CLOSURE

13.1 Premature discontinuation of the study

The sponsor may terminate the study before the scheduled deadline. A written confirmation will be sent to the researcher informing him that the clinical study is terminated.

The investigator will date and sign two copies of the written confirmation (one copy to return to the sponsor and the other copy to file in the Investigator's Study File).

The Ethics Committees and the Competent Authorities will be informed in accordance with local regulations.

13.2 Closure of the center

Any center that has finished including the last patient previously stipulated; and that this has complied with the days of study treatment and the safety visit; It may be closed if there is a common agreement between the sponsor and the study center.

14 DATA SOURCE

The following data (s) will be considered as source:

- The patient's medical file, notes of interconsultation, results of clinical laboratories, results of cabinet examinations.

- Patient's diary,

- Self-qualification questionnaires (subject satisfaction questionnaire)

The patient will directly record the data in the patient questionnaire and in the paper self-assessment questionnaires (subject satisfaction questionnaire), which will be considered source data.

15 SELECTION AND WITHDRAWAL OF SUBJECTS OF STUDY.

Eligibility Criteria

15.1 Inclusion Criteria

All selected subjects:

- They will have an age between 0 to 99 years * see note.
- They will be obtained in the external consultation.
- With diagnosis of bacterial conjunctivitis (signs and / or symptoms and / or culture)

- Signed and dated Informed Consent (Informed Consent and parental consent in case of being a minor)

* NOTE: In the case of inclusion of subjects from 0 years to less 18 years minus 1 day, they will be included progressively as follows:

• Age group of 12 to 18 years.
• Age group from 2 to 12 years old.
• Age group from 0 to 2 years.

This with the intention of integrating patients once the dosage parameters have been established as safe and recommended for the younger age groups.
The indications of the inclusion periods will be made as the results are gathered in the groups of minors.
The Informed Assent will only apply to minors who demonstrate understanding of the study, at the discretion of the researcher.

- Physical examination of patients
In the examination carried out during the baseline visit, a general and ophthalmological clinical history will be performed, initially including and starting treatment with all those patients clinically suspected of bacterial conjunctivitis. If the culture is negative but clinically there is improvement, you can continue with the treatment until the last day of the stipulated study. At the baseline visit a urine pregnancy test will be performed (if applicable).

15.2 Exclusion criteria

General

1. Lack of written informed consent.

2. Women with the possibility of having children, without using contraception (oral contraceptive pill, intrauterine contraceptive device, contraceptive implant, patch or condom).

3. Pregnant women or breastfeeding.

4. Subjects that can not be assessed partially or totally according to the protocol.

5. Subjects with topical, systemic or intravenous medication with any type of antibiotic on the day of the baseline visit.

6. Subjects with topical, systemic or intravenous medication with any type of medication that interferes decisively with the results of the study.

7. Subjects with a history of hypersensitivity to any of the components of the formula of the research product or its analogues.

8. Positive substance abuse (smoking, alcoholism, marijuana). *

9. Subjects who have participated in any clinical research study in the last 40 days, prior to inclusion in the study.

10. Subjects legally or mentally incapacitated to give their consent to participate in this study.

11. Any clinically important abnormalities detected during the clinical examination, tests that could interfere with the conduct of the study or with the evaluations of efficacy and safety.

* Repeated consumption of one or several psychoactive substances, to the point that the consumer (known as an addict) becomes intoxicated periodically or continuously, shows a compulsive desire to consume the preferred substance (or substances), has an enormous difficulty interrupting voluntarily or modify the consumption of the substance and is determined to obtain it in any way. -Definition of WHO *

Related to ophthalmological criteria

1. Eye surgery in the past 6 weeks.
2. Active ulcerative keratitis.
3. Recurrent corneal erosion syndrome.
4. Suspected viral or allergic conjunctivitis.

Related to a therapy or previous and / or concomitant treatments

Current therapy or expected therapy with:

Systemic NSAIDs, corticosteroids, antihistamines or immunosuppressants.

Typically, patients can not be treated at the baseline visit with any other type of antibiotic topical ophthalmic, as well as steroids, NSAIDs, mast cell stabilizers, antihistamines, decongestants. If the patients prior to this day were under treatment with another antibiotic or drugs of those mentioned may be included.

To know the other prohibited treatments and their rest period, please refer to Table 4 "Main prohibited treatments"

Elimination Criteria

• Any complication or lack of control that the doctor considers should be treated differently.

• **Elimination Criteria**

• Clinicians:

a. Any complication or lack of control that the doctor considers should be treated differently. The following points should be considered:

i. The no improvement of the initial clinical signs and symptoms.

ii. Diagnosis added or different to that of acute bacterial conjunctivitis.

iii. Use other medications outside the study.

b. * It is reiterated that they are minimum parameters to be considered, any other case in which the investigator considers necessary the elimination of the patient and suspension of the treatment must be informed and evaluated by the sponsor.

• For the sponsor:

a. By its will, it will not have penalties, nor will it lose benefits to those that it already has right.
b. For the total term of the scheduled visits in the clinical study.
c. For a serious adverse event related to the medication that endangers your health.
d. Why the medication does not work at the doctor's discretion.
and. Why, by sponsor's decision, the study ends earlier.

In case of withdrawal for any of these reasons or any other at the discretion of your doctor, you will be prescribed again the medication of which you were already a user or any other that is of benefit for your best treatment.

15.3 Criteria for the premature withdrawal of the subject
Criteria for premature withdrawal
The following criteria will cause a mandatory withdrawal from the study:

The reasons for a patient leaving the study prematurely may be the following:

- Subject's decision. The patient who wishes to leave the study for any reason can do so at any time, but must inform the researcher. In all cases, the investigator should attempt to establish contact with the patient as soon as possible for a final evaluation in order to:

• Document the patient's decision in clinical notes,

• Obtain the reason (s) for the exit and write them down in the FRC exit format,

• Evaluate the patient's clinical status,

• If necessary, take the appropriate therapeutic measures: management of an adverse event.

In case of failure of all these attempts to contact the patient, the investigator may declare "loss of follow-up" of the patient. The investigator will document all the attempts in the corresponding medical file.

- Decision of the investigator. Especially if an adverse event occurs and the researcher considers that this may threaten the patient's health, or if an important disease occurs that requires the prescription of a medication incompatible with the objective of the study.

- Need for another treatment according to the criteria of the Medical Investigator who will have to document it well in his notes.

- Pregnancy (see procedure in Appendix 2)

- Any deviation to the protocol that affects the patient's safety.

- In all cases, the available data will be saved for the safety analysis (population evaluable by intention to treat).

Process

Whatever the reason for the premature discontinuation of the study treatment, the investigator should immediately inform Laboratorios Sophia S.A. of C.V. and the patient must return the rest of the study treatments to the center.

In case of premature withdrawal of treatment, the investigator should record the reason (s), the exact date of the premature discontinuation of the treatment in the source document and in FRC. If more than one reason is given, the investigator must indicate the main reason.
In case of premature withdrawal from the study due to an adverse event (an event that is serious or not serious), the investigator should make every effort to gather information related to the outcome of the event. If necessary, the information will be collected later.
This information will be recorded in the FRC part related to non-serious adverse events and serious adverse events in a format that will be given separately in case the investigator can not collect the information in a visit, then it will be obtained from the doctor who ensures the patient follow-up
If the study is discontinued / the treatment is discontinued as a result of an event that requires immediate notification, the procedure described in the suspension or discontinuation section of the study will be implemented.

16 TREATMENT OF STUDY SUBJECTS

16.1 Managed treatments

Lagricel Ofteno® Apply one drop 4 times a day for 7 days + any of the following according to the randomization in both eyes.

Apply one drop of PRO157, 2 TIMES a day, from day 1 to day 7
Apply one drop of PRO157, 3 TIMES a day, from day 1 to day 7
Apply one drop of PRO157, 4 TIMES a day, from day 1 to day 7
Apply a drop of Moxifloxacin, 3 TIMES a day, from day 1 to day 7
Apply a drop of Gatifloxacin, 3 TIMES a day, from day 1 to day 7

16.2 Delivery of the treatment

The study drugs will be delivered by a coordinator (not blinded) or person previously designated by the principal investigator, who will indicate how to apply the study medication according to the randomization and will make special emphasis to each subject of not mentioning the principal investigator or person previously designated to perform the treatment evaluations as the drop or characteristic of the delivered bottles is applied.
This is to keep the blind person in the subject's evaluator and avoid bias.

16.3 Previous and concomitant treatments

Prohibited treatments
Table 4 shows the list of prohibited treatments during the study.
If a prohibited treatment is absolutely necessary during the study, the subject should be removed from the study.

Table 4. Main prohibited treatments (during the study)

Medicamento		Vía de administración
Grupo	Prototipo	
Betalactámicos	Penicilinas, Cefalosporinas, Monobactams, Carbapenems.	Tópica
Aminoglucósidos	Gentamicina	Tópica
Azúcares complejos	Clindamicina	Sístemicas
Polipeptídicos	Polimixina	Tópica
Rifamicinas	Rifampicina	Sístemica
Tetraciclinas	Clortetraciclina	Tópica
Amfenicoles	Cloramfenicol	Tópica
Macrólidos	Eritromicina	Sístemico
Misceláneos	Espectinomicina, Virginiamicina, Vancomicina, Teicoplanina, Capreomicina, Cicloserina, Fosfomicina, Novobiocina, Linezolida	Tópica, Sístemico
Quimioterapicos antibacterianos	Sulfonamidas Sulfonamidas + Trimetoprim Nitrofuranos Derivados de Naftiridinay Quinolonas	Tópica, Sístemico
Antiinflamatorios no esteroideos	Ketorolaco. Diclofenaco, nepafenaco, meloxicam,	Tópica
Esteroides	Prednisolona, dexametasona, triamcinolona, fluorometolona, loteprednol.	Tópica, Sístemico
Lagrimas artificiales con conservador		Tópica
Antihistamínicos	Epinastina	Tópica
Descongestionantes	Nafazolina , Oximetazolina, etc	Tópica
Estabilizadores de mastocitos	Cromoglicato de Sodio, etc	Tópica
Quinolonas 3era o 4ta generación	Moxifloxaciono. Gatifloxacino	Tópica
Quinolonas 2da, 3era o 4ta	Ciprofloxacino, Levofloxacino, Ofloxacino.	Sistémicas.

16.4 Authorized treatments during ophthalmologic exploration and / or course of study

Tretacaine hydrochloride (during ophthalmologic exploration)
Tropicamide / Phenylephrine Hydrochloride (during ophthalmologic exploration)
Lagricel Ofteno® (during the whole study time)

16.5 Compliance with treatment

- With the accounting of the study medication returned.

- Patients will have a "diary of the subject" where they will have to write down the time of application of the drop and any incident or setback at the time of the application of the drop, for example, forgetfulness in the application of the drop, application of extra drops, etc.
- The adherence to treatment must be greater than 80%

After the discontinuation of the study treatment, the subject will return with the previously used treatment.

17. Methods and times of measurements.

Scales to fill out by the researcher:

A meeting of researchers will be organized for all those involved in carrying out the study before starting it, and their participation will be mandatory. The objective of these sessions is to train them on the assessment of the efficacy and safety criteria and to ensure reliability among the qualifiers. In addition, detailed qualification rules will be provided to the qualifiers
The scales should always be evaluated by the same evaluating physician, either the principal investigator or an ophthalmologist previously designated in the Delegation of Responsibility format throughout the study, at the beginning of each visit. A guide will be made available for the interview to be carried out in each of the visits.

Self-qualification questionnaires to be completed by the patient:

Initials of the subject	

Mark with an X in any of the following options with which you have identified more in the course of the clinical study.

DEGREE OF SATISFACTION OF THE SUBJECT	ANSWER
Very bad: Intense and unbearable nuisances.	
Mal: Moderate intensity, intermittent, not tolerable.	
Regular: Discomfort of moderate intensity, intermittent and tolerable.	
Good: Mild and occasional nuisances.	
Very good: No discomfort (absent).	

The researcher will apply to the subject a questionnaire that he / she will have to answer at the end of the study where the satisfaction is evaluated upon finishing his / her participation in the study.

Visual acuity

It is a measure of the ability of the visual system to detect and recognize spatial details, it is performed in a high contrast test and with a good level of illumination. To measure visual acuity (VA) a patient will be presented with different high contrast tests and different sizes at a fixed distance, and the value will be noted as far as the patient sees it. The smallest size that the patient recognizes will be taken as a threshold value and expressed in minutes of arc. Visual ability is the best corrected visual acuity.
Bailey and Lovie designed and proposed a primer that would standardize the answers for each letter size in each of the lines. This was achieved by using a logarithmic progression of the size of the optotypes, obtaining equality in the discernment. They proposed that each line of optotypes contain five letters and the space between them is exactly the size of the letters of the same line and the space between the lines is equal to the size of the optotype of the lower line. In such a way that with this booklet, Bailey and Lovie innovated the method of assessing visual acuity through the logarithm of the minimum resolution angle (logMAR). This type of scale establishes: 1) the visual acuity 20/20 is equal to 0.00 in logMAR and 2) the 20/200 represents in log MAR the unit (1,0). Therefore, each successive line change represents a change of 0.10 logarithmic units. In a line of five letters each letter has a value of 0.02 logarithmic units; in this way, the value of the acuity reached within a line can be objectively annotated. This makes the test have a high degree of reliability. In the area of research, it is called a "Golden Proof".

Standardization of the visual examination:

- At a distance of 3 m in a room with dim lighting, the research subject will be evaluated as follows:
- This exam will be held at the research center
- The patient will be asked to always sit in the same place and with the LogMar scale the visual acuity (AV) will be assessed if he / she does not have this type of booklet he / she must carry out the conversion.
- The research subject will keep both eyes open.
- The research subject should gently cover one eye with an occluder while reading aloud the smallest line of letters that can be seen. This test is done on each eye, one at a time, starting with the right eye (RE).
- The doctor must point out, the line that is requested to read the research subject.
- Finally, through the pinhole, the same procedure will be carried out.

Normal values: visual acuity or visual capacity will be expressed in decimals, where 0.0 will be the maximum normal score. In the case of people who do not know how to read, the test will be done with special cards of figures or numbers and the VA will be defined with the same LogMar scale, for patients of very early ages such as RN, infants or uncooperative preschoolers. AV as it perceives and follows light or does not perceive or follow light.
In offices where LogMar is not available, you can measure the VA with the card you normally use and convert it to the LogMar scale for which the following table of equivalences helps.

Equivalence between the different AV scales

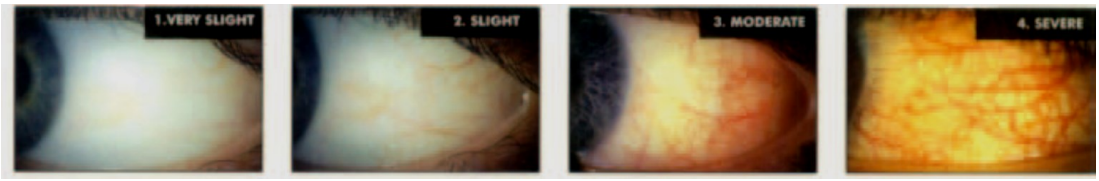
MAR (min arc)	Log MAR	Snellen (d=6m)	Snellen (d=20 ft)	Escala decimal	Keeler A
100	2.0	6/600	20/200	0.01	
79	1.9	6/480	20/1600	0.0125	20*
63	1.8	6/380	20/1250	0.016	19*
50	1.7	6/300	20/1000	0.02	18*
40	1.6	6/240	20/800	0.025	17*
32	1.5	6/190	20/630	0.032	16*
25	1.4	6/150	20/500	0.04	15*
20	1.3	6/120	20/400	0.05	14*
15.8	1.2	6/95	20/320	0.063	13*
12.5	1.1	6/75	20/250	0.08	12
10.0	1.0	6/60	20/200	0.1	11
8.0	0.9	6/48	20/160	0.125	10
6.3	0.8	6/38	20/125	0.16	9
5.0	0.7	6/30	20/100	0.2	8
4.0	0.6	6/24	20/80	0.25	7
3.2	0.5	6/19	20/63	0.32	6
2.5	0.4	6/15	20/50	0.4	5
2.0	0.3	6/12	20/40	0.5	4
1.58	0.2	6/9.5	20/32	0.63	3
1.25	0.1	6/7.5	20/25	0.8	2
1.0	0.0	6/6	20/20	1.0	1
0.8	-0.1	6/4.8	20/16	1.25	
0.63	-0.2	6/3.8	20/12.5	1.6	
0.5	-0.3	6/3	20/10	2.0	

Biomicroscopy Previous

It refers to the revision of the entire anterior segment: cornea, iris, pupil, anterior chamber, crystalline and / or (IOL).
It will be qualified as follows:
Normal.
Abnormal.
Abnormality that does not affect the result of the study.
If any of the structures has any special description that you write down in comments of that same section in the FRC.

Conjunctival hyperemia

Which is defined as the simplest reaction of the conjunctiva to a stimulus, we see a red appearance secondary to the vasodilation of the conjunctival vessels of variable intensity. It will be classified according to the analogous visual scale of hyperemia. Vii



1.- Very Mild 2. Mild 3.- Moderate 4.- Severe

Foreign body sensation

Burning
Lachrymation
Eyelid scales
Eyelid edema
Membranes and / or pseudomembranes
Epitheliopathy
These symptoms will be described as present or absent,
Secretion will also have to be described

Fluorescein and green lysamin stain

Fluorescein staining will be performed, standardization of this scan is done as follows:
1. With the patient in front of the lamp prior instillation of topical anesthesia Ponti Ofteno that will be provided by Laboratorios Sophia, S.A. of C.V.
2.- The lower eyelid of the patient will be gently grabbed, first on the right side and then on the left side, asking the patient to turn upwards so that with this maneuver a greater area of the lower bulbar conjunctiva is exposed, then the filter paper will be placed moistened with a drop of anesthetic and the surface of the eye will be touched with it for a second in the aforementioned area, subsequently the patient will be asked to blink several times and proceed to examine it without specifying corneal region, the same procedure will be performed for the analysis of the conjunctiva with lysamine green:

Absent (without staining)
Medium (less than 10% of the surface with staining)
Moderate (from 10 to 50% with surface staining)
Severe (more than 50% of the surface)

Membranes and pseudomembranes
They are formed by exudates adhering to the inflamed conjunctival epithelium, the difference between one and another is that the latter are removable.
Your presence or absence will be reported.

Subsequent Segment Review
It refers to the revision of the entire posterior segment, particularly: vitreous, retina, macula and optic nerve. It will be qualified as follows:
Normal.
Abnormal.
Abnormality that does not affect the result of the study.
If any of the structures has any special description that you write down in comments of that same section in the FRC.

Sampling for central laboratory:

(This is a general procedure, it does not mean that it should be done as such, that procedure will be punctually described by the central laboratory where the crops will be sent).

1.- After cleaning hands and putting on latex gloves.
2.- Take the swab contained in the package of the means of transport with the index fingers and thumb of the right hand while with the index finger of the left hand the lower eyelid is gently pulled exposing the bottom of the bag and thus be able to take the sample of it
3.- By touching the palpebral conjunctiva the applicator is rotated to take as much sample as possible.
4.- Place the swab in the transport medium.

The central laboratory in charge of the processing of the samples will be asked for Gram stain and special attention to the growth in the culture of the following bacteria:

Staphylococcus aureus, Staphylococcus albus, Pseudomonas aeruginosa, Streptococcus pneumoniae, Haemophilus influenzae, Streptococcus pyogenes, Klebsiella pneumoniae Escherichia coli, Neisseria gonorrhoeae, Streptococcus viridans, Moraxella catarrhalis.

The technique for collecting the sample will be done using a swab. These techniques are not limiting, and it is up to the doctor to select one of them according to the case.

18. VALUATION OF SECURITY

18.1 Safety measurements

Figure (8.2.2) 1 - Research Program indicates safety measurements that are made in each visit or treatment period.

Security criteria
- Adverse events and visual ability

18.2 Times of Measurements

Clinical examination
Basal visit (Day 1)

The principal investigator or the head of the research team of the site duly specified must obtain the letter of informed consent of each of the subjects, before carrying out any procedure of the study.

When the informed consent is obtained and all the inclusion criteria and none of exclusion are met, a unique identification number of the subject will be assigned, this will be used throughout the study for its identification.

Female subjects who are of reproductive age will be tested for pregnancy in urine.

The following evaluations will be made:
Signature of informed consent
Review of inclusion criteria and exclusion criteria,
Demographics,
Urine pregnancy test (if applicable),
General and ophthalmological clinical history,
Clinical Photography,
Sampling of conjunctival sac fundus for culture,
Assigning number to the subject,
Delivery of medication,
Ocular symptoms: burning, tearing, foreign body sensation, pruritus, photophobia
Visual acuity and / or visual ability,
Anterior biomicroscopy: Conjunctival hyperemia, chemosis, secretion, palpebral edema, membranes and / or pseudomembranes, scales, epitheliopathy,
Fluorescein staining,

Green stain of lysine,
Posterior segment revision: Retina, Macula, Vitreous and Optic nerve.
Evaluation of adverse events.

This day the patient will be included, if clinically it suggests a bacterial conjunctivitis, it will be randomized and at that same moment a clinical photograph of his eyes will be made and a sample will be taken for culture of both eyes, immediately he will go with the person previously designated to randomize him , this person will not be masked and will give specific instructions to the patient on how to apply the study medication and will remember the importance of the patient not mentioning the study's evaluating physician how many times the treatment is applied, then he will start with the study medication regardless of the crop results.

Treatment visits:
Visit 1 (Day 3)
Between the days of study there may be a window of ± 1 day. If for any reason an assessment is made on any day not planned in the study, this information should be recorded in the unscheduled visit format found within the FRC.

At each follow-up visit, an ophthalmological examination will be performed in order to evaluate the following parameters.
1. Acuity and / or Visual Ability
2. Clinical Photography,
3. Evaluation of specific symptoms and signs: burning, tearing, foreign body sensation, pruritus, photophobia,
4. Anterior biomicroscopy: conjunctival hyperemia, chemosis, secretion, palpebral edema, membranes and / or pseudomembranes, scales, epitheliopathy.
5. Posterior biomicroscopy (retina, vitreous, macula and optic nerve).
6. Fluorescein staining
7. Green lysine stain
8. Evaluation of adverse events.
9. Evaluation of concomitant medications.

Final Visit (Day 8)
In this the following parameters will be evaluated:
1. Urine pregnancy test (if applicable)
2. Return of medication by the subject
3. Acuity and / or Visual capacity
4. Clinical photography,
5. Ocular symptoms: burning, tearing, foreign body sensation, pruritus, photophobia.
6. Conjunctival sac fundus sampling for culture
7. Anterior biomicroscopy: conjunctival hyperemia, chemosis, secretion, palpebral edema, membranes and / or pseudomembranes, scales, epitheliopathy.
8. Posterior biomicroscopy (retina, vitreous, macula and optic nerve).
9. Fluorescein staining
10. Green lysine stain.
11. Evaluation of adverse events
12. Evaluation of concomitant medications

Follow-up of Adverse Events (EA) (Day 23)

1. A telephone call will be made by the investigating doctor or responsible previously designated for the evaluation of adverse events.

19. PROOF OF PREGNANCY

The urine pregnancy test will be taken in the same facilities of the research center, where the subject will be given a bottle to collect their urine. This will be in private and then deliver the bottle with the urine sample to the investigating doctor or person in charge beforehand, who will introduce a test strip into the sample and wait for the result.

20. ADVERSE EVENTS

All adverse events should be subject to follow-up until their completion and documented in a complete and accurate manner in order to make possible the assessment of the safety of the study drug.

20.1 Events to be registered

An adverse event is defined as any unfavorable medical occurrence in a subject that is participating in a clinical trial, whether or not there is a causal relationship with the study drug and / or experimental procedures, that is present or detected as of the date that the patient signs the form of information and consent, regardless of the period of the study.

Therefore, the investigator will document as an adverse event:

• Any unfavorable and unintended sign, including an abnormal finding of an additional examination that the investigator considers clinically important,
• Any intercurrent symptoms or illness,
• Any worsening during the study of a symptom or disease already present when the patient entered the study (increase in frequency and / or intensity), and which:
-It is detected during a study visit or in an additional examination,
- Be present from the previous visit of the study and notify the patient.

A serious adverse event, that is, an event that, regardless of the dose of the study drug administered:

• How the patient's death results
• Be a threat to life,
Note: the term "threat to life" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically could have caused death if it had been more serious.

• How persistent or important disability / disability results. Note: an event that seriously disrupts the patient's ability to lead a normal life, in other words that causes a significant change, deterioration, injury or alteration of the functions or body structure of the patient, physical activity and / or quality of life.
• Be a congenital anomaly / birth defect. Exposure to the study drug before conception (in man or woman) or during pregnancy that causes an adverse outcome in the child.

Note: any event that may not be an immediate threat to life or result in death or hospitalization but may endanger the patient or may require intervention to avoid one of these outcomes (eg, edema or allergic bronchospasm requiring treatment) intensive at home, blood dyscrasia, seizures that do not cause hospitalization, or development of drug dependence or drug abuse).

Consumption of the study drug by a person other than the patient:

• Minors: any consumption of the study drug with or without medical consequences must be notified immediately to the sponsor.
• Adults: any accidental consumption of the study drug with clinical symptoms and any intentional consumption of the study drug, with or without medical consequences, should be notified immediately to the sponsor.
• In these specific cases, the investigator must inform immediately by telephone or fax, or in non-working hours, to the 24-hour telephone line (see Table (12.3.1.3) 2). These cases should be reported on separate paper pages "Adverse Event" that will be provided to the centers and should be sent immediately by fax to the responsible person.
• A pregnancy that occurs during the study.

20.2 Methods for registration

Adverse events must be documented in an "Adverse Event" form. Some sections of the page must always be filled out in full, whether the event is serious or not serious. The other sections will be filled only when the event requires immediate notification.
In case of progression of the disease by episodes (chronic disease):

-If the disease was already known when the patient entered the study, it will only be documented as an adverse event when there is a worsening (increased frequency and / or intensity of episodes / attacks),

-If the disease is detected during the study and the repetition of the episodes allows diagnosing a chronic disease, episodes that clearly describe the diagnosis will be grouped in the same form "Adverse event".

20.3 Follow-up of adverse events

The researcher must ensure that the patient's follow-up is appropriate to the nature of the event, and that it continues until it is resolved. Any secondary deterioration should be reported immediately to the sponsor.

Any change in terms of diagnosis, intensity, severity, measures taken, causality or result related to an adverse event already reported should be written in a full evaluation of the event.

If the adverse event has not been solved in the patient's final visit, the study can not be closed until it has reached a resolution, which must be followed by the principal investigator or the previously assigned responsible person, who must look for it. detail of

the adverse event and its follow-up only if the researcher indicates that this adverse event is directly related to the study medication. If it is not directly related, then it must be registered and the center can be closed.

20.4 Procedure for a serious adverse event

In the event of a serious adverse event and that is presented:
- During the study.
- During the 15 days following the final visit of the patient's study, regardless of the supposed function of the investigation (drug under study or experimental procedures required according to the protocol of the clinical study) or,
- After these 15 days regardless of whether the start date is after the end of the study, when the event could be related to the investigation.

The researcher must:

Record in the participant's medical record the date on which the event was made known (in a follow-up visit or through telephone contact with the participant or with a third party, ...), immediately after being informed about this event , filling out a "Serious adverse event" form, without waiting for the clinical results or the results of additional research, will be informed by the sponsor (Clinical Research Department and Pharmacovigilance Department) by e-mail, (see Table (12.3.1.3) 1) .Provide people who are designated later, as they are available, anonymous copies of documents that offer useful additional information, such as hospital admission reports, other consultation reports, laboratory test reports, reports. of other tests that help the diagnosis (when possible, pre-treatment assessments should be attached to the stop them against the results obtained with the treatment), or the report of the autopsy, if done.
- Comply with their regulatory obligations before the Competent Authorities and / or before the Ethics Committee, in compliance with local regulatory requirements.

Table 5 - Contact structures in case of a serious or not serious Adverse Event.

First contact

Clinical Study Monitor
QFB. Sandra Carolina Gómez Méndez
Cel. 331 86 21 071
+33 3001 42 00
Ext. 1191

LN. Ana Isabel Alcaraz Ledón
Cel. 331 862 10 72
+33 3001 4200
Ext. 1193

QFB. Jessica L. Mejia Gutierrez

Cel. 331 86 21 070

+33 3001 4200

Ext. 1192

Responsible for Pharmacovigilance:
Dr. Alicia Paulina Melgarejo
Sophia Laboratories, S.A. of C.V.
Av. Paseo del Norte, 5255
Col. Guadalajara Technology Park.
C.P. 45010 Zapopan, Jalisco. Mexico.
Tel. 01 33 30 01 42 83 (Direct)
01 33 3001 4200 Ext. 1029
Cell phone. 044 33 1043 1474
Direct helpline, toll free: 01 800 7102 254
E-mail: farmatec@sophia.com.mx

If an initially non-serious adverse event worsens and becomes serious, this should be reported immediately in the form "Serious adverse event"

Report the initially not serious event on a paper page "Adverse event - Additional information" (see appendix 9),

- Report the deterioration caused by the seriousness on a paper page "Adverse event - Additional information" (see appendix 10), and
- Send them by email immediately to the responsible person indicated above.

If a female patient in the study becomes pregnant, the investigator should:

- Suspend the study treatment for the patient.
- Fill out an "adverse event" form of the FRC.
- Fill out a paper form of pregnancy follow-up report (first page, appendix 11),
- Contribute to the follow-up of this pregnancy and provide the sponsor with the information related to this follow-up (mainly using the second page of the pregnancy follow-up report).

21. EVALUATION OF CAUSALITY

It is important that the investigator of your opinion in relation to the cause-effect relationship between the adverse event and the study drug, for the following reasons: certain adverse events that occur during clinical investigations may be important enough to lead to changes in the drug development program (for example:

Changes in dose, population of the study or in the information provided to patients that may lead to the preparation of new forms of information and consent). This is especially true in case of events that are suspected to be related to the study drug (adverse reaction to the drug) and which, in its most severe form, mean a threat to life.

The causality must be assessed at the time of writing in the patient's file; Subsequently, the reports of a serious and non-serious adverse event will be filled out in its various formats. Only cases marked by the researcher as "related" or according to the opinion of the sponsor have a causal relationship with the investigational medicinal product under reasonable suspicion (relationship of the Adverse Event with the mechanism of action of the drug under study, ...) they will be considered as an Adverse Reaction to the suspect medication.

In general, the expression reasonable causal relationship means communicating that there is evidence or arguments to suggest a causal relationship.

22. RESPONSIBILITIES OF THE SPONSOR

Independently of the normative obligations of the researcher, the sponsor must report the pharmacovigilance data to the pertinent Authorities and to all participating researchers, in accordance with the requirements established in the International Conference on Harmonization (ICH), in the guidelines of the Good clinical practices and local regulations.

23. STATISTICS

Sample size
We conducted a review of published articles regarding the use of medications in the treatment of bacterial conjunctivitis. We found three publications that are the following:

1) “Gatifloxacin Ophthalmic Solution for Treatment of bacterial Conjunctivitis: Safety, Efficacy and Patient Perspective”. Clyde Schultz. En Ophthalmology and Eye Diseases. 2012:4 65-70.
2) “Microbiological Efficacy of a New Ophthalmic Formulation of Moxifloxacin Dosed Twice-Daily for Bacterial Conujnctivitis”. Shachar Tauber et.al. En Adv Ther. (2010) 28(7):566-574.
3) “Clinical use of gatifloxacin ophthalmic solution for treatment of bacterial conjunctivitis”. Lorenzo J. Cervantes y Francis S. Mah. En Clinical Ophthalmology. 2011:5 495.502.

The first of the publications referred to here (Clyde Schultz) is a review article that summarizes the findings regarding the use of gatifloxacin mainly as a treatment for bacterial conjunctivitis but does not give precise figures, it only says, for example, that the Effectiveness reported in an article made in China was around 93%. It is not an original article that gives specific results, but rather comments findings and issues an opinion regarding the convenience of using them as an effective and safe treatment for bacterial conjunctivitis.

The second revised article (Schachar Tauber) is an original article. This is a multicentre study in which 1180 patients were recruited throughout the United States of America, who had a clinical diagnosis of bacterial conjunctivitis. . All patients were given a sample

prior to treatment and another at the end of treatment, which were sent to the clinical laboratory where standard methods of microbiology were used to isolate the biological specimens before and after the treatments. One group was treated with MOXI-AF and the other with placebo (vehicle) instilling in the conjunctival sac one drop twice a day for three days and the most important results of this investigation are summarized in Table 1.

The third article reviewed (Cervantes) describes other studies conducted to test gatifloxacin in two presentations: Zymar (0.3%) tested in 52 patients treated for three days vs. placebo (vehicle) tested in 48 patients and Zymaxid (0.5%) tested in 333 patients for three days vs. placebo (vehicle) tested in 325 patients for three days.

The results reported in these articles regarding efficacy can be summarized in Table 1.

Cuadro 1. Eficacia de medicamentos para erradicación de bacterias en infecciones oculares (Conjuntivitis) reportada en publicaciones.

Tratamiento	Eficacia Absoluta	Total ojos n	Eficacia n	Eficacia %
MOXI-AF[1]		424	316	74.53%
Placebo (Vehículo)[1]		423	237	56.03%
Zymar[2]		52	40	76.92%
Placebo (Vehículo)[2]		48	28	58.33%
Zymaxid[2]		333	193	57.96%
Placebo (Vehículo)[2]		325	148	45.54%
Tratamiento	**Eficacia específica por bacteria**			
MOXI-AF[1]	**Haemophilus influenzae**	67	66	98.51%
	Streptococcus pneumoniae	22	19	86.36%
	Staphylococcus aureous	17	16	94.12%
Placebo (Vehículo)[1]	**Haemophilus influenzae**	52	31	59.62%
	Streptococcus pneumoniae	18	9	50.00%
	Staphylococcus aureous	15	12	80.00%
Zymar[2]	*	52	48	92.31%
Placebo (Vehículo)[2]	*	48	34	70.83%
Zymaxid[2]	*	333	301	90.39%
Placebo (Vehículo)[2]	*	325	228	70.15%

* **Nota:** La eficacia específica por bacteria en los estudios con Zymar y con Zymaxid no se presenta para cada bacteria sino para la totalidad de bacterias que aparecieron en el cultivo inicial y ya no aparecieron en el cultivo post-tratamiento.

[1] Microbiological Efficacy of a New Ophthalmic Formulation of Moxifloxacin Dosed Twice-Daily for Bacterial Conujnctivitis. Shachar Tauber et.al. En Adv Ther. (2010) 28(7):566-574.

[2] Clinical use of gatifloxacin ophthalmic solution for treatment of bacterial conjunctivitis. Lorenzo J. Cervantes y Francis S. Mah. En Clinical Ophthalmology. 2011:5 495-502.

To calculate the sample size, we obtained the overall average of absolute efficacy for patients treated with some medication and for patients treated with placebo. For patients treated with medication, the absolute efficacy (total disappearance of bacteria in the post-treatment culture) was 69.8% and for those treated with placebo it was 53.3%. The specific efficacy (disappearance of a specific bacterium that was present in the pre-treatment culture) for the groups treated with some medication was 92.34% and for patients treated with placebo 66.12%.

With these figures, we can calculate the sample size needed to detect that level of differences reported between patients with bacterial conjunctivitis treated with medication vs. patients treated with placebo.
Annex 1 develops the calculations for the sample size necessary to detect the differences in the percentage of efficacy to eliminate bacteria from patients with bacterial

conjunctivitis found in the articles reviewed between patients treated with any drug vs patients treated with placebo. The Fleiss formula is used for case-control studies.

From the calculations made we can draw the following conclusions and recommendations. The average absolute efficacy found in the articles commented is almost 70% (69.8%) for patients treated with any medication and only 53.3% for patients treated with placebo (in this case vehicle was used as a placebo). According to the Fleiss formula for cases and controls, a sample of 147 cases per group assures us that if the differences that we are going to prove between the treatments is of that magnitude (69.8 %% vs 53.3%) or greater, we will have a 80% probability that the statistical test that we apply to evaluate the differences will be statistically significant (Power or power of the sample), and on the other hand, if the differences between the treatments were not of that magnitude (the differences were of lesser magnitude), when applying a statistical test on the results of a sample of 147 cases with minor differences to the ones presented, it will be not significant and the probability of this happening will be 0.95 (Reliability of the sample).

In summary, to prove differences in the absolute efficacy of two treatments in which one has almost 70% absolute efficacy and the other of only 53.3%, a sample of 147 cases per group will be necessary to have a reliability of 95% and a 80% power.

If instead of calculating the sample size with absolute efficiency we calculate it with the specific efficacy for specific bacteria, using the percentages that we obtained from the review of the articles published and that were 92.34% and 66.12% for patients treated with some medication and for those treated with placebo respectively, the sample according to the Fleiss formula for a 95% reliability and a power of 80% is 44 patients per group.

We can suggest that the minimum sample should be 50 eyes per treatment group and if possible, it would be desirable that the sample per group could reach 150 cases per group.

Of course, the theoretical calculations are a part of the sample size problem, the other part refers to the resources available. Given that 5 medications are going to be tested: Vigamoxi®, Zymar®, and PRO-157 in three posologies and probably a placebo group as long as this does not contravene ethical aspects, if the sample were 50 eyes per group, it would imply 250 or 300 cultures and studies of microbiology or PCR before the treatments and another at the end of them. If the sample increased to 150 eyes per group, then these figures would triple. In short, the theory indicates that an adequate sample to establish and confirm statistically differences in the magnitudes reported in other studies between drug treatments and placebo treatments should be approximately between 50 and 150 eyes.

ANNEX 1. Calculation of sample size.

Fórmula de Fleiss para el cálculo del tamaño de muestra para proporciones.
"Statistical Methods for Rates and Proportions" 2a. Ed. Pp. 38-45 Wiley. 1981. EUA.
Casos y Controles.

r = Razón de: Controles : Casos = **1** : **1** 1.00

P1 = Eficacia absoluta en el grupo tratado con algun medicamento. **0.6980**
Q1 = 1 - P1 0.3020

P2 = Eficacia absoluta en el grupo tratado con placebo. **0.5330**
Q2 = 1 - P2 0.4670

P = Proporción promedio ponderada de eficacia absoluta.

$$P = \frac{(P1 + r * P2)}{r + 1}$$ 0.6155

Q = 1 - P 0.3845

α= **Nivel de significancia o probabilidad de error tipo 1** **0.050**
$1-\alpha/2$= **Percentil bilateral para el nivel de significancia asignado** 0.975
$Z_{1-\alpha/2} = Z_{0.975}$ **de la distribución normal estandarizada que deja un area de 0.975 a la izquierda. Implica una confiabilidad del 95%** 1.960

β= **Probabilidad de error tipo 2** **0.200**
$1-\beta$= **Percentil unilateral para la beta asignada** 0.800
$Z_{1-\beta} = Z_{0.80}$ **de la distribución normal estandarizada que deja un area de 0.80 a la izquierda. Implica un poder del 80%** 0.842

m' = Tamaño de muestra

$$m' = \frac{\left(z_{1-\alpha/2} \sqrt{(r+1) * P * Q} + z_{1-\beta} \sqrt{r * P1 * Q1 + P2 * Q2} \right)^2}{r * (P2 - P1)^2}$$

$$m' = \frac{\left(1.960 \sqrt{(1.00+1)\ 0.62 * 0.38} + 0.842 \sqrt{1.00 * 0.70 * 0.30 + 0.53 * 0.47} \right)^2}{1.00\ (0.53 - 0.70)^2}$$

m' = 135.272

m = Tamaño de muestra corregido

$$m = 0.25\ m' * \left[1 + \sqrt{1 + \frac{2\ (r+1)}{m' * r * |P2 - P1|}} \right]^2$$

m = 147 **Tamaño de muestra para el grupo de referencia (Controles):** $m_1 = r*m$ **147**
Tamaño de muestra para el grupo de estudio (Casos): $m_2 = m$ **147**

Fórmula de Fleiss para el cálculo del tamaño de muestra para proporciones.
"Statistical Methods for Rates and Proportions" 2a. Ed. Pp. 38-45 Wiley. 1981. EUA.
Casos y Controles.

r = Razón de: Controles : Casos = **1** : **1**	1.00
P1 = Eficacia específica en el grupo tratado con algun medicamento.	**0.9234**
Q1 = 1 - P1	0.0766
P2 = Eficacia específica en el grupo tratado con placebo.	**0.6612**
Q2 = 1 - P2	0.3388

P = Proporción promedio ponderada de eficacia específica

$$P = \frac{(P1 + r * P2)}{r + 1}$$ 0.7923

Q = 1 - P 0.2077

α= Nivel de significancia o probabilidad de error tipo 1	**0.050**
1-α/2= Percentil bilateral para el nivel de significancia asignado	0.975
$Z_{1-\alpha/2}$= $Z_{0.975}$ de la distribución normal estandarizada que deja un area de 0.975 a la izquierda. Implica una confiabilidad del 95%	1.960
β= Probabilidad de error tipo 2	**0.200**
1-β= Percentil unilateral para la beta asignada	0.800
$Z_{1-\beta}$= $Z_{0.80}$ de la distribución normal estandarizada que deja un area de 0.80 a la izquierda. Implica un poder del 80%	0.842

m' = Tamaño de muestra

$$m' = \frac{\left(z_{1-\alpha/2} \sqrt{(r+1) * P * Q} + z_{1-\beta} \sqrt{r * P1 * Q1 + P2 * Q2} \right)^2}{r * (P2 - P1)^2}$$

$$m' = \frac{\left(1.960 \sqrt{(1.00+1)\ 0.79 * 0.21} + 0.842 \sqrt{1.00 * 0.92 * 0.08 + 0.66 * 0.34} \right)^2}{1.00\ (0.66 - 0.92)^2}$$

m' = 36.373

m = Tamaño de muestra corregido

$$m = 0.25\ m' * \left[1 + \sqrt{1 + \frac{2\ (r+1)}{m' * r * |P2 - P1|}} \right]^2$$

m =	**44**	**Tamaño de muestra para el grupo de referencia (Controles):**	**m_1=r*m**	**44**
		Tamaño de muestra para el grupo de estudio (Casos):	**m_2=m**	**44**

Analyzed data set
The data will be analyzed in two groups, one will be made up of the population evaluable by Intention to Treat (ITT) in which each of the variables is described, the ITT population will be constituted by all the recruited subjects who have received at least one dose of study treatment.
Others will be the evaluable population Per Protocol (PP) which is the subset of ITT composed of all subjects without any major deviation from the protocol, in which the bivariate analysis will be performed.

24. DIRECT ACCESS TO DATA / DOCUMENTS SOURCE

The researcher will allow the monitors, the persons responsible for auditing, the representatives of the Ethics Committee, and the Competent Authorities to have direct access to the data / source documents.

25. QUALITY CONTROL AND QUALITY ASSURANCE

25.1 Supervision of the study

Before the study
The researcher will allow the monitor to visit the site and the facilities where the study will be conducted to ensure compliance with the requirements of the protocol.
A meeting of researchers will be organized before the start of the study.

The researcher will allow the monitor:
- Inspect the site, facilities and materials used for the study,
- Meet with all the members of your team that participate in the study,
- See all documents related to the study,
- Have access to the FRCs and that they are filled correctly,
- Direct access to the source documents to compare the data contained there against the FRC data,
- Verify that the study is carried out in compliance with the protocols and regulatory requirements.

If computerized medical records are used, the investigator should:
- At the start of the study, print all medical records of all participants,
- During the study, print in real time each of the data entries and each change to the data.

The researcher will personally put the signature and date on the first page of the printout and indicate the number of pages.
At each monitor visit, the investigator will provide you with all the impressions of the medical records of the participants. The Principal Investigator will personally place a date and signature on every page of each printout and indicate on the first page the number of pages.
If the computer system allows tracking of changes made to medical records to be used, the investigator will give the monitor at each visit an impression of the medical records of the participants and the records of the changes made. The researcher will personally place the date and signature on the first page of each printout, and the monitor will do so on all pages. The researcher and the monitor will put the number of pages on the first page.
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.

25.2 Computerized medical record

If computerized medical records are used and the computer system allows it, no change made to medical records by the investigator should hide the original information. The record should clearly indicate that a change was made and provide clear means to locate and read the above information. The researcher will save the data at regular intervals.

The researcher must guarantee the security of the study data in the medical files by implementing security measures to prevent unauthorized access to the data and the computer system.

The researcher undertakes to maintain:
- In the record of the study, all the impressions of the medical file signed and dated by him.
- If the computer system allows it, the documentation of the changes made during the study to the medical records in the study file,
- All original source documents (original of the specific exams, forms of informed consent, ...).

25.3 Audit - Inspection-Verification

The investigator should be informed of the possibility of an audit being conducted during or after the end of the study.

The investigator should be informed that the Competent Authorities may also perform an inspection or verification of the facilities of the sponsor and / or the study center or centers. The sponsor will inform the relevant investigators, immediately upon receiving notification of an inspection to the study centers. Likewise, the investigator will inform the sponsor of any pending inspection.

The researcher will allow the representatives of the Competent Authorities and the people responsible for the audit:
- Inspect the site, the facilities and the material used for the study,
- Meet with all the members of your team participating in the study,
- Have direct access to the study data and source documents,
- See all documents related to the study.

If computerized medical records are used, the researcher undertakes to provide all source documents and impressions of the medical records of the participants, and if the computer system allows it, the record of the changes made during the study.

26.ÉTICA

26.1 Research Ethics Committee

The Principal Investigator will submit to the Research Ethics Committee the study protocol, informed consent, investigator's manual, materials to be delivered to the patient, recruitment materials, and the required documents in accordance with local requirements.
The study will not start in the center without first having obtained the approval of the corresponding Research Ethics Committees, having complied with the local regulatory requirements, having obtained the signing of the confidentiality agreements, economic proposal and signature of the contract of each one of them. the main medical researchers.

26.2 Realization of the study

The study will be conducted in accordance with the ethical principles established in the Declaration of Helsinki of 1964, revised in Seoul, 2008 (see appendix 1).
26.3 Information for the subject and form of informed consent
Informed consent must be obtained before the patient is given 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 principal investigator (or a medical member of the site investigation team duly specified by the principal investigator in delegation of responsibilities format) will provide the prospective participant with all information regarding the characteristics of the study, its potential risks, benefits, objectives and procedures. of the same. This information will be in a language understandable to the subject, it will be explained to the patient that he has the right to interrupt his participation in the study at any stage, without affecting the relationship with the researcher and / or his future assistance. The informed consent will be put to the consideration of the possible participant; This must have enough time to analyze each and every one of the aspects mentioned above and if there is any doubt this will be clarified by the person in charge of obtaining the informed consent. Once the participant agrees to participate in the study, he / she must sign and date the informed consent letter in the presence of two witnesses who have or are not related to the subject of study, who will participate during the informed consent process and will sign endorse that the process was carried out prior to any study procedure, that the study information was clearly explained and doubts were clarified if they existed.
If a patient is illiterate, the acceptance will be with his / her fingerprint, and in the event that the patient is not able to grant an informed written consent, a representative of the "legally authorized" patient can provide such consent. the subject in accordance with applicable laws and regulations.

The principal investigator must also sign and date this consent.

The informed consent must be signed in duplicate by all involved, and two witnesses, one copy will be filed in the researcher's folder and the other will be delivered to the

participant. The Investigator must document in the patient's medical history, the date on which he signed the informed consent.
At the moment in which the informed consent is obtained, a unique identification number of the subject will be assigned, this will be used throughout the study for the identification of the participant.

26.4 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 having complied with local regulatory requirements, with the exception of an amendment that is required to eliminate an immediate danger to study patients.
Each patient affected by the amendment must fill out, date and sign two originals of the new version. The patient will be given a signed original of the amendment and the researcher will keep the second original.

27. DATA MANAGEMENT AND CONSERVATION OF RECORDS

27.1 Data of the study

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

27.2 Case Report Form (FRC)

An FRC 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 allowed for the principal investigator or person responsible for filling in to modify what was written by the subject of the study.

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

All corrections to the data to the FRC must be made by the investigator or the designated person of your team in accordance with the instructions provided, as described below.
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, whether resident within the researcher's, the sponsor's or third party's sites.
The monitor should ensure that all the data in the FRC has been filled. After comparing the data against the source documents, the monitor will ask the researcher to make the

correction / clarification using clarifications, so that they are answered and closed as quickly as possible.

27.3 Data management

The data will be collected in the FRC, once having a copy of the FRC of each of the visits of each patient who has completed the study will be transcribed to a database, the database mask will coincide with the form of report of case and the data of each of the FRCs will be captured. A double data capture will be carried out, in order to validate the information, as the case report forms are being collected from the center and the data have been validated by the clinical monitor.

After the double data capture, a data review will be done, and consistency checks will be made. If there are inconsistencies in the data, the clinical monitor will ask the researcher for its resolution. Whenever necessary, that is, when discrepancies are generated, they will be sent to the researcher for resolution and signature and will be followed up until the corrections are resolved, entered in the database and validated.

27.4 Archive

The investigator will keep all the information related to the study for at least 10 years after the completion of the study.

28. OWNERSHIP OF THE RESULTS - PUBLICATION POLICY

Laboratorios Sophia S.A de C.V., acting as the sponsor of the study, assumes full responsibility for its function and retains exclusive ownership rights to the results of the study, which may be used in the manner it deems appropriate.
Because the study is multicentric, the first publication should be made only with data collected from several centers and analyzed under the responsibility of Laboratorios Sophia S.A. of C.V. The researcher undertakes not to publish or communicate data collected only in a center or in part of the centers before the publication of the full results of the study, unless prior written agreement is given by Laboratorios Sophia S.A. of C.V.

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

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

29. ADMINISTRATIVE CLAUSES

29.1 People to inform

In accordance with local regulations, the investigator and / or sponsor will inform the Director of the Health Care Facility, the pharmacist involved in the study and the Director of the analysis laboratory.

29.2 Substantial amendment to the protocol

If it was necessary to alter the protocol after it was signed, the modification or substantial amendment should be discussed with the investigating physicians and staff that will participate in the clinical study, as well as with the regulatory entities of each region. It should be kept with the initial protocol. On the cover of the protocol kept by the researcher, the number and date of the amendment version must be noted.

All substantive amendments should be sent to the investigators or coordinators or the sponsor, and to the Ethics Committees that reviewed the initial protocol, in accordance with local regulations. Amendments can be implemented only after obtaining the favorable opinion of the Ethics Committee, having met the requirements, and that the document of the amendment was signed, except when a measure is required to eliminate an immediate danger to the patients in the study.

In addition, the substantial amendment must be submitted to the Competent Authorities in accordance with local regulatory requirements.

29.3 Final report of the study

The report of the study will be elaborated by Laboratorios Sophia S.A de C.V. After completing the statistical analysis of the data, a final report will be designed, according to the BCH of ICH.

29.4 Related to the sponsor

The sponsor agrees to:
- Provide the researcher with adequate and sufficient information about the treatment or treatments administered during the study, in order to carry out the study,
- Obtain any authorization to carry out the study and / or the import license for the treatment or treatments administered that might be required by the local authorities before starting the study (if it is international).

30. Confidentiality - Use of information

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 on the computer, are solely for use related to their activities such as 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 investigator may be used by the researcher and by his colleagues to obtain the

informed consent of the patients for the study. The clinical trial protocol, like any information taken from it, should not be disclosed to other parties without the sponsor's written authorization.

The researcher will not disclose any information without the prior written consent of Laboratorios Sophia S.A. of C.V., except to the representatives of the Competent Authorities, and only by request of the same. In the latter case, the researcher undertakes to inform Laboratorios Sophia S.A. of C.V. before revealing the information to these authorities. The researcher will fill out and maintain a selection log of the subjects as well as the identification and enrollment list of each of the patients. 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.

The subject's selection log will begin to be filled from the moment the investigator determines that a patient could participate in the study (through assessment of the patient's medical history during a visit or review of the medical record.)

31. Organization of the center

Any person to whom the researcher delegates a part of the study follow-up (co investigator, assistant researcher, nurse) and any other person participating in the study of this center (cardiologist, pharmacist, ...) must appear in the Delegation format of Responsibilities.

This document must be submitted at the beginning of the study and updated if one of the people participating in the study in the center changes.

32. Documentation to be delivered to the sponsor

The researcher undertakes, before the start of the study:
- To provide your updated Curriculum Vitae (maximum 10 pages) in Spanish (or corresponding language) dated and signed, and send it or deliver it to the sponsor along with that of his or her collaborators or work team,
- Copy of Academic Certifications (undergraduate and postgraduate degrees and federal professional cedulas)
- If you apply a copy of the operation notice (when it is a private practice).

33. APPENDICES

Appendix 1: Declaration of Helsinki of the World Medical Association
DECLARATION OF HELSINKI WORLD MEDICAL ASSOCIATION
Ethical Principles for Medical Research in Human Beings

Adopted by the 18th General Assembly of the AMM, Helsinki, Finland, June 1964, and amended by:
29th General Assembly of the AMM, Tokyo, Japan, October 1975
35th General Assembly of the AMM, Venice, Italy, October 1983
41st General Assembly of the AMM, Hong Kong, September 1989
48th General Assembly of the AMM, Somerset West, Republic of South Africa, October 1996
52nd General Assembly of the AMM, Edinburgh, Scotland, October 2000
53rd General Assembly of the AMM, Washington 2002 (Explanatory note added in paragraph 29)
55th General Assembly of the AMM, Tokyo 2004 (Explanatory note added in paragraph 30)
General Assembly 59th of the AMM, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (AMM) promulgated the Declaration of Helsinki as a statement of ethical principles for medical research in humans, including research with identifiable human material and data.

The Declaration must be read in its entirety and each of the paragraphs that comprise it must not be applied without considering all the other relevant paragraphs.

2. Although the Declaration is intended primarily for physicians, the AMM encourages other participants in medical research involving human subjects to adopt these principles.

3. The doctor's duty to promote and safeguard the health of patients, including those who participate in medical research. The knowledge and conscience of the doctor are dedicated to the fulfillment of this duty.

4. The Geneva Declaration of the AMM forces physicians with the words, "the health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician must act according to what is best for him. the patient when he provides medical attention. "

5. Medical progress is based on research, which must ultimately include studies on human beings. The populations that are underrepresented in medical research should be given access to participate in the research.

6. In medical research involving human beings, the well-being of the research subject must take precedence over all other interests.

Appendix 1: Declaration of Helsinki of the World Medical Association (cont.)

7. The main objective of medical research with human beings is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the most current interventions must be evaluated continuously by means of research into their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.

9. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are especially vulnerable and require special protection. These populations include those who can not give or withhold their consent on their own and those who may be susceptible to coercion or undue influence.

10. Physicians should consider ethical, legal and normative norms and standards for research with humans in their own countries, as well as applicable international norms and standards. No ethical, legal or regulatory requirements, national or international, shall reduce or eliminate any of the protection for the research subjects established in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL INVESTIGATIONS

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right of self-determination, privacy, and confidentiality of the personal information of the research subjects.

12. Medical research with human beings must conform to generally accepted scientific principles, based on a perfect knowledge of the scientific literature, other relevant sources of information, and on correct experimentation in the laboratory, and when relevant in animals. The welfare of the animals used for research purposes must be respected.

13. Appropriate precautions should be taken when conducting medical research that may harm the environment.

1. The design and execution of each research study with human beings should be clearly described in a research protocol. The protocol must contain a statement of the ethical considerations included and must indicate the manner in which this Declaration was handled. The protocol must include information related to the obtaining of funds, sponsors, institutional affiliations, other possible conflicts of interest, incentives for the subjects and provisions on the management and / or compensation to the subjects that are damaged as a consequence of participating in the study. research. The protocol should describe the arrangements for post-study access of subjects to interventions that are identified as beneficial in the study, or access to other appropriate care and benefits.

Appendix 1: Declaration of Helsinki of the World Medical Association (cont.)

2. The protocol in the investigation must be presented for consideration, comment, guidance and approval to a research ethics committee before the start of the study. This committee should be independent of the investigator, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the investigation will be carried out, as well as the applicable international norms and standards, however they should not be allowed to reduce or eliminate any of the protections for the subjects under investigation. are set forth in this Declaration. The committee should have the right to supervise ongoing studies. The investigator should provide supervision research to the committee, especially information about serious adverse events. No change to the protocol can be made without the consideration and approval of the committee.

3. Medical research involving human beings should only be carried out by individuals with the appropriate scientific qualifications and training. Research on patients or subjects in healthy subjects requires the supervision of a competent and appropriately qualified physician or health care professional. The responsibility for the protection of research subjects always rests with the doctor or the health care professional and never with the research subjects, even when they have given their consent.

4. Medical research that implies a disadvantage or a vulnerable population or community will only be justified if the research is in response to health needs and priorities of this population or community obtain a benefit from the results of the research.

5. Any study of medical research with human beings should be preceded by a careful assessment of the predictable risks and burdens for the individuals and communities that participate in the research, compared to the benefits provided for them and for other affected individuals or communities. for the condition under investigation.

6. Clinical studies should be recorded in a database with access to the public before recruiting the first subject.

7. Physicians will not be able to participate in a research study with human beings unless they have confidence that the risks involved were properly assessed and that they can be handled satisfactorily. Physicians should immediately suspend a study when it is discovered that the risks outweigh the possible benefits, or when there is conclusive evidence of positive and beneficial results.

8. Medical research with human beings can only be carried out if the importance of the objective exceeds the risks and burdens inherent to the subjects under investigation.

9. The participation of competent individuals as subjects of medical research must be voluntary. Although it may be appropriate to consult with family members or community leaders, no competent individual can participate in a research study unless he or she freely agrees.

Appendix 1: Declaration of Helsinki of the World Medical Association (cont.)

10. Every precaution must be taken to protect the privacy of the research subjects, as well as their personal information, in order to minimize the impact of the study on their physical, mental and social integrity.

11. In medical research with human beings, each possible subject should be adequately informed about the goals, methods, sources of funds, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefit and the possible risks of the study, and the discomforts that could imply, as well as any other important aspects of the study. The possible subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be paid to the specific information needs of the possible subjects, as well as to the methods used to offer the information. Once having made sure that the possible subject understood the information, the doctor or another duly qualified individual should try to obtain the informed consent of the subject, granted freely and preferably in writing. If it can not be expressed in writing, the unwritten consent must be formally documented and witnessed.

In the case of medical research that uses identifiable human material or data, physicians should normally seek consent to collect, analyze, store and / or reuse samples. There may be situations in which it is impossible or impractical to obtain consent for such an investigation, or that could imply a threat to the validity of the investigation. In such situations, the investigation may be carried out only after it has been submitted to the research ethics committee for approval.

26. When trying to obtain "Information for the patient and form of informed consent" for participation in a research study, the doctor should be especially cautious if the possible subject has a relationship of dependence with the doctor or could give his consent under duress In such situations, informed consent should be sought by a qualified individual who is completely independent of this relationship.

27. In the case of a possible research subject who is incompetent, the doctor will try to obtain the informed consent of a legally authorized representative. These individuals should not be included in a research study if there is no likelihood of benefit to them, unless it is intended to promote the health of the population represented by the potential subject and the research can not be carried out with competent persons, and research involves only risks and minimum burdens.

28. When a potential research subject, who considers himself incompetent, can give his consent to participate in the investigation, the doctor must also seek the consent of the legally authorized representative. The denial of the possible subject must be respected.

Appendix 1: Declaration of Helsinki of the World Medical Association (cont.)

29. Research involving individuals who are physically or mentally disabled to give their consent, for example unconscious patients, may be performed only if the physical or mental condition that prevents their informed consent is a necessary characteristic of the research population. In such circumstances, the physician must seek the informed consent of the legally authorized representative. If such a representative is not available and the investigation can not be delayed, the study will proceed without informed consent, as long as the specific reason for including a subject with a condition that causes him or her not to give informed consent has been established in the research and study protocol has been approved by a research ethics committee. The consent must be obtained to continue in the investigation as soon as possible, the subject or the legally authorized representative.

30. All authors, publishers and printers have ethical obligations regarding the publication of research results. The authors have the duty to make publicly available the results of their research with human beings and will be responsible for the integrity and accuracy of their reports. They must adhere to the accepted guidelines for the ethical report. Negative and inconclusive results should be published, as well as positive results, or made publicly available. The publication should include sources of funds, institutional affiliations and conflicts of interest. Reports of an investigation that are not in accordance with the principles of this Declaration shall not be accepted for publication.

Appendix 1: Declaration of Helsinki of the World Medical Association (cont.)

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL ATTENTION

31. The physician may combine medical research with medical care only to the extent that the research is justified by its possible preventive, diagnostic or therapeutic value and the physician has good reason to believe that participation in the research study will not adversely affect the health of patients who serve as research subjects.

32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best intervention currently tested, except in the following circumstances:
• It will be acceptable to use a placebo or not to administer treatment when there is no currently proven intervention; or
• When for methodological and scientific reasons the use of placebo is necessary to determine the efficacy or safety of an intervention, and patients who are given placebo or no treatment are not at risk of serious or irreversible damage. Care should be taken to avoid abuse of this option.

33. At the end of the study, patients who participated in the study will have the right to be informed of the results of the study and to share with them the resulting benefits, for example, access to interventions identified as beneficial in the study, or other care or adequate benefits.

34. The physician must fully inform the patient which aspects of the care are related to the investigation. The refusal of the patient to participate in a study, or the decision of the patient to withdraw from the study should never interfere with the patient-doctor relationship.

35. In the treatment of a patient, when there are no proven interventions or have been ineffective, the doctor, after seeking expert advice and with the informed consent of the patient or the legally authorized representative, may use an unproven intervention if in his opinion the doctor offers hope to save lives, restore health or relieve suffering. When possible, this intervention should be part of the object of the investigation, designed to assess its safety and efficacy. In all cases, the new information must be recorded and, when appropriate, made publicly available.

Appendix 2: Format for Pregnancy Follow-up

Any fetal exposure to the product or products of the study triggers a procedure for monitoring pregnancy, especially to identify:
- cases in which pregnancy occurs unexpectedly, when an interaction with the method of contraception used is suspected (oral contraceptives, especially)
- any pregnancy termination during the study: either spontaneous or induced abortion, regardless of the reason,
- birth of a product, infant with deformations or abnormal, during or after the study. The latter always constitutes a serious adverse event.

The first page of the format for pregnancy follow-up should be filled out by the researcher starting from the beginning of the pregnancy and forward, if necessary with the help of other doctors who attended to the patient. The second sheet will be filled later when the pregnancy has ended, with the help of the researcher, other doctors, obstetricians, midwives, etc.

Appendix 2. Format for Pregnancy Tracking (cont.)

A - INFORMANT

Name: Population: Country:

Telephone No.: Center No.:

B - INFORMATION RELATED TO PREGNANT WOMEN

First Name: ... Last Name: ... Date of Birth (DD-MM-YYYY):
Participant No.: Last menstruation date (DD-MM-YYYY):
• Positive pregnancy test ⟹ Date (DD-MM-YYYY):

Exposure of the patient to the study product (1

No. Protocol:
Dosage *: Indication:
Via:

Date taken first (DD-MM-YYYY): Date last taken (DD-MM-YYYY):

Concomitant medications (including oral contraceptives)

	②	③	④	⑤	⑥
First name					
Daily dose					
First date taken					
Date taken last **					

Substances taken by recreation by the pregnant woman
Tobacco: cigarettes / day: Alcohol:

Illicit drugs:

Obstetric history

Pregnancy or previous pregnancies: • Yes • No

If the answer is yes: number of pregnancies Number of deliveries at term:

Appendix 2. Format for Pregnancy Tracking (cont.)

Number of premature births: Number of abortions:

• Previous fetal / neonatal abnormalities ⇨ Specify:

• Complications during previous pregnancies ⇨ Specify:

Medical history of the pregnant woman

Date of filling:

First name:

* In case of dose modification during the study, specify the dates of the first and last dose of each dose of the study product.
** Report NA (Not Applicable) if it is in progress

Appendix 2: Format for Pregnancy Tracking (Cont.)

Protocol No.: Center No.: 2/2
Participant No.:

C - RESULT OF PREGNANCY

Complications of the mother

• High blood pressure: • Diabetes:
• Infection: • Other ⟹ Specify:

Other medications administered during pregnancy

First name					
Daily dose					
First date taken					
Date taken last					

Pregnancy monitoring (relevant examinations / biological results)

Result

• Live birth ⟹ Proceed with section D - NEONATO INFORMATION
• Spontaneous abortion / dead birth ⟹ Date (DD-MM-YYYY):
Were congenital anomalies detected? • No • Yes ⟹ Specify:

• Elective termination ⟹ Date (DD-MM-AA)

• Therapeutic termination ⟹ Date (DDMMAA):
Results of fetal tests and reason for termination:

D - NEONATO INFORMATION

Date of birth (DD-MM-YYYY): Gestational age at birth: weeks

Physical examination at birth:
• Dysmorphic features were not identified
• Minor anomalies ⟹ Specify:
• Major malformations
• Syndrome / diagnosis ⟹ Specify:
• Other important findings ⟹ Specify:
Apgar Ratings: 1min: 5min:

Finish date:

First name:

Appendix 3. Report Format of Serious Adverse Events

SOPHIA®

Excelencia en oftálmicos

REPORTE DE
EVENTO ADVERSO SERIO (EAS)

NO. DE PROTOCOLO:		☐ INICIAL
NO. EVENTO ADVERSO SERIO:		☐SEGUIMIENTO

DATOS DEL CENTRO

NO. DE SITIO:		NOMBRE DEL INVESTIGADOR PRINCIPAL:	
DIRECCIÓN:		CIUDAD/PAÍS:	
TELÉFONO:		FAX:	
NOMBRE DE QUIEN REPORTA EL EAS:			

DATOS DEL SUJETO

NO. DE SUJETO:		INICIALES:		FECHA DE NACIMIENTO: ___/__/____ (DD/MM/AAAA)			
SEXO: ☐MASCULINO ☐FEMENINO		RAZA:		PESO (Kg):		ESTATURA (m):	

EVENTO ADVERSO SERIO. *Favor de llenar el formato de EA en el FCR.*

FECHA EN QUE OCURRIÓ EL EAS: ___/__/____ (DD/MM/AAAA)	**FECHA EN QUE EL INVESTIGADOR PRINCIPAL TUVO CONOCIMIENTO DEL EAS:** ___/__/____ (DD/MM/AAAA)
DIAGNÓSTICO:	**EXÁMENES DE LABORATORIO** (Fecha, prueba, resultados, unidades):
SIGNOS Y SÍNTOMAS:	**EXÁMENES DE GABINETE** (Fecha, prueba, resultados, unidades): **HISTORIA CLÍNICA:**
FECHA DE INICIO: ___/__/____ (DD/MM/AAAA)	**FECHA DE TÉRMINO:** ___/__/____ (DD/MM/AAAA)
CRITERIOS DE SERIEDAD: ☐MUERTE FECHA: ___/__/____ (DD/MM/AAAA) AUTOPSIA: ☐NO ☐SI ☐ DESCONOCIDO ☐HOSPITALIZACIÓN FECHA: ___/__/____ (DD/MM/AAAA) ALTA HOSPITALARIA: ☐NO ☐ SI. FECHA: ___/__/____ (DD/MM/AAAA) ☐CLÍNICAMENTE IMPORTANTE ☐RIESGO DE VIDA ☐DISCAPACIDAD/INCAPACIDAD ☐ ANORMALIDAD CONGÉNITA ☐ OTRO EVENTO SERIO: ☐ SOBREDOSIS ☐ EMBARAZO ☐OTRO EVENTO ADVERSO MENCIONADO EN EL PROTOCOLO	**RELACIÓN CON EL MEDICAMENTO DE ESTUDIO:** ☐NO ☐ PROBABLE ☐FALTA DE EFICACIA DEL MEDICAMENTO DE ESTUDIO ☐POSTERIOR A LA SUSPENSIÓN DEL MEDICAMENTO ☐RELACIONADO. ESPECIFIQUE: ☐TIEMPO DE INICIO SUGESTIVO ☐EFECTO RECONOCIDO ☐EFECTO CONOCIDO DEL MEDICAMENTO ☐ SIN RELACIÓN CON MEDICAMENTOS CONCOMITANTES ☐ SIN FACTOR DE CONFUSIÓN ☐OTRA RAZÓN. ESPECIFIQUE: _____ **RESOLUCIÓN DE EAS:** ☐RESUELTO. FECHA: ___/__/____ (DD/MM/AAAA) ☐RESUELTO CON SECUELAS. FECHA: ___/__/____ (DD/MM/AAAA) ☐RESOLVIÉNDOSE ☐NO RESUELTO ☐FATAL
DESCRIPCIÓN Y MANEJO DEL EAS (*Favor llenar formato de tratamiento concomitante):* _____ _____	

Appendix 3: Report Format of Serious Adverse Events (Cont.)

Excelencia en oftálmicos

REPORTE DE EVENTO ADVERSO SERIO (EAS)

MEDICAMENTO DE ESTUDIO	
MEDIDAS TOMADAS CON EL MEDICAMENTO DE ESTUDIO EN RELACIÓN AL EAS: ☐ LA DOSIS NO CAMBIÓ ☐ LA DOSIS INCREMENTÓ ☐ LA DOSIS SE REDUJO ☐ TEMPORALMENTE INTERRUMPIDO ☐ INTERRUPCIÓN DEL MEDICAMENTO ☐ NO APLICA	**TIPO DE MEDICAMENTO:** ☐ CIEGO ☐ ETIQUETA ABIERTA **ADMINISTRACIÓN DE PRIMERA DOSIS:** FECHA: ___ /__ / ____ (dd/mmm/aa)
INFORMACIÓN DEL MEDICAMENTO DE ESTUDIO DOSIS ADMINISTRADA CUANDO OCURRIÓ EL EA: _____ FECHA DE ÚLTIMA DOSIS ADMINISTRADA: FECHA: ___ /__ / ____ (dd/mmm/aa)	
SI FUE INTERRUMPIDO TEMPORALMENTE EL MEDICAMENTO DE ESTUDIO: FECHA DE INTERRUPCIÓN: FECHA: ___ /__ / ____ (dd/mmm/aa) FECHA DE REINICIO: FECHA: ___ /__ / ____ (dd/mmm/aa)	
SI SE SUSPENDIÓ EL MEDICAMENTO DE ESTUDIO: SI EL MEDICAMENTO SE ADMINISTRÓ NUEVAMENTE, ¿EL EA OCURRIÓ NUEVAMENTE? ☐NO ☐SI ☐NO APLICA SI LA RESPUESTA ES SÍ, ESPECIFIQUE LA DOSIS DE CON LA QUE REINICIÓ EL TRATAMIENTO:	
NARRATIVA DE CASO (NARRATIVA DETALLADA DEL EVENTO ADVERSO SERIO):	

NOMBRE/PUESTO: _____ **FIRMA:** _____
FECHA: ___/___/_____ (dd/mmm/aa)

Appendix 4. Medication Inventory and Accounting Format

SOPHIA
Excelencia en oftálmicos

INVENTARIO Y CONTABILIDAD DEL MEDICAMENTO

NO. DE ESTUDIO:	
INVESTIGADOR PRINCIPAL:	
MEDICAMENTO DE ESTUDIO:	

No. DE MEDICAMENTO DE ESTUDIO	No. DE LOTE	No. DE SUJETO	FECHA DE ENTREGA (DD/MM/AAAA)	No. DE FRASCOS ENTREGADOS	ENTREGADO POR: (Iniciales)	FECHA DE DEVOLUCIÓN (DD/MM/AAAA)	NO. DE FRASCOS DEVUELTOS	RECIBIDO POR (Iniciales):	VERIFICACIÓN	
									Iniciales	(DD/MM/AAAA)
									Iniciales	(DD/MM/AAAA)
									Iniciales	(DD/MM/AAAA)
									Iniciales	(DD/MM/AAAA)
									Iniciales	(DD/MM/AAAA)
									Iniciales	(DD/MM/AAAA)
									Iniciales	(DD/MM/AAAA)
									Iniciales	(DD/MM/AAAA)
									Iniciales	(DD/MM/AAAA)
									Iniciales	(DD/MM/AAAA)
									Iniciales	(DD/MM/AAAA)
									Iniciales	(DD/MM/AAAA)
									Iniciales	(DD/MM/AAAA)
									Iniciales	(DD/MM/AAAA)
									Iniciales	(DD/MM/AAAA)

COMENTARIOS : ____

____

____

INVESTIGADOR PRINCIPAL	MONITOR CLÍNICO
FIRMA:	FIRMA:
FECHA: (DD/MM/AAAA)	FECHA: (DD/MM/AAAA)

Appendix. 5 Humidity and temperature record of medication for clinical studies.

LABORATORIOS SOPHIA S.A DE C.V

REGISTRO DE HUMEDAD Y TEMPERATURA DE MEDICAMENTO PARA ESTUDIOS CLINICOS

NO DE PROTOCOLO			
PERIODO DE REGISTRO (dd/mmm/aa – dd/mmm/aa)			
MEDICAMENTO		LOTE / CAD	
UBICACIÓN DEL MEDICAMENTO		CÓDIGO SAP DEL DATA LOGGER	
*TEMPERATURA PROGRAMADA °C		*HUMEDAD PROGRAMADA %	

FECHA (dd/mmm/aa)	HORA (24 h)	TEMPERATURA (°C)	HUMEDAD (%)	VALIDADO (iniciales)

*Aplica cuando el medicamento se encuentre dentro de la cámara climática

Observaciones_____

Tiempo de resguardo: 10 años Lugar: Gaveta de Investigación Clínica Responsable: Investigación Clínica
Código: FRG-DD0110 Rev. 1

34. REFERENCES

i. Diamant JI, Hwang DG. Therapy for bacterial conjunctivitis. *Ophthalmol Clin North Am*. 1999;12(1):15–20.

ii. Mueller JB, McStay CM. Ocular infection and inflammation. Emerg Med Clin North Am. 2008 Feb;26(1):57-72, vi. Review

iii. Ramesh S, Ramakrishnan R, Bharathi MJ, Amuthan M, Viswanathan S. Prevalence of bacterial pathogens causing ocular infections in South India. Indian J Pathol Microbiol. 2010 Apr-Jun;53(2):281-6.

iv. Data on File. Laboratorios Sophia, S.A. de C.V.

v. Data on File. Laboratorios Sophia, S.A. de C.V.

vi. Data on file. Laboratorios Sophia, S.A. de C.V.

vii. The Institute for Eye Research Scale. Referida a partir de C.C.L.R.U. Centre for Contact Lens Research Unit.

viii. Assessment of musculoskeletal toxicity 5 years after therapy with levofloxacin. Bradley JS et al. Pediatrics. 2014 Jul;134(1):e146-53. doi: 10.1542/peds.2013-3636. Epub 2014 Jun 2.

ix. Gatifloxacin, moxifloxacin, and balofloxacin resistance due to mutations in the gyrA and parC genes of Staphylococcus epidermidis strains isolated from patients with endophthalmitis, corneal ulcers and conjunctivitis. Betanzos-Cabrera et al. Ophthalmic Res. 2009;42(1):43-8. doi: 10.1159/000219684. Epub 2009 May 28

x. Wu X. et al. Prophylactic effect of topical fluoroquinolones in a rabbit model of Staphylococcus aureus endophthalmitis. J Ocul Pharmacol Ther. 2012 Apr; 28(2):186-93. doi:10.1089/jop.2011.0136. Epub 2011 Nov 11.

xi. Estimate of the direct and indirect annual cost of bacterial conjunctivitis in the United States. *BMC Ophthalmol*. 2009;9:13.

xii. Udeh BL, Schneider JE, Ohsfeldt RL. Cost effectiveness of a point-of-care test for adenoviral conjunctivitis. *Am J Med Sci*. 2008;336(3):254-264.

Shields T, Sloane PD. A comparison of eye problems in primary care and ophthalmology practices. *FamMed*. 1991;23 (7):544-546.

i. Amir A. Conjunctivitis a Systematic Review of Diagnosis and Treatment, JAMA 2013; 310, (16).

ii. American Academy of Ophthalmology; Cornea/External Disease Panel. *Preferred Practice Pattern Guidelines, Ed. Elsevier 2011: Conjunctivitis-Limited Revision.* San Francisco, CA: American Academy of Ophthalmology.

iii. *Høvding G. Acute bacterial conjunctivitis. Acta Ophthalmol. 2008;86 (1):5-17.*

iv. *Bielory BP, O'Brien TP, Bielory L. Management of seasonal allergic conjunctivitis: guide to therapy. Acta Ophthalmol. 2012;90 (5):399-407.*