Excelencia en oftálmicos

Zebesten ® (Bromfenac 0.09 %) efficacy and safety on inflammation of the conjunctival surface in subjects with grade I-III Pterygium vs placebo

Drug Product Code:	PRO-155
Study Drug:	Bromfenac 0.09 %
Therapeutic Indication:	Ophthalmic non-steroid anti-inflammatory
Development Phase:	Phase IV
Protocol Code:	SOPH155-0415/IV
Sponsor:	Laboratorios Sophia, S.A. de C.V.
Version: Date:	2 June 2016

1. INDEX

2. GLOSSARY

ABC	Area under the curve
AINE	Non-steroid anti-inflammatory
BAK	Benzalkonium chloride
Cmax	Maximum concentration
COX1	Cyclooxygenase 1
COX2	Cyclooxygenase 2
FDA	Food and Drug Administration
HFB	Hydroxyfluoroprednisolone
PGE2	Prostaglandin E2
PIO	Intraocular pressure
T1/2	Half life
Tmax	Time to reach the maximum concentration
OSDI	Ocular Surface Disease Index
TRL	Tear film breakup time
mmHg	Millimeter of mercury
FRC	Case report form
UV rays	Ultraviolet rays
LOCS III	Lens Opacities Classification System

3. BACKGROUND

The manipulation of the ocular structures during surgery, infectious phenomena, trauma in the ocular globe, allergies, etc., are events that cause an inflammatory cascade, due to the release of a large number of chemical mediators, after cell lysis, and induce the expression of cyclooxygenase 1 and 2 (COX1 and 2). The COX-2 products are prostaglandins, which have different effects on the damaged tissue (see figure 1).

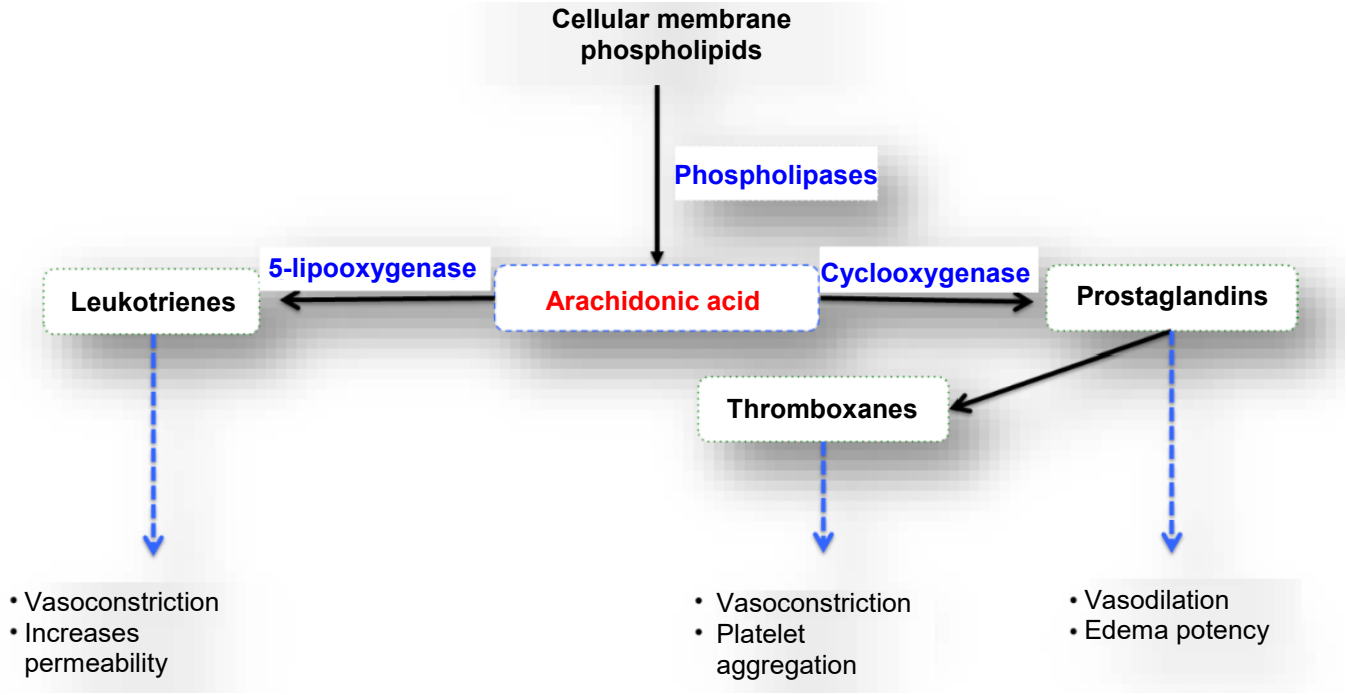


Figure 1. The loss of integrity of the cellular membrane as consequence of the surgical manipulation of the ocular structures causes an increase in the bioavailability of membrane phospholipids, which are biotransformed by phospholipids into arachidonic acid. 5-lipooxygenase acts on the arachidonic acid and synthesizes leukotrienes, which increase the vascular permeability and vasoconstriction. Cyclooxygenases, upon acting on the arachidonic acid, synthesize prostaglandins and thromboxanes, which

Prostaglandins cause the filtration of fluid from the perifoveal capillary networks to the extracellular space of the macular region. Some of the main ocular signs and symptoms in which prostaglandins have been involved are inflammation, pain, conjunctival hyperemia, posterior synechiae, opacity of the posterior capsule, changes in ocular tension, glaucoma, and cystic macular edema.

Considering the role taken on by the inflammation in the development of this process, the use of two groups of drugs to prevent the deteriorating effects of its onset has been proposed:

1. Non-steroid anti-inflammatory agents that directly inhibit COX1 and COX2 enzymes.
2. Topical corticoids that act on the A2 phospholipase level, inhibiting the release of prostaglandins.

Non-steroid anti-inflammatories present higher safety in chronic dosing schedules compared to corticoid anti-inflammatories; however, in terms of anti-inflammatory potency they are superior to the latter.

Currently, there are four FDA-approved ophthalmic AINES for treatment of inflammation following cataract surgery: diclofenac 0.1 % solution, ketorolac 0.5 % suspension, nepafenac 0.1 % suspension, and bromfenac 0.09 % solution. Bromfenac is a non-steroid anti-inflammatory byproduct of phenylacetic acid related to diclofenac. Its unique chemical structure confers high lipophilicity, quick penetration, and higher immediate and sustained bioavailability in all ocular tissue.[1]

Bromfenac 0.9 mg/ mL eyewash is intended for treating post-surgery ocular inflammation after the extraction of cataracts in adults, based on good preclinical and clinical results.

The ophthalmic bromfenac 0.09 % solution has demonstrated its safety and efficacy as a topical ocular AINE, specifically, in a controlled inflammation model such as surgical trauma in the anterior chamber (phacoemulsification); said study demonstrated its efficacy in reducing the swelling of different structures in the post-surgery period, such as corneal edema, conjunctival hyperemia, chemosis, intracameral cellularity, and retinal edema.[2]

In comparison with other AINES available on the market, it was also demonstrated that its efficacy is similar and its tolerability is satisfactory as well as its safety.

Currently, thanks to the diversity of available drug products for the treatment of ocular inflammation, we as ophthalmologists can be more precise in the treatment scheme granted to the subject; that is to say, we can choose, depending on the gravity of the inflammatory symptoms, the anti-inflammatory with the desired effect and the lowest number of possible adverse events.

Chronic pathologies with an inflammatory component, such as Pterygium, occur with recurrent aggravations in which symptoms and signs that, while they may not permanently affect the structure of the eye, do diminish the visual quality, are exacerbated.

The ideal AINE is that which reaches therapeutic concentrations in the anterior and posterior segment levels, has an excellent anti-inflammatory activity, is analgesic, safe, and well-tolerated. Different types of AINES are formulated and sold for their use in ophthalmology: indomethacin 1 %, diclofenac 0.1 %, ketorolac 0.5 %, nepafenac 0.1 %, and bromfenac 0.09 %; among these the most innovative are nepafenac and bromfenac. All are organic acids except nepafenac, which is an amide analog and is formulated as a suspension instead of a solution. All of them reach therapeutic concentrations in the aqueous humor, iris, and ciliary body. However, most are not able to reach the posterior pole. Only the next-generation AINES – bromfenac and nepafenac – are able to reach therapeutic concentrations in the posterior segment and are the most inhibitory for COX2, which has the highest expression at the retina level.

4. JUSTIFICATION

Steroids are considered the “golden standard” for treating inflammation and may cause multiple adverse events such as: increase in intraocular pressure, susceptibility to infection, delay in the healing of corneal injuries, glaucoma, and posterior subcapsular cataracts, among others; for which reason AINEs represent a safer alternative for the treatment of long-term post-surgery inflammation.

Most AINEs are weak acids and are ionized with the tear pH, limiting their permeability towards the anionic cornea. Due to their pharmacological characteristics, AINES must be combined with insoluble cationically-charged complexes, as is the case with benzalkonium chloride, to facilitate their penetration and solubility.

Currently, four topical non-steroid anti-inflammatories are approved by the Food and Drug Administration (FDA) for the treatment of inflammation: diclofenac 0.1 %, ketorolac 0.5 %, nepafenac 0.1 %, and bromfenac 0.09 %. Of these, bromfenac is the only one approved at a dosage of twice a day and which is currently used to treat post-surgery inflammation, blepharitis, conjunctivitis, and escleritis.[3]

The use of topical ocular AINES was limited to their chronic use, which also presents adverse events such as corneal abrasion, tear film dysfunction, or even corneal melting. Recent evidence regarding bromfenac being used for 3 weeks indicates that its dosage of twice a day appears to be safe for the ocular surface.

There is a report by Frucht J, et al. which compares the use of indomethacin 0.1 % versus dexamethasone 0.1 % to handle ocular signs and symptoms associated with Pterygium and Pinguecula, under a dosing schedule of 1 drop 6 times a day for 3 days, followed by 1 drop 4 times a day for 11 days for both drug products.

Although the authors assert that both drug products are efficient and safe, the dosing schedule entails the frequent administration of the drug products, which represents an increase in the risk of the subject's failure to follow the treatment, for which reason we propose bromfenac as a useful drug in the control of clinical signs such as hyperemia in an inflammatory disease model that requires a drug with less adverse events and a lower frequency of administration that other AINES.[4]

5. PURPOSES

5.1 General purpose:

Evaluate the efficacy and safety of Zebesten ® (bromfenac 0.09 %) ophthalmic solution in the treatment of conjunctival hyperemia and ocular surface inflammation in a clinical grade I to III Pterygium model.

5.1.1 Specific purpose 1:

Evaluate the efficacy of Zebesten ® in the control of conjunctival hyperemia in subjects with Pterygium through its qualitative assessment through the validated analogous scale of the cornea unit and contact lenses of the University of South Wales.[5]

5.1.2 Specific objective 2:

Evaluate the safety of Zebesten ® through the evaluation of the corneal and conjunctival epithelium through fluorescein and lissamine green staining, the measurement of intraocular pressure, and the Tear film breakup time.

6. SUMMARY

Drug Product Code:	PRO155
Study Drug:	BROMPHENAC 0.09 % OPHTHALMIC SOLUTION
Therapeutic Indication:	Ocular non-steroid anti-inflammatory
Protocol Code:	SOPH155-0415/IV
Sponsor:	Laboratorios Sophia, S.A. de C.V.
Version: Date:	2 June 2016
Study Title:	Evaluation of the efficacy and safety of Zebesten ® (Bromfenac 0.09 %) ophthalmic solution on the treatment of conjunctival hyperemia and inflammation of the ocular surface in a clinical grade I-III Pterygium model
Study Design:	Controlled, randomized, double blind, masked clinical study, comparing the safety and efficacy of Zebesten ® for the treatment of conjunctival hyperemia in grade I to III Pterygium compared to placebo

Variables to Evaluate:	Primary outcome
	- Conjunctival hyperemia
	- Tear film breakup time
	- Adverse events
	Secondary outcome
	- Ocular symptomatology
	  o Burning sensation
	  o Foreign body sensation
	  o Photophobia
	- OSDI questionnaire scoring
	- Evaluation of epithelial defects with fluorescent dye (cornea and conjunctival)
	- Evaluation of epithelial defects with lissamine green dye (cornea and conjunctival)
	- Visual capacity
	- Intraocular pressure

Groups	Subjects diagnosed with grade I to III Pterygium will be included in 2 study groups. Group 1 will receive Zebesten ® ophthalmic solution together with Na hyaluronate. Group 2 will receive placebo plus Na hyaluronate.

7. MATERIALS AND METHODS

7.1 Study design

Multicentric, controlled, randomized, double blind clinical study, which compares the safety and efficacy of Zebesten ® for the treatment of conjunctival hyperemia in grade I to III Pterygium compared to placebo.

7.2 Sample

The total population will be 166 cases, which will be randomly included and distributed in 2 study groups. Both with diagnosis of grade I to III Pterygium.

Subjects with bilateral Pterygium, in which both eyes meet the selection criteria, can participate with both eyes, taking each eye as one case.
Group 1 will receive Zebesten ® ophthalmic solution together with Na hyaluronate.
Group 2 will receive placebo (formulation with no drug substance) together with Na hyaluronate.

7.3 Blinding

The double blind study is a procedure in which the subject and treating physician do not know which study subjects were assigned to which treatment group. To achieve blind conditions for the drug product, the investigational drug product and the placebo are both packaged in identical bottles with the same legends on the label. The blinding codes are kept by an individual uninvolved in the study designated by the sponsor. The codes are also available in the research center (completely sealed), so the Researcher may refer to them should a subject present a serious adverse event, after being authorized by the study sponsor. The blind conditions are strictly upheld during the data analysis.

7.4 Pharmacological approach

The pharmacological approach consists in the instillation of the ophthalmic solution in the bottom of the conjunctival sac during the waking period in any of the following study groups:

- Group 1:
    - Sodium hyaluronate 0.4 % [Lagricel Ofteno ®] 1 drop 3 times a day in the waking period in the bottom of the conjunctival sac (the following application method is recommended: start: 7:00 ± 1 h; following: 15:00 ± 1 h; end: 19:00 ± 1 h) for 20 days
    - Bromphenac 0.09 % [Zebesten ®] 1 drop 2 times a day in the waking period in the bottom of the conjunctival sac (the following application method is recommended: start: 7:15 ± 1 h; end: 19:15 ± 1 h) for 20 days
- Group 2:
    - Sodium hyaluronate 0.4 % [Lagricel Ofteno ®] 1 drop 3 times a day in the waking period in the bottom of the conjunctival sac (the following application method is recommended: start: 7:00 ± 1 h; following: 15:00 ± 1 h; end: 19:00 ± 1 h) for 20 days
    - Placebo 1 drop 2 times a day in the waking period in the bottom of the conjunctival sac (the following application method is recommended: start: 7:15 ± 1 h; end: 19:15 ± 1 h) for 20 days

7.5 Distribution into treatment groups

The subjects are distributed into the study groups on the visit indicated in the study timetable, through simple 1:1 randomization, closed envelope technique, through a specialized software that uses random number tables to achieve a uniform distribution in each of the treatment groups.

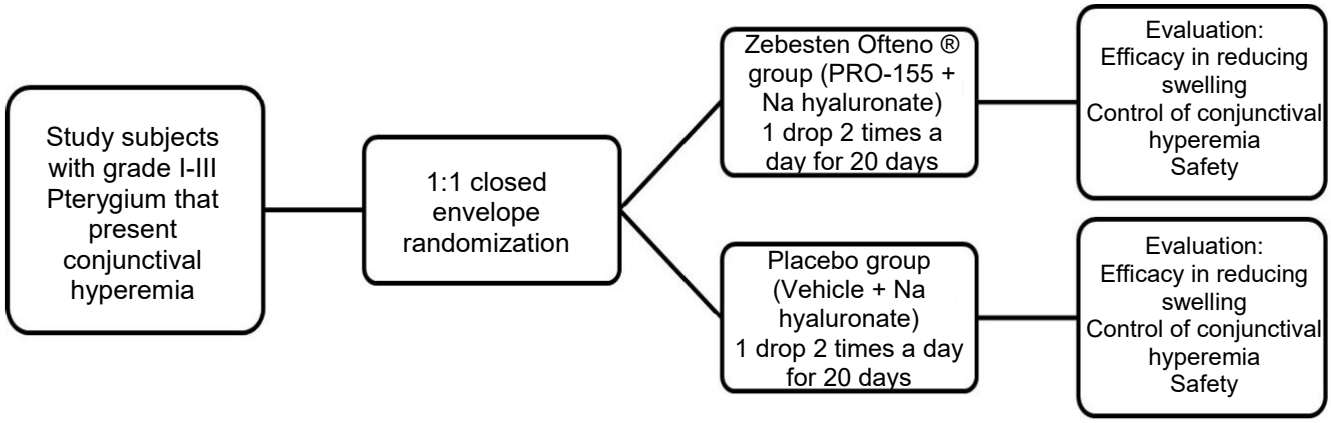


Fig. 1. DISTRIBUTION OF STUDY SUBJECTS. Shows the randomized distribution of the study subjects in the research protocol using a computing system through the closed envelope technique.

7.6 Ethical considerations

This protocol follows the Good Clinical Practices (GCP) and the principles originated in the 18th Medical Assembly of Helsinki, Finland in 1964 and the modifications carried out in Tokyo, Japan in 1975, Venice, Italy in 1983, Hong Kong in 1989, and the 48th General Assembly in Somerset West, South Africa in 1996. 59th General Assembly in Seoul, South Korea, 2008, 64th General Assembly in Fortaleza, Brazil, 2013, where the medical investigation (clinical investigation) was discussed.

Also, the protocol follows the specifications of the General Health Law of Mexico as regards research in the healthcare field, which as per article 17 considers this study, under subsection III, as having a risk higher than the minimum and the administration of drugs. Under said legal framework, the integrity of the individuals, their life, and their safety is respected.

We also follow National Mexican Standard NOM-012-SSA3-2012, which establishes the criteria to carry out investigational projects in the field of human healthcare.

7.6.1 Research Ethics Committee

The main researcher shall submit the study protocol, informed consent, researcher's manual, materials to be handed to the subjects, recruiting materials, and necessary documents to an investigational ethics committee approved by the National Bioethics Commission and currently registered before the Federal Commission for Protection against Sanitary Risks (COFEPRIS), as per local requirements.

The study shall not be initiated in the research center without prior approval of the relevant investigational ethics committees and research committee, compliance with the local regulatory requirements, signing of the confidentiality agreements, economic proposal, and signing of the contracts of each of the main medical researchers.

7.6.1.1 Information for subjects and informed consent form

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

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

The main researcher (or a physician who is a member of the site's research team, duly specified by the main researcher as far as delegation of responsibility) shall provide the possible participant with all the information regarding the study characteristics, potential risks, benefits, objectives, and procedures. This information shall be communicated in a language the subject can comprehend, and the subject will be informed that they have the right to interrupt their participation in the study at any time,

without it affecting the relationship with the researcher and/ or their future support. The informed consent shall be given to the possible participant for their consideration, and they must be given enough time to analyze each of the previously mentioned aspects. Should they have any doubts, these must be clarified by the person responsible for obtaining the informed consent. Once the participant agrees to participate in the study, they must sign and date the informed consent letter in the presence of two witnesses that may or may not have a relationship with the study subject, who shall participate during the informed consent process and sign affirming that the process was carried out before any study procedure, that the study information was clearly explained, and that doubts (if any) were clarified.

If a subject is illiterate, their agreement shall be indicated with their fingerprint, and should the subject not be able to grant their adequate written informed consent, a “legally authorized” representative of the subject may provide said consent on behalf of the subject, as per applicable laws and regulations.

The main researcher must also sign and date this consent.

The informed consent must be signed in duplicate by all involved parties and two witnesses. A copy shall be archived in the researcher’s files and another shall be provided to the participant. The researcher must document the date on which the informed consent was signed within the subject’s medical record.

After having obtained the informed consent, a unique identification number shall be assigned to the subject, which will be used during the entirety of the study for the purpose of identification of the participants.

7.6.2 Modifications to the “informed consent”

Any change to the “informed consent” constitutes a modification to this document and must be presented for approval before the Research Ethics Committees and, if applicable, before the competent authorities.

In the modification, a copy of the new version shall be included in the country's language or languages. Said modifications may be implemented only after having obtained written approval of the Research Ethics Committee and having complied with the local regulatory requirements, except for modifications required to eliminate an immediate danger for the study subjects.

Each subject affected by the modification must fill out, date, and sign two original copies of the new version. The subject will receive a signed original copy of the modification and the researcher will keep the second original copy.

7.7 Confidentiality – use of information

All documents and information provided to the researcher by the sponsor are strictly confidential. The researcher expressly agrees that the information regarding their professional and clinical experience provided to the sponsor physically and stored in the computer are only for use related to their activities with the clinical study sponsor, according to the Good Clinical Practices. The researcher accepts that they and the members of their team will only use the information within the study framework to carry out the protocol. This agreement is obligatory while the confidential information has not been disseminated to the public by the sponsor. The clinical study protocol provided to the researcher may be used by them and their colleagues to obtain the subjects' informed consent for the study. The clinical study protocol, as with any information taken from it, shall not be revealed to other parties without the sponsor's written authorization.

The researcher shall not reveal any information without the prior written consent of Laboratorios Sophia S.A. de C.V., except to representatives of the competent authorities and only upon their request. In this last case, the researcher is required to inform Laboratorios Sophia S.A. de C.V., before revealing the information to the authorities. The researcher shall fill out and maintain a subject screening logbook, as well as the identification and recruitment listing of each of the subjects.

The researcher agrees to grant access to the site to the auditor and/ or representatives of the competent authorities. The information shall be handled in compliance with trade confidentiality.

The subject screening logbook shall begin to be filled out starting from the moment in which the researcher determines that a subject can participate in the study (through an assessment of the subject's medical record during a visit or review of the medical file), once the research center is opened.

7.8 Organization of the center

All individuals to whom the researcher delegates part of the follow-up of the study under their responsibility (co-researcher, sub-researcher, nurse) and any other person participating in this center's study (cardiologist, pharmacist, …) must appear in the delegation of responsibility form. This document must be submitted at the start of the study and updated if there are changes in any of the individuals participating in the center's study.

8. STUDY DRUG PRODUCT

8.1 Codes, labelling, storage

The dropper bottles shall be issued in their primary and secondary packaging to the various participating research centers, identified with the protocol code, under the specific dosage form and contents in milliliters, as shown in the following image, among others:

8.1.1 Primary packaging

PRO 155 Ophthalmic solution Content: 5 mL	**CAUTION: STUDY DRUG**	**FOR RESEARCH**	**PURPOSES ONLY**	Subject No.	Initials:____	ME No.:	Batch: Cad:

8.1.2 Secondary packaging

Drug products No. Batch: Expiration date:	**0.09** **Protocol: SOPH155-0415/IV** **Subject No.:_____** **Subject initials:_____** **Researcher:_____** Ophthalmic route. Give as per the protocol. Storage at room temperature at not more than 30 ºC. Do not freeze. Sample for clinical research. Investigational drug product Not for sale. Keep out of reach of children. **"Return this container and unused drug products"** Laboratorios Sophia S.A. de C.V. Av. Paseo del Norte No. 5255, Col. Guadalajara Technology Park C.P. 45010. Zapopan, Jalisco, México. Tel. +52 (33) 3001-4200. Content: 1 bottle	REMOVE LABEL PRO-155 Protocol: SOPH155-0415/IV Drug products No.:_____ Subject initials:_____ Researcher:_____ PRO-155 Protocol: SOPH155-0415/IV Drug products No.:_____ Subject initials:_____ Researcher:_____

8.2 Study Drug Product

- The formulation of Zebesten® is composed of the following active agent: Bromfenac 0.09 mg/mL, and inactive agents: povidone, boric acid, sodium borate decahydrate, sodium sulfite, polysorbate 80, disodium edetate dihydrate, benzalkonium chloride, sodium hydroxide, hydrochloric acid, water for injection. It is dispensed in low-density polyethylene dropper bottles for multidose administration as a 5 mL ophthalmic solution. Sanitary record: 108M2014.
- Drug product Lagricel Ofteno® is composed of the following active agent: sodium hyaluronate 0.4 mg (4 mg/mL). It is dispensed in a dropper bottle (with a container closure system that allows to preserve the solution) for unit-dose administration as a 0.5 mL preservative-free ophthalmic solution. Sanitary record: 0208C99 SSA
- Placebo is composed of Zebesten® formulation additives: povidone, boric acid, sodium borate decahydrate, sodium sulfite, polysorbate 80, disodium edetate dihydrate, benzalkonium chloride, sodium hydroxide, hydrochloric acid, water for injection. It is dispensed in low-density polyethylene dropper bottles for multidose administration as a 5 mL ophthalmic solution.

8.3 Study Drug Handling

Previously weighted and packed drug products will be sent from the storage center located at Laboratorios Sophia S.A. de C.V.

The main researcher at the research center is responsible of handling the study drug, including:

- Receipt and storage of the study drug (ME). The receipt of the study drug will be acknowledged by signature and return of the relevant form. The study drug must be kept in a safe area with restricted access. Some special

storage conditions are requested, such as storage at room temperature ≤ 30 ºC, do not freeze, and no refrigeration required. The researcher must have a thermohygrometer that records:

- Current temperature
- Minimum temperature
- Maximum temperature
- Percentage of relative humidity

- The main researcher or designated pharmacist must read daily the 4 parameters indicated and record them in the corresponding documentation.

-The expiration date will appear on each box and label.

- The researcher or pharmacist of the research center must use the provided treatment only for subjects participating in the study.

- The study drug must be kept locked and with restricted access throughout the period it remains at the research center.

- Study drug count:

- The researcher and/or pharmacist of the research center and/or a designated team member must fill on real time all the documents provided by the sponsor for the study drug hamdling.

The study monitor will verify regularly the study drug handling and count.

- At the end of the study, the researcher and study monitor will make a final inventory of the drug products and will record it in the relevant form.

After counting the amount of remaining study drug products returned in every container, the study monitor will pick them for storage and subsequent destruction.

Any defect or deterioration of the study drug or their packaging must be notified to the study monitor. The researcher will notify the monitor all the complaints received from the subjects.

If the study drug is returned to the sponsor before expected (batch withdrawal), the sponsor will prepare an informative letter addressed to the researcher and/or pharmacist of the research center. Local persons responsible of the study will sent this letter to each one of the study centers. When receiving the letter, the researcher and/or pharmacist will identify the subjects that own the treatment when the incident is observed and will contact them immediately. The monitor will organize the return of the study drug to destroy it.

9. STUDY SCHEDULE

Procedure	SCHEDULE (window periods)				
	Baseline visit	Visit 1	Visit 2	Final visit	Follow-up call
	Day 1	Day 7 (± 2)	Day 15 (± 2)	Day 21 (± 2)	Day 36 (± 2)
Eligibility criteria (inclusion and exclusion)	X				
Pregnancy test (if applicable)	X			X	
Informed consent signature	X				
General and ophthalmic medical record	X				
Ocular symptomatology (A, B, C)	X	X	X	X	
OSDI questionnaire	X	X	X	X	
Subject code assignment	X				
Visual capacity	X	X	X	X	
Previous biomicroscopy (D)	X	X	X	X	
Testing of epithelial defects with fluorescein dye	X	X	X	X	
Testing of epithelial defects with lissamine green dye	X	X	X	X	
Breakup time	X	X	X	X	
PIO measurement	X			X	
Posterior ophthalmoscopy under mydriasis	X			X	
Treatment delivery	X				
Start of drug application	X				
End of drug application				X[1]	
Drug return				X	
Subject diary submission	X				
Subject diary review		X	X	X	
Evaluation of adverse events		X	X	X	X
Evaluation of concomitant drug	X	X	X	X	
Follow-up call					X

9.1 Annotations to Activities Schedule:

A. Burning

B. Foreign body sensation

C. Photophobia

D. Includes testing of conjunctival hyperemia variable

[1] The application ends one day before to fulfill the 20 days indicated in the treatment.

10. DESCRIPTION OF THE PROCEDURES

10.1 General and Ophthalmic Medical Record

It refers to a systems review highlighting the medical and surgical history, indicating the start, evolution and, if applicable, the end of previous conditions.

List the drug products taken and the dates of the last dose; specify their administration route.

A general clinical examination will be performed, including vital signs (blood pressure, body temperature, breaths per minute and heart rate) and anthropometric parameters (weight, size, complexion).

Patients will be asked about previous, chronic or acute ocular conditions, specifying onset or diagnosis time, and their evolution.

If applicable, the optical correction devices used by the subject will be listed, such as frame glasses, contact lenses, magnifying glass, etc. Similarly, the evolution time and use period will be stated.

Then, topical drug products used in eyes and eye adnexa will be investigated. In the case of any systemic drug product directly related to a condition of the eyes or eye adnexa (eyelids, eye socket, lacrimal duct, glands, etc.), it must also be recorded in this section.

Any finding that prevents the protocol procedures from being carried out or the subject from remaining in the study must be recorded. Yes/ No must be indicated in the FRC. In the case of any finding, it must be specified.

It must also be recorded if the subject performs outdoor activities for more than 8 hours (Yes/ No) and if they perform activities in a place with air conditioning for more than 8 hours a day (Yes/ No).

The grade of pterygium must be recorded according to the above classification.

10.2 Pregnancy Test

A urine pregnancy test will be performed in the same facilities of the contracted research center, where the participant of the study will be provided with a home pregnancy test-type device for private use. The subject will be indicated to pour the urine on the absorbing end for 10 seconds, and then to place the included plastic cover and let it stand for 3 minutes on a flat surface with the results window facing upwards. It is important to mention that the device must not be moved during this period.

The result will appear after 3 to 15 minutes. A line will appear in the control window indicating that it is working correctly. Then, a pink line will appear in the results window. Its intensity may vary, but if it appears it indicates that pregnancy is very probable.

The test must be recorded in the FRC, indicating it was performed, the date and results (positive/ negative). If the test is not performed, the reason must be specified.

10.3 Ophthalmic Exploration

10.3.1. Visual Capacity Measurement

Basal visual acuity must be tested without using optical correction devices, using a Snellen card in a room with adequate natural or artificial lighting. The result must be documented in the form of a fraction according to the number of lines that the subject was able to read. This information will be reported as visual acuity.

Afterwards, the subject's visual acuity will be tested using the best optical refraction and it will also be recorded in the form of a fraction in the Snellen card. Both values will be reported for statistical purposes (LogMAR). A fraction conversion table is attached to LogMAR.

In the FRC, the result will be recorded as 20 / number for Snellen and as decimal for LogMAR.

- **Visual Examination Standardization**

- At a distance of 3 meters in a well-lit room the research subject will be evaluated as follows:

- This examination will be performed within the research center

- The subject will be asked to sit always at the same place and their visual acuity (AV) will be tested using the LogMAR chart. If this chart is not available, the conversion must be performed (Fig. 10.3.1.1). The research subject must keep both eyes open.

- The research subject must gently cover an eye with the occluder provided by Laboratorios Sophia S.A. de C.V., (all the research subjects must use the same occluder to cover their eye) while they read aloud the smallest line of letters they are able to see. This examination is performed in each eye, one at a time, starting with the right eye (OD).

- The physician must point to the line the research subject must read.

- The same steps are applied for the visual capacity test.

LogMAR	VAR	Snellen (m)	Decimal Snellen (ft)	
1.0	50	6/60	0.10	20/200
0.9	55	-	-	20/150
0.8	60	6/36	0.15	20/120
0.7	65	-	0.20	20/100
0.6	70	6/24	-	20/80
0.5	75	6/18	0.30	20/60
0.4	80	-	0.40	20/50
0.3	85	6/12	0.50	20/40
0.2	90	6/9	-	20/30
0.1	95	-	0.75	20/25
0.0	100	6/6	1.00	20/20
-0.1	105	6/5	-	20/15
-0.2	110	6/4	1.50	-
-0.3	115	6/3	2.00	20/10

Fig. No. 10.3.1.1. LogMAR conversion table

10.3.2 Previous Biomicroscopy

This test will be performed in consecutively from the eyelids and eyes adnexa to the ocular surface and anterior chamber. The following items must be tested:

- Description of eyelids, eyelashes and adnexa glands.
- Description of lid wiper, bulbar and fornix: in this item, the qualitative characteristics will be classified as follows.
- Conjunctival hyperemia:
    - Bulbar hyperemia: it will be compared to the images of Fig. 10.3.3.1, which shows different grades of venous turgor: very slight, slight, moderate and severe.

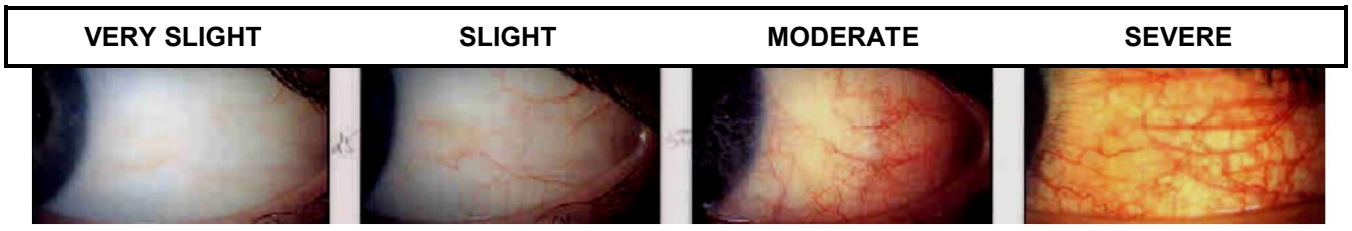


Fig. 10.3.3.1 [10]

- Tarsal hyperemia: similarly, tarsal hyperemia will be compared with the images shown in Fig. 10.3.3.2, which shows the venous turgor in the palpebral mucosa.
- Documentation in the FRC: the most severe hyperemia must be recorded.

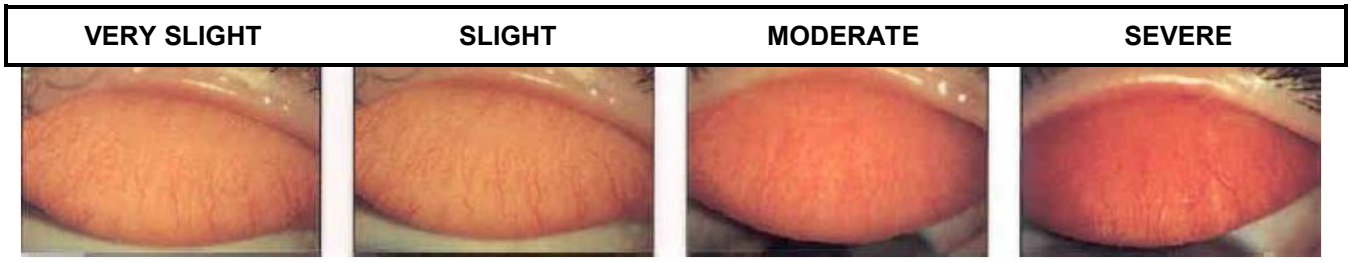
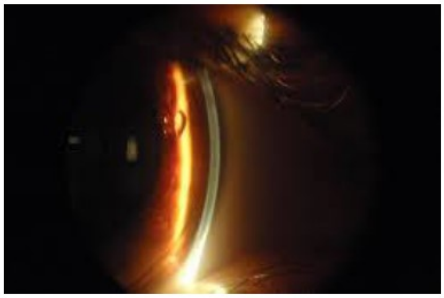


Fig. 10.3.3.2 [10]

10.3.2.1 Anterior Segment:

- The photometer and consensual pupilar reflexes must be reviewed, as well as the iris constitution, highlighting pathological aspects, such as inflammatory membranes, anterior and posterior synechiae, among others.
- The width of the anterior chamber will be qualitatively graded using the Van Herick technique, which consists of grading the space between the iris and posterior side of the cornea by subjective appreciation, locating the beam of light of a slit lamp in the external third of the anterior chamber:

Example: Van Herick II



- Lens: the items to be evaluated are the integrity of the anterior capsule of the lens and its composition characteristics, highlighting only pathological aspects, for example: pseudoexfoliation, pigment, synechiae, etc.

- Opacities: will be analyzed, if applicable, according to the LOCS II scale.

It will be recorded in FRC as normal/abnormal. If abnormal, it must be specified if this finding affects the protocol procedures and if it prevents the subject from remaining in the study.

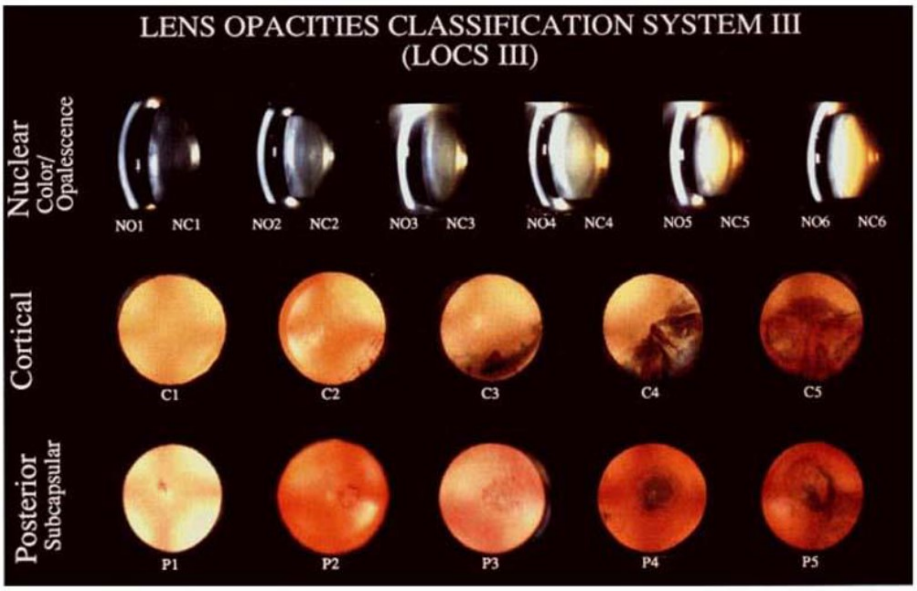


Image 2. LOCS III [6]

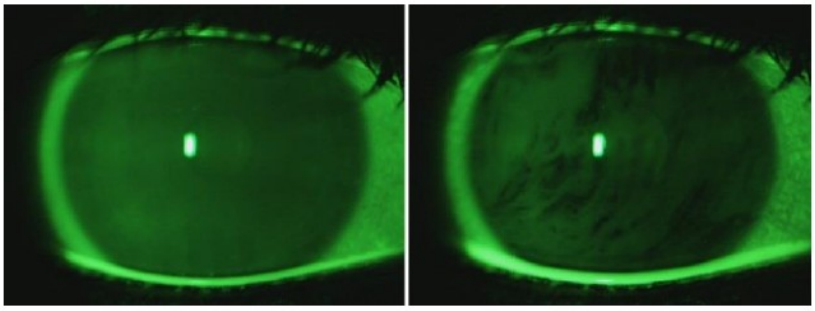
10.3.2.2 Fluorescein Dye

Sodium fluorescein dye dissolved in tetracaine will be used on the ocular surface (billiard conjunctiva and cornea). After staining the surface, the following explorations will be performed:

10.3.2.2.1 Tear Film Breakup Time

It will be measured after blinking once and the patient will be asked to not blink again until the tear film breaks on the cornea. If it is more than 10" it will be regarded as normal. The whole number value will be recorded on the FRC.

Example:

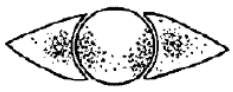


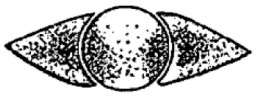
10.3.2.2.2 Epithelial Defects

After the TRL test, the grade of epithelial staining in the cornea and conjunctiva will be tested according to the Oxford University scale, as it has been shown to be the scale closest to the OSDI score.[7] The record in the FRC must correspond to this scale. It must be recorded in the FRC with the roman numeral corresponding to the grade.

10.3.2.3 Lissamine Green Dye

Lissamine green dye dissolved with tetracaine will be used on the ocular surface (bulbar conjunctive and cornea). Once the surface is stained, the cornea and conjunctive epithelium will be testes according to the Oxford University scale. It must be recorded in the FRC with the roman numeral corresponding to the grade.

Panel	Grade	Criteria
A 	0	Equal or less than panel A
B 	I	Equal or less than panel B, more than A
C 	II	Equal or less than panel C, more than B
D 	III	Equal or less than panel D, more than C

E 	IV	Equal or less than panel E, more than D
> E	V	More than panel E

10.3.3 Measurement of Intraocular Pressure

After testing the ocular surface using fluorescein dye, PIO will be measured using a Goldman tonometer and cobalt-blue filter.

The whole number value will be recorded in the FRC.

10.3.4 Posterior Segment Exploration

The posterior segment will be reviewed to verify that there are no pathological processes requiring attention and/or preventing the participation of the subject in the clinical trial.

The posterior segment and the rest of the retina will be explored under medicinal mydriasis, recording the following aspects:

1. Appearance of vitreous humor
2. Retina completely applied
3. Vascular alterations
4. Appearance of clinical macular area
5. Appearance of the foveolar area
6. Characteristics of the optical nerve
    a) Emergence of vessels
    a. Neuroretinal rim
    b. Cup-to-disc ratio expressed in decimals
7. Report any other clinical finding in the retina.

It must be reported in the FRC as normal/abnormal. If it is abnormal, it should be specified if this finding affects the protocol procedures preventing the subject from remaining in the study.
The optical nerve must be reported in decimals.

10.4 Ocular Symptomology

It refers to the enquiry performed by the researcher for the presence or absence of the following symptoms: burning, foreign body sensation and photophobia, related to pterygium. It must be recorded as present or absent. Symptomology directly related to the administration of the drug product must not be reported in this section. Post-instillation symptoms shall be recorded in the instrument “subject's diary”.

10.5 OSDI Questionnaire

It refers to the application of the OSDI questionnaire. The obtained score must be recorded. The score is obtained as follows:

$$OSDI = \frac{(score\ sum)25}{\#\ of\ answered\ questions}$$

10.6 Subject's Diary Submission and Review

During the baseline visit, the subject will be provided with the instrument “subject's diary” and it will be explained how to fill it out.

During the following visits, the completeness of the diary will be reviewed, and questions that might have arisen during its completion will be answered.

10.7 Adverse Events Evaluation

It refers to the evaluation performed by the main researcher for the presence of adverse events according to item 17. Adverse Events.

If the subject presents any adverse event it must be recorded in the file and FRC.

10.8 Evaluation of Concomitant Drugs

The main researcher will question the subject on the use of drug products other than those indicated in the protocol.

If the subject uses any other drug it will be documented in the file and FRC.

11. PROCEDURES TO BE PERFORMED ON EACH VISIT

The procedures to be performed on each visit are listed below. The study day on which the visit must be performed appears in brackets and the permitted window period in parentheses.

11.1 Baseline Visit

1. During this visit it will be evaluated if the subject meets the eligibility criteria.
2. First, the informed consent will be reviewed clarifying any doubt the subject wishes to review, and documenting in the clinical note the subject's possible questions and the answers given to them. This procedure will be performed strictly by the healthcare personnel, preferably by the main researcher.
    a. Afterwards, the informed consent will be signed, jointly with two witnesses (if applicable).
3. If applicable (female subject in reproductive age), pregnancy test.
4. The medical staff will generate a medical record based on the systems review of the subject, specifying signs and symptoms related to systemic inflammatory diseases. A complete ophthalmic medical record will be generated, including at least the items required in the case report form plus the items required by the usual medical record used for the first time in the subject's research center.
5. OSDI questionnaire will be applied.
6. Ocular symptomology enquiry.
7. Complete ophthalmic exploration, indicating pterygium.
8. Subject code designation (as per item 16. Identification Procedures).
9. Treatment deliverance (as per item 8. Study Drugs).
10. Start of the treatment.
11. Subject diary submission.
12. Concomitant drug products assessment.
13. Scheduling subsequent visits.

11.2 Visits 1 and 2 [Days 7 and 15 (±2 Days])

1. Ophthalmic physical exploration:
    a. Visual capacity testing
    b. Previous biomicroscopy
2. OSDI questionnaire application
3. Enquiry regarding ocular symptomology
4. Subject diary review
5. Adverse events evaluation
6. Concomitant drug products assessment

11.3 Final Visit [Day 21 (+2 Days)]

1. If applicable (female subject in reproductive age), pregnancy test
2. OSDI questionnaire application
3. Ocular symptomology enquiry
4. Complete ophthalmic exploration
5. Return of drug
6. Adverse events evaluation
8. Concomitant drug products assessment

11.4 Follow-up Phone Call [Day 36 (±2)]

1. Investigate any adverse events related to the drug.

12. POPULATION CHARACTERISTICS

- Adults ≥ 18 years and < 90 years.
- Both sexes.
- Clinical diagnosis of pterygium grade I to III (temporary and/or nasal).
- Enrollment duration of 6 months.

- Enrollment potential: once the research centers are opened, it is estimated that during the first month, inclusion will cover 30% of the size of the total sample.

12.1 Inclusion Criteria

- Age ≥18 and <90 years
- Both sexes
- Clinical diagnosis of pterygium grade I to III (temporal and/or nasal). According to the classification proposed by Johnston.[9] (See attachment)
- Availability to attend check-ups when indicated.

12.2 Exclusion Criteria

12.2.1 General Criteria:

1. Subjects with topical or systemic medication that interferes significantly with the study results, such as topical immunomodulators, AINEs, antihistamines, corticosteroids, artificial tears with preservative, vasoconstrictors, etc. (see list of prohibited drug products).

2. Subjects (female) with an active sex life that do not use a hormonal contraceptive method, intrauterine device or bilateral tubal occlusion.

3. Female subjects that are pregnant or lactating.

4. Female subjects that tested positive in a urine base pregnancy test.

5. Positive for addiction* (verbal interview).

6. Subjects that have participated in any research clinical study in the last 40 days.

7. Legally or mentally incapacitated subjects unable to give their informed consent for their participation in this study.

8. Subjects that cannot keep appointments or follow through with all the protocol requirements.

*Definition: routine consumption of one or several psychoactive substances, till the point where the consumer (known as addict) periodically intoxicates themselves or does so in a constant manner,

shows a compulsive desire of using the preferred substance (or the substances), suffers an enormous difficulty to interrupt voluntarily or modify the consumption of the substance and seems determined to obtain it at any cost. –OMS definition*.

*** Addiction explanatory note: in the case of socially accepted drugs like tobacco and alcohol, their repetitive or continuous use is considered as addiction as well. In case of it being occasional (less than once per week) it must be completely suspended during a month prior to the study and during the study. In the case of ex-smokers (with more than one year without smoking) they shall not use substitutes like nicotine patches nor electronic cigarettes. In the case that there was another condition please consult the scientific committee of Laboratorios Sophia S.A. de C.V. to analyze each case in particular.*

12.2.2 Exclusion criteria related to ophthalmologic conditions:

Grade IV pterygium. According to the classification proposed by Jonhston9. (See addendum)

Dellen of the cornea.

Ocular surface neoplasia

Symblepharon.

Any type of corneal ulcers

Ocular surface disorders that result in scarring.

Metaplastic lesions in the ocular surface or adnexa.

History of autoimmune diseases that potentially can present ocular manifestations, like: rheumatoid arthritis, juvenile rheumatoid arthritis, Sjörgen syndrome, seronegative spondyloarthropathies, Systemic lupus erythematosus, multiple sclerosis, arthritis of giant cells, Graves' disease, among others.

Infectious diseases

Ophthalmologic diseases that can potentially require treatment in the following 3 months.

Ocular surgical procedures (in the last 3 months)

Diseases in the previous segment that require treatment or endanger the visual prognosis (posterior uveitis, diabetic retinopathy, macular degeneration, etc.)

History of penetrating corneal transplantation.

History of scarring inflammatory diseases such as Steven-Johnson syndrome, pemphigus etc.

History of ocular allergic reaction and/or adnexa.

12.2.3 Elimination criteria of the subject included in the study:

1. Corneal damage clinically perceptible or evidenced in the staining of the surface (lissamine green and fluorescence) for example:

(a) Corneal de-epithelisation grade V (according to the Oxford scale)

(b) Corneal Melting.

(c) Corneal Dellen.

2. Added ocular surface diseases that require a treatment different to Zebesten ® or added treatments that are indicated for the new diagnostic.

3 Opacities in ocular transparent mediums (cornea, clear, vitreous body) that prevents the assessment of the anterior chamber or the following segment.

4. The subject's own decision.

5. Unable to keep the follow-up appointments.

6. Added not authorized treatment or self-medicated

7. Herbal treatments that affect the course of the disease or that produce other complications not related to the disease.

8. Systematic diseases that require immunomodulatory treatment or biologics that affect each line of the inflammatory cascade.

9. Retinal diseases secondary to chronic-degenerative diseases that require treatment to preserve the function and/or anatomy.

10. Inflammatory retinal diseases

11. Installation of uveitic picture in any ocular uveal level.

12. Uveitic picture that mean an ophthalmologic emergency that requires immediate treatment.

13. Ocular diseases that require surgical treatment.

14. Ocular diseases that require intravitreal injections.

12.3 PROHIBITED DRUG PRODUCTS

For purposes of this protocol, all drug products belonging to the groups listed in the 12.3.1 table are considered as prohibited, the drug product in the prototype column are examples of the most representative drug product of the group, however, they are not the only ones that are prohibited.

Table 12.3.1

Drug product group	**Prototype**	**Route of administration**	**Resting period**
Non-steroidal anti-inflammatory drugs	Ketorolac Diclofenac	Topical	8 weeks
Steroidal anti-inflammatory drugs	Dexamethasone, Prednisolone, Fluorometholone.	Topical and systematic	8 weeks
prostaglandin analogue	Latanoprost, Travaprost	Topical	12 weeks

Immune modulators	Ciclosporin	Topical	12 months
Vasoconstrictive	Naphazoline	Topical and systematic	2 weeks
Alpha 2 agonists	Brimonidine	Topical	4 weeks
Beta blockers	Timolol, betaxolol	Topical	4 weeks
Carbonic anhydrase:	Dorozlamide brinzolamide	Topical	4 weeks
Lubricants with conservatives	Hypromellose, Propylene glycol	Topical	2 weeks

12.4 SAMPLE SIZE CALCULATION

Sample size protocol SOPH155-0415/IV

According to the objectives of the study to evaluate the Zebesten ® effect in subjects with primary pterygum, the variables of primary outcome stipulated in the design were:

- Conjunctival hyperemia
- TRL

Both variables are considered, using similar literature, to perform the calculation of the sample size to meet with the study objectives.

Conjunctival hyperemia

The sample size was calculated according to the formula for the continuous quantitative variables:

$$n = 2\frac{(Z \propto -Z_1 - \beta)(\delta)}{d^2}$$

With a statistical trust of 95% that corresponds to the type I error, and is the same as 1.96, with a potency of 80% that corresponds to the type II error, and equals to 0.84. It is considered as a standard deviation for the increase of 0.4 degrees of severity1 in the scale of conjunctival hyperemia after a pterygium surgery, with an expected difference of at least 2.9 degrees of severity.

Based on the previous the result was 69 cases (eyes) per group, which was incremented 20% by consideration of the losses (14 subjects), with **a total of 83 cases per group**, with a total population of study of **166 eyes to treat.**[8]

Tear film breakup time

The sample size was calculated according to the formula for continuous quantitative variables:

$$n = 2\frac{(Z \propto -Z_1 - \beta)(\delta)}{d^2}$$

With a statistical trust of 95% that corresponds to the type I error, and is the same as 1.96, with a potency of 80% that corresponds to the type II error, and equals to 0.84. It's considered as a standard deviation for the increase of 1.47 seconds 2 in the tear film breakup time posterior to 60 days of ciclosporin application A, with an expected difference of at least 10.2 seconds.

Based on the previous the result was of 120 cases per group, which was incremented 20% per consideration to the losses (24 cases), with a total of **144 cases per group**, with a total population of study of **288 eyes to treat**.

13. STUDY VARIABLES

Independent variables

- Pharmacological intervention
    - Zebesten® + Sodium hyaluronate 4 mg/ml
    - Placebo (vehicle + Sodium hyaluronate 4 mg/ml)

Dependent variable

- Primary outcome variable
    - Conjunctival hyperemia
    - Tear film breakup time
    - Adverse events

- **Secondary outcome variable**
    - burning
    - Foreign body sensation
    - Photophobia
    - Questionnaire score OSDI
    - Fluorescein stain
    - Visual capacity
    - Intraocular pressure

Intervening variables

- Work activity with sun exposure without ocular protection.
- Areas with air conditioner.
- Use of ocular devises that modify the lubrication.

13.1 Tolerability study

The security variables of the use of Zebesten ® will be evaluated in the appointed visits in the chronogram, by means of the following parameters.

1. burning
2. Foreign body sensation
3. Photophobia

13.2 Security evaluation

The security variables of the use of Zebesten ® will be evaluated in the appointed visits in the chronogram, by means of the following parameters.

1. Tear film breakup time
2. Visual capacity
3. Intraocular pressure
4. Epithelial defects
5. Adverse events.

13.3 Efficacy assessment

The efficacy variables of Zebesten® use will be evaluated in the appointed visits in the chronogram, by means of the following parameters:

1. Conjunctival hyperemia
2. OSDI score

Table of scales and variables measurement method

Variable	Unit	Symbol	Type	Measurement method	Normal value
Age	Years	--	Continuous	Calculated as of the date of birth	NA
Gender	Female Male	F/M	Nominal	Direct questioning	NA
Pterygum	Grade 0 Grade I Grade II Grade III Grade IV	--	Ordinal	Direct observation	Grade 0
Adverse events	Number of cases	N	Discreet	Counting	NA
Intraocular pressure	Mercury millimeters	MmHg	Continuous	Goldman applanation tonometry	11-21
Visual capacity	Fraction	Snellen	Nominal	Card	
Tear film breakup time	Seconds	s	Continuous	Direct counting	> 10
OSDI questionnaire	Points	--	Discreet	Questionnaire	
epithelial defects	Grade I Grade II Grade III Grace IV Grade V	--	Discreet	Direct observation with fluorescent staining and lissamine green	Oxford scale

Signs and ophthalmologic symptoms					
conjunctival hyperemia	Very mild Mild Moderate Severe	--	Ordinal	Direct observation. Efron classification.	Normal
burning	Present absent	--	Nominal	Direct questioning	Absent
Foreign body sensation	Present Absent	--	Nominal	Direct questioning	Absent
Photophobia	Present Absent	--	Nominal	Direct questioning	Absent
Prior segment	Normal Abnormal	--	Nominal	Direct observation	Normal

14. PROPOSED STATISTICAL ANALYSIS

The statistical analysis will be performed by a researcher blinded to the intervention groups.

The continuous quantitative variables will be expressed and presented via measures of central tendencies and of dispersion (media, standard deviation and ranges).

The nominal qualitative variables and ordinals will be presented via frequencies and proportions.

The Kolmogorov-Smirnov test will be performed in order to know the normal distribution or not of the obtained results in each study group. Also, the Levene test will be performed in order to know if the variables are the same or different.

Assuming a normal distribution of the data, the intra-group differences will be determined via the t test for paired samples, in the case of the quantitative variables. For the quantitative variables the χ^2 test (chi squared) will be used and in case that the expected frequencies are less than 5 the exact Fisher test will be used.

The differences among the groups will be analyzed via the t test in case of quantitative variables. For the quantitative variables tables of contingency 2x2 will be made and the differences will be calculated via χ^2 (chi squared) with Yates correction in case that the expected frequencies are less than 5 the exact Fisher test will be used).

The level of significance will be alpha of 0.05 or less.
A final statistical analysis will be included to all the subjects that complete 3 visits in the chronogram of activities.

15. Results report

The results obtained during the development of the investigation's protocol will be the responsibility of the sponsor, who is under obligation of reporting them to the pertinent authorities. Plus each one of the participating researchers will receive a results report.
The objective is to achieve the publication of the study on an international magazine with the objective of disseminate the scientific knowledge obtained.

16. IDENTIFICATION PROCEDURES, SECURITY AND THERAPEUTIC ADHERENCE OF THE INVESTIGATION SUBJECTS

16.1 Recruitment

The subject will be recruited in the ophthalmologic consultation of the participating research centers, in which a goal of scrutinized and randomized subjects are contemplated according to their scrutiny and recruitment capacity.

16.2 Subject identification

All the subject of the study will be identified through a number and their initials.

In the scrutiny stage a number will be assigned to the participant in a consecutive manner, employing 3 digits and once included the subject will be assigned with the subject's number (CFR number) which will be conformed of 3 digits of the molecule, 2 of the center's number, and 3 digits of the consecutive number assigned at the research center.

For example:

155/01/001 (molecule number/ center's number/ subject's number at the center).

16.3 Subject discontinuation

The following are the reasons why a subject may leave the study prematurely:

Subject's decision. The subject that desires to leave the study for any reason is allowed to do so at any moment, but they must inform the researcher. In all cases, the researcher musty try to establish contact with the subject as soon as possible for a final evaluation with the purpose of:
Documenting the subject's decision in clinical notes, obtaining the motive/s of the departure and writing them down in the exit format of the CRF, evaluate the clinical state of the subject, take timely therapeutic measures if required: handling of an adverse event or concomitant illness.

Researcher's decision. Especially if adverse events occur and the researcher considers that this can risk the subject's health, the indications in the adverse events section must be followed, or if an important disease occurs that needs medical prescription incompatible with the objective of the study. It will be reported in the clinical notes and a reporting format of the serious adverse events will be filled and the Ethics committee will be informed, clinical monitor and pharmacovigilance of Laboratorios Sophia.

An erroneous inclusion according to the protocol. The decision on whether the subject will remain in the study will be made conjunctly by the researcher and the sponsor.
Other motives (insufficient response, need of another treatment)
In all the cases, the available data will be kept for the security analysis (intention-to-treat population)

16.4 Research products recall

In case of research products recall (decided by the competent authorities of the sponsor) the sponsor will immediately inform the researcher.

The researcher in collaboration with the sponsor's representatives (clinical monitor) must with haste:

- Interrupt the supply of the affected research products to the subjects.
- Inform the involved subjects that they must stop the application of these research products immediately and take them to the center.
- The monitor will organize the return in order to carry on with the destruction of the study drug, both the used as the not used to Laboratorios Sopihia S.A. de C.V., according to procedures.

16.5 Adherence to the treatment

Compliance of the administration of the study drugs by the subjects will be evaluated at the facilities of Laboratorios Sophia once the dropper bottle of each subject are returned by the researcher. Each bottle with be weighed in an analytical balance and the difference with respect to the initial weight of the bottle; all values above 70% will be considered as adequate adherence to the treatment with respect to the posology described in the present protocol for Zebesten® and the buyer. It will also be evaluated in the research center by the researching physician

In the event that the adherence to the study drug is under 70 %, it will be considered that the results obtained from the participant are analyzed by intention to treat, see the section for the statistical analysis.

17. ADVERSE EVENTS

17.1 Adverse event, definition and communication

17.1.1 Overview

Adverse events (EA) may appear during the study, these may be associated or not with the study drug. If at any time any of the subjects may present any adverse event classified as serious that is derived from the drug's administration, the guidelines of the Official Mexican Norm 220 SSA1 2012 Installation and Operation of the Pharmacovigilance shall apply. The administration of the drug will be interrupted and the administration of an alternative therapy will be prescribed, as per the judgement of the main researcher.

An adverse event is any medical occurrence in a subject or subjects of a medical research, to whom a pharmaceutical product was administered and that does not necessarily have a causal relation with this treatment. Therefore. An EA can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (research) product, whether it is or not related to this.

The researcher must report the adverse events occurred during the study from the moment in which the subject signs the informed consent to be included in the clinical trial until the conclusion of the last procedure described in the approved version of the study protocol.

In all cases the etiology must be identified as far as possible and the sponsor must be notified. An "unexpected adverse event" is understood as any EA that is not identified in the nature, severity or frequency in the Researcher's Manual or in the information of the risks described in this protocol.

17.2 Classification and severity

17.2.1 Classification

The adverse events are divided in two categories according to their importance: "serious" and "not serious", this classification determines the procedures that must be used to report and document the adverse event.

A **serious adverse event** is that which:

- Threatens the life or causes the death of the subject.
- Makes it necessary to hospitalize or prolong the hospital stay
- It is the cause for persistent or meaningful incapacity
- It is the cause of alterations or malformations in the newly born

A non-serious adverse event is that which does not comply with any of the previous criteria.

17.2.2 Severity of the Adverse Events

The grade of severity of the adverse events must be evaluated by the researcher in charge or the person delegated for such task, as per the intensity of the clinical manifestations.

- **Mild intensity** is considered for those adverse events that do not interfere with everyday activities; these that may or may not require the suspension of the drug's administration.
- **Moderate intensity** is considered for those adverse events that interfere with everyday activities; (may provoke sick leave at work or school), but do not directly threaten the subject's life, they may or not require the suspension of the drug's administration.

- **Severe intensity** is considered for those adverse events that prevent the subject from performing their everyday activities.

17.3 Report of non-serious adverse events

The reports of adverse events classified as “non-serious” must be reported in the specific section of the case report form of the clinical protocol, as per what is indicated in the guide for the filling of the case report form.

During each monitoring visit, the correct filling of the non-serious adverse event report in the specific section of the case report form will be verified. It must be assured that before base closure of the study the non-serious adverse events are completed with a final resolution of adverse events and the totality of the information requested in the form of case report.

17.4 Characteristics of the report of serious adverse events

The researcher in charge and/ or person delegated for such task must report every adverse event, serious or non-serious that are presented during the development of the study, providing a diagnosis (name) to the condition(s) the subject presents.

It must be assured that the adverse events are correctly reported, grouping the signs and symptoms of the subject in clinical diagnosis.

In those cases in which the presence of several adverse events at once, and in which there is evidence that none of them correspond to the same pathological entity, each of the adverse events must be separately reported. For those surgical interventions programmed, the clinical diagnosis that caused the surgery must be reported instead of only the surgical event as such. For example: cholecystectomy (surgical event -NOT reported as adverse event); acute cholecystitis (Clinical diagnosis -reported as adverse event).

The reports of adverse events must indicate the date/ time of start, date/ time of conclusion, evolution and measures taken, as per the following:

- Solved
- Solved with aftereffects
- Being solved
- Unresolved
- Unknown

The information on the adverse events must be updated indicating the date of the kind of final solution of the adverse event or indicate as “being solved” for those cases in which the adverse event is still active.

17.5 Causality

The main researcher based on physical exploration, signs and symptoms referred by the study subject must indicate, based on a clinical judgement, if there is or not causal relation between the study drugs and the adverse events presented by the subject.

The way to classify the causal relation to the study drug will be the following:

17.5.1 Definitely related:

There is certainty that the adverse event is related with the product being researched.

17.5.2 Probably related:

There is a high probability that the adverse event is related to the product being researched.

17.5.3 Possibly related:

There is a probability that the product being researched is the cause of the adverse event, but other causes cannot be discarded.

17.5.4 Not related:

There is evidence that the adverse event is related to another cause different from the product being researched.

17.5.5 Unknown:

Adverse event for which causal evaluations were not possible.

The relation between the study drug product with the adverse events is stablished as per the following criteria:

- Previous experience with the drug.
- Knowledge of the adverse reactions with its use.
- Explanations for the adverse reactions.
- Use of other drug products, concomitant diseases, non-pharmacological therapies, diagnostic tests or other procedures or, in its case, confusion patterns.
- Time passed between the administration of the drug and the adverse event.
- Concentrations of the drug.
- Effects with re-exposition to the drug.

17.5.6 Reporte de los Eventos Adversos Serios

An active search of EAs must be performed using the spontaneous reports of the subject and physical explorations and interviews performed by the researcher during the visits.

If the EA ends up interrupting the study, the researcher must complete the FCR, in the section corresponding to Termination of the study, and specify if the event is serious or not.

A form of serious adverse events must be completed by the main researcher or the physician in charge and sent to the sponsor within the 24 hours following the notification; even if not all the required information is yet available at the moment. All the information gathered afterwards must be sent immediately once it is available. The researcher must provide an adequate and complete follow-up of the EAs. At any time they must provide an updated report of the EAs and report in writing when there is a final result for it.

In the same manner, all the EAs must be reported to the Committees of Ethics in Research, as well as the Regulatory authorities.

All the EAs as per the previous definitions and independently of the treatment or relationship with the study drug must be notified as soon as the event is known.

The researcher must notify the sponsor of the event sending the form "Serious Adverse Event Report" ("first notice") within the 24 hours after knowing about it **via email** with all the available information on the serious adverse event to the department of Pharmacovigilance of Laboratorios Sophia, S.A. de C.V as well as attaching a copy by email to the monitor in charge of the center.

17.5.7 Pharmacovigilance responsible:

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Email: farmacovigilancia@sophia.com.mx

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

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Direct assistance line, toll-free number: 01 800 7102 254

Non-serious adverse events (mild and moderate) are reported to the regulatory authority by the end of the study (after the report or in the report) and the serious adverse events immediately.

18. MONITORING AND AUDITING PROCEDURES.

Each research center as well as each researcher will have a clinical monitor assigned and authorized to revise, monitor and procure the information obtained from the study subjects.

Each research center will be submitted to an evaluation previous to its inclusion to grade its human, technological and logistic resources and determine their capacity to perform the study.

Periodic monitoring visits will be performed for the revision of the files and the emptying of the information required in the case report forms (CRF), this will be done physically in paper within the clinical file and in electronic format in the forms located in the online electronic information portal, to which the researchers and coordinators will have access to perform such procedure within the following 72 hours to the date of the visit by the subject, so as to maintain the fidelity of the data obtained and implement more timely actions.

The audits will be performed with an external supplier, by which the visit will be previously notified to the research center. The result of the audit will be evaluated by the Department of Clinical Operations of Laboratorios Sophia S.A. de C.V., together with the auditors and the main researcher. The findings will be described in a report of Corrective and preventive actions (CAPA) that will be filed in the general folder of the clinical study of the Department. All the findings detected in the audit will have a proper follow-up until their conclusion.

Audit - Inspection - Verification

The researcher must be informed that the competent authorities can also perform an inspection or verification of the facilities of the sponsor and/or the center or research centers.

The sponsor will inform the pertinent researchers immediately after receiving the notification of an inspection to the study centers. In the same manner, the researcher will inform the sponsor of any pending inspection.

The researcher will allow the representatives of the competent authorities and the people responsible of the audit:

- Inspect the site, the facilities and the material used for the study,
- Meet with all the members of their team that partake in the study,
- Have direct access to the study data and the source documents,
- Consult all the documents related with the study.

If there are computer medical files, the researcher commits to provide all the source documents and printings of the medical files of the participants, and if the computer system allows it, the registration of the changes performed during the study.

19. BIOSAFETY CONSIDERATIONS

NO BIOSAFETY IMPLICATIONS

This protocol, titled: “Efficacy and safety of Zebesten® (bromfenac 0.09 %) on the inflammation of the conjunctival surface on subjects with pterygium grade I- III vs placebo” with number: SOPH155-0415/I HAS NO BIOSAFETY IMPLICATIONS, since NO infectious - contagious biological material, pathogen

strains of bacteria or parasites, any kind of virus, radioactive material of any kind, animals or cells or vegetables modified genetically, toxic, dangerous o explosive substances, any other kind of material that may risk the health of physical integrity of the personnel of the center of research or the subjects of the study or the environment will be used. As well, we declare that in this project no cell, tissue or organs transplant procedures nor cellular therapy will be performed, no laboratory, farm or wild animals will be used.

20. ATTACHMENTS

Classification of pterygium

Grade 0	Posterior to the limbus, pinguecula
Grade I	The tissue involves the limbus
Grade II	The tissue is only above the limbus
Grade III	The tissue is between the limbus and the pupil's margin
Grade IV	The tissue overtakes the pupil's margin

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22. APPENDICES

Appedix 1: Declaration of Helsinki of the World Medical Association

DECLARATION OF HELSINKI OF THE WORLD MEDICAL ASSOCIATION

Ethical Principles for Medical Research in Humans

Adopted by the 18th General Assembly of the World Medical Association, Helsinki, Finland, June 1964, and modified by the:

29th General Assembly of the World Medical Association, Tokyo, Japan, October 1975

35th General Assembly of the World Medical Association, Venice, Italy, October 1983

41st General Assembly of the World Medical Association, Hong Kong, September 1989

48th General Assembly of the World Medical Association, Somerset West, South Africa, October 1996

52nd General Assembly of the World Medical Association, Edinburgh, Scotland, October 2000

53rd General Assembly of the World Medical Association, Washington, 2002 (added clarifying note in paragraph 29)

55th General Assembly of the World Medical Association, Tokyo, 2004 (added clarifying note in paragraph 30)

59th General Assembly of the World Medical Association, Seoul, October 2008

64th General Assembly of the World Medical Association, Fortaleza, Brazil, October 2013

Introduction

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

The Declaration must be considered in its entirety and a paragraph must be applied taking into account all other pertinent paragraphs.

2. As per the mandate of the AMM, the Declaration is mainly intended for physicians. The AMM urges others involved in medical research in humans to adopt these principles.

General principles

3. The Declaration of Geneva of the World Medical Association binds physicians to “attentively preserve above all the health of their subject” and the International Code of Medical Ethics states that “physicians must consider what is best for the subject when providing healthcare”.

4. The physician’s duty is to promote and preserve the health, well-being, and rights of the subjects, including those who participate in medical research. The knowledge and awareness of the physician must be dedicated to complying with said duty.

5. The progress of medicine is based on research that, ultimately, must include studies in humans.
6. The main objective of medical research in humans is to understand the causes, evolution, and effects of illnesses and improve the preventive, diagnostic, and therapeutic interventions (methods, procedures, and treatments). Also, the best tested medical interventions must be continuously evaluated through research to ensure their safety, efficacy, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect to all human beings and to protect their health and personal rights.
8. Although the main objective of medical research is to generate new knowledge, this objective must never be prioritized over the rights and interests of persons participating in the research.

9. In medical research, the physician’s duty is to protect the life, health, dignity, right to self-determination, intimacy, and confidentiality of personal information of the persons participating in the research. The responsibility to protect the persons taking part in the research must always be in the hands of a physician or another healthcare professional and never in the hands of the research participants, even after having granted their consent.

10. Physicians must consider ethical, legal, and judicial norms and standards for research in humans in their own countries, as well as the current international norms and standards. It must be ensured that a national or international ethical, legal, or judicial requirement never reduces or eliminates means of protection of the persons participating in the research established in this Declaration.

11. Medical research must be carried out in a way that reduces the possible damage to the environment to the minimum level.

12. Medical research in humans must be carried out solely by persons who have the appropriate education, knowledge, and scientific and ethical qualifications. Research in healthy subjects or volunteers requires the supervision of a competent and appropriately qualified physician or other healthcare professional.

13. Groups that are underrepresented in medical research must have an appropriate access to participate in the research.

14. Physicians who combine medical research with medical attention must involve their subjects in the research only as far as this is justified by a preventive, diagnostic, or therapeutic potential value and if the physician has adequate justification for believing that their participation in the study will not adversely affect the health of the subjects participating in the research.
15. Appropriate compensation and treatment must be ensured for persons harmed during their participation in the research.

Risks, Costs and Benefits
16. In the medical practice and in medical research, most medical interventions entail some costs and risks.
Medical research in humans should only be carried out when the importance of its objective is higher than the risks and costs for the person participating in the research.

17. All medical research in humans must follow a careful comparison of the risks and costs for persons and groups participating in the research, compared to the foreseeable benefits to them and other persons or groups affected by the disease under investigation.

Measures must be implemented to reduce the risks to the minimum level. Risks must be monitored, assessed, and documented continuously by the researcher.

18. Physicians must not involve themselves in research studies in humans unless they are sure that the risks have been adequately assessed and that it is possible to confront them in a satisfactory manner.

When the entailed risks are more significant than the expected benefits, or if there are conclusive tests of definitive results, physicians must assess whether to continue, modify, or immediately suspend the study.

Vulnerable Groups and Persons

19. Some groups and persons subjected to the research are particularly vulnerable and may have a higher possibility to suffer abuse or additional harm.

All vulnerable groups and persons must receive dedicated protection.

20. Medical research in a vulnerable group is only justified if the research responds to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. Additionally, this group may benefit from the knowledge, practices, or medical interventions derived from the investigation.

Scientific requirements and research protocols

21. Medical research in humans must be made up of generally accepted scientific principles and must be supported in a profound knowledge of scientific literature, other pertinent sources of information, as well as correctly performed laboratory experiments and animals, as the case may be. Care must also be given to the well-being of the animals used in the experiments.

22. The project and method of all studies in humans must be clearly described and justified in a research protocol.

The protocol must always make reference to the ethical considerations that may apply and must indicate the manner in which the principles indicated in this Declaration have been taken into account. The protocol must include information regarding financing, sponsors, institutional affiliations, possible conflicts of interest, and incentives for the persons in the study and information on provisions for treating or compensating persons who suffer harm as a consequence of their participation in the research.

In clinical trials, the protocol must also describe the appropriate arrangements for the post-trial provisions.

Research Ethics Committee

23. The research protocol must be sent, for consideration, comment, advice and approval to the pertinent ethics committee before the start of the study. This committee must be transparent in their workings, must be independent from the researcher or of any other type of undue influence and must be properly qualified. The committee must consider the current laws and guidelines of the country where the research study is taking place, as well as the current international standards, but it must be ensured that the protection of the participants of the study as described in this Declaration is not reduced or eliminated.

The committee has the right to control the ongoing trials. The researcher is obligated to provide control information to the committee, especially any serious adverse event. No modifications to the protocol may be done without the consideration and approval of the committee. After the study is complete, the researcher must present a final report to the committee with a summary of the results and conclusions of the study.

Privacy and Confidentiality

24. All possible precautions must be taken in order to protect the privacy of the individuals that participate in the research as well as the confidentiality of their personal information.

Informed Consent

25. The participation of individuals capable of giving their informed consent in the medical research must be voluntary. Although it may be appropriate to consult with the families or community leaders, no person able to give their informed consent may be included in the study without having accepted personally and freely.

26. In medical research involving humans able to give their informed consent, each potential individual must receive adequate information about the objectives, methods, financial sources, possible conflict of interests, institutional affiliations of the researcher, expected benefits, foreseeable risks and discomforts derived from the experiment, post-study provisions and any other aspect pertinent to the research. The candidate must be informed of the right to participate or not in the research and of withdrawing their consent at any moment without punishment. Special attention must be paid to the specific needs of information of each potential individual, as well as the methods employed to deliver the information.

After ensuring that the individual has understood the information, the physician or another properly qualified person must then request, preferably through writing, the informed and voluntary consent of the person. If the consent cannot be granted via granting, the process to achieve it must be formally documented and witnessed.

All the participant in the medical research must have the option of being informed about the general results of the study.

27. When asking for the informed consent for participating in the research, the physician must pay special attention when the potential individual is linked with him by a dependent relationship or if they consent under pressure. In a situation such as this, the informed consent must be lost by an adequately qualified person that has nothing no relation to that situation.

28. When the candidate is unable to give informed consent, the physician must ask for the informed consent of their legal representative. These individuals must not be included in the research study if there is no possible benefit to them, unless that the study has as an objective to promote the health of the represented group for the potential individual and this investigation cannot be performed in individuals able to give their informed consent and the research entails just a minimal risk and cost.
29. If a candidate that takes part in the research study who is deemed unable to grant their informed consent is able to grant their consent about participating in the research, the physician must be the one to ask for it, in addition to the consent of their legal representative. The refusal of the potential individual must be respected.
30. Research on individuals without the physical or mental capacity to grant their consent, for example unconscious subjects, may be done only if the physical/mental condition that prevents the individual from granting their informed consent is a necessary characteristic of the group being research. In these circumstances, the physician must ask the informed consent of the legal representative. If the aforementioned representative is not available and if they research cannot be delayed, the study can take place without informed consent, as long as the specific reasons for including the individuals with a disease that does not allow them to grant informed consent have been stipulated in the research protocol and the study has been approved by a research ethics committee. The consent to remain in the research study must be obtained as soon as possible from the individual or from a legal representative.
31. The physician must fully inform the subject of the aspects of the care that are related to the research. The refusal of the subject to participate in a research study or their decision of withdrawing must not negatively affect the physician-patient relationship.

32. For medical research where identifiable human material or human data is used, such as research about the material or data contained in biobanks and similar repositories, the physician must request the informed consent for the collection, storage, and reuse. There might be an exceptional situation where it is impossible or impractical to obtain the consent for such research. In this situation, the research can only be done after being considered and approved by an investigational ethics committee.

Placebo Use

33. The possible benefits, risks, costs and effectiveness of any new intervention must be evaluated via their comparison with the best proven interventions, except for the following circumstances:
When there is no proven intervention, the use of placebo, or any intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons it is necessary to determine the efficacy or safety of an intervention the use of any intervention less effective that the best proven one, the use of placebo, or no intervention.

Subjects that receive any sort of medical intervention less effective that the best proven one, the placebo or no intervention, will not run additional risks of serious injury or irreversible damage as a consequence of not receiving the best proven intervention.

Extreme care must be taken to avoid abusing this option.

Post-trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make available provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make the results of their research on human subjects publicly available and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Research reports that do not comply with the principles of this Declaration should not be accepted for publication.

Unproven interventions in the clinical practice

37. In the treatment of a patient, when proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Afterwards, these interventions should be made the object of research to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

Appendix 2. Good Clinical Practices

Good Clinical Practices directives of the International Conference on Harmonization include 13 basic principles, which are based on the Declaration of Helsinki. These principles are as follows:

1. The first principle indicates that clinical trials should be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practices and the applicable regulatory requirement(s).

2. The second principle states that before a trial is initiated, foreseeable risks and inconveniences should be weighed against anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

3. The third principle of Good Clinical Practices indicate that the rights, safety and well-being of the trial subjects are the most important considerations and should prevail over interest of science and society.

4. The fourth principle states that the information available before the trial about an investigational product should be adequate to support the proposed clinical trial.

5. The fifth principle establishes that clinical trials should be scientifically sound, and described in clear, detailed protocol. The requirements of this clinical trial protocol are also described in the directive guidelines of Good Clinical Practices of ICH.

6. The sixth principle indicates that the trial should be conducted in compliance with the protocol that has received prior Institutional Review Board or Independent Ethics Committee approval. This implies that a study can not be started until it has been approved by these institutions.

7. The seventh principle states that the medical care given to, and medical decisions made on behalf of subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist. The medical care responsible should always be qualified physicians.

8. The eighth principle indicates that each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s). Usually the sponsor is the responsible of ensuring that all the people involved in the performance of the trial are sufficiently trained

to carry it out, regarding their education and work experience, as well as their training. This evaluation is performed based on a previous trial, in which the sponsor meets and interviews the staff to ensure that they are adequately prepared to perform the trial. As part of this evaluation, the sponsor reviews the *curriculums vitae* (CV) of the staff involved in the trial.

9. The ninth principle specified that freely given informed consent should be obtained from every research subject prior to the clinical trial and the participation of the subject. It is worth mentioning that the freely given informed consent must be ready before the trial and that the subjects that might participate should not start any exploration with selection purposes to participate in the trial before they have given their freely given informed consent.

10. The tenth principle establishes that all clinical trial information should be recorded, handled, and stored in a way that allows its reporting, interpretation and verification. In other words, this principle states that the information provided to the sponsor must be able to be accurately reported, interpreted and verified.

11. The eleventh principle indicates that the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

12. The twelfth principle of Good Clinical Practices indicates that Investigational products should be manufactured, handled and stored in accordance with applicable Good Manufacturing Practice for industrial manufacturing. Good Manufacturing Practices have existed long before than Good Clinical Practices and many countries of the world have followed the Good Manufacturing Principles to manufacture and storage the investigational products. The investigational products used in a clinical trial should be used in accordance to the approved protocol. The protocol includes a section that contains the detailed instructions to manufacture, handle and store the investigational product in a clinical trial.

13. The thirteenth principle indicates that systems with procedures that assure the quality of every aspect of the trial should be implemented. Generally, this is the sponsors' responsibility.

In summary, we have addressed the directives of Good Clinical Practices established by the International Conference on Harmonization, and described their historical development, as well as the current content. We have addressed the different sections of these rules and we have established that the glossary is useful as a common language for the clinical global research. We have also described the current version of the directives of Good Clinical Practices dated on January 17th, 1997, which include an addendum titled Guidelines notes from September 8th, 1997.

Document consulted in the international normative instrument of the Bioethical National Commission at: http://www.conbioeticamexico.salud.gob.mx/interior/normatividad/normainter.html on March 12th, 2015.

Appendix 3. Ocular Surface Disease Index

The OSDI (ocular surface disease index) test is a simple test created to establish the severity and classification of dry eye according to its symptomology.

Answer the following questions by checking the box that best represents your answer:

1. Have you experienced any of the following during the last week?

	FREQUENCY				
	All of the time	Most of the time	Half of the time	Some of the time	None of the time
Eyes that are sensitive to light?	4	3	2	1	0
Eyes that feel gritty?	4	3	2	1	0
Painful or sore eyes?	4	3	2	1	0
Blurred vision?	4	3	2	1	0
Poor vision?	4	3	2	1	0
				Subtotal:	

2. Have problems with your eyes limited you in performing any of the following during the last week?

	FREQUENCY				
	All of the time	Most of the time	Half of the time	Some of the time	None of the time
Reading?	4	3	2	1	0
Driving at night?	4	3	2	1	0
Working with a computer or bank machine (ATM)?	4	3	2	1	0
Watching TV?	4	3	2	1	0
				Subtotal:	

3. Have your eyes felt uncomfortable in any of the following situations during the last week?

	FREQUENCY				
	All of the time	Most of the time	Half of the time	Some of the time	None of the time
Windy conditions?	4	3	2	1	0
Places or areas with low humidity (very dry)?	4	3	2	1	0
Areas that are air conditioned?	4	3	2	1	0
				Subtotal:	

OSDI score: total points × 25/Nº of answered questions.