# A Multicentric, Prospective, Crossover, Double-Blind Clinical Study, to Evaluate the Non-inferiority of the PRO-122 ophthalmic solution, after treatment with Krytantek Ofteno ®, in subjects with primary open-angle glaucoma (POAG) and / or intraocular hypertension (OHT). CONFORT Study K.

Drugs under study: Brimonidine 2 mg, Dorzolamide 20 mg, Timolol 5 mg.

Therapeutic indication: Antiglaucomatous

Development phase: Phase 3

Protocol code: SOPH122-0914 / III

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

Version: No.2

Date: March 2017

## 2. STUDY SHEET SUMMARY

Sponsor's name: Laboratorios Sophia, S.A. of C.V.

Active Ingredient Name: Brimonidine 2 mg, Dorzolamide 20 mg, Timolol 5 mg.

Study title: A Multicentric, Prospective, Crossover, Double-Blind Clinical Study, to Evaluate the non-inferiority of the PRO-122 ophthalmic solution, after treatment with Krytantek Ofteno ®, in subjects with Primary Open-angle Glaucoma (POAG) and / or intraocular hypertension (OHT). CONFORT Study K. No.: SOPH122-0914 / III

National multi-center study

 Study period:

Duration of the study for the participant: 75 days once the treatment.

 Development phase of

Study: Phase 3

Goals:

Aim:

To evaluate the non-inferiority of the PRO-122 ophthalmic solution versus Krytantek Ofteno® through its efficacy, tolerability, and safety on intraocular pressure in subjects with POAG and / or OHT.

Primary objective of efficacy:

To evaluate the efficacy of the PRO-122 ophthalmic solution versus the Krytantek Ofteno® ophthalmic solution applied on the ocular surface in subjects diagnosed with POAG and / or OHT by control and maintenance of a Target Intraocular Pressure (TIOP).

Primary objective of tolerability:

To evaluate the tolerability of the PRO-122 ophthalmic solution versus the Krytantek Ofteno® ophthalmic solution in subjects diagnosed with POAG and / or OHT through the evaluation of ocular symptoms such as burning, red eye, lacrimation, foreign body sensation; fluorescein stain, Visual Function Index (VF-14) questionnaire score and ocular comfort index.

Primary security objective:

To evaluate the safety of the PRO-122 ophthalmic solution versus the Krytantek Ofteno® ophthalmic solution in subjects diagnosed with POAG and / or OHT by better corrected visual acuity, anterior segment biomicroscopy, fundus examination and frequency of adverse events.

Hypothesis Ha: There is a difference between the efficacy and safety of the PRO-122 ophthalmic solution versus the efficacy and safety of the Krytantek Ofteno® ophthalmic solution.

H0 hypothesis: There is no difference between the efficacy and safety of the PRO-122 ophthalmic solution versus the efficacy and safety of the Krytantek Ofteno® ophthalmic solution.

Methodology:

A Multicentric, Prospective, Crossover, Double-Blind Clinical Study, with fixed dose.

**Number of participants:** 120 subjects.

**Diagnosis and main criteria for inclusion:** Older than 18 years old, both genders, with primary open angle glaucoma and / or intraocular hypertension, classified as mild, moderate, or severe, who achieved their TIOP for 2 months prior to treatment under Krytantek Ofteno®, with an informed consent signature obtained during the first visit.

**Medication under study:**
PRO-122 Ophthalmic solution. It will be applied with the following dosage:

1 drop every 12 hours for 30 days, alternating therapy with 30 more days of Krytantek Ofteno® with the same frequency.

**Sponsor's name**: Laboratorios Sophia, S.A de C.V.

**Active Ingredient Name**: Brimonidine 2 mg, Dorzolamide 20 mg, Timolol 5 mg.

**Comparator:**

1 drop of Krytantek Ofteno ® Ophthalmic Drops every 12 hours for 30 days in the sequence corresponding to your assigned group.

**Treatment duration:**

- Inclusion period: 3 months.

- Treatment period: 30 days. 2 sequences.

- Follow-up period: 75 days.

**Evaluation criteria:**

**Efficacy measurements:**

**Main efficacy criterion**

Efficacy will be determined by maintaining the TIOP (like the IOP goal corresponding to its degree of damage) during the study.

**Primary tolerability criterion**

Specific signs and symptoms such as burning, hyperemia, lacrimation, foreign body sensation, chemosis, anterior segment biomicroscopy, better corrected visual acuity as well as measurements with fluorescein staining, VF-14 visual function questionnaire and ocular comfort index will be evaluated.

**Primary security criteria:**

Adverse events frequency

**INDEX**

4. GLOSSARY AND DEFINITIONS

 AE Adverse Event

 VA Visual acuity

- VC Visual Capacity
- CRF Case Report Form
- GCP Good Clinical Practices
- ICH International Conference on Harmonization
- IC Informed Consent
- RM Researcher's Manual
- ERC Ethics and Research Committee
- ICL Informed Consent Letter
- EPIT Estimated Population by Intent to Treat
- IOP Intraocular Pressure
- EPPP Estimated Population by Proper Protocol
- SAE Serious Adverse Event
- RC Rear Camera
- SM Study Medication
- Cr Committee of the researcher
- OHT Intraocular hypertension
- POAG Primary Open-angle Glaucoma
- FMI File Master of the Investigator
- MSF Master Studio File
- LRT Lacrimal rupture time
- TBD Timolol, brimonidine, dorzolamide
- ABC Area below the curve
- CMC Camax Maximum concentration

**5. ADMINISTRATIVE STRUCTURE OF THE STUDY**

Sponsoring parties

**Table 1. - Laboratorios Sophia S.A. of C.V.**

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| Scientific Comittee | Dr. at C. Ricardo Alonso Llamas ricardo.llamas@sophia.com.mx | Clinical Pharmacologist |
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| Monitor | QFB Priscilla Muriel Lima Mateos priscilla.lima@sophia.com.mx | Clinical Operations Assistant |
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## 6. BACKGROUND

Glaucoma is an optic neuropathy characterized by progressive coping of the optic nerve

whose main risk factor is the increase in intraocular pressure, which causes alterations in the visual fields, although in the pre-perimetric stages of glaucoma there is no evidence of functional damage. ii Glaucoma is one of the main causes of irreversible blindness in the world, it is estimated that until the year 2000, there were approximately 6.7 million blind people in the world, secondary to glaucoma, it is estimated that by the year 2020 this figure will be increase by 11.1 million.

Epidemiological studies reveal that the race with the highest prevalence of glaucoma is black, as well as a consensus that after 40 years there is a greater risk of developing the disease. The male sex is affected 3: 1 with respect to the female sex, especially when there is an affected first-line relative. iv, v

Besides age, race, sex and family history, other important risk factores include intraocular pressure vi, high myopia vii, central corneal thickness viii, characteristics of the optic nerve ix, use of steroids ix, diabetes mellitus, and arterial hypertension, among others.

Open-angle glaucoma (POAG) and angle-closure glaucoma (ACG) are classified as primary and secondary.

The classification of secondary POAG includes the subjects with pseudoexfoliation, and pigmentation because of steroid and facolytics use. In the primary ACG there is a population who present with pupillary block and those who do not, this includes: inflammatory, neovascular, facomorphic factors and those with ciliary body cysts or retinal tumors.

There are different lines of medications for the treatment of glaucoma which are described below:

**Alpha adrenergic**

Brimonidine

**Analogs of prostaglandins**

Bimatoprost

Latanoprost

Travaprost

Unoprostone

**Beta-blockers**

Timolol Maleate

 Carbonic anhydrase inhibitors

 Systemic: Acetazolamide.

 Topics: Brinzolamide, Dorzolamide.

 Myotics: Parasympathomimetics: pilocarpine.

There is a consensus regarding the start of treatment: subjects with a diagnosis of glaucoma should start medical treatment; monotherapy with first-line drugs is recommended for subjects with suspected high-risk glaucoma, subjects with IOP greater than 25 mmHg are susceptible to treatment, the first therapeutic step to reach the TIOP is monotherapy and finally that the diagnosis of POAG is an indication for surgical treatment. Xi

However, in many cases, two or more concomitant medications are required to achieve the TIOP. This leads to poor adherence to treatment, due to the number of doses and a higher cost. For this reason, the use of fixed combinations represents a more comfortable posology for the subject and with fewer adverse effects.

Krytantek Ofteno® is a medication useful in glaucoma treatment for cases where more than one medication is required to control intraocular pressure. When used, it will have an additive effect since the drugs act by different mechanisms.

JUSTIFICATION

For these subjects in whom the TIOP cannot be reached according to the therapeutic consensus (IOP <14 mmHg +/- 2 mmhg or 30% reduction in baseline IOP), a fixed combination therapy is the treatment of choice.

In this sense, Laboratorios Sophia, S.A. of C.V. offers the only fixed triple combination Krytantek Ofteno® (dorzolamide 20 mg, brimonidine 2 mg, timolol 5 mg) which has already proven its effectiveness, tolerability, and safety in phase 1, 2 and 3 studies. The rapid evolution in medical treatment for glaucoma subjects is a topic that Laboratorios Sophia S.A de C.V maintains as a priority.

For this reason, Laboratorios Sophia S.A de C.V now presents a reformulation free of conservative to this same triple combination which aims to demonstrate the same efficacy in the control of IOP and better tolerability in the ocular surface of the subjects diagnosed with glaucoma through this clinical study.

All these characteristics are maintained by the same components without containing benzalkonium chloride or any other preservative xvii, xviii, xix.

In a preclinical study in which Krytantek Ofteno® and PRO-122 ophthalmic solution versus the same components (TDB) were administered in New Zealand rabbits separately, their availability in the aqueous humor was determined by the AUC and Camax, which showed similar values without significant differences between availability with conservative versus without conservative 20.

The reasoning by which a formula is proposed with the same effectiveness starts from the conclusions enunciated by Dr. Boudin et al. about of the conservator’s effects on the ocular surface in which the inflammation factors that lead to histological changes were measured. In these studies, first performed on the conjuntiva of healthy patients, then in patients diagnosed with primary glaucoma, it was possible to conclude that the following differences existed:

 The goblet cells are depleted by 60% after one month of being exposed to ophthalmic solutions with benzalkonium chloride xvii, xviii, xix.

 Tear rupture time is altered after 7 days of exposure and peaks at abnormal times after 3 weeks xviii.

Likewise, the migration of pro-inflammatory cells from the innate response promotes secondary immunological reactions, such as:

 HLA-DR antigens and pro-kinetic molecules I-cam – 3 are the main molecules found in the conjunctival proper substantia and tenon. xix

 As a result there is a significant increase in CD-20/22/23 as well as CD 4 (Th2) xviii, xix.

These changes in the cellular population of the ocular surface produce the following histopathological changes, which are proportional to the time of exposure and the amount of BAK to which the tissues have been exposed:

 Corneal de-epithelization.

 Loss of epithelial microvilli.

 Subconjunctival fibrosis.

 Reduction of the number of goblet cells.

 Epithelial keratinization.

 Squamous metaplasia.

 Increase in the number of desmosomes.

 Bullous epithelium dystrophy.

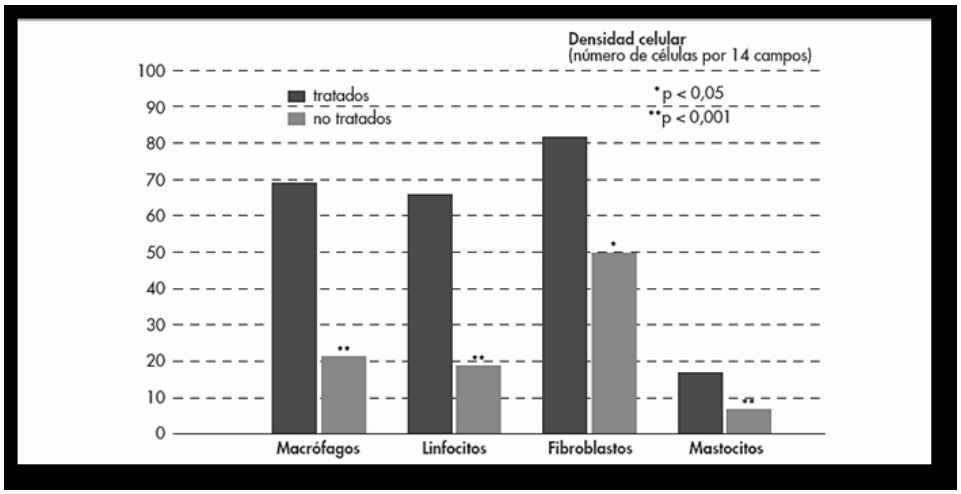
 Subepithelial fibrosis.

 Increase in subepithelial lymphocytes and plasma cells

 Thickening of the basement membrane.

Subsequently, the previous changes were correlated with the results of filtering surgeries in subjects in whom it was performed of first intention (without previous treatment) and compared with those who underwent filtering surgery after receiving chronic topical treatment with a conservative. 23

In this study a conjunctive sample was taken in which the immunohistochermical markers related to apoptosis and metaplasia of ocular surface tissues were analyzed, finding the following results. xviii, xix.:




Conjunctival biopsies and their cellular infiltrates in surgically treated antiglaucomatous user patients and nonusers. xix

| | Non-users | Monotherapy | Multi-theraphy |
|---|---|---|---|
| Normal | 80% | 59% | 12% |
| Markkers inmunohistochemical | 20% | 27.3% | 42% |
| fibrosis | 0% | 12.7% | 46% |

Percentage of patients in whom cell changes and / or fibrosis were compared according to exposure to BAK. xix.

With this, we can estimate that 40% of patients will use more than 2 drugs after 5 years of treatment, so that providing the user with eye antihypertensive drugs that remove adverse events while retaining the qualities that provide effectiveness to the drug will be very useful in the treatment of chronic diseases such as primary open-angle glaucoma.

In our Cross Over study model, the washout period was calculated with 5 times the average life time of the medication, which is max. 20 hrs, therefore, is not necessary to add a transfer effect period to the period of medication application.

## NON-CLINICAL PHARMACOLOGY

The bioavailability of antiglaucoma drugs in ophthalmic solution depends on their ability to pass through the cornea. To achieve its action, it is necessary to reach the site of action in optimal concentration. In the case of topical ophthalmic medications, the drug must cross hydrophilic and lipophilic barriers to reach the target tissue. The corneal epithelium and the endothelium are lipophilic barriers while the stroma is only permeable to

hydrophilic compounds. The permeability to different chemical entities is greater if a drug presents hydrophobic and hydrophilic regions in the same molecule. This is characteristic of weak acids and bases, which can exist in a nonionic form soluble in lipids as in a water-soluble ionic form. In addition, the continuous renewal of the tear film creates an important obstacle to prevent chemical substances of different kinds from penetrating the interior of the eye. This reasoning allows us to consider that the active ingredients in ophthalmic solutions have high concentrations. Both Dorzolamide, Timolol and Brimonidine are hypotensive drugs commonly used in the treatment of ocular hypertension and glaucoma. Dorzolamide ([4S, 6S] -2 ethylamino-4-methyl-5,5-dioxo-5λ, 7- dithiobicyclo [4.3.0] nona-8,10-di en-8-sulfonamide) is an inhibitor of carbonic anhydrase that has its effect on the inhibition of bicarbonate synthesis and consequently reduces the formation of HA; in the case of Timolol (S) -1- (tert-butylamino) -3 - [(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl) oxy] propan-2-ol), a beta blocker adrenergic, reduces the production of HA by blocking the adrenergic receptors in the ciliary body and Brimonidine (5-bromo-N- [4,5-dihydro tartrate]-1H-imidazol-2-yl] quinoxalin-6-amine), a selective agonist of alpha adrenergic receptors, decreases the synthesis of HA by reducing cyclic AMP (cAMP) and thereof increases the uveoscleral flux. In ophthalmology, the dynamics of how a drug reaches its therapeutic target is a controversial issue, mainly because of the limited accessibility to measure concentrations in different ocular structures in a subject, in addition to its specific mechanism of blood supply. The passage of a solute through a membrane has as a limiting speed diffusion in the lipid bilayer, which is characterized by the diffusion coefficient. However, an experimental way to know the concentration of a solute in an aqueous solution and its adjacent compartment, such as a membrane, is to calculate the partition coefficient between two immiscible solvents. The Partition Coefficient is the relationship between the affinity of the solute in a solvent / water system. A very polar solute will have a very small partition value, while a hydrophobic one will have values greater than unity. Therefore, the diffusion rate of a solute depends proportionally on the difference in its concentration.

These data are important during the design of ophthalmic application products since they help to predict their behavior when applied to the ocular surface. For this reason, Laboratorios Sophia, S.A. of CV, conducted a study to analyze the partition coefficient of the components of an ophthalmic solution in fixed combination (Brimonidine, Timolol and Dorzolamide) and the maximum concentration achieved in the aqueous humor (AH), a model of rabbits in an octanol-water system was used for each of them. The final concentration for each drug in AH was assessed by diffusion, where it was found that the order of solubility was Brimonidine > Timolol > Dorzolamide. The maximum concentrations reached in aqueous for Brimonidine, Dorzolamide and Timolol were at 15, 90 and 60 minutes respectively. With these results, we can conclude that the fixed combination of Brimonidina-Dorzolamida-Timolol is compatible and bioavailable for the control and management of intraocular pressure and glaucoma. Xii

On the other hand, a preclinical, unicentric, prospective, longitudinal, comparative, and double-blind study of ninety days was conducted in 30 ophthalmologically healthy albino New Zealand rabbits to evaluate the safety of Krytantek Ofteno® and its effectiveness in the control of intraocular pressure (IOP) versus the separate but concomitant application of its three active ingredients -dorzolamide, timolol and brimonidine (DTB).

In phase 1 (day 1 to 30) a drop of Krytantek Ofteno® and two drops of polyvinyl alcohol were applied to the right eye; a minimum period of 5 minutes was established between each application. In the wash period (day 31 to 60) the application of the drug was suspended. In phase 2 (day 61 to 90) a drop of DTB was applied to the right eye, each drop was applied in the same way as in the first stage. The rabbits were evaluated on days 0, 4, 11, 18 and 25 in each phase before starting the application of the medicine. The IOP was assessed at 08:00 h, 12:00 h and 16:00 h in both eyes.

According to the results, it could be seen that with Krytantek Ofteno® the IOP decreased from basal day 0 to the final day of the study by 40% compared to 20% in those treated with DTB. Likewise, Krytantek Ofteno® demonstrated greater security. Xiii

Clinical data of phase I:

We conducted a safety study about the tolerance of dorzolamide, brimonidine and timolol in a fixed combination applied to the ocular surface of ophthalmologically healthy human volunteers, 30 subjects were studied in total, to which the fixed combination was applied every 12 hours during a 7 days period, evaluations were made on days 2, 4, 7 and 10 of the study. At each visit, the physical examination was performed, and the findings were recorded in the following order: 1) visual capacity. 2) revision of the anterior segment with slit lamp 3) investigation of specific signs 4) tonometry and 5) indirect ophthalmoscopy under drug-induced mydriasis. According the observations during the study, there were no changes in the ocular surface of any eye after the application of the study article for 10 days, in the same way there were no changes with respect to the ocular surface stains in any day of study. Therefore, it was concluded that the fixed combination of 2% dorzolamide, 0.5% timolol and 0.2% brimonidine is safe and well tolerated when administered topically ophthalmic at the indicated dosage in ophthalmologically healthy volunteers. Xiv

## 7. STUDY DESIGN

### 7.1. Point or limit points

Main efficacy criterion

The efficacy of the PRO-122 ophthalmic solution versus the Krytantek Ofteno® ophthalmic solution applied on the ocular surface in subjects diagnosed with POAG and / or OHT by maintaining the target IOP will be evaluated.

Tolerability criteria

Ocular symptoms such as burning, red eye, lacrimation, foreign body sensation, chemosis, better corrected visual acuity, anterior segment biomicroscopy, fundus examination will be evaluated; fluorescein staining, VF-14 questionnaire score and ocular comfort index will be evaluated.

Security criteria

Frequency of adverse events.

## 7.2. Experimental design

### 7.2.1. Study plan

This is a Phase 3, National, Multicentric, Prospective, Crossover, Double-Blind, fixed-dose study.

This study will be carried out with 120 subjects from the ophthalmological consultation with diagnosis of primary open angle glaucoma with mild, moderate, or severe damage and / or with intraocular hypertension and a previous two-month period use of Krytantek Ofteno® and current control of the corresponding TIOP.

If the subject meets all the inclusion criteria and none of exclusion, they can be included in the study. In the same occasion a study group A or B will be assigned randomly, in group A the therapy with Krytantek Ofteno® will continue for 30 days, in which the subject will be evaluated again, and he will change from therapy to PRO-122 solution which will be used for 30 days after the 60th day, date of the final visit.

In the case of those assigned to group B on day 1, the change to PRO-122 solution will be made for 30 continuous days until the date of revision on day 30, day on which the treatment with Krytantek Ofteno® will be restored to continue until the day 60 for the final evaluation.

The selected subjects will be observed for 60 days. No subject may use the mentioned treatment for more than the established time.

The valuation days indicated in the activity schedule should be carefully observed. Table 2. A window variation period of + - 2 days can be accepted in relation to the revision visits and +/- 1 day in the safety visits.

Figure 1- Study plan

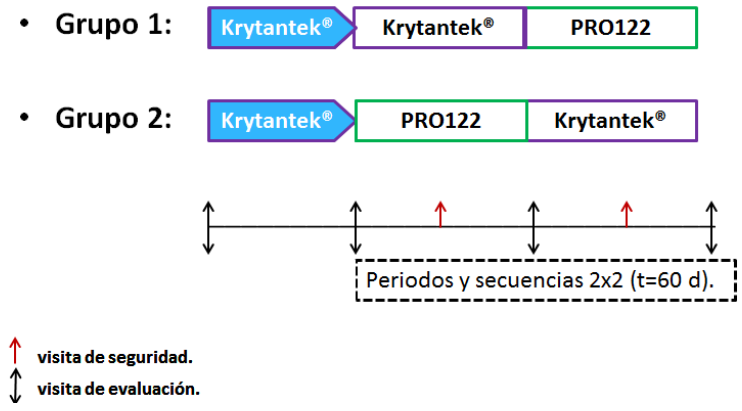
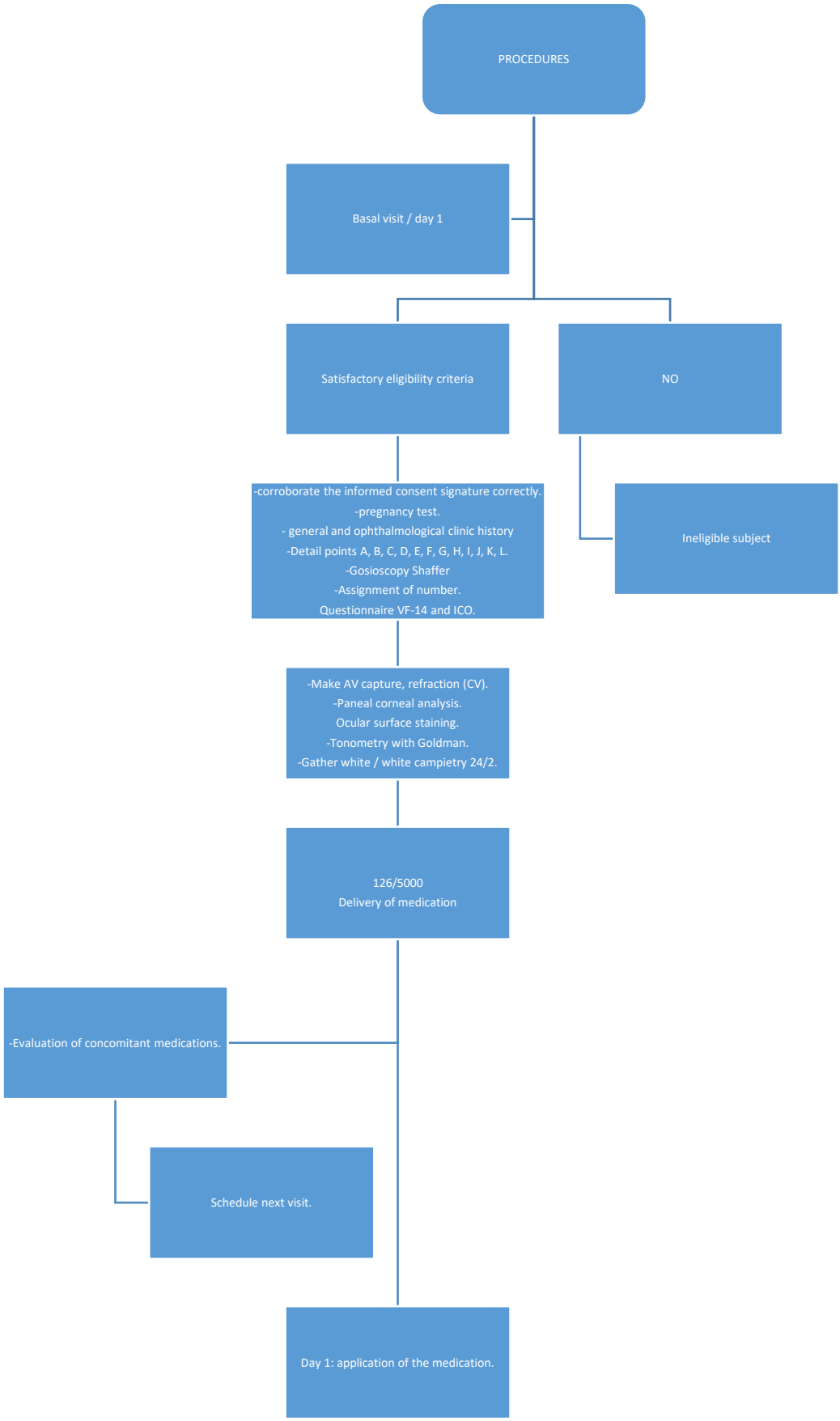


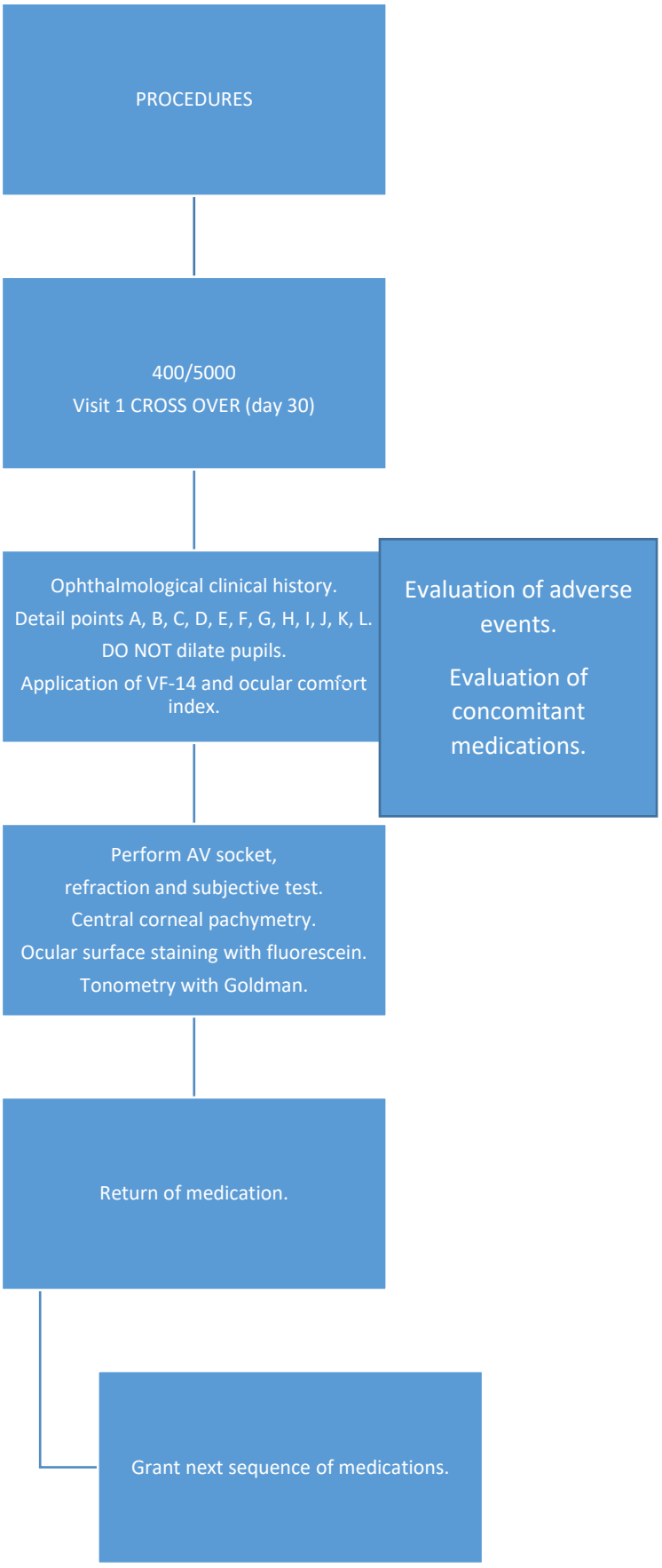

Table 2. Study Schedule

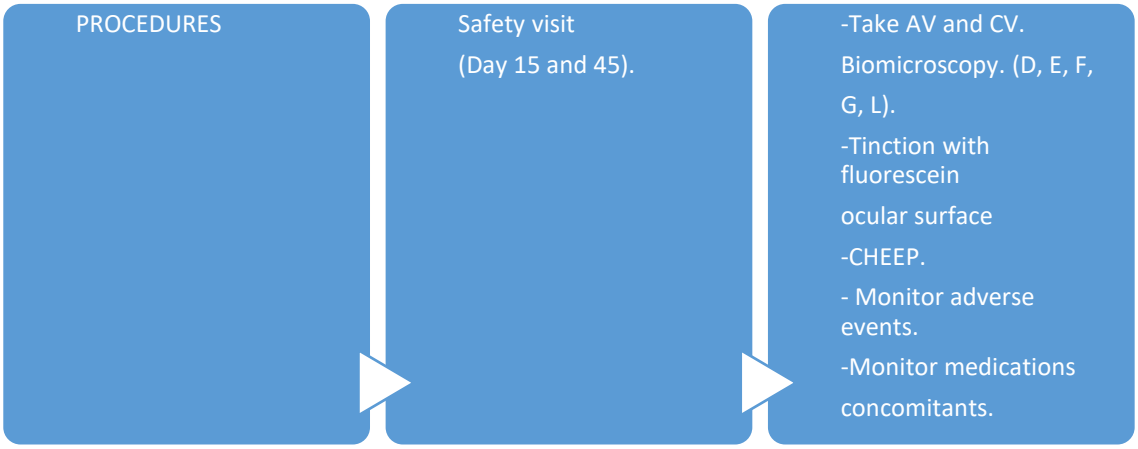
* if you have Humphrey visual fields of <6 months of completion these can be considered.

| Procedimiento | SEGUIMIENTO | | | | | | |
|---|---|---|---|---|---|---|---|
| | Visita de selección | Visita Basal | Visita seguridad 1 (± 1 días) | Visita 1 Cross over. (± 2 días) | Visita seguridad 2 (± 1 días) | Visita Final (± 2 días) | Llamada de vigilancia (± 2 días) |
| | | Día 1 | Día 15 | Día 30 | Día 45 | Día 61 | Día 75 |
| Criterios de elegibilidad (inclusión y exclusión). | | X | | | | | |
| Prueba de embarazo (si aplica). | | X | | | | X | |
| Firma de consentimiento informado. | X | | | | | | |
| Historia clínica general y oftalmológica. | X | | | | | | |
| Cuestionario VF-14 | | X | | X | | X | |
| Cuestionario índice de confort ocular V.1. | | X | | X | | X | |
| Asignación de código al sujeto. | | X | | | | | |
| Campos Visuales | | X* | | | | X | |
| Agudeza y capacidad visual. | X | X | X | X | X | X | |
| Entrega de tratamiento. | | X | | X | | | |
| Síntomas oftalmológicos ( A,B,C,D) | X | X | | X | | X | X |
| Gonioscopía Shaffer. | | X | | | | X | |
| Biomicroscopía anterior (D,E,F,G,L) | X | X | X | X | X | X | |
| Tinción fluoresceína. | X | X | X | X | X | X | |
| Paquimetría corneal central | X | X | | X | | X | |
| Medición de PIO. | X | X | X | X | X | X | |
| Biomicroscopía posterior bajo midriasis (H,I,J,K) . | X | | | | | X | |
| Devolución del medicamento. | | | | X | | X | |
| Evaluación de eventos adversos | | X | X | X | X | X | X |
| Evaluación de medicamentos concomitantes | X | X | X | X | X | X | |
| Evaluación final por parte del investigador principal. | | | | | | X | |

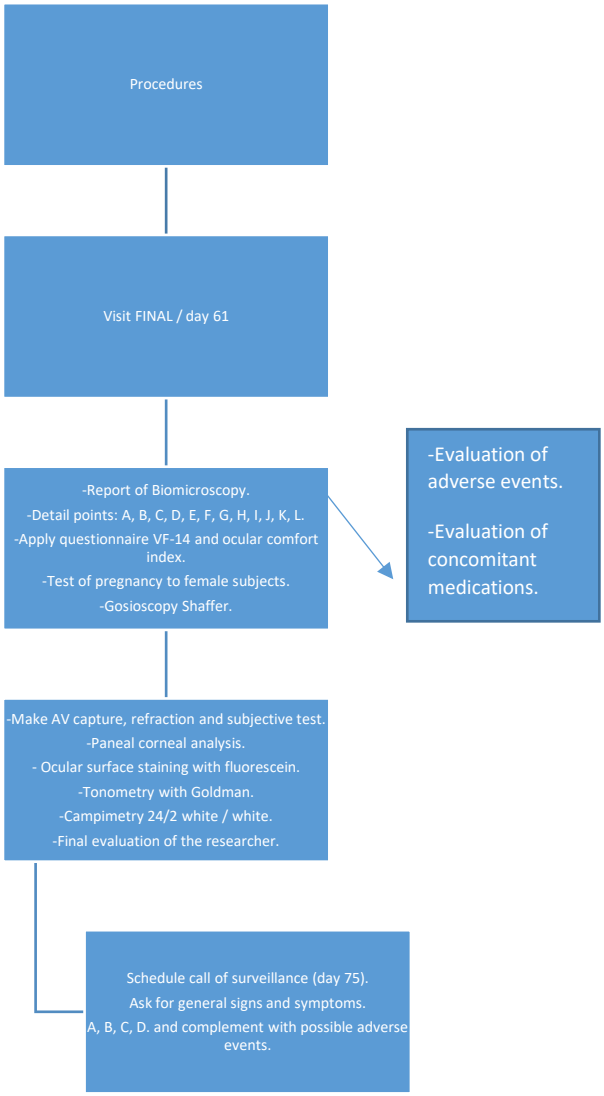
A) Ardor B) Sensación de cuerpo extraño C) lagrimeo D) Hiperemia conjuntival E) Quemosis F) Cristalino G) Iris H) Retina I) Mácula J) Vítreo K) Excavación de nervio óptico en decimales L) TRL.


PROCEDURES
Basal visit / day 1
Satisfactory eligibility criteria
NO
-corroborate the informed consent signature correctly.
-pregnancy test.
- general and ophthalmological clinic history
-Detail points A, B, C, D, E, F, G, H, I, J, K, L.
-Gosioscopy Shaffer
-Assignment of number.
Questionnaire VF-14 and ICO.
Ineligible subject
-Make AV capture, refraction (CV).
-Paneal corneal analysis.
Ocular surface staining.
-Tonometry with Goldman.
-Gather white / white campietry 24/2.
126/5000
Delivery of medication
-Evaluation of concomitant medications.
Schedule next visit.
Day 1: application of the medication.


PROCEDURES
400/5000
Visit 1 CROSS OVER (day 30)
Ophthalmological clinical history.
Detail points A, B, C, D, E, F, G, H, I, J, K, L.
DO NOT dilate pupils.
Application of VF-14 and ocular comfort index.
Evaluation of adverse events.
Evaluation of concomitant medications.
Perform AV socket,
refraction and subjective test.
Central corneal pachymetry.
Ocular surface staining with fluorescein.
Tonometry with Goldman.
Return of medication.
Grant next sequence of medications.




Note: A) Burning B) Foreign body sensation C) Lachrymation D) Conjunctival hyperemia E) Chemosis F) Crystalline G) Iris H) Retina I) Macula J) Vitreous K) optic nerve excavation in decimals L) TRL * ICO = ocular comfort index.




A) Burning B) Foreign body sensation C) Lachrymation D) Conjunctival hyperemia E) Chemosis F) Crystalline G) Iris H) Retina I) Macula J) Vitreous K) Optical nerve optic nerve excavation in decimals. L) TRL * ICO = ocular comfort index.

### 7.3. Measures to minimize deviations

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

- Once the dropper bottles of each subject are returned by the researcher, each bottle will be weighed on an analytical balance and the difference will be obtained with respect to the initial weight of the container; any value above 80% will be considered as an adequate attachment treatment.

- The subjects will have a "subject's diary" in which they will answer a questionnaire based on analogous visual scales with the main signs and symptoms perceptible to the subject and if there is one out of this questionnaire, you can write it down in the space designated for its description.

A meeting of researchers will be organized for the physicians involved in the study before starting with the inclusion of subjects, their attendance will be mandatory.

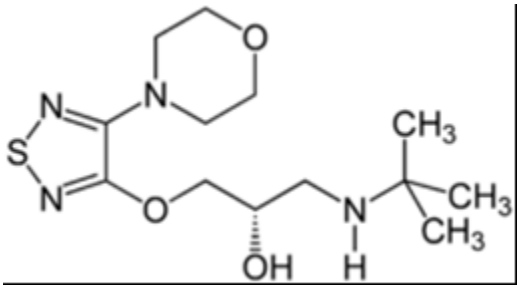
At the end of the study the subjects will answer a questionnaire of satisfaction of the subject in the local language and the researcher will explain the subject. It is not authorized for the researcher to report / correct the score of the subject in the self-score questionnaires.

## 7.4. Products and system to determine the study blind

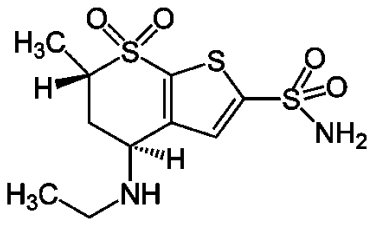
### 7.4.1. Managed products

**Table 3 - Description of study drugs**

Ophthalmic drops of 0.5% timolol maleate, 2% dorzolamide and 0.2% brimonidine.
Timolol Maleate: 0.5% timolol
- Chemical Name: (S) -1- (tert-butylamino) -3 - [(4-morpholin-4-yl-1,2,5-thiadiazol-3-yl) oxy] propan-2-o
- Molecular weight: 316,421 g / mol
- Molecular formula: C13H24N4O3S
- Chemical structure:



Dorzolamide: 2% dorzolamide
- Chemical name: (4S-trans) -4- (ethylamino) -5,6-dihydro-6-methyl-4H-thieno [2,3-b] thiopyr-2-sulfonamide-7,7-dioxide monohydrochloride.
- Molecular weight: 360.9
- Molecular formula: C10H16N2O4S3 • HCl.
- Chemical structure:



Brimonidine: 0.2% brimonidine.

Chemical Name: 5-Bromo- N - (4,5-dihydro-1H-imidazol-2-yl) quinoxaline-6-amine

Molecular weight: 292,135 g / mol

Molecular formula: C11H10Br1N5

Chemical structure:

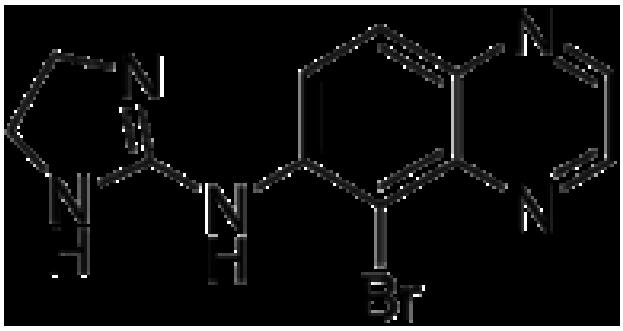
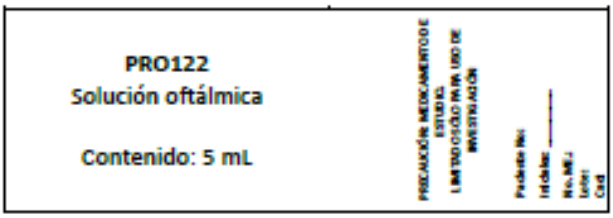


Table 4 - Packaging description

Primary packaging

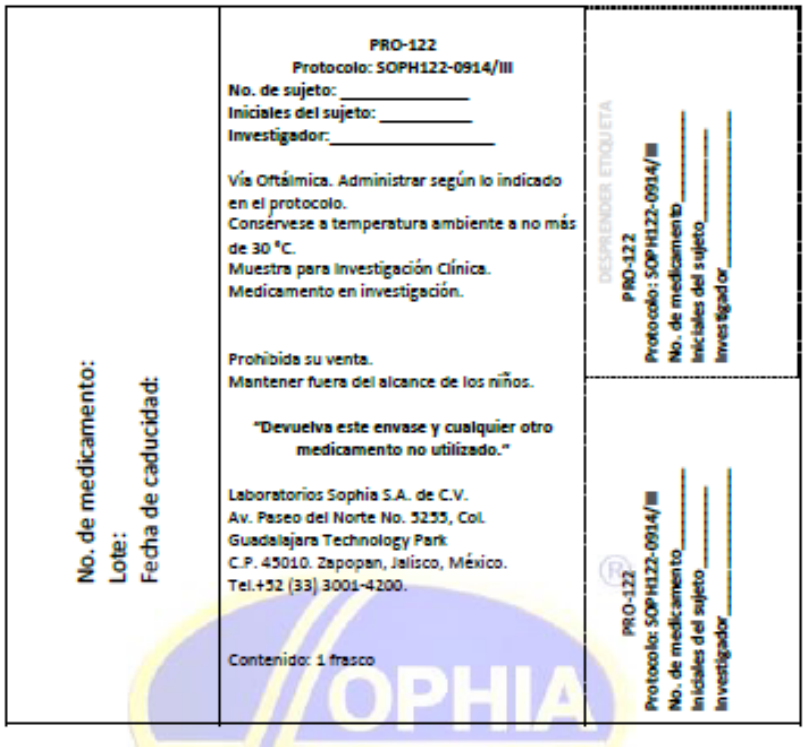
The bottles will be delivered in their primary packaging and they will be identified with the protocol code, below the specification of solution or suspension and content in milliliters, among others as illustrated below.

Example:




Secondary package:

The specifications of the study drugs will be described in the secondary packaging. Example:




### 7.4.2. Treatment management

The treatments will be provided from the manufacturing site (Laboratorios Sophia, S.A. de C.V.) previously weighed.

Treatment management will be under the responsibility of the researcher and / or pharmacist of the health care establishment (when applicable), including:

- The reception and storage of the study medication (SM). The study medication must be stored in a secure area with restricted access. Some special storage conditions are requested, such as keeping them at room temperature to no more than 30º Celsius, for which the investigating physician will be provided with a humidity and temperature recorder as a loan during the study.

- Data download of the recorder will be done by the clinical monitor in the monitoring visits and in turn the previously designated responsible will make a reading of the day directly from the recorder's screen.

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

- The delivery of the treatments will be in accordance with the study plan and following the delivery methods that are described in the section. The researcher and / or pharmacist

of the healthcare establishment should use the treatment delivered only for the subjects participating in the study.

- The study medication count.

The researcher and / or pharmacist of the health care establishment and / or a designated person of his study team must fill in in real time all the documents that the sponsor provides for treatment handling.

The study monitor will periodically check the management and recounting of the treatment. At the end of the study, the researcher and the study monitor will make a final inventory of the medicines, and they will write down the corresponding format.

The study monitor will collect the remaining treatments for storage and subsequent destruction, after quantifying the amount in each container.

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

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

### 7.5. Discontinuation of the study

#### 7.5.1. Premature discontinuation of the study

The sponsor may terminate the study before the scheduled deadline. A written confirmation will be sent to the researcher.

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

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

#### 7.5.2. Closure of the center

The closure of the research center will be carried out once the last subject visit has been included, previously agreed upon between Laboratorios Sophia SA de CV and the Investigator.

A center that does not include subjects in the three months after the initial visit may be closed by decision of Laboratorios Sophia S.A. of C.V.

### 7.6. Source data

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

- The subject's medical record

- Journal of the subject

- The self-score questionnaires (VF-14 and ocular comfort index).

The subject will directly record the data of the self-rating questionnaires in paper form, which will be considered source data.

## 8 SELECTION AND REMOVAL OF STUDY SUBJECTS.

### 8.1 Selection Criteria

#### 8.1.1 All subjects included:

- 18 years of age or older

- Male or female.

- Obtained in the external consultation.

- Diagnosis of primary open angle glaucoma and / or hypertension classified as mild, moderate, or severe glaucomatous damage, users of Krytantek Ofteno® for at least two months before inclusion and under control of the target IOP.

- Signed informed consent.

Physical examination of the subjects

In the physical examination carried out during the baseline visit, the absence of any anomaly that could interfere with the conduct of the study will be reviewed:

At the baseline visit, white on white 24-2 Humphrey campimetry data should be collected with no more than 6 months after having been carried out and considered in reliable parameters, in case of not having such characteristics, please realize this study.

#### 8.1.2 Informed consent

Obtained as described in section 14.2 of the protocol.

### 8.2 Exclusion criteria

#### 8.2.1 General criteria

1. Subjects with topical or systemic medication that interferes decisively in the results of the study. (Such as topical immunomodulators, tamponade of lacrimal punctures, corticosteroids, ocular hypotensives other than those indicated above, artificial tears with conservative).

2. Subjects (female and male) with active sexual life who are not using a contraceptive method.

3. Subjects of the female sex in a state of pregnancy or who are breastfeeding.

4. Subjects of the female sex with pregnancy test in positive urine.

5. Positive substance abuse (illegal drugs).

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

7. Subjects legally or mentally incapacitated to give their informed consent for their participation in this study.

8. Subjects who cannot comply with the appointments or with all the requirements of the Protocol.

### 8.2.2 Medical and therapeutic criteria

Related to ophthalmological criteria

1. Subjects with only one eye with vision.

2. Subjects with visual acuity of 20/200 or worse in either of the two eyes.

3. Subjects with a narrow angle glaucoma history without treatment, with or without total or partial closure of the angle in either of the two eyes.

4. Subjects with corneal abnormalities that prevent tonometry by applanation.

5. Subjects with ocular surgery or ocular trauma resolved in the last 6 months prior to inclusion.

6. Any eye laser surgery in the last 3 months.

7. Any progressive retinal disease or without control.

8. Inflammatory diseases of any kind.

9. Subjects who wear contact lenses.

Related to various conditions

1. Subjects with a history of hypersensitivity to any of the ingredients of the research product or its analogues.

2. Subjects who can not comply with the study appointments and / or protocol requirements.

Related to a therapy or previous and / or concomitant treatments

Previous therapy

Subjects can not be treated at the time of inclusion with any other type of antiglaucomatous than Krytantek Ofteno ®.

To know the other prohibited treatments and their rest period, please refer to table 5

"Main prohibited treatments - Rest period to be respected".

### 8.3 Discontinuation criteria

### 8.3.1 Withdrawal criteria

The following criteria will result in the mandatory exclusion of the study:

The reasons that a subject leaves the study prematurely may be the following:

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

 Document the subject's decision in clinical notes.

 Obtain the reason (s) for the exit and write them down in the corresponding format.

 Evaluate the clinical status of the subject.

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

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

- Decision of the investigator.

 Especially if an adverse event occurs and the investigator believes that this may threaten the subject's health, or if a major disease requires the prescription of a medication incompatible with the purpose of the study occurs.

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

- Pregnancy.

- Any deviation to the protocol that affects the safety of the subject.

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

### 8.3.2 Procedure

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

In case of premature withdrawal of treatment, the investigator should record the reason (s), the exact date of the premature discontinuation of the treatment in the source document and in CRF. If more than one reason is given, the investigator must indicate the main reason.

In case of premature exclusion of the study due to an adverse event (serious or not), the investigator should make every effort to gather information related to the outcome of the event. If necessary, the information will be collected later.

This information will be recorded in the CRF part related to non-serious adverse events; and the serious adverse events in a format that will be given separately in case the researcher can not collect the information in a visit, then it will be collected from the doctor who will ensure the follow-up of the subject.

### 8.4 Managed treatments

Subjects with previous treatment with Krytantek Ofteno® every 12 hours for at least 2 months prior to study and under control of the TIOP for mild, moderate, or severe damage will begin to apply PRO-122 or Krytantek Ofteno® without leaving wash period as follows:

1 drop every 12 hours (e.g. 9 am – 9 pm) for 30 days; at the end of the stablished period they will change to the opposite formula respectively. Application of the indicated treatment will begin at the baseline visit. In the crossover visit, the morning application will correspond to the initial sequence of the medication and the second application of the day, will correspond to that of the second sequence.

#### 8.4.1 Treatment delivery

At the baseline visit, the principal investigator or the previously designated responsible person will give the subjects the box with the treatment for the study.

The researcher will give the subjects the box with the corresponding treatment.

#### 8.4.2 Previous and concomitant treatments

Prohibited treatments

Table 5 shows the list of prohibited treatments before and during the study.

In case of uncertainty, the researcher will verify the corresponding treatments.

If a prohibited treatment is absolutely necessary during the study, the subject should be removed.

**Table 5. Main prohibited treatments** -Periods of rest to respect.

| Medicine | | Route of administration | Rest period |
|---|---|---|---|
| Group | Prototype | | |
| Artificial tears with conservative. | Anyone | Ophthalmic | 2 weeks |
| Carbonic anhydrase inhibitor | Acetazolamide | Oral or I.V | 1 month |
| Prostaglandin analogues | Latanoprost<br>Travaprost<br>Bimatoprost | Ophthalmic | 2 months |
| Parasympathomimetics | Pilocarpine | Ophthalmic | 2 moths |

#### 8.4.3 Authorized treatments before and during the study

Tretacaine Hydrochloride

Tropicamide / Phenylephrine Hydrochloride

Antibiotics of any kind

### 8.4.4 Treatment compliance

Compliance will be assessed through the measurement of the bottle weight before and after the start of the study, in the same way the subject will have to fill in the "subject's diary" where it will record the time at which the medication should be applied.

After the discontinuation of the study treatment, the investigator will propose an alternative treatment if necessary, or the appropriate care adapted to the nature of the clinical condition of the subject.

## 9 VALUATION OF EFFECTIVENESS

### 9.1 Efficacy measurements

Table 2 - Research schedule shows the effectiveness measurements made at each visit or period of treatment.

Primary efficacy parameters are:

Maintaining control of the TIOP during the time elapsed between the baseline day and day 60.

Secondary efficacy parameters:

Fluorescein staining, VF-14 questionnaire score and ocular comfort index evaluation, signs and symptoms such as such as burning, tearing, foreign body sensation, conjunctival hyperemia and / or chemosis.

Primary security parameters:

Frequency of adverse events, visual capacity, data of the anterior segment biomicroscopy and fundus examination.

### 9.2 Measurement methods and times

Scales to fill out by the researcher:

A meeting of researchers will be organized for all those involved in carrying out the study before starting it, and their participation will be mandatory. The objective of these sessions is to train them on the assessment of the efficacy and safety criteria and to ensure reliability among the qualifiers. In addition, detailed qualification rules will be provided to the qualifiers.

The same qualified physician should evaluate at the start of each visti the scales previously designated in the Delegation of Responsibility format throughout the study.

Self-qualification questionnaires to be completed by the subject:

The researcher will explain to the subject the self-score questionnaires; the subjects will fill them in the visits of days 1 (basal visit), 30 (crossover) and 61 (final day). Since the subject will fill out the self-score questionnaires, these will be provided in local language. Only the subject must fill out these questionnaires.

**Visual acuity**

It is a measure of the ability of the visual system to detect and recognize spatial details, it is performed in a high contrast test and with a good level of illumination. To measure visual acuity (VA) a subject will be presented with different high contrast tests and different sizes at a fixed distance, and the value will be noted as far as the subject sees. The smallest size that the subject recognizes will be taken as a threshold value and expressed in arc minutes. Visual ability is the best visual acuity with optical correction.

Bailey and Lovie designed and proposed a primer that would standardize the answers for each letter size in each of the lines. This was achieved by using a logarithmic progression of the size of the optotypes, obtaining equality in the discernment. They proposed that each line of optotypes contain five letters and the space between them is exactly the size of the letters of the same line and the space between the lines is equal to the size of the optotype of the lower line. In such a way that with this booklet, Bailey and Lovie innovated the method of assessing visual acuity through the logarithm of the minimum resolution angle (logMAR). This type of scale establishes: 1) the visual acuity 20/20 is equal to 0.00 in logMAR and 2) the 20/200 represents the unit in log MAR (1,0). Therefore, each successive line change represents a change of 0.10 logarithmic units. In a line of five letters each letter has a value of 0.02 logarithmic units; in this way, the value of the acuity reached within a line can be objectively annotated. This makes the test have a high degree of reliability. In the area of research, it is called a "Gold Standard".

Standardization of the visual examination:

- At 3 m distance in a room with dim lighting, the research subject will be evaluated as follows:

- This exam will be held at the research center

- The subject will be asked to always sit in the same place and with the LogMar scale, the visual acuity (AV) will be assessed. If he does not have this type of booklet he must carry out the conversion (a table is provided below).

- The research subject will keep both eyes open.

- The research subject should gently cover one eye with the occluder (always use the same occluder to cover the eye, with all research subjects) while reading aloud the smallest line of letters you can see. This exam is done in each eye, one at a time, starting with the right eye (RE).

- The doctor must point out the line that the research subject is requested to read.

- Finally, the same procedure will be performed through the stenopic.

Equivalence between the different AV scales

| 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 |

**Previous Biomicroscopy**

It refers to the revision of the entire anterior segment: cornea, iris, pupil, anterior chamber, crystalline and / or (IOL).

It will be qualified as follows:

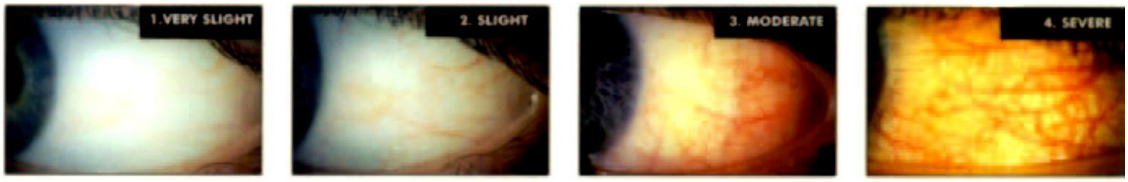
Normal.

Abnormal.

Abnormality that does not affect the result of the study:

**Conjunctival hyperemia / hyperemia:**

defined as the simplest reaction of the conjunctiva to a stimulus, a red appearance secondary to the vasodilation of the conjunctival vessels of variable intensity. It will be classified according to the analogous visual scale of hyperemia of The Institute for Eye Research Scale.ix




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

-Foreign body sensation

-Burning

-Lachrymation

- Chemosis

These symptoms will be described as present or absent, in case there is a discharge, it will have to be described.

Gonioscopy with Shaffer classification:

The classification of Shaffer will be carried out with a Goldman gonioscope to establish the open-angle (grade III and IV) and its characteristics.

The 3-lens Goldman type lens will be placed on the cornea, after instillation of topical tetracaine and 2% hypromellose as a lubricant, the quadrants will be observed and described starting with the superior, then temporal, inferior and ending with the nasal side.

Fluorescein stain

Fluorescein staining will be performed, standardization of this scan is done as follows:

1- Subject will be in front of the lamp prior instillation of topical anesthesia that will be provided by Laboratorios Sophia S.A. of C.V.

2.- The subject's lower eyelid will be gently grabbed, first on the right side and then on the left side asking the subject to look upwards so that with this maneuver a greater area of the lower bulbar conjunctiva is exposed, then the fluorescent filter paper moistened with a drop of anesthetic will be placed in the surface of the area previously mentioned, subsequently the subject will be asked to blink several times and proceed to examine it without specifying the corneal / conjunctival region and will be evaluated with the following classification :

Absent (without staining)

Medium (less than 10% of the surface with staining).

Moderate (from 10 to 50% with surface staining).

Severe (more than 50% of the surface).

**Central corneal pachymetry**

Under local topical anesthesia with tetracaine, the central corneal thickness will be examined with an ultrasonic pachymeter. This value will be used for the adjustment of IOP that will be adjusted based on the conversion tables validated for each device that is counted in the research center. Note: it is important that in all the visits that require it, the same pachymeter used as in the initial visit.

**Applanation tonometry**

The measurement of intraocular pressure will be based on the method of "applanation" which is the most commonly used method and is based on the Imbert Fick principle, which establishes that the pressure inside a dry and thin-walled ideal sphere is equivalent to the force needed to flatten its surface divided by its flattening area. Normally the intraocular pressure ranges from 10 to less than 21 mmHg.

The methodology for taking the pressure will be as follows:

1.- After having instilled a drop of topical anesthetic on the surface of both eyes of the subject.

2.- A strip of fluorescein will be placed on the surface of the lower bulbar conjunctiva, first of the right eye, and then the whole procedure will be performed on the left eye.

3.- Through the Goldman tonometer the cornea will be indented with the biprism and the intraocular pressure will be determined based on the force and flattened area. In this sense the medical ophthalmologist or the person previously designated will make the shot without observing the knob, which will be read by another doctor previously designated to avoid mistakes in the reading.

5.- The intraocular pressure will be expressed in mmHg which is the flattening force multiplied by 10.

Subsequent Segment Review

It refers to the revision of the entire posterior segment, particularly: vitreous, retina, macula, and optic nerve. It will be qualified as follows:

Normal.

Abnormal.

Abnormality that does not affect the result of the study (explaining situation in the FRC).

Optic Nerve Excavation

It includes the revision of the optic nerve, having to determine mainly the excavation or cupping vertically and must be expressed in a decimal way.

This ophthalmological exploration will be analyzed as an independent parameter of the revision of the posterior segment, the rest of the optic nerve structure is also evaluated.

24-2 Humphrey campimetry:

Prior to inclusion, the subject must have a 24-2 white / white campimetry as a diagnostic method for primary open angle glaucoma, this must be no more than 6 months old after being performed, the ophthalmologist will evaluate it only to corroborate the diagnosis. In the case report format, the average deviation (DM) and standard deviation of the model (DSM) will be recorded. According to the general evaluation by the ophthalmologist, the subjects will be classified in mild, moderate, or severe damage corresponding to the preferred practice guidelines (PPP).

## 10 SECURITFY

### 10.1 Safety measurements

The following safety measurements made in each visit or treatment period must be included in the schedule of activities

The safety measurements are the following:

- Adverse events.

- Visual acuity and visual ability.

- Previous biomicroscopy data.

- Concomitant medications.

- Fluorescein staining.

- Taking IOP with Goldman.

**10.2 Measurement methods and times**

**10.2.1 Basal visit (day 1)**

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

When the informed consent is obtained, a unique identification number of the subject will be assigned, this will be used throughout the study for its identification.

The female sex subjects who have presented their menarche will undergo a urine pregnancy test.

The following evaluations will be made to ALL enrolled subjects:

1. Complete general and ophthalmological clinical history.

2. VF-14 questionnaire and ocular comfort index.

3. Visual Acuity and Visual Ability

4. Visual Fields (validity in the last 6 months, if not, realize a new one).

5. Evaluation of specific signs and symptoms of burning, foreign body sensation, lacrimation, conjunctival hyperemia.

6. Anterior segment biomicroscopy (conjunctival hyperemia, chemosis, crystalline, iris, TRL, corneal surface, anterior chamber angle measurement).

7. Posterior segment biomicroscopy (retina, vitreous, macula, optic nerve) under mydriasis.

8. Vertical excavation of the optic nerve.

9. Fluorescein staining.

10. Taking intraocular pressure (IOP) with Goldman tonometer.

11. Corneal pachymetry.

12. IOP adjustment with corneal thickness.

13. Subject number assignment

14. Evaluation of concomitant medications.

15. Evaluation of acute adverse events.

All subjects will begin with the application of the study medication in the corresponding dose without leaving a washout period.

All procedures will be recorded in the subject's clinical record.

**10.2.2 Safety visit 1: (day 15).**

The subject will attend the review 15 days after the start of treatment, a window period of +/- 1 day is allowed.

In this visit, the following will be evaluated:

1. Visual acuity and visual capacity.

2. Anterior segment biomicroscopy.

3. Taking intraocular pressure (IOP) with Goldman tonometer.

4. Fluorescein staining of the ocular surface.

5. Evaluate concomitant medications and adverse events.

**10.2.3. Visit crossover 1 (Day 30)**

A window of ± 2 days is allowed while continuing to apply the study medication as stipulated.

At each follow-up visit, an ophthalmological examination will be performed in order to evaluate the following parameters.

1. Visual acuity and visual capacity.

2. VF-14 questionnaire and ocular comfort index.

3. Evaluation of symptoms and specific signs, foreign body sensation, burning, lacrimation, conjunctival hyperemia.

4. Previous biomicroscopy. (conjunctival hyperemia, chemosis, crystalline, iris, TRL, corneal surface).

5. Ultrasonic pachymetry

6. Fluorescein staining

7. Taking intraocular pressure (IOP) with Goldman tonometer.

8. Evaluation of concomitant medications.

9. Evaluation of adverse events

10. Delivery of new treatment.

11. Return of medication granted as first treatment.

**10.2.4 Safety visit 2 (Day 45):**

The subject will go to review 15 days after the start of the new treatment (day 45), a window period of +/- 1 day will be allowed for the visit.

In this visit, the following will be evaluated:

1. Visual acuity and visual capacity.

2. Anterior segment biomicroscopy.

3. Taking intraocular pressure (IOP) with Goldman tonometer.

4. Fluorescein staining of the ocular surface.

5. Evaluate adverse events and concomitant medications.

### 10.2.5 Final visit 5 (Day 61)

A window period of ± 2 day will be allowed for this visti. The following parameters will be evaluated:

1. Acuity and visual ability.

2. Visual Fields 24/2 Humphrey, white / white.

3. VF-14 questionnaire and ocular comfort index day 01, 30 and 60.

4. Evaluation of symptoms and specific signs foreign body sensation, burning, tearing, hyperemia.

5. Previous biomicroscopy. (conjunctival hyperemia, chemosis, crystalline, iris, TRL, corneal surface, anterior chamber angle measurement.

6. Ultrasonic corneal pachymetry.

7. Posterior biomicroscopy (retina, vitreous, macula and optic nerve).

8. Vertical excavation of the optic nerve.

9. Fluorescein staining.

10. Taking intraocular pressure (IOP) with Goldman tonometer.

11 Urine pregnancy test (if applicable).

12. Evaluation of concomitant medications.

13. Evaluation of adverse events.

14. Return of the second treatment.

15. Final evaluation by the researcher.

### 10.2.6 Laboratory tests

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

### 10.3 Adverse events

All adverse events should be a matter of follow-up and must be documented in a complete and accurate manner to make possible the assessment of the safety of the study drug.

The same procedure will be applicable if the subject is given the drug under study or the comparators.

### 10.3.1 Record of adverse events in the Case Report Form

#### 10.3.1.1 Events to be registered

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

Therefore, the investigator will document as an adverse event:

 Any unfavorable and unintended sign, including an abnormal finding of an additional examination that the investigator considers clinically important,

 Any intercurrent symptoms or illness,

 Any worsening symptom or disease during the study or already present when the subject entered the study (increase in frequency and / or intensity)

- Detected during a study visit or in an additional examination,

- Be present from the previous study visit and notify the subject.

Adverse Events at the time of application: the subject will document in the diary the possible adverse events that arise at the time of the application of the product under investigation. The Investigator will periodically review these journals, giving timely follow-up to the symptoms.

Concomitant diseases: are all those diseases that are recorded in the baseline visit of the subject.

Adverse Events of Special Interest: within the research protocol there are certain signs, symptoms or diseases characteristic of the disease or treatment that are of special interest to the sponsor.

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

 **Results in the death of the subject**

 **Represents a threat to life**

Note: the term "threat to life" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically could have caused death if it had been more serious.

 **Hospitalization or prolongation of the hospital stay.**

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

 **How persistent or important disability / disability results.**

Note: an event that seriously alters the ability of the subject to lead a normal life, in other words that causes a significant change, deterioration, injury or alteration of the functions or body structure of the subject, physical activity and / or quality of life.

 **Is a congenital anomaly / birth defect.** Exposure to the study drug before conception (in man or woman) or during pregnancy that causes an adverse outcome in the child.

**Consumption of the study drug by a different person to the subject:**

 Minors: any consumption of the study drug with or without medical consequences must be notified immediately to the sponsor.

 Adults: any accidental consumption of the study drug with clinical symptoms and any intentional consumption of the study drug, with or without medical consequences, should be notified immediately to the sponsor.

In these specific cases, the investigator must immediately report by telephone or fax, or in non-working hours to the 24-hour telephone line (see Table 6).

### 10.3.2.2 Follow-up of adverse events

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

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

If the adverse event has not been resolved in the final visit of the subject in the study, the subject must be followed up correctly, noting any information about the outcome of the event in an "Adverse Event" form.

If it is not the researcher who carries out the subject's follow-up (hospitalization, follow-up by a specialist or the general practitioner of the subject) the researcher will do everything possible to keep in contact with the person / department in charge of the subject's follow-up, so that you can obtain additional information to report it in an "Adverse Event" form.

### 10.3.2.3 Procedure for a serious adverse event

In the setting of a serious adverse event that is presented:

- During the study or
- During the 15 days after the final study visit of the subject, regardless of the supposed function of the investigation (study drug or required experimental procedures according to the protocol of the clinical study) or,
- After these 15 days regardless of whether the start date is after the end of the study when the event could be because of the investigation.

The researcher must:

Record in the participant's medical record the date on which the event was made known (in a follow-up visit or through telephone contact with the participant or with a third party, ...), immediately after or within 24 hours after being informed about this event, the sponsor will be informed by email and / or by telephone through his clinical monitor, to fill out the "Serious Adverse Event Report" form.

If an initially non-serious adverse event worsens and becomes serious, this should be reported immediately in the corresponding format.

Report the initially not serious event on a paper page "Adverse event - Additional information".

- Report the deterioration caused by the seriousness on a paper page "Adverse event - Additional information", and

- Send them by email immediately to the person responsible indicated above, with opia to the assigned study monitor.

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

- Suspend the study treatment for the subject.

- Fill out an "adverse event" form of the CRF.

### 10.3.2.4 Causality assessment

It is important that the researcher provide his or her opinion regarding the cause-effect relationship between the adverse event and the study drug, for the following reasons: certain adverse events that occur during clinical investigations may be important enough to lead to changes in the drug's development program (for example: changes in dose, population of the study or in the information provided to subjects that may lead to the preparation of new information and consent forms). This is especially true in case of events that are suspected to be related to the study drug (adverse reaction to the drug) and which, in its most severe form, could mean a threat to life.

The causality must be assessed at the time of reporting the adverse event. Only cases marked by the researcher as "related" or according to the opinion of the sponsor to have a causal relationship with the investigational medicinal product under reasonable suspicion (relationship of the Adverse Event with the mechanism of action of the drug under study...) they will be considered as an Adverse Reaction to the suspect medication.

In general, the reasonable causal expression relationship means linking evidence or arguments to suggest a causal relationship.

### 10.3.3 Responsibilities of the sponsor

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

## 11 STATISTICS

### Sample size

Sample calculation:

To calculate the sample size, we used the average and the general standard deviation of the two quantitative variables mentioned (the intraocular pressure and the decrease of the intraocular pressure with respect to the basal pressure during and at the end of the treatments) and the percentage of cases that presented adverse events.

The reliability of the study was established at 95% and the power at 80%.

The sampling error was established as follows: in the case of the variable "intraocular pressure at the end of treatment" we established a sampling error of ± 1.00 mm Hg, that is, if the mean intraocular pressure at the end of the presents differences less than or equal to 1.00 mm Hg, we will conclude that the two treatments are equal, we will not be in a position to reject the null hypothesis of equal intraocular pressure at the end of treatment; but if the difference was higher than 1 mm of Hg in favor of Krytantek Ofteno® compared to PRO-122, we could assure with a $p < 0.05$ that PRO 122 is superior to Krytantek Ofteno®, given that the former presented lower values than the second and vice versa.

In the case of the variable "change in intraocular pressure with respect to the baseline value prior to treatment", the sampling error proposed is also 1.00 mm Hg. This leads us to the following reasoning: if the differences in the decrease in intraocular pressure between the treatments in this study were less than ± 1.00 mm Hg, we would conclude that there are no differences in this efficacy parameter, if this limit were exceeded, then we could speak of superiority of some of these treatments with respect to the rest.

Finally, for the case of the variable "Percentage of subjects who presented adverse events", the sampling error was established at ± 15.0%. If the difference between the percentage of adverse events between one treatment and another (Krytantek Ofteno® versus. PRO-122) was less than 15%, then we will say that the treatments are equal with this parameter and if the difference was greater than 15 percent, then we will conclude that there are significant differences between treatments for this variable.

In Appendix 4 (Tables 5, 6 and 7) the calculations are developed for the sample size needed to detect the indicated differences and to reach a conclusion about the efficacy of these two treatments.

The study will allow to know if the efficacy (measured in terms of "intraocular pressure" and "change in intraocular pressure") is equal or better for PRO-122 when compared to Krytantek Ofteno® (null hypothesis) or if PRO-122 is worse than Krytantek Ofteno® (alternative hypothesis).

It will also uncover if the security is the same or better for PRO-122 compared to Krytantek Ofteno® (in case the percentage of adverse events of PRO-122 is equal to or

less than Krytantek's) or worse (if the percentage of adverse events for PRO-122 results in more than 15% above the subjects treated with Krytantek®).

The resulting sample calculated for the variable "intraocular pressure" was found to be 91 and 84, for the variable "change in intraocular pressure" and for "percentage of cases with adverse events", respectively.

We propose a sample of 90 cases per group for this study. Table 4 shows the results of the sample size calculated for each of the variables with the sampling errors which appear in subsection (A) of that table. We did an additional exercise proposing sampling errors of 1.5 mm Hg for intraocular pressure variables and 20% for the percentage of adverse events. For those sampling error sizes, the appropriate sample is proposed in 60 cases per group.

4. Comparison of the sample size required for a 95% reliability and a power of 80% considering different levels of sampling error.

| | Variable | Error de Muestreo | Tamaño de Muestra |
|---|---|---|---|
| A) | PIO | 1.0 mm Hg | 91 |
| | Disminución en PIO | 1.0 mm Hg | 84 |
| | % de Eventos Adversos | 15% | 85 |
| B) | PIO | 1.5 mm Hg | 41 |
| | Disminución en PIO | 1.5 mm Hg | 37 |
| | % de Eventos Adversos | 20% | 57 |

For the sampling errors indicated in subsection (A), one sample per group of 90 patients would be recommended.

For the sampling errors indicated in subsection (B), one sample per group of 60 patients would be recommended.

In conclusion we could say that the study sample could be at least 60 subjects per arm, which would have sampling errors of 1.5 mm Hg for intraocular pressure variables and 20% for the percentage of adverse events. We can increase it to 90 cases per group to reduce the errors to 1.0 mm Hg and 15% respectively, in all cases we assume a 95% reliability and an 80% power.

## 12 DIRECT ACCESS TO THE DATA / DOCUMENTS SOURCE

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

# 13 QUALITY CONTROL AND QUALITY ASSURANCE

## 13.1 Supervision of the study

### 13.1.1 Before the study

The researcher will allow the monitor to visit the site and the facilities where the study will be conducted to ensure compliance with the protocol requirements.

A meeting of researchers will be organized before the study starts.

The researcher will allow the monitor:

- Inspect the site, facilities and materials used for the study,

- Meet with all the members of your team that participate in the study,

- See all documents related to the study,

- Have access to the CRFs and that they are filled correctly,

- Direct access to the source documents to compare the data contained there against the CRF data,

- Verify that the study is carried out in compliance with the protocols and regulatory requirements.

If electronic medical records are used, the investigator should:

- Print all medical records of all participants at the start of the study,

- Print in real time each of the data entries and each change to the data during the study,

The researcher will personally put the signature and date on the first page of the printout and indicate the number of pages. At each monitor visit, the investigator will provide you with all the impressions of the participant's medical records.

If the computer system allows tracking of changes made to medical records, the investigator will give the monitor an impression of the medical records of the participants and the records of the changes made at each visit. The researcher will personally place the date and signature on the first page of each printout, and the monitor will do so on all pages. The researcher and the monitor will put the number of pages on the first page.

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

## 13.2 Audit – Inspection - Verification

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

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

inspection to the study centers. Likewise, the investigator will inform the sponsor of any pending inspection.

The researcher will allow the representatives of the Competent Authorities and the people responsible for the audit to:

- Inspect the site, the facilities and the material used for the study,

- Meet with all the members of the team participating in the study,

- Have direct access to the study data and source documents,

- See all documents related to the study.

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

## 14 ETHICS

### 14.1 Research Ethics Committee

The Principal Investigator will submit to the Research Ethics Committee the study protocol, informed consent, investigator's manual, materials to be delivered to the subject, recruitment materials, and the required documents in accordance with local requirements.

The study will not begin in the center without first having obtained the approval of the corresponding Ethics Committees, having complied with the local regulatory requirements, and having obtained the signature of the confidentiality agreements and economic proposal of each of the principal investigating physicians.

The study will be conducted in accordance with the ethical principles established in the Declaration of Helsinki of 1964, revised in Seoul, 2008 (see appendix 1).

### 14.2 Information for the subject and form of informed consent

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

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

The principal investigator will provide the potential participant with all the information regarding the characteristics of the study, its potential benefits, risks, objectives, and procedures. This information will be with a language understandable to the subject, the right to interrupt their participation in the study at any stage will be explained to the subject, this, without affecting the relationship with the researcher and / or their future assistance. The informed consent will be put to the consideration of the possible participant; and must have enough time to analyze each and every one of the aspects

mentioned above and if there is any doubt, this will be clarified by the person in charge of obtaining the informed consent. Once the participant agrees to participate in the study, he / she must sign and date the letter of informed consent in the presence of two witnesses who have or are not related to the subject of study, who will participate during the informed consent process and will sign endorse that the process was carried out prior to any study procedure, that the study information was clearly explained, and, if present, doubts were clarified.

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

The principal investigator must also sign and date this consent.

The informed consent must be signed in duplicate by all involved, and two witnesses, one copy will be filed in the researcher's folder and the other will be delivered to the participant. The Investigator must document the date on which the informed consent was signed in the subject's medical history.

When the informed consent is obtained, a unique identification number of the subject will be assigned, this will be used throughout the study for the identification of the participant.

The letters of informed consent are made in duplicate, a copy is kept by the investigator and a second one will be delivered to the subject.

### 14.3 Modification to "informed consent"

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

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

Such amendments may be implemented only after having obtained the written approval of the Ethics Committee and having complied with the local regulatory requirements, except for an amendment that is required to eliminate an immediate danger to the subjects of the study.

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

# 15 DATA MANAGEMENT AND CONSERVATION OF RECORDS

## 15.1 Study data

The investigator or the designated person on your team will complete the Case Report Format (CRF) as well as all other documents provided by the sponsor (e.g., documents related to the handling of the treatment).

### CRF

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

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

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

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

To ensure the confidentiality and security of the data, user names and access codes will be used to restrict access to the system only to authorized personnel, whether resident within the researcher's, the sponsor's or third party's sites.

The monitor should ensure that all the data in the CRF has been filled. After comparing the data against the source documents, the monitor will ask the researcher to make the correction using clarifications, so that they are answered and closed as quickly as possible.

The scientific review team of Laboratorios Sophia S.A. of C.V. will give the latest medical-scientific review, and will set the pattern to freeze the database.

## 15.2 Data management

The data will be collected in the CRF, once having a copy of the CRF of each of the visits of each subject that has completed the study, they will be transcribed to a database, the database mask will match the form of report of case and the data of each of the CRFs will be captured. A double data capture will be carried out to validate the information, as the case report forms are being collected from the center and the data have been validated by the clinical monitor.

### 15.3 File

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

## 16. OWNERSHIP OF RESULTS PUBLICATION POLICY

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

Because the study is multicentric, the first publication should be done only with data collected from several centers and analyzed under the responsibility of Laboratorios Sophia S.A. of C.V. The researcher undertakes not to publish or communicate data collected only in a center or in part of the centers before the publication of the full results of the study, unless Laboratorios Sophia S.A. of C.V. gives prior written agreement.

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

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

## 17. ADMINISTRATIVE CLAUSES

### 17.1 Related to the sponsor and the researcher

#### 17.1.1 People to inform

In accordance with local regulations, the investigator and / or sponsor will inform the Director of the Health Care Facility, the pharmacist involved in the study. The researcher will inform in advance, with their consent, the participating general practitioner.

#### 17.1.2 Substantial amendment to the protocol

If it was necessary to alter the protocol after it was signed, the modification or substantial amendment should be discussed with the investigating physicians and staff that will participate in the clinical study, as well as with the regulatory entities of each region. It

should be kept with the initial protocol. On the cover of the protocol kept by the researcher, the number and date of the amendment version must be written.

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

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

### 17.1.3 Final report of the study

Laboratorios Sophia S A de C.V. will elaborate the study report after completing the statistical analysis of the data, a final report will be designed, according to the ICH's PCBs.

### 17.2 Related to the sponsor

The sponsor agrees to:

- Provide the researcher with adequate and sufficient information about the treatment or treatments administered during the study, in order to it carry out

- Obtain any authorization to carry out the study and / or the import license that might be required by the local authorities to administer the treatment before starting the study (if it is international).

### 17.3 Related to the researcher

### 17.3.1 Confidentiality - Use of information

All documents and information provided to the researcher by the sponsor are strictly confidential.

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

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

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

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

### 17.3.2 Organization of the center

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

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

### 17.3.3 Documentation to be delivered to the sponsor

The researcher undertakes, before the start of the study:

- To provide an updated Curriculum Vitae (maximum 10 pages) in Spanish (or corresponding language) dated and signed, and send it or deliver it to the sponsor along with your or your collaborators or work team,

- Copy of Academic Certifications (undergraduate and postgraduate degrees and federal professional cedulas)

- A copy of the operation notice, if applies. (when it is a private practice).

## 18. APPENDICES

### Appendix 1: Declaration of Helsinki of the World Medical Association

### DECLARATION OF HELSINKI OF THE AMM

Ethical Principles for Medical Research in Human Beings

Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964

and amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975

35th World Medical Assembly, Venice, Italy, October 1983

41st World Medical Assembly, Hong Kong, September 1989

48th General Assembly Somerset West, South Africa, October 1996

52nd General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification of Paragraph 29, added by the WMA General Assembly, Washington 2002

Note of Clarification of Paragraph 30, added by the General Assembly of the AMM, Tokyo 2004

59th General Assembly, Seoul, Korea, October 2008

### A. INTRODUCTION

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

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

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

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

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

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

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

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

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

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

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

## B. PRINCIPLES FOR ALL MEDICAL INVESTIGATIONS

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

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

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

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

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

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

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

18. Every study of medical research with human beings should be preceded by a careful assessment of the predictable risks and burdens for the individuals and communities participating in the research, compared to the benefits foreseen for them and for other affected individuals or communities. for the condition under investigation.

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

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

21. Medical research involving human subjects may be carried out only if the importance of the objective exceeds the risks and burdens inherent to the subjects under investigation.

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

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

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

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

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

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

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

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

and study protocol has been approved by a research ethics committee. The consent must be obtained to continue in the investigation as soon as possible, the subject or the legally authorized representative.

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

**C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL ATTENTION**

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

32. The benefits, risks, burdens, and effectiveness of a new intervention must be tested against those of the best intervention currently tested, except in the following circumstances:

 It will be acceptable to use a placebo or not to administer treatment when there is no currently proven intervention; or

 When for methodological and scientific reasons the use of placebo is necessary to determine the efficacy or safety of an intervention, and subjects who are given placebo or no treatment are not at risk of serious or irreversible damage. Care should be taken to avoid abuse of this option.

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

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

35. In the treatment of a subject, when there are no proven interventions or have been ineffective, the doctor, after seeking expert advice and with the informed consent of the subject or the legally authorized representative, may use an unproven intervention if in his opinion the doctor offers hope to save lives, restore health or relieve suffering. When possible, this intervention should be part of the object of the investigation, designed to

assess its safety and efficacy. In all cases, the new information must be recorded and, when appropriate, made publicly available.

## Appendix 2: questionnaire VF14

**Apéndice 2: cuestionario VF14**

**Nombre del sujeto:** _____.
**Fecha de nacimiento:** _____. **Fecha de visita:** _____.

**¿A causa de su visión, cuanta dificultad tiene para realizar las siguientes actividades?**
***Si NO realiza alguna actividad porfavor circule la opción N/A (no aplica).**

| ACTIVIDAD | | Ninguna | Poco | Moderada | Muy difícil | No puedo |
|---|---|---|---|---|---|---|
| Leer letras pequeñas. (como las de los medicamentos, etiquetas de comida etc.) | N/A | | | | | |
| Leer el periódico o un libro | N/A | | | | | |
| Leer letras grandes en el periódico (encabezados) o en un libro, o los números del teléfono. | N/A | | | | | |
| Reconocer a la gente cuando se acercan | N/A | | | | | |
| Ver escalones, banquetas, o desniveles. | N/A | | | | | |
| Leer señales de tránsito, letreros en la calle o de las tiendas. | N/A | | | | | |
| Realizar actividades como costura, tehído o bordado. | N/A | | | | | |
| Llenar formularios de datos o cheques. | N/A | | | | | |
| Jugar juegos de mesa (lotería, cartas). | N/A | | | | | |
| Practicar deportes | N/A | | | | | |
| Cocinar | N/A | | | | | |
| Ver televisión. | N/A | | | | | |
| Manejar carro durante el día. | N/A | | | | | |
| Manejar carro durante la noche. | N/A | | | | | |

Firma del sujeto: _____
_____.

Para uso exclusivo del aplicante:

| | | | | | | |
|---|---|---|---|---|---|---|
| C= | No. De casillas seleccionadas en esta columna. | | | | | |
| F= | Cantidades factorizadas | X4= | X3= | X2= | X1= | 0= |

Puntaje final: (F _____ / C _____ ) x 25 = V

V=

Firma del médico aplicante: _____.

**VF-14 Rating:**

**F = results from multiplying the number of boxes in said column by the corresponding X value.**

**It will be done like this with each column.**

**Subsequently, the values of all the columns will be added and divided by the value of C.**

**The value of C corresponds to the sum of the number of squares answered except those that do not apply, the maximum being 14.**

## Appendix 3: Eye comfort index questionnaire.

Version 1.0 / September 2014

**Apéndice 3: Cuestionario índice de confort ocular.**

**Versión 1.0 / Septiembre 2014**

**Nombre:**_____. **Iniciales:**_____.

**Fecha de aplicación:** ___ /_____/___ **(día/mes/año).**

*Instrucciones:* Marque con una cruz un número del 0 al 10, calificando las molestias que ha sentido a lo largo del uso de este medicamento, siendo 0 (cero) ninguna molestia y 10 molestias insoportables.

1.-¿Durante el uso de este medicamento ha sentido **cansancio** en sus ojos?

0____1____2____3____4____5____6____7____8____9____10

2.- ¿Durante el uso de este medicamento ha sentido **ardor** en sus ojos?

0____1____2____3____4____5____6____7____8____9____10

3.- ¿Durante el uso de este medicamento ha sentido **comezón** en sus ojos?

0____1____2____3____4____5____6____7____8____9____10

4.- ¿Durante el uso de este medicamento ha sentido **resequedad** (arenillas) en sus ojos?

0____1____2____3____4____5____6____7____8____9____10

5.- ¿Durante el uso de este medicamento ha sentido **dolor** en sus ojos?

0____1____2____3____4____5____6____7____8____9____10

**Nombre del médico que aplicó:**_____.

**Firma:**_____.

## Appendix 4: Sample calculation

### Table 5

Formula to calculate the sample size considering parameters recorded in periodicals for the variable: "Final intraocular pressure in patients with glaucoma or ocular hypertension, treated with Krytantek".

$$n = \frac{2Sp^2}{(X1-X2)^2} (Z1-a/2 + Z1-b)^2$$

Sp = Average standard deviation of the test variable in patients treated with Krytantek. 2.40

X1 = Average of the reference population (Krytantek) 14.68

X2 = Average of the experimental population (Other) 15.68

(X1 - X2) = Difference of expected means, that wants to be contrasted (Sampling error) 1.00

a = Level of significance or probability of error type 1 = 0.05

1-a / 2 = Bilateral percentages for the level of assigned significance. = 0.975

Z0.975 = Z of the standardized normal distribution that leaves an area of 0.975 to the left. It implies 95% reliability. 1.96

b = Probability of error type 2 = 0.20

1-b = Unilateral percents for the assigned beta = 0.80

Z0.80 = Z of the standardized normal distribution that leaves an area of 0.80 to the left. It implies a power of proof of 80%. 0.842

n= 90.4458701

Minimum necessary sample size that assures us with a probability of 0.80 (Power of 80%) that if the difference you want to contrast is true (1 mm Hg or more difference), the study confirms it rejecting the null hypothesis and that if this difference is less than 1 mm Hg (less than the magnitude of the expected difference - sampling error), then do not reject the null hypothesis, and confirm that the difference is not of the magnitude that arises, with a probability of: 0.95 which implies a 95% Reliability.

Table 6

Formula to calculate the sample size considering parameters recorded in periodicals for the variable: "Decrease in final intraocular pressure in patients with glaucoma or ocular hypertension, treated with Krytantek".

$$n = \frac{2Sp^2}{(X1-X2)^2} (Z1-a/2 + Z1-b)^2$$

Sp = Average standard deviation of the change in intraocular pressure in patients treated with Krytantek 2.30

X1 = Average of the reference population (Krytantek) 10.20

X2 = Average of the experimental population (Other) 11.20

(X1 - X2) = Difference of means expected, that wants to be contrasted

(Sampling error) 1.00

a = Level of significance or probability of error type 1 = 0.05

1-a / 2 = Bilateral percentages for the level of assigned significance. = 0.975

Z0.975 = Z of the standardized normal distribution that leaves an area of 0.975 to the left. It implies 95% reliability. 1.96

b = Probability of error type 2 = 0.20

1-b = Unilateral percents for the assigned beta = 0.80

Z0.80 = Z of the standardized normal distribution that leaves an area of 0.80 to the left. It implies a power of proof of 80%. 0.842

n = 83.0657383

Minimum necessary sample size that assures us with a probability of 0.80 (Power of 80%) that if the difference you want to contrast is true (1 mm Hg more, or less change in IOP), the study confirms it by rejecting the null hypothesis and that if this difference is less than 1.00 mm Hg (less than the magnitude of the expected difference - sampling error), then do not reject the null hypothesis, and confirm that the difference is not of the magnitude that arises, with a probability of: 0.95 which implies a 95% Reliability.

Table 7. Fleiss' formula for calculating the sample size for proportions. "Statistical Methods for Rates and Proportions" 2a. Ed. Pp. 38-45 Comparison of two proportions.

**Cuadro 7. Fórmula de Fleiss para el cálculo del tamaño de muestra para proporciones.**
**"Statistical Methods for Rates and Proportions" 2a. Ed. Pp. 38-45**
**Comparación de dos proporciones.**

| | | |
|---|---|---|
| r = Razón de: | Krytantek : Krytantek [Otros] 1 : 1 | 1.00 |
| P1 = Proporción de casos con eventos adversos (Krytantek) | | 0.0448 |
| Q1 = 1 - P1 | | 0.9554 |
| P2 = Proporción de casos con eventos adversos (Otros) | | 0.1848 |
| Q2 = 1 - P2 | | 0.8054 |
| P = Proporción promedio ponderada de mejoría en el universo | | |
| $P = \frac{(P1 + r * P2)}{r + 1}$ | | 0.1196 |
| Q = 1 - P | | 0.8804 |
| $\alpha$= Nivel de significancia o probabilidad de error tipo 1 | | 0.050 |
| $1-\alpha/2$= Percentila bilateral para el nivel de significancia asignado | | 0.975 |
| $Z_{1-\alpha/2}$= $Z_{0.975}$ de la distribución normal estandarizada que deja un area de 0.975 a la izquierda. Implica una confiabilidad del 95% | | 1.960 |
| $\beta$= Probabilidad de error tipo 2 | | 0.200 |
| $1-\beta$= Percentila unilateral para la beta asignada | | 0.800 |
| $Z_{1-\beta}$= $Z_{0.80}$ de la distribución normal estandarizada que deja un area de 0.80 a la izquierda. Implica un poder del 80% | | 0.842 |

m' = Tamaño de muestra

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

$$m' = \frac{\left( 1.960 \sqrt{(1.00+1)\ 0.12 * 0.88} + 0.842 \sqrt{1.00 * 0.04 * 0.96 + 0.18 * 0.81} \right)^2}{1.00\ (0.18 - 0.04)^2}$$

m' = 72.272

m = Tamaño de muestra corregido

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

| | | | | |
|---|---|---|---|---|
| m = | 85 | Tamaño de muestra para el grupo de referencia (Krytantek): | $m_1 = r*m$ | 85 |
| | | Tamaño de muestra para el grupo de estudio (Otros): | $m_2 = m$ | 85 |

## 19. REFERENCES


i. i Leske M. Early Manifest Glaucoma Trial. Design and baseline data. Ophthalmology 1999; 106: 2144-2153.

ii. ii Sample PA, Bosworth CF, Blumenthal EZ, et al. The loss of visual function in glaucoma. Seminars in Ophthalmology . 2000: 15(4): 182-193.

iii. iii Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. Br J Ophthalmol. 2006 Mar;90(3):262-7.

iv. iv Bowd C, Weinreb RN, Zangwil LM. Evaluating the Optic Disc and Retinal Nerve Fiber Layer in Glaucoma I: Clinical examination and photographic Methods. *Seminars in Ophthalmology.* 2000: 15(4): 194-205.

v. v Kwon YH, Caprioli J. Primary open angle glaucoma. En: Tasman W, Jaeger EA, eds. Duane's clinical ophthalmology. Philadelphia: J.B. Lippincott, 1999:pp.1-30.

vi. vi Jiménez-Román J, Paczka J, Lineamientos y Recomendaciones para el manejo del Glaucoma, 2da Edición, México DF, Intersistemas SA de CV, 2005, pp. 15-19.

vii. vii Perkins ES, Phelps CD. Open-angle glaucoma, ocular hypertension, low-tension glaucoma, and refraction. *Arch Ophthalmol* 1982; 100:1464.

viii. viii Emre M, Orgui S, Gucleta K, *et al*. Ocular blood flow alteration in glaucoma is related to systemic vascular dysregulation. *Br J of Ophthalmology* 2004; 88(5):662-666.

ix. ix Gordon M; Beiser J, Brandt J, *et al*. The Ocular Hypertension Treatment Study. Baseline factors that predict the onset of primary open angle glaucoma; *Archives of Ophthalmology* 2002; 120(6):714–720.

x.x Distelhorst J, Hugues G. Open Angle Glaucoma. *American Family Phisician.* 2003; 67(9):1937-1944.

xi. xi Colegio Mexicano de Glaucoma, Grupo Mexicano de investigación en Glaucoma Consenso Nacional para el Diagnóstico y Tratamiento del Glaucoma México 2009. Reporte Final del Grupo Mexicano de Investigación en Glaucoma.

xii. xii Laboratorios Sophia S.A. de C.V. Estudio farmacocinética de una solución oftálmica en combinación fija de brimonidina, dorzolamida y timolol.

xiii. xiii Laboratorios Sophia S.A de C.V Estudio preclínico de la eficacia de Krytantek ofteno® vs terapia separada concomitante en conejos albinos nueva zelanda. Data on file.

xiv. xiv Laboratorios Sophia S.A. de C.V. "Estudio clínico de la seguridad y la tolerancia de una solución tópica oftálmica de dorzolamida, brimonidina y timolol en combinación fija, aplicada en la superficie ocular de voluntarios humanos oftalmológicamente sanos" Data on file.
xv. xv IER Grading Scales. Institute for Eye Research, Sydney, Australia. Available at: http://www.siliconehydrogels.org/grading_scales/SETUP.HTM. Accessed July 20, 2007

xvi. Clin Ophthalmol. 2014 May 14; 8:927-35. doi: 10.2147/OPTH.S49467. eCollection 2014. Patient adherence and persistence with topical ocular hypotensive therapy in real-world practice: a comparison of bimatoprost 0.01% and travoprost Z 0.004% ophthalmic solutions. Campbell JH1, Schwartz GF2, LaBounty B3, Kowalski JW1, Patel VD1.

xvii. Pisella, P.J., Pouliquen, P., Baudouin, C., 2002. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication.Br.J.Oph-thalmol. 86,418e423.
xviii. Sherwood MB, Grierson I, Millar L, Hitchings RA. Long-term morphologic effects of antiglaucoma drugs on the conjunctiva and Tenon's capsule in glaucomatous patients. Ophthalmology 1989; 96 (3): 327-35.
xix. Christophe Baudouin, Antoine Labbé, Hong Liang, Aude Pauly, Françoise Brignole-Baudouin, Preservatives in eyedrops: The good, the bad and the ugly, Progress in Retinal and Eye Research, Volume 29, Issue 4, July 2010, Pages 312-334 , ISSN 1350-9462.