Excelencia en oftálmicos

Protocol:

SOPH122-0420/IV

Proposed title for the study: Phase IV clinical study, to compare the efficacy of the combination of Krytantek Ofteno PF® plus Gaap Ofteno PF® against the combination of Eliptic Ofteno PF® plus Gaap Ofteno PF®, in patients with primary open-angle glaucoma or ocular hypertension.

Information on the molecules under study

Name of pharmaceutical products: Gaap Ofteno PF® (GOF), Krytantek Ofteno PF® (KOF), Eliptic Ofteno PF® (EOF).

Generic name: GOF: latanoprost 0.005% preservative-free ophthalmic solution. KOF: fixed combination of timolol 0.5%, dorzolamide 2%, and brimonidine 0.2% preservative-free ophthalmic solution. EOF: fixed combination of timolol 0.5% and dorzolamide 2% preservative-free ophthalmic solution.

Indication: Treatment of primary open-angle glaucoma and ocular hypertension.

Protocol information

Development phase: IV

Version: 2.0

Data version: 21-jul-20

Clinical Trials Code: NCT04702789

This protocol has been developed in accordance with the principles of the Declaration of Helsinki and will be carried out in accordance with Good Clinical Practices and in compliance with ICH guidelines and current local legislation.

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

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Changelog

Changes from version 1.0 dated May 15, 2020, to version 2.0 dated July 21, 2020.

1. Cover. – The following text has been changed: “Design/Summary for the Study” to “Protocol for the Study”; “Version: 1.0” to “Version: 2.0”; and “Version Date: May 15, 2020” to “Version Date: July 21, 2020.”
2. Change History. – The Change History sheet has been added.
3. Headers. – Change the text from “Version 1.0, Date: May 15, 2020” to “Version 2.0, Date: July 21, 2020.”
4. Contents. – The table of contents has been updated.
5. Table of Tables and Figures. – A space has been added between the table of contents to facilitate review.
6. Study Manager – The name and email address of the operational manager are added.
7. Sponsor signature pages. – The name of the operational manager is added.
8. Summary of the protocol for study SOPH122-0420/IV. – The following texts have been changed: “Protocol version: 1.0” to “Protocol version: 2.0”; and “Version date: May 15, 2020” to “Version date: July 21, 2020.”
9. 9.1.11 Adverse events. – The following modifications have been made to specify the reason for collecting adverse events from the date of signing the informed consent.

   The paragraph:

   “An AE is defined as any adverse medical occurrence in a subject administered an investigational product, regardless of causal attribution.”

   It is changed to the following:

   “An EA is defined as "Any adverse medical occurrence in a subject administered an investigational product, regardless of causal attribution. However, Good Clinical Practices, Mexican Regulation (NOM-220-SSA1-2016), and the need to establish the patient's baseline status, including adverse events caused by treatment prior to the study and disease manifestations, in order to compare adverse events after treatment, require the researcher to collect and report all adverse events and suspected adverse events from the moment informed consent is obtained."

   The following paragraph is deleted:

   One month after treatment, adverse events occurring with concomitant treatment should be recorded, and adverse events recorded with experimental and concomitant treatment should be assessed at subsequent visits.

10. The numerals in sections 9.1.12 to 9.1.24 are corrected, since section 9.1.11 was repeated twice.

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Content

Index of Tables and Figures

Study leader

The administrative structure of the sponsoring party, corresponding to Laboratorios Sophia, SA de CV, is shown in Table 1. Study managers .

Table 1. Study leaders

Function	Name/Contact	Membership ¥
Medical Director of the study	[redacted]	Medical Director
Director of the study		Medical Manager
Operations Manager		Regional Clinical Research Manager
Author of the Protocol		Medical Editor
Biostatistics		Biostatistics Manager

¥ Employees of Laboratorios Sophia, SA de CV, Av. Paseo del Norte No. 5255, Col. Guadalajara Technology Park, Guadalajara-Nogales Highway Km13.5 CP 45010 Zapopan, Jalisco, Mexico Tel +52(33) 3000 4200

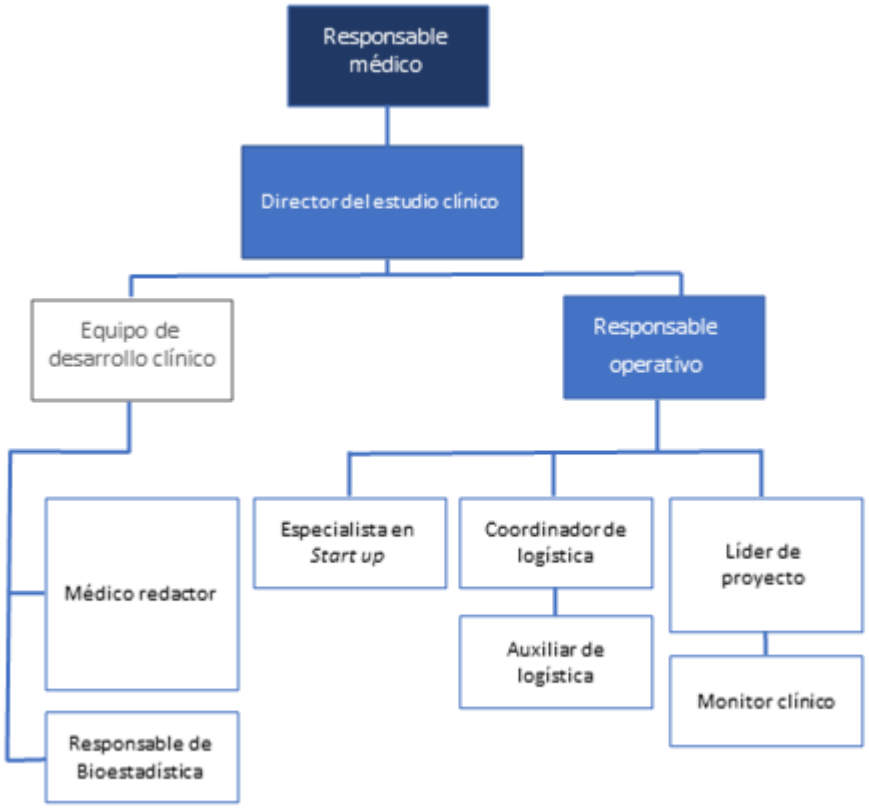

Figure1 Administrative structure

Sponsor's Signature Page

Name:	
Qualification: Medical Director of the study	**Signature** **Date**

Name:	
Qualification: Director of the study	**Signature** **Date**

Name:	
Qualification: Operations Manager	**Signature** **Date**

Name:	
Qualification: Author of the protocol	**Signature** **Date**

Researcher Agreement

I agree to conduct this clinical study according to the design and guidelines of this protocol, adhering to its provisions. I declare that I will conduct the study in accordance with the standards of Good Clinical Practice and will report all information and data as indicated in the protocol, particularly any adverse events. I will also manage clinical supplies provided by the sponsor strictly in accordance with this protocol. I understand that the information that identifies me may be used by the sponsor. Because the information contained in this protocol and the Investigator's Manual is confidential, I understand that sharing it with any third party not involved in the approval, supervision, or conduct of the study is prohibited. I will ensure that necessary precautions are taken to protect the information from loss, inadvertent disclosure, or access by unauthorized third parties.

Name: [Write the full name of the researcher	**Signature**
Qualification: Principal Investigator	**Date**
Name of the center: [Write name of study center]	
Geographic location (city/state/country) [Write the geographic data of the center]	

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List of abbreviations

AA	Alpha-adrenergic agonist
APG	Prostaglandin analogue
AVMC	Best corrected visual acuity
BAK	Benzalkonium chloride
BB	Beta-blocker
IDB	Twice a day
BPC	Good clinical practices
CV	Visual capacity
CEI	Research Ethics Committee
CI	Informed consent
ICC	Informed consent letter
CIGTS	Glaucoma Initial Treatment Collaborative Initial Glaucoma Treatment Study)
CRF	Case Report Form Form)
DM	Mean deviation
DSM	Standard deviation of the model
EA/EAS	Adverse event / serious adverse event
EOF	Elliptic Ofteno PF ®
FDA	Food and Drug Administration
GOF	Gaap Ofteno PF ®
GAA	Open-angle glaucoma
GPAA	Primary open-angle glaucoma
GCAC	Chronic angle-closure glaucoma
GCC	Central corneal thickness
GPAC	Primary angle-closure glaucoma
GTN	Normal tension glaucoma
HTO	Intraocular hypertension
IAC	Carbonic anhydrase inhibitors
ICH	International Conference on Harmonization (for its acronym in English) International Conference on Harmonization)
ICO	Eye comfort index
IP	Principal investigator of the clinical study
ITT	Intention-to-treat population
KOF	Krytantek Ofteno PF ®
MAO	Monoamine oxidase

NO	Optic nerve
NOM	Mexican Official Standard
OCT	Optical coherence tomography
WHO	World Health Organization
PIO	Intraocular pressure
PNA	Unanticipated problems
PP	Population by protocol
RAM	Adverse drug reaction
RCD	Cup/disc ratio
SRAM	Suspected adverse drug reaction
TID	Three times a day
TMM	Maximum medical therapy
TMMT	Maximum tolerated medical therapy
QD	Once a day
VDF	Verification of source documents

1. Summary of the study protocolSOPH122-0420/IV

1.1 Synopsis

Title of the study: Phase IV clinical study, to compare the efficacy of the combination of Krytantek Ofteno PF® plus Gaap Ofteno PF® against the combination of Eliptic Ofteno PF® plus Gaap Ofteno PF®, in patients with primary open-angle glaucoma or ocular hypertension.	
Protocol code: SOPH122-0420/IV	**Creation date :** April 20, 2020
Protocol version : 2.0	**Version date:** July 21, 2020
Therapeutic indication: Tratamiento del glaucoma primario de ángulo abierto e hipertensión ocular.	**Use:** Reduction and control of intraocular pressure.
Estimated duration of the study (from the first visit of the first patient to the preparation of the final report) **:** 14 meses	**Development phase :** IV

Aim:

To determine the superiority in additional lowering of mean intraocular pressure of the preservative-free fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2% (Krytantek Ofteno PF ®), compared with the effect obtained by the preservative-free fixed combination of timolol 0.5%/dorzolamide 2% (Elliptic Ofteno PF ®), in patients with primary open-angle glaucoma or ocular hypertension treated with preservative-free latanoprost (Gaap Ofteno PF ®).

Goals secondary

- To determine the efficacy of adding the preservative-free fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2% (Krytantek Ofteno PF ®) to patients with primary open-angle glaucoma or ocular hypertension treated with preservative-free latanoprost (Gaap Ofteno PF ®).
- To determine the efficacy of adding the preservative-free fixed combination of timolol 0.5%/dorzolamide 2% (Elliptic Ofteno PF ®) to patients with primary open-angle glaucoma or ocular hypertension treated with preservative-free latanoprost (Gaap Ofteno PF ®).

Hypothesis:

H_0 = The mean final reduction in intraocular pressure obtained by adding the preservative-free fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2% (Krytantek Ofteno PF ®) is not superior to the effect obtained by adding the preservative-free fixed combination of timolol 0.5%/dorzolamide 2% (Elliptic Ofteno PF ®), in patients with primary open-angle glaucoma or ocular hypertension treated with preservative-free latanoprost (Gaap Ofteno PF ®). $A\ difference \geq 1.5$ mmHg between treatments is considered superior .

H_1 = The mean final reduction in intraocular pressure obtained by adding the preservative-free fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2% (Krytantek Ofteno PF ®) is superior to the effect obtained by adding the preservative-free fixed combination of timolol 0.5%/dorzolamide 2% (Elliptic Ofteno PF ®), in patients with primary open-angle glaucoma or ocular hypertension treated with preservative-free latanoprost (Gaap Ofteno PF ®). Considering a difference ≥ 1.5 mmHg between treatments as superior .
Study design : Phase IV, double-blind, multicenter, parallel-group, randomized clinical study.

Number of subjects:	**Main inclusion criteria:**
n= 116 cases. 58 cases per group. One case equals one eye. A subject may contribute one or two cases.	Glaucoma primario de ángulo abierto y/o hipertensión ocular no controlados por un solo agente hipotensor ocular.

Selection criteria:

Inclusion criteria:

- Subjects with primary open-angle glaucoma (according to the American Academy of Ophthalmology preferred practice pattern guidelines) or ocular hypertension, not controlled by a prostaglandin analogue or β -blocker in the eye to be included in the study.
- Treatment prior to the eligibility visit for ≥ 30 days with a prostaglandin analogue or β -blocker , in the eye to be included in the study.
- Intraocular pressure by Goldmann tonometry ≥ 19 and ≤ 26 mmHg in the eye to be included in the study.
- Ability to voluntarily grant informed consent.
- Be able and willing to comply with scheduled visits, treatment plan, and other study procedures.
- Age equal to or greater than 18 years.

Exclusion criteria :

- Being pregnant, breastfeeding, or planning to become pregnant during the clinical study.
- For women of reproductive age, not having access to a hormonal contraceptive method, intrauterine device, or bilateral tubal obstruction for a period of 30 days or more.
- Anterior chamber angle < 2 in the Shaffer Classification or presence of peripheral anterior synechiae in the eye to be included in the study.
- Being treated with any systemic ocular hypotensive (e.g. mannitol, glycerin, isosorbide).
- Best Corrected Visual Acuity less than 20/200 in the eye to be included in the study.
- Severe central visual field loss (sensitivity ≤ 10 dB at ≥ 2 of the 4 points central to the fixation point of the visual field), in the eye to be included in the study.
- History of ocular surgery or ocular laser procedure within the last 6 months in the eye to be included in the study.
- History of ocular trauma in the last 6 months in the eye to be included in the study.
- History of chronic uveitis in the eye to be included in the study.
- retrobulbar , subconjunctival or subtenon injection in the last 6 months in the eye to be included in the study.

- Patients with silicone, or who have had silicone, in the anterior or posterior segment of the eye to be included in the study
- Diagnosis of aphakia in the eye to be included in the study.
- Any corneal alteration that decreases the reliability of Goldmann tonometry in the eye to be included in the study.
- Known hypersensitivity to the active ingredients to be used in the study (prostaglandin analogues, β -adrenergic blockers, α2 - adrenergic agonists, carbonic anhydrase inhibitors).
- Diseases that contradict the use of the active ingredients to be used in the study (e.g. severe asthma or COPD, 2nd or 3rd degree atrioventricular block not controlled with a pacemaker, sinus bradycardia, manifest heart failure, Chronic Kidney Disease with a CrCl < 30 ml/min).
- Patients requiring the use of monoamine oxidase inhibitors (MAOIs), and patients treated with antidepressants that affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin).
- Patients who use, or have used in the last month, topical ophthalmic steroids in the eye to be included in the study, or by oral, intravenous, intramuscular, dermal, or intralesional routes.
- Have participated in another clinical research study within 30 days prior to signing the FCI.
- Having previously participated in this study.
- Having a history of drug addiction within the last two years prior to signing the FCI.
- Have any type of surgical intervention scheduled during the study period.
- Be or have an immediate family member (e.g., spouse, parent/legal guardian, sibling, or child) who is a member of the research site or sponsor staff.

<u>Elimination criteria</u>

- Intraocular pressure ≤ 18 mmHg at the baseline visit, in the eye to be included in the study.
- Intraocular pressure > 26 mmHg at the baseline visit, in the eye to be included in the study.
- Subject 's decision .
- Pregnancy .
- Presence of a serious adverse event.
- Lack of efficacy of maximum medical therapy (less than 20% decrease when any of the experimental treatments were added to treatment with latanoprost).
- Adherence less than 90% to the treatments provided in the study.
- Subject who does not attend two consecutive visits.

Experimental (investigational) treatment :

- <u>Investigational product, dosage and route of administration:</u>
  Krytantek Ofteno PF®. Fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2%. Sterile, preservative-free ophthalmic solution.Laboratorios Sophia, S.A. de C.V.
  Posology: 1 drop in the eye to be treated every 12 hours.
  Route of administration:Ophthalmic topical.

- <u>Comparator product, dose and route of administration (reference product):</u>

Eliptic Ofteno PF®. Fixed combination of timolol 0.5%/dorzolamide 2%. Sterile preservative-free ophthalmic solution.Laboratorios Sophia, S.A. de C.V.
Posology:1 drop in the eye to be treated every 12 hours.
Route of administration:Topical ophthalmic.

Concomitant treatment:

- Concomitant product in both groups:
  Gaap Ofteno PF®. Latanoprost 0.005%. Sterile preservative-free ophthalmic solution.Laboratorios Sophia, S.A. de C.V.
  Posology:1 drop in the eye to be treated every 24 hours at night.
  Route of administration:Topical ophthalmic

Duration of treatment :	**Approximate duration of the subject in the study:**
90 days.	105 days.

Evaluation criteria :

Effectiveness :

- Average reduction in intraocular pressure achieved with the experimental treatment when added to patients treated with preservative-free latanoprost (Gaap Ofteno PF ®).
- Percentage of patients treated with preservative-free latanoprost (Gaap Ofteno PF ®), who when one of the experimental treatments is added, achieve a reduction of ≥20%, ≥25%, ≥30%, ≥35% in their intraocular pressure.
- Percentage of patients treated with preservative-free latanoprost (Gaap Ofteno PF ®), who when one of the experimental treatments is added, achieve an intraocular pressure of ≤12, ≤13, ≤14, ≤15, ≤18 mmHg.

Security :

- Best corrected visual acuity (BCVA).
- Cup/disc ratio measured by the researcher and by OCT.
- Nerve fiber layer and ganglion cell thickness measured by OCT.
- Evaluation of the optic nerve by optic nerve photography.
- Visual fields determined by computerized campimetry.
- Central corneal thickness determined by pachymetry.
- Integrity of the ocular surface:
  - Hyperemia conjunctival
  - Chemosis
  - staining with fluorescein
- Events adverse .

Tolerability :

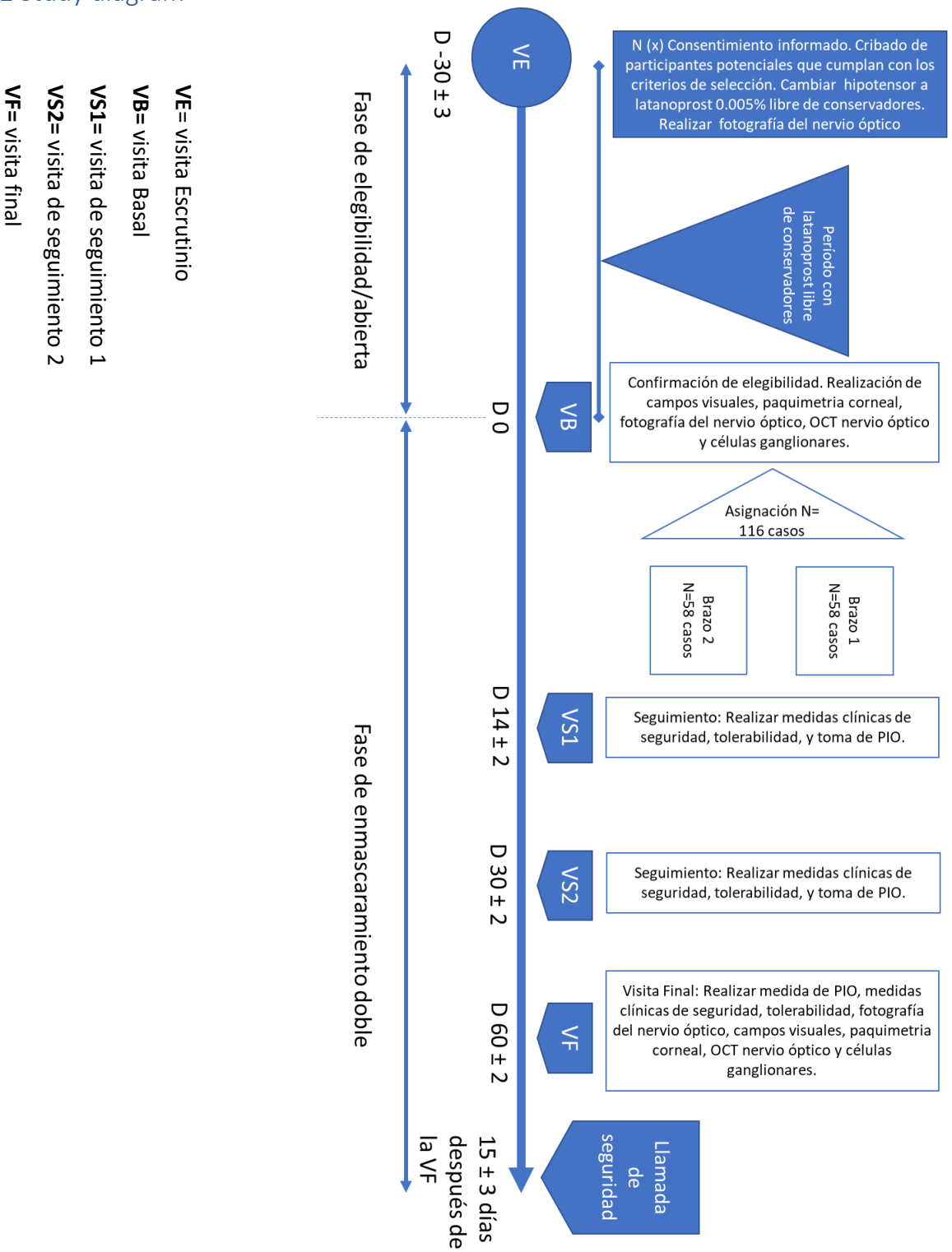
- Eye comfort index .

Statistical methodology:

The Kolmogorov-Smirnov (KS) and Shapiro-Wilk (SW) tests will be performed, as applicable, to determine whether the distribution presents normality in the results obtained in each study group. The data will be expressed with measures of central tendency: mean and standard

deviation for quantitative variables. Qualitative variables will be presented in frequencies and percentages. Statistical analysis will be performed using the Student's t-test for quantitative variables, considering a 95% confidence interval (95% CI) for the non-inferiority/superiority criteria based on the study objectives. The difference between qualitative variables will be analyzed using the X^2 (chi-square) test or Fisher's exact test. An alpha (α) ≤ 0.05 will be considered significant.

1.2 Study diagram



1.3 Subject schedule

	Eligibility Phase		Double-masking PHASE			
Procedures	Visit of		VISIT of			Safety call D 75 ± 3
	SCRUTINY D -30 ± 3	BASAL D 0	FOLLOW -up 1 D 14 ± 2	FOLLOW -up 2 D 30 ± 2	FINAL D 60 ± 2	
SIGNING of informed consent form	X					
HISTORY (general and ophthalmological)	X					
STOMATOGRAPHY (weight and height)	X					
Vital signs	X	X	X	X	X	
Evaluation of concomitant medications	X	X	X	X	X	X
Evaluation of adverse events	X	X	X	X	X	X
Pregnancy test (if applicable)	X				X	
Eye Comfort Index	X	X	X	X	X	
AVMC	X	X	X	X	X	
Assessment of ocular surface integrity (conjunctival hyperemia, chemosis, and corneal fluorescein staining)	X	X	X	X	X	
Goldmann type ocular tonometry	X	X	X	X	X	
Gonioscopy	X	X				
Fundoscopy in mydriasis (evaluation of the optic nerve, its cup, and the retina)	X	X			X	
EVALUATION of Eligibility CRITERIA	X	X				
optic nerve PHOTOGRAPHY	X	X			X	
Subject code assignment	X					
Delivery of the Identification Card	X					
Submission of the subject and training diary	X	X		X		

Delivery of concomitant treatment	X	X		X		
Return of concomitant treatment		X		X	X	
Assessment of treatment adherence (review of subject diary and weight of bottles)		X	X	X	X	
Corneal pachymetry		X			X	
Visual fields		X			X	
OCT optic nerve and ganglion cells		X			X	
RANDOMIZATION to experimental treatment group		X				
Delivery of experimental treatment		X		X		
Fundoscopy without mydriasis, unless the Investigator considers mydriasis necessary (evaluation of the optic nerve, its cup, and the retina)			X	X		
Return of experimental treatment				X	X	
Continuity assessment			X	X		

2. Theoretical framework

2.1 Introduction

Glaucoma is a progressive optic neuropathy characterized by the loss of retinal ganglion cells and their respective axons, resulting in the distinctive appearance of the optic disc and concomitant loss of visual function. [1]It is the second leading cause of blindness worldwide, and it is estimated that by 2020, 79.6 million people will have glaucoma, with 74% of them presenting with primary open-angle glaucoma (POAG). [2]The Latin American population, especially those of Mexican origin, is more prone to developing POAG compared to Anglo-Saxons. [3] [4]

The mechanism by which glaucoma damages the optic nerve is likely multifactorial; however, elevated intraocular pressure (IOP) is the main risk factor and the only one that can currently be modified to prevent the progression of glaucoma damage, including normal-tension glaucoma. [5] [6] [7] [8] [9]Reducing IOP has also been shown to decrease the conversion rate of ocular hypertension (OHT) to glaucoma. [7] Chauhan et al. reported that for every 1 mmHg increase in IOP, the risk of glaucoma progression increases by 19%.[5]

Despite significant advances in surgical filtration treatments, implants, and laser procedures that improve trabecular drainage, drug therapy remains the initial intervention for most patients with OHT and glaucoma; this treatment typically includes topical application of antihypertensive agents. [10]

Currently, pharmacological options in Latin America for topical IOP reduction include prostaglandin analogues (PAGs), β -blockers (BBs), α2 - adrenergic agonists (AAs), carbonic anhydrase inhibitors (CAIs), and parasympathomimetics. Pharmacotherapy commonly begins with the application of a single antihypertensive agent, usually one of the so-called first-line agents (prostaglandin analogues or β- blockers). [11]However, monotherapy may be insufficient in many cases due to the inability to achieve the target IOP and/or prevent glaucoma progression. In some other cases, the same medication may lose its effectiveness over time due to tachyphylaxis . [12]*The Ocular Hypertensive* Treatment Study (*THTSS) Treatment Study*) reported that, at 5 years, approximately 40% of patients require two medications to achieve a 20% IOP reduction from baseline, while an additional 9% require more than two medications. [7]Therefore, more than one medication is frequently required for adequate medium- and long-term IOP control. This can be achieved with the concurrent use of two or more medications from different classes, either concomitantly or in a fixed combination. [12]

In addition to their IOP-lowering efficacy, fixed combinations offer multiple benefits when compared with concomitant administration of their active ingredients: 1) lower cost, 2) simpler treatment regimen, 3) better treatment adherence, and 4) decreased risk of washout. [13] [14] [15]

For he treatment of the HTO and he GPAA he use of a only medicine can result insufficient when trying to reach the target IOP, so it is necessary to resort to the use of 2 or more ocular hypotensive agents of different families. [5] [11] [12]

A simplified glaucoma treatment regimen proposes starting with monotherapy, based on a first-line drug such as an APG or a BB, the former being the most commonly used by ophthalmologists today. If this initial therapy is not sufficient to achieve the target IOP, but does significantly reduce IOP, a second drug is added, preferably the other first-line drug not previously used. This intermediate therapy would already be requiring three daily instillations, theoretically compromising treatment adherence. Therefore, the treating physician may decide to migrate to a fixed combination of two drugs. If the target IOP is not achieved, a third drug can be added to achieve the maximum tolerated

medical therapy (MTMT) regimen stipulated by Zimmerman of three drugs in three daily instillations. [16]

As previously postulated, the use of fixed combinations offers advantages over the concomitant application of its components and a fixed combination of three drugs can broaden the horizon towards he new plan of TMMT postulate by *Sampaolesi* , he which contempla fixed triple therapy (timolol, dorzolamide, brimonidine) + an APG. [16]

2.2 Glaucoma and its classification

The term glaucoma encompasses a variety of conditions that all have in common the characteristic of being an acquired, degenerative, and progressive optic neuropathy. Glaucoma-related optic neuropathy is characterized by a specific pattern of optic nerve abnormalities, and although glaucoma is frequently associated with elevated IOP, elevated IOP is not necessary for diagnosis. [11] [17] [18]

This disease is classified according to the underlying anatomy and pathophysiology, with open-angle glaucoma (OAG) and angle-closure glaucoma being the two main subtypes (*see Figure 2 Classification of glaucoma*). Both can occur without an identified cause, resulting in idiopathic, or primary, glaucoma. Secondary glaucoma is a form of glaucoma in which there is an identifiable cause of the increased intraocular pressure and optic nerve damage. Pseudoexfoliation glaucoma is the most common type of secondary glaucoma.[17]

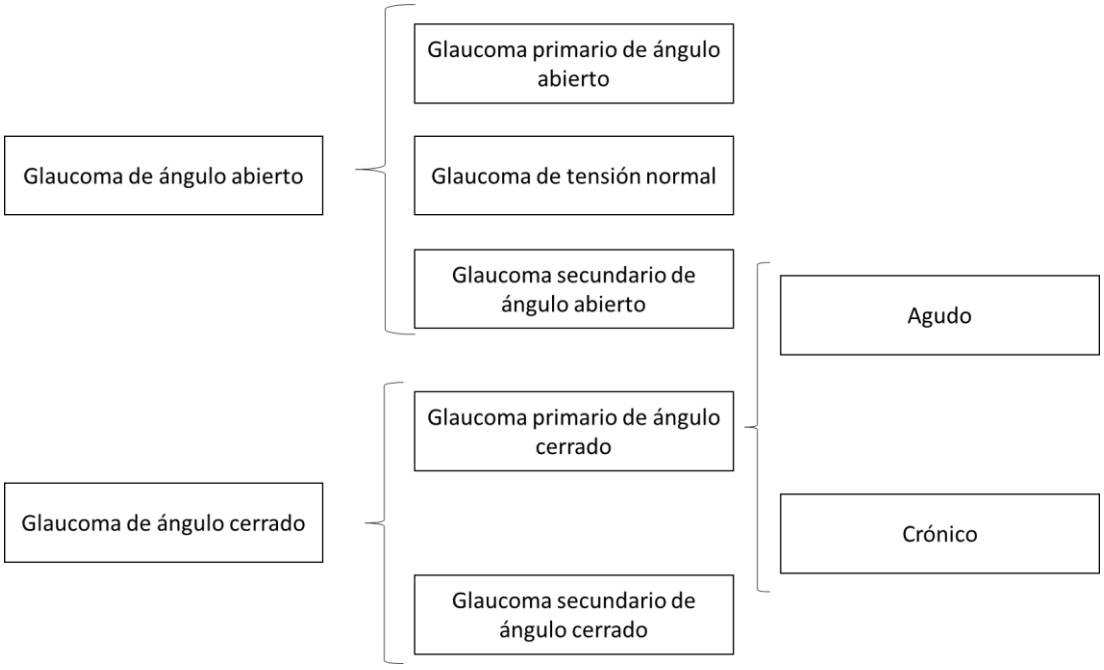


*Figure 2*Classification of glaucoma

The American Academy of Ophthalmology defines primary open-angle glaucoma (POAG) as a chronic and progressive optic neuropathy in adults where there is a characteristic acquired atrophy of the optic nerve, with loss of retinal ganglion cells and their axons, and with an open iridocorneal angle by gonioscopy.[17] [18]

Normal-tension glaucoma is a type of open-angle glaucoma, but where the IOP is within normal limits. Some consider this subgroup of patients to be a separate entity from POAG, while others

consider it to be part of primary open-angle glaucoma. In general, patients with normal-tension glaucoma have a high propensity for optic nerve damage related to low IOP. The amount of visual loss in patients with normal-tension glaucoma tends to be greater than would be expected based on the appearance of the optic nerve.[17] [18]

Chronic angle-closure glaucoma (CACG) occurs when there is a physiological obstruction of the trabecular meshwork, typically by the iris. Although it is a less common form of glaucoma, CACG accounts for 50% of glaucoma-related blindness.[17]

POAG can be classified as suspected glaucoma, and as mild, moderate, and advanced glaucoma, depending on the stage of the disease.[17]

Finally, ocular hypertension, although not an optic neuropathy, is a glaucoma-related entity. It is defined as intraocular pressure above 21 mmHg in patients with a normal-appearing visual field and optic nerve. Patients with ocular hypertension are at risk of developing POAG and are therefore considered glaucoma suspects. There is no standardized consensus on when these patients should be treated; however, it is reported that 12% to 63% of optic nerve fibers may be lost before a visual field defect can be detected. For this reason, treatment of ocular hypertension is considered to be directed toward selected individuals at high risk of developing POAG, such as patients with an IOP ≥ 24 mmHg or those with a ≥ 2% annual risk of developing glaucoma . [19] [20] [21]

2.3 Clinical manifestations and diagnosis of primary open-angle glaucoma

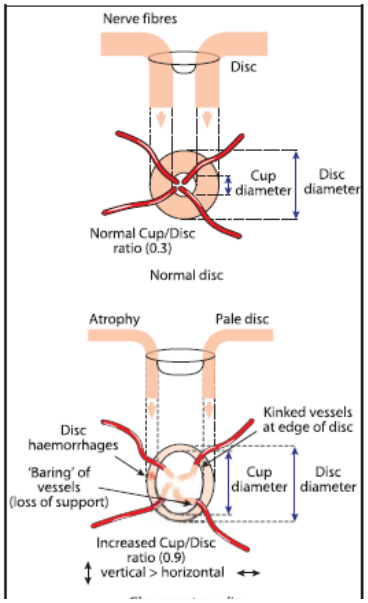


Figura 3 Cambios en el nervio óptico causados por glaucoma

In POAG, vision loss is gradual, and patients may not realize it until the damage has become severe. The disease is often detected during routine screenings. [22]

The best clinical sign we can find with the disease is changes in the optic nerve. The cup-disc ratio increases as the nerve fibers atrophy *(see Figure 3. Changes in the optic nerve caused by glaucoma)* . Asymmetry of the optic nerves is important because the disease is often more advanced in one eye than in the other. Finding hemorrhages in the optic nerve is a sign of a poor prognosis. [22]

Changes in the optic nerve that occur over time are best detected in serial photographs. Loss of peripheral vision is difficult to detect initially because it requires considerable loss of nerve fibers. The classic sign of glaucoma (visual field loss and increased cupping of the optic nerve) usually occurs in patients with pressure below the upper limit of normal (21 mmHg). Therefore, it is sometimes important to take several measurements throughout the day to detect any increase in pressure. [22]

Glaucoma screening should be part of your eye exam. The ability to diagnose the disease in its two main forms, open angle or angle closure, and assess its severity are critical for treatment and prevention of blindness. [23]

In the medical history, it is important to inquire about ocular history (refractive errors, trauma, surgery); family history of vision loss or glaucoma; systemic diseases; review previous notes or evaluations to assess IOP levels, optic nerve status, and visual fields; and review the use of drug therapies for the eye.[23] [18]

The equipment needed for the evaluation is described in *Table 2 Equipment needed for glaucoma evaluation* .

Board2 Equipment needed for glaucoma evaluation

Clinical evaluation	Minimum equipment required	Optional or recommended equipment
Visual acuity	Near or distance vision chart. Pinhole	3-4 meter visual acuity chart with contrast assessment chart
Refraction	Trial frame and lenses, retinoscope, Jackson cross cylinder	Phoropter Autorefractometer
Pupils	Pen-type pocket lamp	
Anterior segment	Slit lamp, keratometer	Corneal pachymeter
Intraocular pressure	Goldmann tonometer, portable tonometer, Schiotz tonometer	Tonopen Pneumotonometer
Angle	Slit lamp and lens for gonioscopy	Anterior segment optical coherence tomography. Ultrasonic biomicroscopy
Optic nerve	Direct ophthalmoscope Slit lamp with 78 or 90 diopter lens	Fundus camera Optic nerve analyzer (optical coherence tomography, confocal laser ophthalmoscopy, laser polarimetry)
Fundoscopy	Direct ophthalmoscope Indirect ophthalmoscope with 20 or 25 diopter lenses Slit lamp with 78 diopter magnifying glass	12 and 30 diopter lenses 60 and 90 diopter lenses
Visual fields	Manual perimetry or automated white-white campimetry	Automated shortwave campimetry, or with dual-frequency technology

What should be examined during the consultation is:[23] [18]

- Visual acuity: Inspect undilated and with best correction (BCVA), both at distance and near. Central vision may be affected in advanced glaucoma.

- Refractive errors: Refractive error can help determine the risk of open-angle glaucoma (myopia) or angle-closure glaucoma (hyperopia). Neutralizing this error is important for correctly assessing visual acuity and fields.
- Pupils: Reactivity and the presence of an afferent pupillary defect (a decreased response to miosis of the pupil when stimulated by direct light, but with a greater response to consensual stimulation) should be assessed. An afferent pupillary defect may be a sign of moderate or advanced asymmetric damage.
- Eyelids, sclera, conjunctiva: Examination may reveal signs of inflammation, redness, damage to the ocular surface, local pathology that may be related to poor IOP control, or possible medication allergies.
- Cornea: It should be assessed to rule out edema, which can be seen in acute or high-pressure glaucoma. Furthermore, IOP readings are underestimated in the presence of corneal edema. Corneal precipitates may indicate inflammation.
- Corneal thickness: This measurement can help us interpret IOP. Thick corneas tend to overestimate IOP, and thin corneas tend to underestimate it.
- Intraocular pressure: It should be measured in each eye before gonioscopy and mydriasis. It is recommended that the time of the assessment be recorded to monitor diurnal variations.
- Anterior segment: The anterior segment should be examined with or without mydriasis. The anterior chamber depth should be examined if secondary glaucoma evidence such as pseudoexfoliation, pimento, inflammation, or neovascularization is present.
- Iridocorneal angle: The angle should be examined to determine whether the iris is in contact with the trabecular meshwork, and to assess its location and extent. *See Figure 4 Iridocorneal angle* .

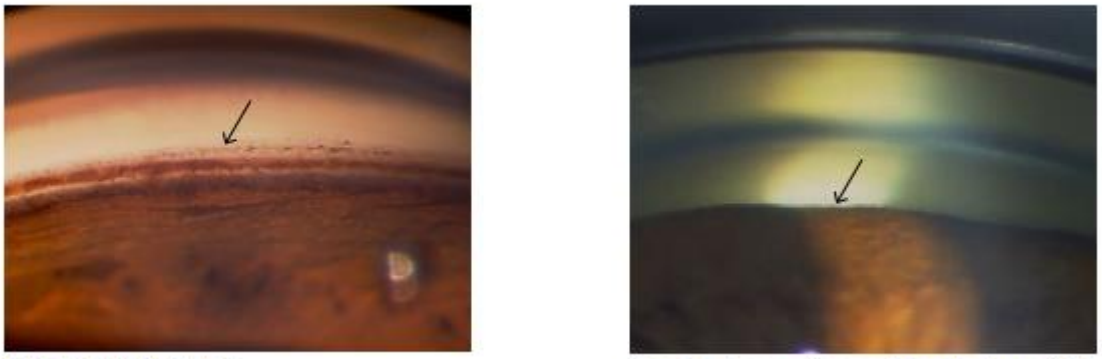


*Figure 4*Iridocorneal angle

- Iris: It should be examined for mobility and irregularity, the presence of synechiae and pseudoexfoliation at the margin, and its configuration (bulged, concave, flat). Its attachment height should be recorded.
- Lens: The lens should be examined to rule out cataracts, and to see its size, position, and whether there are synechiae or pseudoexfoliation material.
- Optic nerve: Review the characteristic signs of glaucoma *(see Figure 5. Optic nerve changes secondary to glaucoma)* . The degree of optic nerve damage helps guide treatment.

- Mild damage should include a cup ≥ 0.5, focal defects in nerve fibers, focal thinning in the neuroretinal rim, increased vertical cupping, cup/disc asymmetry, notching, hemorrhages, and non-compliance with the ISNT rule (the inferior side is thicker than the superior, the superior than the nasal, and the nasal than the temporal).
- Moderate to advanced damage shows a ≥ 0.7 cup, diffuse defect in nerve fibers, diffuse thinning of the neuroretinal rim, optic nerve pseudopits, and hemorrhages.

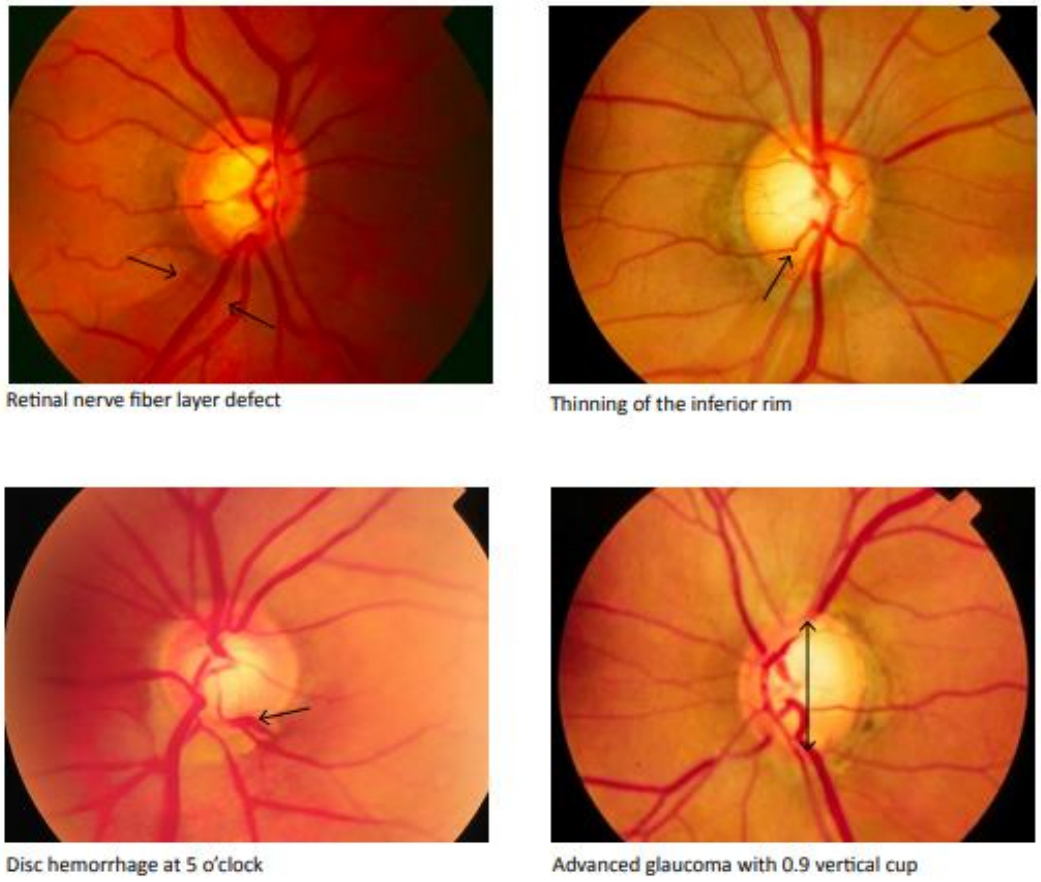


*Figure 5*Changes in the optic nerve secondary to glaucoma

- Fundoscopy: Evaluate the posterior pole to rule out other pathologies such as diabetic retinopathy, macular degeneration.
- Visual fields: The goal of treatment is to preserve visual function. Visual fields should be measured to identify, localize, and quantify the extent of visual loss. The presence of visual field damage could indicate moderate to advanced disease. Monitoring visual fields is important to determine disease stability. *See Figure 6 Progression of visual field defect* for an example of disease progression.

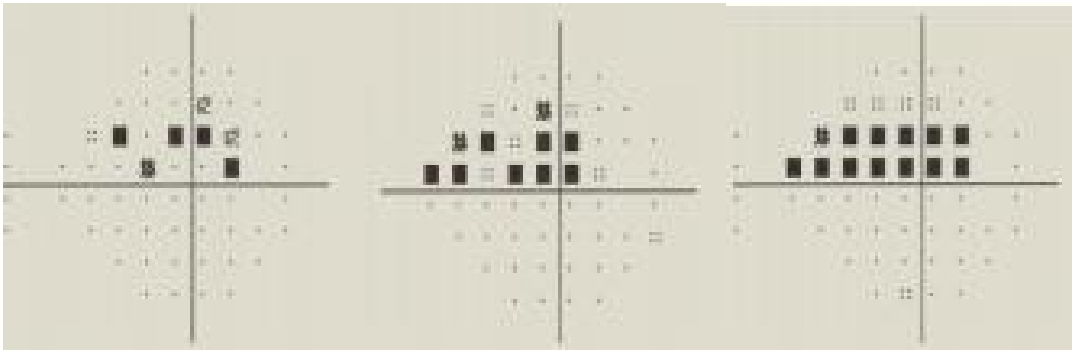


Figure6 Progression of the campimetric defect

2.4 Pharmacological management of glaucoma

The Collaborative Initial Glaucoma Treatment Study (CIGTS) demonstrated no difference between initial medical therapy and surgical therapy for preserving vision in glaucoma patients. However, glaucoma patients prefer medical therapy because adverse reactions associated with surgery are more problematic than those associated with drug therapy. Overall, initial medical therapy remains the treatment of choice for most patients with primary open-angle glaucoma. [24]

When glaucoma is diagnosed , the doctor does his or her best to assess the patient's likelihood of losing vision over the course of his or her lifetime. From this perspective, it's important to stage the disease to determine this likelihood. [24]

2.4.1 Establishing the target intraocular pressure

Despite significant progress in the field of neuroprotection, lowering IOP remains the only option available for treating glaucoma patients. Several studies have shown that lowering IOP is beneficial for glaucoma patients, even those with normal blood pressure. [25]Therefore, it is important to establish a target intraocular pressure, assuming that glaucoma progression is unlikely.

The European Glaucoma Society defines target IOP as the assessment of intraocular pressure achieved with treatment that could help prevent future glaucoma damage. The American Academy of Ophthalmology defines it as the appropriate intraocular pressure range to halt progressive pressure-induced damage. Therefore, target IOP is the pressure that will prevent the progression of visual loss without compromising the patient's quality of life. [26]

To determine the target IOP, it is necessary to pay attention to: the absolute cut-off value, percentage reduction, and values based on formulas. [26]

The absolute cutoff value is the IOP value that is relatively fixed and can be applied to a large number of patients with similar glaucoma-related damage. For example, the Advanced Glaucoma Intervention Study (AGIS) established that an IOP <18 mmHg in eyes with -10 dB of visual field damage did not progress over 8 years of follow-up. However, further analysis showed that these eyes actually had an average IOP of 12.3 mmHg. Author Palmberg demonstrated a 30% chance of progression if the pressure is maintained around 15 mmHg, and a 70% chance if it is maintained at 20 mmHg. For the treatment of mild-moderate-severe glaucoma, the initial pressure is generally staged at 18 mmHg, 15 mmHg, or 12 mmHg. [26]

The percentage of IOP reduction is an important value demonstrated in clinical studies. In patients whose IOP was reduced by 25% or 5.1 mmHg with medical therapy, progression was reduced by 45%, while in patients without this reduction, progression was reduced by 75%. In the Normal Tension Glaucoma Treatment Collaborative study, when a 30% IOP reduction was achieved, disease

progression was observed in 12% of patients at 5 years, while in untreated patients, progression was 35%. [26]

The following table shows the percentage of progression found in different studies as IOP was lowered. [26]

Board3 Percentage of intraocular pressure reduction in clinical studies

Study (names of studies in English, or authors)	Type of glaucoma	Basal IOP	Percentage of reduced IOP	Progression		Target IOP level
				With Tx	No Tx	
Ocular Hypertension Treatment Study	Open angle	24.9	20%	4.4%	9.5%	19.3
Early Manifest Glaucoma Trial	GPAA	20.6	25%	45%	62%	Decrease of 5.2 mmHg
Collaborative Normal Tension Glaucoma Study	GTN		30%	12%	35%	
Collaborative Initial Glaucoma Treatment Study Medical	GPAA	27	38%	15% progress with treatment and 15% improvement with treatment		17-18 mmHg
Surgicall		27	46%			14-15 mmHg
Stewart et al.						
Early	GPAA and GPAC	24.9±8	32-43%	18.7% progress with treatment		<18 mmHg
Moderate		28.3±5	44%	21.3% progress with treatment		<18 mmHg
Advanced		27.7±9	50%	2.3% progress with treatment		12 mmHg

Tx = treatment, GPAA = primary open-angle glaucoma, NTG = normal-tension glaucoma, PACG = primary angle-closure glaucoma.

There are several formulas for estimating target IOP values. These formulas attempt to incorporate the patient's risk factors into the assessment to estimate the target IOP. One of the most widely used formulas is the modified Jamper formula. *See Figure 7. Formula for target intraocular pressure* . [26] [25]

Pio Meta= Presión inicial (1-presión inicial/100) – Z ± 2

Z-0 Sospechoso de glaucoma
Z-1 Alto sospechoso de gluacoma
Z-2 Glaucoma leve
Z-3 Glaucoma moderado
Z-4 Glaucoma grave
Z-5 Glaucoma en estadío final

*Figure 7*Formula for target intraocular pressure

Establishing and achieving the target IOP helps to better define a disease management algorithm, since a patient's quality of life can be affected by the use of medications, which in some cases may be unnecessary. In patients with mild disease, an IOP of around 15 mmHg may be sufficient initially, while patients with moderate disease should have an IOP <15 mmHg to stabilize their visual field. Patients with advanced glaucoma need an IOP <14 mmHg, preferably 12 mmHg, with minimal fluctuations over time. In patients with normal-tension glaucoma, a 30% reduction in IOP is expected. [26]

It is important to remember that patients who require lower intraocular pressure require aggressive treatment to lower it, and that adherence to treatment may be difficult in some cases due to the complexity of the treatments. [26]

2.4.2 Initial management to control intraocular pressure

Glaucoma management is more an art than a science. The introduction of several new classes of antihypertensive medications and the completion of several randomized clinical trials have not changed this fact. While we now have more options for initiating glaucoma treatment than our predecessors, the principles of therapy have not changed much during this period. Our tools for detecting and monitoring the disease have improved, but they are still insufficient to prospectively predict which patients will have a better and worse outcome.[24]

In many cases, starting with monotherapy (a single antihypertensive agent) is recommended. Treatment is considered effective when it achieves an IOP reduction comparable to the range achieved by the medication in a similar population. However, it should be emphasized that the antihypertensive effect depends on baseline IOP, with a greater reduction in patients with higher levels. Therefore, it is important to consider baseline or pretreatment IOP.[11]

If initial therapy reduces IOP to target IOP levels and is well tolerated, the therapy can be continued unchanged, but the patient needs regular monitoring. However, if the therapy appears ineffective, or the medication is not tolerated, the medication should be changed. However, if monotherapy is effective and tolerable, but the target IOP is not achieved, adding another drug is recommended.[11]

2.4.3 Ocular hypotensive agents

Ocular hypotensive agents have been available since 1875. There are six pharmacological classes for topical use in Latin America, and an additional family for systemic use only.

The first-line agents are: [11] [27]

Prostaglandin/prostamide analogues: These drugs increase uveoscleral outflow. They have a 25–35% reduction in IOP. Latanoprost is part of this family, along with travoprost, tafluprost, and bimatoprost (prostamide).

β -Adrenergic antagonists (β-blockers): This group includes non-selective β-blockers (timolol, levobunolol , metipranolol , carteolol , befunolol), which reduce intraocular pressure by 20–25%; and β1 receptor selective blockers (betaxolol), which reduce intraocular pressure by ±20%. Both selective and non-selective blockers act by decreasing aqueous humor production.

Carbonic anhydrase inhibitors: This group includes topical inhibitors (brinzolamide and dorzolamide), which reduce intraocular pressure by 20%; and systemic inhibitors (acetazolamide, methazolamide, dichlorphenamide), which reduce pressure by 30–40 %. Both topical and systemic inhibitors reduce aqueous humor production as a mechanism of action.

2 -adrenergic agonists : These include apraclonidine, brimonidine, and clonidine. These drugs lower IOP by decreasing aqueous humor production, although brimonidine can also increase uveoscleral outflow. The IOP reduction is 18–25% for brimonidine and clonidine, but 25–35% for apraclonidine.

See the table below for a summary of first-line IOP-lowering medications.

Board4 Classes of first-line medications used to lower IOP

Classes of medications	Examples	Usual dosage	Mechanism of action	Local adverse effects
Prostaglandin analogues	Latanoprost, travoprost, tafluprost, bimatoprost	1 time a day at night	Increases the outflow of aqueous humor through the uveoscleral pathway	Conjunctival hyperemia, eyelash growth, eyelash blackening, iris pigmentation, uveitis, macular edema
β-blockers	Timolol, levobunolol , Carteolol, metipranolol , betaxolol	1 time a day in the morning or 2 times a day	Reduces the production of aqueous humor	Eye irritation and dryness
α 2 -adrenergic	Brimonidine, apraclonidine	3 times a day (sometimes 2 times a day)	Initially they reduce the production of aqueous humor with subsequent increase in outflow	Irritation, dryness, and allergy

Carbonic anhydrase inhibitors	Dorzolamide, brinzolamide, acetazolamide (oral)			Irritation, dryness, burning

Second-line agents are: [11] [27]

Nonselective adrenergic agonists: Epinephrine and dipivefrin . These drugs decrease intraocular pressure by 15–20% by decreasing aqueous humor production and may also increase the uveoscleral pathway.

Parasympathomimetic agents: Direct-acting agents such as pilocarpine and carbachol facilitate aqueous humor outflow and reduce IOP by 20-25%. Indirect-acting agents such as demecarium bromide , echothiophate , and disopropylfluorophosphate reduce IOP by 15-25%.

Osmotic agents: Oral agents include glycerol, isosorbide, and alcohol, and intravenous agents include mannitol and urea. The mechanism for lowering intraocular pressure is through dehydration and reduction of vitreous volume. Oral agents lower pressure by 15-20%, and intravenous agents by 15-30%.

2.4.4 Fixed combinations of ocular hypotensive agents

Topical ocular hypotensive medications are considered the first line of initial treatment for ocular hypertension. However, the desired intraocular pressure level is not always achieved with a single medication, and patients frequently require multiple medications, which can lead to poor compliance. According to the Ocular Hypertension Treatment Study, after 5 years of ocular hypotensive treatment, 40% of patients will require at least two different medications. [28] If initial therapy appears ineffective, or the first choice is tolerated and effective in reducing intraocular pressure but does not achieve the target intraocular pressure, an additional active ingredient is added to the therapeutic regimen. Patients are usually prescribed multiple medications from different classes to maintain intraocular pressure control. There are several concerns regarding the use of multiple drops for glaucoma, such as increased toxicity from preservatives, treatment adherence, cost, and the washout effect. The washout effect depends not only on the high tear fluid turnover but also on the addition of a second drop in a short period of time. When more than one drop is used, patients do not allow adequate time for ocular absorption of their first medication before administering the second. [29]

Combining several medications in a single container can improve adherence by reducing the time required to administer drops. Furthermore, for those who require multiple doses to control intraocular pressure, fixed-dose combinations offer convenience, efficacy, and safety. Fixed-dose combinations reduce daily drop use, the number of containers, and the amount of preservatives, which can improve tolerability. [29]

<u>Fixed combination of timolol 0.5%/dorzolamide 2%</u>

The fixed combination of timolol 0.5%/dorzolamide 2% has been available since 1998 in the USA, and is used in patients who do not respond adequately to β-blockers. [14]

Clinical studies of 3 to 15 months duration compared the blood pressure lowering effect of the timolol 0.5%/dorzolamide 2% fixed combination with the individual components or concomitant combination therapy. The blood pressure lowering effect of the combination was greater (1 to 3 mmHg) than that of dorzolamide 2% monotherapy three times daily or timolol 0.5% twice daily. The

blood pressure lowering effect of the timolol 0.5%/dorzolamide 2% fixed combination was approximately 1 mmHg less than that of concomitant administration of the active ingredients. [14] [30]

Fixed combination of timolol 0.5%/brimonidine 0.2%

The fixed combination of timolol 0.5%/brimonidine 0.2% It has been available in the USA since 2007 to reduce intraocular pressure in patients who require the combination due to inadequate control of intraocular pressure. [14]

Clinical studies were conducted to compare the hypotensive efficacy of the fixed combination of timolol 0.5%/brimonidine 0.2% administered twice daily with that of the individual components. The timolol-brimonidine combination showed an additional reduction in intraocular pressure of 1 to 3 mmHg over brimonidine three times daily, and an additional 1 to 2 mmHg over timolol. However, the reduction in intraocular pressure was approximately 1-2 mmHg lower than that achieved by the concomitant administration of both active ingredients. [14] [31]

Fixed combination of timolol 0.5%/ brinzolamide 1%

In a 12-month controlled clinical study in patients with open-angle glaucoma or ocular hypertension who, in the opinion of the investigator, might benefit from treatment with timolol 0.5%/brinzolamide 1% fixed combination and who had mean baseline IOPs of 25 to 27 mmHg, the mean IOP-lowering effect of this fixed combination administered twice daily was 7 to 9 mmHg. Non-inferiority of timolol 0.5%/brinzolamide 1% fixed combination to timolol 0.5%/dorzolamide 2% fixed combination with respect to mean IOP reduction was demonstrated at all visits across all follow-up visits. [32]

In a 6-month controlled clinical study in patients with open-angle glaucoma or ocular hypertension and a mean baseline IOP of 25 to 27 mmHg, the mean IOP-lowering effect of the fixed combination timolol 0.5%/brinzolamide administered twice daily was 7 to 9 mmHg and was up to 3 mmHg greater than brinzolamide alone administered twice daily and up to 2 mmHg greater than timolol 5 mg/mL administered twice daily. A statistically superior reduction in mean IOP was observed compared to both brinzolamide and timolol at all times and at all visits throughout the study. [32]

Fixed combination of brinzolamide 1%/brimonidine 0.2%

fixed combination of brinzolamide 1%/brimonidine 0.2% was formulated as a timolol-free combination to treat patients with glaucoma or ocular hypertension who were intolerant to β-blockers. This combination demonstrated its efficacy compared to the individual components in clinical study **C-10-040** , which included 560 patients, who were classified into three distinct groups according to the treatment they received: fixed combination of brinzolamide 1%/brimonidine 0.2% , brinzolamide, or brimonidine. The results are shown in the following table. [33]

*Table 5*Clinical study of the fixed combination of brinzolamide 1%/brimonidine 0.2%

C-10-040 **. Primary endpoint: Change in mean diurnal intraocular pressure* from baseline at month 3**		
Treatment group	N	Mean change in intraocular pressure 3rd month (SD)
Brinzolamide/Brimonidine	191	-7.9 mmHg (0.21)

Brinzolamide	191	-6.5 mmHg (0.24)
Brimonidine	174	-6.4 mmHg (-0.24)
Mean difference in intraocular pressure at 3 months		
Brinzolamide-brimonidine vs brinzolamide	191-191	-1.3 mmHg, 95%CI (-1.9, -0.6), p<0.0001
Brinzolamide-brimonidine vs brimonidine	191-174	-1.5 mmHg, 95%CI (-2.0,-1.0), p<0.001
***The result is an average of the 3 daily measurements taken (9 am, +2 am, +7 am)**		

Although the study showed significant values in the reduction of intraocular pressure of the fixed combination of brinzolamide 1%/brimonidine 0.2% versus the individual components, the reduction was not ≥2 mmHg. [33]

Study **C-010-041** was conducted to assess the non-inferiority of the fixed combination of brinzolamide 1%/brimonidine 0.2% versus coadministration of both active ingredients separately. The study included 890 patients, and a non-inferiority margin of <1.5 mmHg was established. Both the per-protocol and intention-to-treat analyses, performed at month 3 of treatment, showed that the reduction in daytime intraocular pressure compared to baseline was similar in both treatment groups. [33]

Fixed combination of prostaglandin analogues and timolol

The reduction in intraocular pressure when the β-blocker was added separately to latanoprost was 2.5 mmHg, which is slightly significant, but the same applies to intraocular pressure when the β-blocker is added to a prostaglandin analogue in a fixed combination and compared with the reduction in intraocular pressure achieved by the prostaglandin analogue alone. One study showed that the least squares difference between latanoprost and the latanoprost-timolol combination was only 1 mmHg (p=.005), a result that was not significant. [14]

In Study **C-01-69** , the effectiveness of the fixed combination of travoprost-timolol was compared with timolol and travoprost. The fixed combination produced a 32% to 38% reduction in intraocular pressure, and decreased it 2 to 3 mmHg more than timolol, but when compared with travoprost, it only decreased it 0.5 to 1.8 mmHg more. [34]

Study **192024-018T** assessed the effectiveness of the bimatoprost-timolol combination versus timolol and bimatoprost. The results for the bimatoprost-timolol combination and bimatoprost were not significant. Study **192024-021T** only showed significant changes between the combination and bimatoprost at one endpoint, and no significant changes at the others. Another study, **192024-504T** , also showed no significant changes between the use of bimatoprost-timolol and bimatoprost. [35]

There are some implications with the use of combinations of prostaglandin analogues with timolol, because in most studies it has been shown that they do not offer a really important change in intraocular pressure, although they have demonstrated non-inferiority against prostaglandin

analogues, and in terms of lowering intraocular pressure they lower more than prostaglandin alone, the difference has not been greater than 2 mmHg at all measurable points.[14]

An important point to mention is that in combinations of prostaglandin analogues with timolol, the timolol dose is reduced to just once a day.

Fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2% (Krytantek Ofteno ® and Krytantek Ofteno PF ®)

The fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2% with preservatives (Krytantek Ofteno ®) has been shown in two clinical studies to be more effective than combinations of two ocular hypotensive agents (the combinations of timolol 0.5%/dorzolamide 2% and timolol 0.5%/brimonidine 0.2%). When compared with the fixed combination of timolol 0.5%/dorzolamide 2%, it decreased IOP by 42.3% (10.2 ± 2.1 mmHg), while the fixed combination of timolol 0.5%/dorzolamide 0.2% decreased IOP by 28.4% (6.7 ± 2.8 mmHg). In contrast, when compared with the fixed combination of timolol 0.5%/brimonidine 0.2%, it decreased IOP by 6.1 mmHg at 8 am and 4.3 mmHg at 4 pm, while the fixed combination of timolol 0.5%/brimonidine decreased it by 4.0 mmHg at 8 am and 2.3 mmHg at 4 pm. In both studies, the Krytantek Ofteno ® combination was shown to lower IOP more in a clinically significant way than the dual combinations. [28] [36]

In a clinical study, the non-inferiority of the preservative-free fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2% (Krytantek Ofteno PF ®) was compared with the preservative-containing version (Krytantek Ofteno ®), in order to demonstrate that there was no decrease in effectiveness when benzalkonium chloride was discontinued. In this study, patients already controlled with Krytantek Ofteno ® were randomized to continue treatment for one month or switch to the preservative-free combination, and then switch to the other treatment after one month of treatment. In this way, both groups were exposed to treatment with and without preservatives. In the study, the patients already controlled did not have any significant changes in their blood pressure, so it was concluded that the treatment was equally effective. [37]

A prospective study evaluated whether the fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2% (Krytantek Ofteno ®) did not lose effectiveness if benzalkonium chloride was withdrawn (Krytantek Ofteno PF ®). The study was a multicenter, double-blind, randomized, crossover study in which patients previously treated with Krytantek Ofteno ® were randomly assigned to receive Krytantek Ofteno PF ® for 30 days, or continue on Krytantek Ofteno ® . On day 31, patients receiving Krytantek Ofteno PF ® were switched to Krytantek Ofteno ® for 30 days, while the other group was switched to Krytantek Ofteno PF ® . The primary efficacy variable was maintenance of IOP control, and the safety and tolerability of both products were assessed by the presence of adverse events (AEs), ocular findings, an ocular comfort questionnaire, and the VF-14 index. [37]

A total of 51 patients participated. After twice-daily application of Krytantek Ofteno PF®, its efficacy in maintaining IOP control was demonstrated in patients previously treated with Krytantek Ofteno® . Crossover between treatments after day 30 did not affect IOP control. Krytantek Ofteno PF® was shown to be non-inferior to Krytantek Ofteno® in controlling IOP. [37]

The safety of both products was similar, with no drug-related adverse events or safety differences. The tolerability of the two therapies evaluated, based on ocular findings, the ocular comfort questionnaire, and the VF-14 index, was also similar. [37]

The study demonstrated that Krytantek Ofteno PF ® has similar effectiveness, safety, and tolerability to Krytantek Ofteno ® . [37]

2.4.5 Maximum tolerated medical therapy

With the increasing availability of medications to treat elevated IOP and glaucoma, maximal medical therapy (MMT) has the potential to improve IOP control in patients whose control is insufficient with two antihypertensives. Ideally, MMT should increase the likelihood of patients achieving their target IOP and, consequently, slow disease progression. Ultimately, the goal is to design more effective and tolerable therapies that can be realistic alternatives to surgery. It is important to mention that the blood pressure lowering effect demonstrated by each class of antihypertensives is additive; however, the magnitude of the reduction achieved by adding a medication to an existing therapy is less than the effect achieved when starting with that medication. However, antihypertensives from different classes can be combined to optimize treatment. [38]

Maximum medical therapy is not specific to any one combination of antihypertensives, and several options are available. This therapy may consist of three or four active ingredients, depending on treatment tolerance and regional availability of the drugs. Combinations of three antihypertensives may include a fixed triple combination, a fixed double combination plus monotherapy, or three antihypertensives concomitantly. In contrast, combinations of four antihypertensives may consist of two double combinations, a fixed triple combination plus monotherapy, or even the concomitant use of all four antihypertensives. [38]

3. Problem statement

3.1 Delimitation of the problem

Glaucoma is the leading cause of irreversible blindness worldwide, and lack of treatment leads to disease progression. Despite this, the factor that most influences disease deterioration is poor patient adherence to treatment. Because the disease produces few symptoms, there is little patient motivation to seek treatment, especially in the early stages, when vision-threatening complications have not yet begun. [39]

Since their introduction in ophthalmology, prostaglandin analogues have become the cornerstone of glaucoma treatment. By reducing intraocular pressure over 24 hours with a single application, they have simplified patient care. However, as previously mentioned, 40% of patients will require more than one drop to achieve a 20% reduction. Before the existence of prostaglandin analogues, the most widely used treatment for glaucoma was timolol, and although prostaglandin analogues have become the most widely used medications, many physicians consider β-blockers the preferred adjunctive therapy with prostaglandins (intermediate therapy). [28] [40] [40]

However, there are cases where intermediate therapy, or from the start of treatment, requires a significant reduction in IOP. In these cases, maximally tolerated medical therapy can be used, which consists of adding a double fixed combination to a prostaglandin analogue, thus creating three antihypertensive agents. Previously, a fourth medication was not used, as the patient had to apply a significant number of drops that could reduce their adherence. However, the incorporation of a triple fixed combination such as Krytantek Ofteno PF® makes simplified treatment possible with four active ingredients by adding a prostaglandin analogue, creating a new maximally tolerated medical therapy. [16]

Although understanding the actual effectiveness of maximum medical therapies is essential for determining treatment success in glaucoma therapy, little attention has been paid to studying their effectiveness, tolerability, and adherence. [38]

The aim of this study is to determine the efficacy of a new four-active ingredient maximal medical therapy using two drugs: preservative-free latanoprost 0.005% (Gaap Ofteno PF®) and the preservative-free fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2% (Krytantek Ofteno PF®), comparing it to one of the most widely used maximal medical therapies, latanoprost 0.005% therapy (Gaap Ofteno PF®) and the combination of timolol 0.5%/dorzolamide 2% (Elliptic Ofteno PF®).

The reason is to scientifically support the benefit of having an active ingredient over traditional maximum medical therapy, in this case brimonidine.

3.2 Research question

In patients on latanoprost, does adding Krytantek Ofteno PF ® reduce intraocular pressure more than adding a dual fixed combination of timolol 0.5%/dorzolamide 2%?

3.3 Background on this research

There are no previous studies comparing Krytantek Ofteno PF ® with the fixed combination of timolol 0.5%/dorzolamide 2%. However, there are studies comparing the efficacy of Krytantek Ofteno ® (a combination with the same principles as Krytantek Ofteno PF ® , but without preservatives) against the fixed combination of timolol 0.5%/dorzolamide 2%, and against another dual combination of antihypertensive agents . Therefore, the results of these studies could serve as background for this research. [37]

3.3.1 Krytantek Ofteno ® against double combinations

Krytantek Ofteno ® against the fixed combination of timolol 0.5%/dorzolamide 2%

In 2009, a prospective, randomized, multicenter, double-blind clinical study was conducted to assess the efficacy and safety of using Krytantek Ofteno ® compared with the use of the fixed combination of timolol 0.5%/dorzolamide 2% (Cosopt ®), in patients with primary open-angle glaucoma and ocular hypertension. [36]

A total of 112 patients were studied, divided into two groups of 56 patients each. One group received the fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2%, and the other received the fixed combination of timolol 0.5%/dorzolamide 2% for 180 days. Both groups started with very similar intraocular pressure (24.1 ± 2.6 mmHg and 23.6 ± 2.2 mmHg), and a reduction in intraocular pressure was observed in both groups from the seventh day of treatment. However, the group treated with Krytantek Ofteno ® showed a greater reduction in intraocular pressure from day 15 of the study to the end of the study compared to the dual combination group. From the third month onwards, the Krytantek Ofteno® group saw a 42.3% reduction in intraocular pressure, while the dual combination group saw a 28.8% reduction. Seven patients in the study (four in the dorzolamide-timolol group and three in the dorzolamide-timolol-brimonidine group) withdrew from the study and were not included in the statistical analysis. [36]

The following table details the behavior of intraocular pressure in the study. [36]

Board6 Comparison of the effectiveness of Krytantek Ofteno® and a fixed combination of timolol 0.5%/dorzolamide 2%

Effectiveness	**Changes in intraocular pressure (mmHg)**	
	Dorzolamide-timolol-brimonidine group	Dorzolamide-timolol group
Average baseline intraocular pressure (± SD) (before treatment)	24.1 ± 2.6	23.6 ± 2.2
Average intraocular pressure at 3 months	13.9 ± 2.3	16.8 ± 2.7
Average decrease in intraocular pressure at 3 months	10.2 ± 2.5	6.8 ± 2.9
Percentage reduction in intraocular pressure at 3 months	42.3%	28.8%
Average intraocular pressure at 6 months	10.2 ± 2.1	6.7 ± 2.8
Average decrease in intraocular pressure at 6 months	13.9 ± 2.9	16.9 ± 3.4

Percentage reduction in intraocular pressure at 6 months	42.3%	28.4%

As we can see in the table, the decrease in intraocular pressure was significantly greater with the use of Krytantek Ofteno ® compared to the double combination. [36]

No significant differences were found in adverse events between the two combinations. Two patients reported adverse events with Krytantek Ofteno® , and six patients with the dual combination. The most common adverse events were ocular pain, burning, and keratitis. [36]

This study concludes that the fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2% (Krytantek Ofteno ®) is safe and more effective than the double combination (Cosopt ®) in reducing intraocular pressure in patients with primary open-angle glaucoma or ocular hypertension. [36]

Krytantek Ofteno ® against the fixed combination of timolol 0.5%/dorzolamide 2%

A three-month, double-blind, multicenter clinical study was conducted in 2012 comparing the efficacy and safety of Krytantek Ofteno® versus the fixed combination of timolol 0.5%/brimonidine 0.2% (Combigan D®) for reducing intraocular pressure. Patients with an average intraocular pressure of 21–30 mmHg and a diagnosis of primary open-angle glaucoma and ocular hypertension were included. [28]

Fifty-six patients per group were enrolled from a total of 11 research centers in Mexico. A total of 106 patients were included in the statistical analysis. Their mean age was 62.5 ± 10.2 years in the dorzolamide-timolol-brimonidine group and 60.6 ± 12.7 years in the timolol-brimonidine group. [28]

*Table 7*Comparison of effectiveness at 8 am between Krytantek Ofteno ® and a fixed combination of timolol 0.5%/brimonidine 0.2%

Visits	**Difference in intraocular pressure between groups at 8 am**		
	Dorzolamide-timolol-brimonidine (n=108)	Timolol-brimonidine (n=104)	P
Basal	22.3 ± 0.9	22.4 ± 1.8	0.558
Day 15	18.0 ± 2.0	19.5 ± 3.4	0.000
Day 30	16.4 ± 1.5	18.4 ± 1.3	0.000
Day 60	16.3 ± 2.5	18.3 ± 2.0	0.000
Day 90	16.2 ± 2.0	18.4 ± 1.4	0.000

Board8 Comparison of the effectiveness at 4 pm between Krytantek Ofteno ® and a fixed combination of timolol 0.5%/brimonidine 0.2%

Visits	**Differences in intraocular pressure between groups at 4 pm**		
	Dorzolamide-timolol-brimonidine	Timolol-brimonidine	P
Basal	19.0 ± 1.3	19.1 ± 1.2	0.536

Day 15	15.4 ± 1.2	17.8 ± 0.9	0.000
Day 30	15.3 ± 1.3	17.5 ± 1.7	0.000
Day 60	15.0 ± 2.3	17.0 ± 2.6	0.000
Day 90	14.7 ± 2.4	16.8 ± 1.4	0.000

As reflected in the tables above, the difference between the groups was statistically significant, with a greater decrease in IOP in the Krytantek Ofteno ® group from the first visit after starting treatment, at both times of taking this variable. [28]

At the last follow-up, a decrease of approximately 6.1 mmHg vs. 4.0 mmHg at 8 a.m., and 4.3 mmHg vs. 2.3 mmHg at 4 p.m., was observed for the Krytantek Ofteno ® group and the timolol 0.5%/brimonidine 0.2% fixed combination group, respectively. [28]

Adverse effects were documented in eight patients, six of whom were excluded from the study. These effects included ocular burning (mild in one patient and moderate in another), hyperemia (severe in one patient), dizziness (severe in one patient), headache (mild in one patient), and bradycardia (mild in one patient); no relationship was found with the drug studied in this protocol. [28]

This study demonstrated that treatment with the Krytantek Ofteno ® fixed combination is more effective than treatment with the timolol 0.5%/brimonidine 0.2% fixed combination in patients diagnosed with POAG or ocular hypertension, making it an effective option that can reduce the risk of visual loss secondary to glaucoma in patients who require more than one medication to achieve adequate IOP reduction, while taking advantage of the multiple advantages offered by fixed combinations, especially for glaucoma patients who will be chronic users of different medications. [28]

3.3.2 Krytantek Ofteno ® as part of maximum tolerable medical therapy

In a three-arm, double-blind clinical study, conventional maximal tolerable medical therapy (prostaglandin analogue plus the fixed combination of timolol 0.5%/dorzolamide 2%) was compared in the first arm; a three-active ingredient fixed combination (Krytantek Ofteno®) in the second arm ; and a new maximal tolerable medical therapy with four active ingredients, using Krytantek Ofteno® plus a prostaglandin analogue, in the third arm . The prostaglandin analogue used in this clinical study was travoprost. [16]

In this study of three groups of 30 eyes each, two triple therapies and one quadruple therapy were evaluated by performing a diurnal intraocular pressure hourly curve one day before treatment, and another hourly curve 30 days after treatment. [16]

The first group, treated with travoprost plus the fixed combination of timolol 0.5%/dorzolamide 2%, presented the following results. [16]

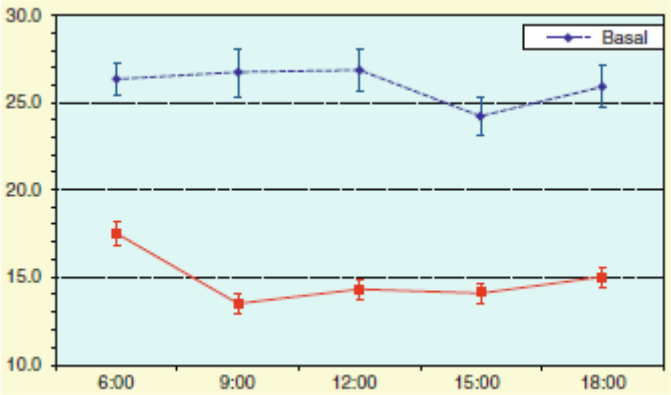


*Figure 8*Comparison of the hourly curve of baseline intraocular pressure with post-treatment with travoprost plus the fixed combination of timolol 0.5%/dorzolamide 2%

The second group, treated with Krytantek Ofteno ®, presented the following results. [16]

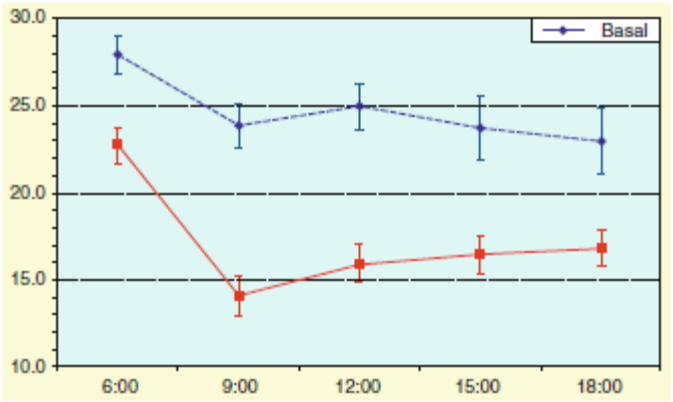


*Figure 9*Comparison of the hourly curve of basal intraocular pressure with post-treatment with Krytantek Ofteno ®

The third group, treated with the combination of travoprost plus Krytantek Ofteno ®, presented the results. [16]

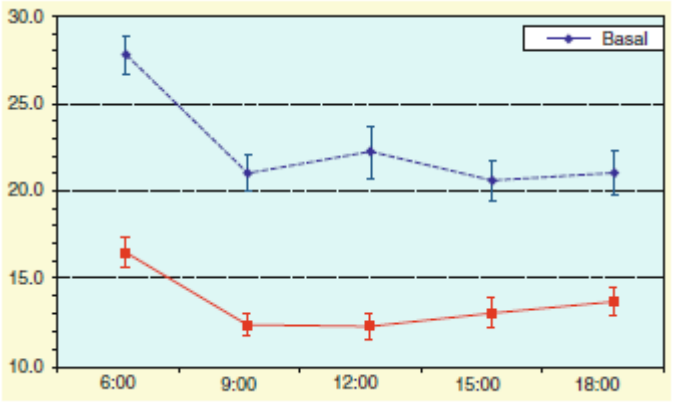


Figure10 Comparison of the hourly curve of basal intraocular pressure with post-treatment with travoprost plus Krytantek Ofteno ®

While the effectiveness in all three treatment arms was very good, the only therapy that was able to normalize the intraocular pressure profile at 6:00 am at the patient's bedside was Krytantek Ofteno ® plus travoprost.

3.3.3 Other studies on maximum medical therapy with four ocular hypotensive agents

A retrospective study evaluated the benefit of adding brimonidine (the antihypertensive agent that differentiates the treatments in this study) to a treatment with three ocular antihypertensives. In the study of 53 patients, 46 were followed for one month, and 28 for one year. Of the patients followed for one month, 61% showed an IOP decrease ≥20 %, while of the 28 followed for one year, 50% showed an IOP decrease ≥20 %. [41]

In a prospective clinical trial, maximal four-agent drug therapy using a fixed combination of travoprost 0.004%/timolol 0.5% plus a fixed combination of brinzolamide 1%/brimonidine 0.2% was studied in patients with POAG or ocular hypertension treated with a combination of travoprost 0.004%/timolol 0.5%. These patients were compared with a treatment group that continued using travoprost 0.004%/timolol 0.5% alone. Patients in both groups had similar baseline IOPs of 21.6 ± 1.78 and at treatment level of 21.8 ± 1.90 mmHg. Patients on the four-agent therapy achieved a -4.25 mmHg reduction in IOP, whereas those continuing the two-agent therapy achieved a -2.11 mmHg reduction. This showed clinical relevance in adding this combination of brinzolamide 1%/brimonidine 0.2% to a treatment with travoprost 0.004%/timolol 0.5%. [42]

Juncal et al. evaluated 25 patients receiving a combination of four active ingredients. Upon withdrawal of a carbonic anhydrase inhibitor, 20% of patients had an increase in intraocular pressure of ≥20 % after the washout period. [38]

3.3.4 Other studies on maximum medical therapy with three ocular hypotensive agents

There is more information on maximal medical therapy with three ocular hypotensive agents than with four. The following table summarizes some of the most significant studies. [38]

Board9 Clinical studies of maximal medical therapies comparing treatment with different antihypertensives

Study	Subjects	Study design	Treatment	Washing period	Results
Fixed combinations of three ocular hypotensive agents					
Baiza-Duran 2012	GPAA, HTO	Randomized, double-blind	• Timolol/brimonidine/dorzolamide (n=56) • Timolol/brimonidine (n=56)	6 weeks before the basal	The triple combination lowered IOP more at 8 am and 4 pm, significantly at 3 months.
Baiza-Duran 2009	GPAA, HTO	Randomized, double-blind	• Timolol/brimonidine/dorzolamide (n=56) • Timolol/dorzolamide (n=56)	I don't know specific	From day 15, the triple combination significantly reduces IOP.
Garcia-Lopez 2014	GPAA, HTO	Cross-linking, single masking	• Timolol/brimonidine/dorzolamide (n=26) • Bimatoprost/timolol (n=30)	One month between treatments	Both combinations significantly reduced IOP from baseline three months after switching therapy. The reduction was greater in the bimatoprost/timolol group.
Combination of three ocular hypotensive agents (multiple bottles)					
Fechtner 2011	GPAA, HTO	Randomized, single-masked	• Latanoprost + brimonidine/timolol (n= 102) • Latanoprost + timolol (n= 102)	4 weeks of washout of all medications	The triple combination produced

				except latanoprost	significant IOP reduction at 12 weeks.
Goldberg 2012	GPAA, HTO	Randomized, double-blind	• Brinzolamide + travoprost/timolol (n= 75) • Placebo + travoprost/timolol	Patients switched their therapy to travoprost/timolol for 4 weeks	The triple combination significantly reduced IOP at 8 am and 4 pm after 4 weeks.
Feldman 2016	GPAA, HTO	Randomized, double-blind	• Travoprost + brinzolamide/brimonidine (n=113) • Travoprost + placebo (n= 116)	2- to 28-day washout, where patients discontinued previous therapies and started travoprost	The triple combination significantly decreased daytime IOP after 6 weeks.
Fechtner 2016	GPAA, HTO	Randomized, double-blind	• APG + brinzolamide/brimonidine (n=88) • APG + placebo (n= 94)	Patients discontinued other therapy and received APG during the 28-day open-label phase prior to screening	The triple combination produced an additive effect, decreasing IOP after 6 weeks.
Topouzis 2018	GPAA, HTO	Randomized, masked	• APG + brinzolamide/brimonidine (n= 96) • APG + placebo (n=92)	Washout of other medication before randomization	The triple combination produced a significant diurnal IOP reduction after 6 weeks.
Konstas 2013	GPAA, HTO	Masked observer, crossover	• Travoprost + brinzolamide/timolol (n= 23) • Travoprost + brimonidine/timolol (n= 27)	No washing	The triple combination significantly reduced 24-h IOP from baseline with travoprost.

3.4 Justification

Traditionally, maximum medical therapy has consisted of the application of three different active ingredients, each with an additive effect in reducing intraocular pressure. However, today, with the incorporation of fixed combinations of three active ingredients, a maximum medical therapy with four active ingredients can be easily designed.

The combination of three antihypertensives is the current standard for optimal maximal medical therapy, with evidence indicating that these treatments are effective and well tolerated, and that they provide better 24-hour IOP control than treatment with two ocular antihypertensives. The next logical step for these therapies is the addition of a fourth antihypertensive agent. [38]

There are few studies evaluating maximum medical therapies for the treatment of glaucoma and ocular hypertension, and although there is little information on the maximum tolerable medical therapy with four antihypertensive agents, it is considered that adding a fourth antihypertensive agent may be clinically useful in 20% to 50% of patients , according to retrospective evaluations. [41]

Triple-ingredient therapies that do not contain a prostaglandin analogue, such as Krytantek Ofteno PF® , are effective in lowering daytime IOP, but their effect may not be as significant in morning hypertension spikes, and adding a prostaglandin analogue may normalize hypertension spikes.

Furthermore, they can achieve an IOP reduction greater than 50%, a significant reduction compared with triple therapy alone. [16]

Previous studies have demonstrated the greater effectiveness of a fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2% compared to dual combinations. However, these studies were conducted in patients who were not receiving other antihypertensive therapies. In a real-life setting, the most commonly used medications are prostaglandin analogues, and when the IOP reduction achieved with these drugs is not sufficient, a dual combination is often added to achieve a greater effect. Therefore, it is important to understand the effect of the triple combination added to the prostaglandin analogue. In this case, the decision was made to conduct the study with latanoprost (Gaap Ofteno PF®) because latanoprost is the most widely distributed prostaglandin analogue, and patients who use it are more compliant with treatment than those who use bimatoprost and travoprost. [43] [44]

4. Objectives and hypotheses

4.1 Main objective:

To determine the superiority in additional lowering of mean intraocular pressure of the preservative-free fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2% (Krytantek Ofteno PF ®), compared with the effect obtained by the preservative-free fixed combination of timolol 0.5%/dorzolamide 2% (Elliptic Ofteno PF ®), in patients with primary open-angle glaucoma or ocular hypertension treated with preservative-free latanoprost (Gaap Ofteno PF ®).

4.2 Secondary objectives:

- To determine the efficacy of adding the preservative-free fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2% (Krytantek Ofteno PF ®) to patients with primary open-angle glaucoma or ocular hypertension treated with preservative-free latanoprost (Gaap Ofteno PF ®).
- To determine the efficacy of adding the preservative-free fixed combination of timolol 0.5%/dorzolamide 2% (Elliptic Ofteno PF ®) to patients with primary open-angle glaucoma or ocular hypertension treated with preservative-free latanoprost (Gaap Ofteno PF ®).

4.3 Hypothesis

H_0 = The mean final reduction in intraocular pressure obtained by adding the preservative-free fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2% (Krytantek Ofteno PF ®) is not superior to the effect obtained by adding the preservative-free fixed combination of timolol 0.5%/dorzolamide 2% (Elliptic Ofteno PF ®), in patients with primary open-angle glaucoma or ocular hypertension treated with preservative-free latanoprost. Considering a difference ≥ 1.5 mmHg between treatments as superior.

H_1 = The mean final reduction in intraocular pressure obtained by adding the preservative-free fixed combination of timolol 0.5%/dorzolamide 2%/brimonidine 0.2% (Krytantek Ofteno PF ®) is superior to the effect obtained by adding the preservative-free fixed combination of timolol 0.5%/dorzolamide 2% (Elliptic Ofteno PF ®), in patients with primary open-angle glaucoma or ocular hypertension treated with preservative-free latanoprost. Considering a difference ≥ 1.5 mmHg between treatments as superior .

5. Study design

5.1 General description of the study

Phase IV, double-blind, multicenter, parallel-group, randomized clinical study.

Main inclusion criterion for the study: Subjects with uncontrolled primary open-angle glaucoma and/or ocular hypertension.

The study will consist of two treatment phases (*see Figure 11 Study design)* :

- First phase (eligibility/open-label phase): In this approximately 30-day phase, participants who meet the eligibility criteria will be assigned to concomitant IOP-controlling therapy (Gaap Ofteno PF®) . The purpose of this phase is to homogenize patients on a single treatment before exposing them to the experimental treatment.
- Second phase (double-blind phase): In this approximately 60-day phase, participants who again meet the eligibility criteria will be assigned to the experimental treatment (investigational treatment [Krytantek Ofteno PF®] or comparator treatment [Elliptic Ofteno PF®]), while continuing concomitant treatment (Gaap Ofteno PF®) . It is during this phase that patients are exposed to maximum medical therapies.

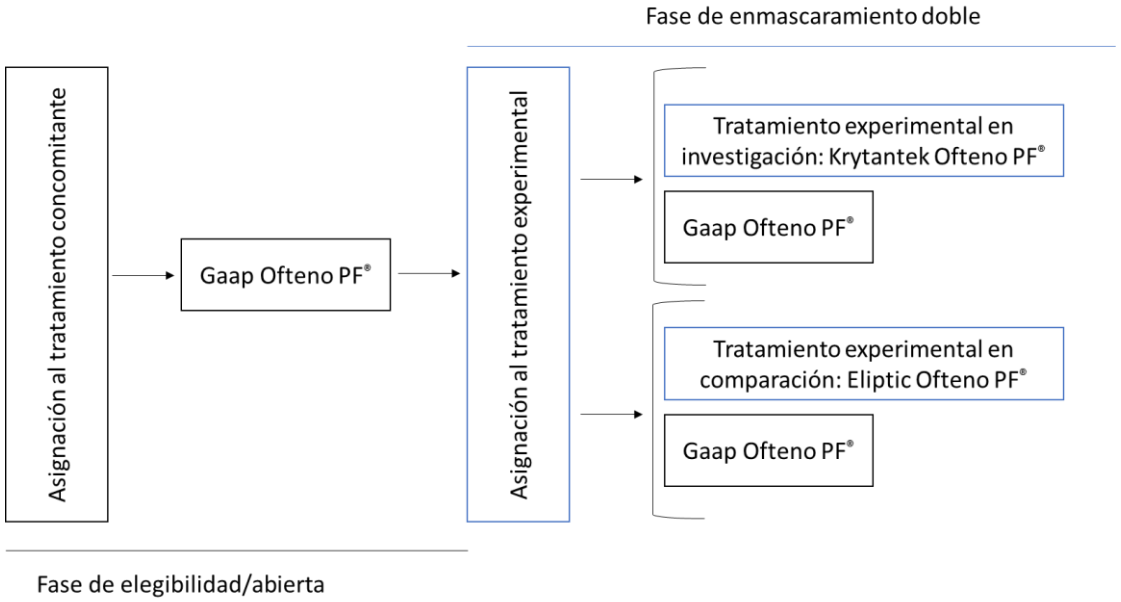


Figure11 Study design

5.2 Justification of the study design

The clinical trial is the ideal model for evaluating the effectiveness of two interventions, providing the highest quality evidence among the different types of research. The randomization and double-blinding characteristics help avoid biases (selection, evaluation, etc.) that cannot be avoided with other models. The controlled nature of the trial and its parallel groups allow for the effects of the interventions to be distinguished in isolation.

This study determined that to determine whether the investigational treatment is superior to the comparator treatment, it must decrease IOP by at least 1.5 mmHg more than the comparator treatment. It should be noted that for every millimeter of mercury a patient decreases in IOP, there is a lower risk of disease progression. [45]

Since these are uncontrolled patients, it is preferable to continue treatment for one month, which can serve as a washout of the previous treatment and as an adaptation to concomitant treatment with a prostaglandin analogue. This will ensure that, by the start of the experimental treatment phase, a significant reduction in the prostaglandin analogue has already been achieved, making it easier to interpret the IOP reduction during the experimental treatment.

5.3 Expected duration of the study

The total duration of the study, from the first patient visit to the final report, is estimated to be approximately 14 months.

The planned recruitment period is 30 weeks (7.5 months) plus a 16-week (3.5-month) period for the final subjects to complete their participation. Considering the proposed study sample of 116 cases, the average total recruitment rate during the study should be approximately 4 cases per week or 16 cases per month. Competitive recruitment will be conducted among approved research centers.

The approximate duration of each patient in the study is approximately 105 days.

6. Study population and sample size

6.1 Population or universe of the study

Our study universe includes all subjects aged 18 or older, diagnosed with primary open-angle glaucoma or ocular hypertension, and who are not controlled with their current therapy.

6.2 Eligibility criteria

6.2.1 Inclusion criteria

- Subjects with primary open-angle glaucoma (according to the American Academy of Ophthalmology preferred practice pattern guidelines) or ocular hypertension, not controlled by a prostaglandin analogue or β -blocker in the eye to be included in the study.
- Treatment prior to the eligibility visit for ≥ 30 days with a prostaglandin analogue or β -blocker , in the eye to be included in the study.
- Intraocular pressure by Goldmann tonometry ≥ 19 and ≤ 26 mmHg in the eye to be included in the study.
- Ability to voluntarily grant informed consent.
- Be able and willing to comply with scheduled visits, treatment plan, and other study procedures.
- Age equal to or greater than 18 years.

6.2.2 Exclusion criteria

- Being pregnant, breastfeeding, or planning to become pregnant during the clinical study.
- In the case of women of reproductive age, not having a hormonal contraceptive method, intrauterine device or bilateral tubal obstruction.
- Anterior chamber angle < 2 in the Shaffer Classification or presence of peripheral anterior synechiae in the eye to be included in the study.
- Being treated with any systemic ocular hypotensive (e.g. mannitol, glycerin, isosorbide).
- Best Corrected Visual Acuity less than 20/200 in the eye to be included in the study.
- Severe central visual field loss (sensitivity ≤ 10 dB at ≥ 2 of the 4 points central to the fixation point of the visual field), in the eye to be included in the study.
- History of ocular surgery or ocular laser procedure within the last 6 months in the eye to be included in the study.
- History of ocular trauma in the last 6 months in the eye to be included in the study.
- History of chronic uveitis in the eye to be included in the study.
- retrobulbar , subconjunctival or subtenon injection in the last 6 months in the eye to be included in the study.
- Patients with silicone, or who have had silicone, in the anterior or posterior segment of the eye to be included in the study
- Diagnosis of aphakia in the eye to be included in the study.
- Any corneal alteration that decreases the reliability of Goldmann tonometry in the eye to be included in the study.
- Known hypersensitivity to the active ingredients to be used in the study (prostaglandin analogues, β -adrenergic blockers, α2 - adrenergic agonists, carbonic anhydrase inhibitors).
- Diseases that contradict the use of the active ingredients to be used in the study (e.g. severe asthma or COPD, 2nd or 3rd degree atrioventricular block not controlled with a pacemaker, sinus bradycardia, manifest heart failure, Chronic Kidney Disease with a CrCl < 30 ml/min).

- Patients requiring the use of monoamine oxidase inhibitors (MAOIs), and patients treated with antidepressants that affect noradrenergic transmission (e.g. tricyclic antidepressants and mianserin).
- Patients who use, or have used in the last month, topical ophthalmic steroids in the eye to be included in the study, or by oral, intravenous, intramuscular, dermal, or intralesional routes.
- Have participated in another clinical research study within 30 days prior to signing the FCI.
- Having previously participated in this study.
- Having a history of drug addiction within the last two years prior to signing the FCI.
- Have any type of surgical intervention scheduled during the study period.
- Be or have an immediate family member (e.g., spouse, parent/legal guardian, sibling, or child) who is a member of the research site or sponsor staff.

6.2.3 Elimination criteria

- Intraocular pressure ≤ 18 mmHg at the baseline visit, in the eye to be included in the study.
- Intraocular pressure > 26 mmHg at the baseline visit, in the eye to be included in the study.
- Subject's decision.
- Pregnancy.
- Presence of a serious adverse event.
- Lack of efficacy of maximum medical therapy (less than 20% decrease when any of the experimental treatments were added to treatment with latanoprost).
- Adherence less than 90% to the treatments provided in the study.
- Subject who does not attend two consecutive visits.

6.2.4 Subject substitution

Subjects discontinued from the study due to withdrawal of consent, selection failures, or loss to follow-up, or failure to meet criteria at the baseline visit, may be replaced if it is necessary to balance the study groups to ensure they are evaluable or to complete the minimum population to be evaluated for the efficacy analysis.

The results obtained from the replaced subjects will continue to be used for safety analysis.

6.3 Identification of subjects in the study

Patients in the study will be identified by a number and their initials.

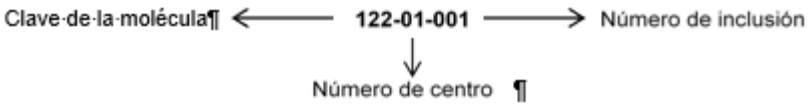
The initials of the subject of study will be obtained starting with the first letter of the name, followed by the first letter of the first surname and the first of the second, obtaining a maximum of three letters. In case the person has two names or a compound surname, the first letter of the first name or compound surname will always be used.

Example:

1. Adolfo Daniel Mercado Carrizalez
    a. Initials: AMC
2. Juan D e la Torre O rozco
    a. Initials: JDO
3. L uis Carlos P érez-Gómez R amírez
    a. LPR Initials

During the screening phase, participants will be assigned a consecutive three-digit number. Once the subject has been selected, they will be assigned a number that will identify them throughout the study. This code will consist of eight numbers in the following order, from left to right:

- three digits of the molecule under study according to the name given by the sponsor.
- two digits corresponding to the research center number
- three digits of the consecutive number assigned to your inclusion in the research center. Example:



6.4 Strategies for recruiting and retaining research subjects

The research centers conducting the study are expected to be responsible for patient recruitment.

If during the development of this research protocol the principal investigator needs to publish or disseminate the invitation to participate in the study in the media, he or she must request approval from the Research Ethics Committee and the Research Committee, as well as authorization from the relevant regulatory body.

It is possible to discuss with other health professionals, especially those who evaluate patients with chronic-degenerative diseases, the opportunity for the latter to receive free treatments, pertinent ophthalmological evaluation at no cost, as well as office examinations that will allow a more precise determination of their clinical ocular status by participating in a clinical research protocol sponsored by Laboratorios Sophia, SA de CV.

Some established strategies for retaining research subjects in the study are:

- Clearly communicate the importance of the study and the potential benefits that the population to which it belongs could obtain from it.
- Calling, emailing, or texting to remind you of appointments or activities to be carried out (with the prior consent of the research subject).
- Provide an ID card to record future appointments, and a journal/calendar to record activities.
- Optimize patient visit processes so that the visit doesn't last longer than necessary.

6.5 Procedure in case of loss of tracking

For this protocol, loss to follow-up is defined as those patients who were randomized, who at some point were active patients in the study, but their final evaluation could not be completed.

If a participating patient does not attend their appointment, the research center will call to determine the reason and attempt to schedule a new appointment within the established window or an unscheduled appointment. If an appointment cannot be scheduled, the patient will be asked about the presence of AEs and the reason for withdrawing from the study, as minimum information.

6.6 Sample size

6.6.1 Number of subjects or cases calculated

An estimated 58 evaluable cases per treatment arm are estimated (patients may contribute one or two cases [eyes]), 116 cases (eyes) in total.

6.6.2 Justification of the sample calculation

The sample size calculation was based on the study by Joh and Jin (2019), where they evaluated the efficacy of triple maximum medical therapy (MMT) versus double MMT in lowering IOP after 1 year of follow-up. [46]

This was a retrospective, consecutive case series study, in which 82 eyes of 82 subjects were included. 45 eyes received triple MMT consisting of tafluprost or brimonidine + brinzolamide/timolol (fixed combination) vs 37 eyes treated with tafluprost/timolol or brinzolamide/brimonidine (fixed combination). The primary efficacy variable was the decrease in mean IOP from initial to final. The reduction rate for the triple MMT group at 12 months was 52.7% vs 50.4% for the double MMT group. At three months, the IOP in triple MMT was 16.1 ± 2.2 mmHg vs 35.5 ± 4.5 mmHg at baseline, while for double MMT it was 16.5 ± 2.7 mmHg vs 33.7 ± 5.8 mmHg at baseline.

For the present protocol, a reduction in IOP of ≥20% compared to the initial IOP with a single agent (latanoprost) is expected after two months of treatment with 3 or 4 pharmaceutical agents, and a difference between groups of ≥1.5 mmHg. The difference of -2.0 ± 3.8 mmHg observed in the study by Joh and Jin, at 3 months of treatment with respect to the initial value between triple MMT and double MMT, was considered for the calculation. The expectation is that in subjects treated with KOF + GOF the difference with respect to EOF + GOF will be 1.5 mmHg. According to the working hypotheses:

$$H_0: \mu_A - \mu_B \leq \delta$$

$$H_1: \mu_A - \mu_B > \delta$$

The relationship between the sample size of the two groups is:

$$k = \frac{n_A}{n_B}$$

The sample size was calculated using the equation for two means, to prove that the mean of group A (GOF + KOF) is greater than the mean of group B (GOF + EOF). [47]

The sample size and power estimates were performed using an online tool and following the equations described in Proposal II. [48]The calculation was performed considering a power of 80% (β), a significance level of 0.05 (α), and a non-inferiority/superiority margin (δ) of 1.5.

$$n_A = kn_B \; y \; n_{B=} \left(1 + \frac{1}{k}\right)\left(\sigma \frac{z_{1-\alpha} + z_{1-\beta}}{\mu_A - \mu_B - \delta}\right)^2$$

$$1 - \beta = \Phi(z - z_{1-\alpha}) + \Phi(-z - z_{1-\alpha}) \; , z = \frac{\mu_A - \mu_B - \delta}{\sigma\sqrt{\frac{1}{n_A} + \frac{1}{n_B}}}$$

Where:

k= n_A / n_B is the coincidence relationship,

σ is the standard deviation

Φis the function of the standard normal distribution,

Φ^{-1} is the normal standard quantile function,

α is the Type I error,

β is the Type II error, which means that, 1-β is the power, and

δ is the test margin.

According to the previous calculation, the result was 45 cases (eyes); this calculation was increased by 30% to account for potential losses. The total suggested sample size is 58 cases (eyes) per treatment arm (**116 eyes in total**).

7. Therapies and products under investigation

7.1 Investigational Products

These are the medications given to patients once they are enrolled in the study. All patients will receive the single concomitant treatment medication, but will be randomized to receive one of the two experimental treatment medications. Randomization will be 1:1.

7.1.1 Concomitant treatment

Concomitant product:

- Gaap Ofteno PF®. Latanoprost 0.005%. Solución oftálmica estéril libre de conservadores.Laboratorios Sophia, S.A. de C.V.
- Posology:1 gota en el ojo a tratar cada 24 horas por la noche.
- Route of administration:Tópica oftálmica.

7.1.2 Experimental treatment

Investigational product, dose and route of administration (investigational treatment):

- Krytantek Ofteno PF®. Combinación fija de timolol 0.5%/ dorzolamida 2%/ brimonidina 0.2%. Solución oftálmica estéril libre de conservadores.Laboratorios Sophia, S.A. de C.V.
- Posology:1 gota en el ojo a tratar cada 12 horas.
- Route of administration:Tópica oftálmica.

Comparator product, dose and route of administration (comparator treatment):

- Eliptic Ofteno PF®. Combinación fija de timolol 0.5%/dorzolamida 2%. Solución oftálmica estéril libre de conservadores.Laboratorios Sophia, S.A. de C.V.
- Posology:1 gota en el ojo a tratar cada 12 horas.
- Route of administration:Tópica oftálmica.

7.2 Investigational Therapies

During the first month, patients will receive only Gaap Ofteno PF® , and if they meet the selection criteria at the baseline visit, they will be randomized to receive one of the experimental treatments. *See Figure 12 Investigational Therapies* .

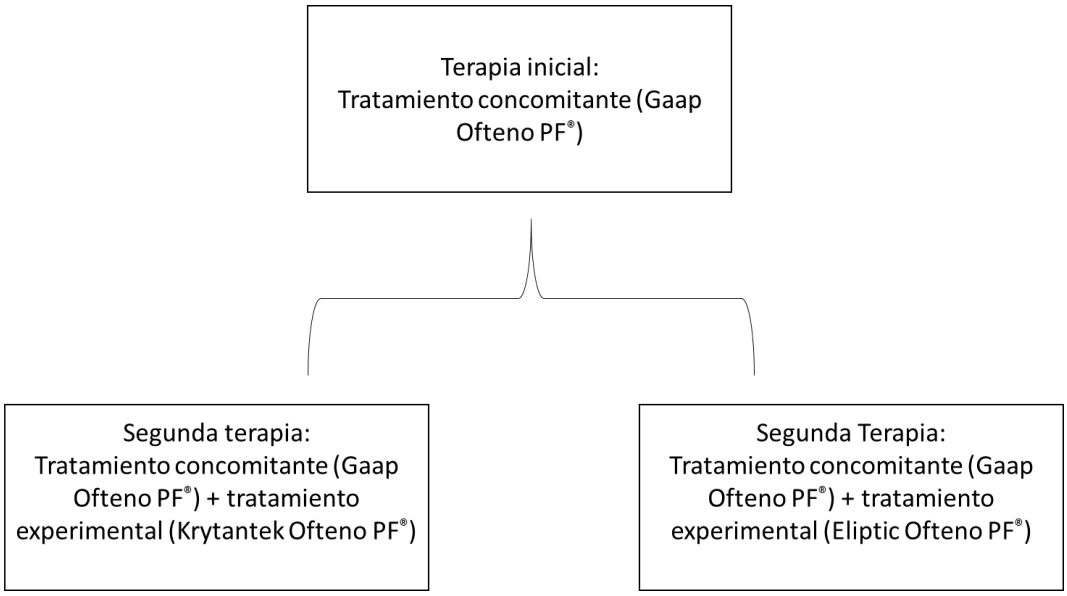


Figure12 Investigational therapies

There will be two groups, one with a maximum medical therapy of 4 ocular hypotensive agents (latanoprost plus timolol 0.5%/dorzolamide 2%/brimonidine 0.2%), and the other with a maximum medical therapy of 3 ocular hypotensive agents (latanoprost plus timolol 0.5%/dorzolamide 2%).

7.3 Justification of comparator therapy

Eliptic Ofteno PF ® is a preservative-free fixed combination of timolol 0.5%/dorzolamide 2%, available in the multidose bottle Novelia ® from the company Remera, as well as Krytantek Ofteno PF ® and Gaap Ofteno PF ® .

Because the experimental treatment bottles share the same presentation, it may be easy to mask the researcher and study subjects.

7.4 Randomization and blinding of investigational products

After signing the FCI, the subject will receive a patient number under which all information will be coded pseudo -anonymously during collection and completely anonymized during analysis.

Treatment allocation/randomization will be performed in two steps, using an integrated web-based response system (IWRS). In the first step, all patients will be assigned to the same treatment at the eligibility visit, but after one month, patients who again meet the eligibility criteria will be randomly assigned to one of the two experimental treatments. The allocation to the experimental treatments will be randomized 1:1 to either the Krytantek Ofteno PF® or the Eliptic Ofteno PF® .

Treatments masked to the investigator, the patient, and the sponsor will be the experimental treatments.

Furthermore, the statistical analysis will be performed in a blinded manner.

The masking of the bottles will be carried out by the personnel indicated by the Regional Clinical Research Management of Laboratorios Sophia, SA de CV. This will consist of removing the primary (commercial) label in the case of Krytantek Ofteno PF® and Eliptic Ofteno PF® and placing an identical label. The primary packaging will also be identical for both medications.

7.4.1 Implementing randomization

The allocation sequence will be generated by the Regional Clinical Research Management of Laboratorios Sophia SA de CV. The research center will receive a set of envelopes each containing the intervention number. The envelopes will be identical on the outside. Each envelope will be shown to the participants for their selection by the principal investigator or a designated member of their team.

7.4.2 Opening the blind

Blinding may be opened in the following cases:

- Presence of serious adverse event
- Safety alert due to the use of the study drugs
- In case the sponsor or the researcher determines it for some reason of security or other reason that is considered pertinent

7.5 Storage and handling of investigational products

The treatments will be provided by Laboratorios Sophia, SA de CV, for each research center. They will be labeled, reconciled, and weighed in advance. Treatment management will be the responsibility of the PI or a designated member of their team.

7.5.1 Delivery and receipt

The sponsor will be responsible for delivering the study treatments to the research center according to internal procedures. Delivery will be made in sealed boxes by courier service or directly by sponsor staff to the research center's address, in accordance with the study plan.

Reception will be handled exclusively by the research center team, including the PI. They must verify the condition of the primary packaging (the box). If it shows alterations or defects in its integrity that, in their judgment, could have damaged the contents, they must report this to the sponsor. If the package shows no significant defects, they will proceed to open it.

Inside, you should locate the receipt and temperature and humidity *data logger* . You should verify that the recorded temperature and humidity meet the specifications for transport and storage. You will then verify the contents (treatments) with what is reported on the document. If the document matches the contents, you will sign the receipt and send it to the sponsor. If not, you will notify the sponsor.

At the study center, staff assigned by the PI will administer the appropriate treatment to admitted subjects, sufficient for the study period. The medication for concomitant treatment will be administered at the eligibility, baseline, and follow-up visits; and the medication for experimental treatment will be administered at the baseline and follow-up visits.

7.5.2 Storage

Medications must be stored in a secure area with restricted access. They must be stored at room temperature, no more than 30° Celsius.

The research center is required to record the temperature and humidity recorded on the data logger in the format designated by the sponsor. This record must include the current temperature and humidity, as well as the minimum and maximum values for each. This must be done at least once a day on weekdays.

These data will be compared by the clinical monitor according to the record in the *data logger* .

7.5.3 Return

Research subjects will return their concomitant treatments to the PI-approved staff at the center at the baseline visit, the second follow-up visit, and the final visit; while they will receive the experimental treatment at the second follow-up visit and the final visit.

The research center will process the return when the sponsor so indicates. Prior to the return, the research center must perform a count of the assigned medication and the remaining medication, in order to create an inventory that will be used to complete the final medication return form.

8. Intervention during the study

8.1 Application of investigational products/medicines

Patients who meet all inclusion criteria and none of the exclusion or elimination criteria may be randomized after the eligibility visit to concomitant treatment (Gaap Ofteno PF ®) of the study.

The concomitant treatment is the same for all patients. It will be administered at 9:30 p.m. (9:30 p.m.), and patients will have ± 15 minutes to administer it.

At the baseline visit, when patients have been on concomitant treatment for approximately 30 days, the inclusion, exclusion, and elimination criteria will be reassessed. If the patient again meets the inclusion criteria, but none of the exclusion or elimination criteria, they may be randomized to the experimental treatment. Therefore, after the baseline visit, patients who remain in the study will receive concomitant treatment plus the experimental treatment.

The experimental treatment is not the same for all patients, as there are two treatments: the investigational product and the comparator product. Patients may receive either therapy depending on their randomization. The experimental treatment will be administered at 9:00 a.m. and 9:00 p.m. (9:00 p.m.); patients will have ± 10 minutes for the treatment.

While patients are using the experimental treatment, they will continue with concomitant treatment, which is essential for assessing the efficacy of the study. Evening applications of both products must be given at the established times, with a minimum of 10 minutes between them.

*Table 10*of Study Drug Administration Schedule

Phases of the study	**Therapies to administer**	
	Concomitant treatment: Gaap Ofteno PF ®	Experimental treatment: Krytantek Ofteno PF ® or Eliptic Ofteno PF ®
Eligibility/Open Phase (First Month)	• 9:30 p.m. ± 15 minutes	• It will not be applied
Double-blind phase (second and third month)	• 9:30 p.m. ± 15 minutes	• 9:00 hours ± 10 minutes • 9:00 p.m. ± 10 minutes

8.2 Replacement of ocular hypotensive agents used prior to the study

Patients will be receiving treatment with an ocular hypotensive agent (β-blocker or prostaglandin analogue) before starting the study. It is important that this medication be substituted for the concomitant treatment provided for the study at the eligibility visit.

If a patient is using a β-blocker, they should apply the corresponding morning drop on the day of the eligibility visit, before coming to the center, and if they are included in the study, they should no longer apply the evening drop.

8.3 Strategies to improve adherence and monitor adherence

Strategies:

- At the baseline, follow-up 2, and final visits, the research subject will return the concomitant treatment with the goal of assessing adherence by weighing the returned vial at the site.
- At follow-up visits 2 and 3, the research subject will return the experimental treatment for the purpose of assessing adherence by weighing the returned bottle at the site.
- At each visit, the PI will reinforce the importance of following the prescribed regimen with the research subject and ask if they have had any problems following the instructions. If necessary, the PI will retrain the subject in administering the medications.
- Subjects with an email address will be sent emails by the PI or designated person to remind them of their treatment adherence and the importance of it. The content of the emails will be submitted to the Research Ethics Committee for approval.
- Printed reminder.
- Through the subject's diary tool.

Procedure for monitoring adherence:

- Procedure at the research center. Before dispensing the medication to the research subject, the pharmacist must weigh the vials to be dispensed. After the subject returns the medication, the pharmacist must also weigh the vials. Guidelines to follow:
    - The pharmacist will use the scale authorized by the sponsor
    - You will place the bottle in the center of the scale and obtain the measurement.
    - Remove the bottle from the scale and replace it, confirming that the measurement is the same. If it is different, weigh it again and average the 3 measurements.
    - The result will be recorded in a log provided by the sponsor explicitly for this function.

Adhesion will be calculated considering the following: the weight of the empty bottle, the weight of the drop, the weight of the bottle with its contents, the total number of drops to be applied during the entire procedure, and the total weight of the drops applied. The following simplified formula will be used:

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

Where:

Ad= adhesion
P_1 = weight of the bottle given to the subject at the beginning
P_f = weight of the bottle returned by the subject
P_T = weight of the dosage indicated for the intervention

$$P_T = (P_g)G$$

Where:
P_g = weight of the intervention drop, determined by the research and development department

G= number of drops indicated for the intervention
Adherence will be assessed at each visit where the research subject returns the intervention. This result will allow the PI to determine whether the subject will continue in the study according to the elimination criteria.
The assessment of adherence through the subject's diary will be carried out as follows:

$$Ad = (Ar)100/ Ai$$

Where:
Ad = Adhesion
Ar = Registered Applications
Ai = Applications indicated for the intervention
The final (overall) adherence will be determined by the average adherence of each of the visits.

8.4 Authorized or prohibited medicines and medical devices

8.4.1 Medications and medical devices permitted prior to and during the study

Subjects successfully enrolled in the study and who meet the eligibility criteria may continue systemic treatment for their underlying conditions (provided these conditions are not contraindicated for the use of β -blockers, α2 - agonists, carbonic anhydrase inhibitors, or prostaglandin analogues). If, during the course of the study, they require the implementation of a new authorized medication, they may do so. All concomitant medications used must be duly reported in the clinical record notes and in the corresponding section.

Permitted ophthalmic medications:

- Ophthalmic topics:
    - Tetracaine 0.5% (office only)
    - Tropicamide 0.8% / Phenylephrine 5% (office only, and after Goldmann tonometry)
    - Any antibiotic
    - Eye lubricants
    - Nonsteroidal anti-inflammatory drugs
    - Ocular reepithelializing agents
    - Antihistamines

All permitted ophthalmic medications may only be applied at least 10 minutes after the study treatment. In the case of ointments or gels, these must be applied after the study products to avoid a decrease in absorption.

8.4.2 Medications and medical devices prohibited before and during the study

Ophthalmic medications prohibited during the study:

- Ophthalmic topics:
    - Steroidal anti-inflammatory drugs
    - Parasympathomimetic agents (e.g. pilocarpine)
    - Mydriatics and cycloplegics (not for office use)

  - Vasoconstrictors (e.g. naphazoline, oxymetazoline, phenylephrine, tetrahydrozoline)

- Intraocular or paraocular route:
  - During the course of the study, and for six months prior to the study, no medication will be administered via these routes.
  - Silicon

Prohibited medications that are administered by a route other than ophthalmic:

- During the study:
  - Mannitol
  - Isosorbide
  - Glycerin
  - Acetazolamide
  - Methazolamide
  - Aminooxidase inhibitors (MAOIs)
  - Tricyclic antidepressants
  - Mianserin
  - Steroidal anti-inflammatory drugs
- Prior to the study:
  - Any of the medications prohibited during the study may not have been used during the month prior to the study.

Important: Although they are not prohibited during the study, it is important to note that if the patient is using any type of antiarrhythmic, it is important to inquire about the type of cardiac arrhythmia they have, since most cardiac arrhythmias that require treatment could have the use of β-blockers as a contraindication, and therefore they would not be patients that can be included in the study.

9. Procedures during the study

9.1 Description of the procedures or assessments during the study

The different procedures that will be performed during the study are described below. The list may not be in order, but could be arranged in the most optimal way according to the needs of each research center.

9.1.1 Signature of informed consent

Procedure that ensures that the research subject has voluntarily expressed his or her intention to participate in this research, after having understood the information given to him or her about the objectives of this research, benefits, discomforts, and possible risks.

9.1.2 Taking a general and ophthalmological clinical history

This includes questions about medical history, symptoms, or diagnosed conditions, as well as any medications currently being used, regardless of their route of administration. It includes measurements of body weight and height (somatometry), and a complete ophthalmological evaluation.

9.1.3 Measuring vital signs

This involves measuring heart rate, respiratory rate, blood pressure, and body temperature. These measurements can be taken with a stethoscope, a sphygmomanometer, a mercury thermometer, or their digital counterparts.

9.1.4 Ophthalmological evaluation

Evaluation of the eyeball, eyelids, eyelashes, and other ocular structures through inspection, slit lamp (biomicroscopy), and palpation (touch). This evaluation includes best-corrected visual acuity, assessment of ocular surface integrity, intraocular pressure, and possible gonioscopy and fundoscopy.

9.1.5 Best-corrected visual acuity

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

Snellen notation is described as the distance at which the test is performed divided by the distance at which the letter vertically equals 5 minutes of arc. Thus, at 6 meters, a letter 6/6 (20/20) equals 5 minutes of arc, a letter 6/12 (20/40) equals 10 minutes, and a letter 6/60 (20/200) equals 50 minutes. The Snellen fraction can also be expressed as a decimal (i.e., 20/20 = 1 and 20/40 = 0.5). [49]

VA will be assessed at baseline, without refractive correction, using the Snellen chart. This chart will be placed in a location with adequate natural or artificial lighting and at a distance of 3 m from the subject being assessed. Visual acuity will be measured in each eye, starting with the right eye (RE), asking the subject to keep both eyes open and using an occluder to cover the left eye (LE); the subject will read aloud the lines indicated by the evaluator. The evaluator will record the smallest line of letters visible as the RE VA in the clinical record. The LE is then assessed using the same method.

The subject's best refractive correction will then be performed, and the examination will be repeated using the obtained refraction. This result will be reported as best-corrected visual acuity

(BCVA). It will be recorded as a fraction in the clinical record and on the CRF, and it will also be recorded as a decimal on the CRF. By definition, BCVA cannot be less than VA.

9.1.6 Integrity of the ocular surface

This will be performed using biomicroscopy using the research center's slit lamp. A complete assessment of the anterior segment will be recorded in the clinical record. The lighting techniques used will be at the discretion of the PI.

The variables that will be recorded in the CRF are:

- Conjunctival hyperemia. Defined as the simplest reaction of the conjunctiva to a stimulus, a red appearance is observed secondary to vasodilation of the conjunctival vessels of varying intensity. It is graded using the Efron scale. [50]See *Appendix 1 8.2 Efron scale for conjunctival hyperemia* .
- Chemosis. Defined as conjunctival edema resulting from an inflammatory reaction. It is graded as present or absent. The evaluator will use a narrow 60° beam and measure whether the conjunctiva separates from the sclera by ≥ 1/3 of the entire eyelid opening or whether it extends beyond the gray line. [51]
- Fluorescein staining. A drop of topical anesthetic will be instilled in the conjunctival fornix. A second drop will then be applied to the tip of the fluorescein strip and allowed to run into the fornix. It is essential to rapidly assess the staining, sequentially, first in the left posterior region and then in the right posterior region, so that the observed patterns are equally bright. This assessment will be performed using a cobalt blue filter. Grading will be using the Oxford scale. [52]*See Appendix 18.3 Oxford Scale.*

9.1.7 Intraocular pressure

Tonometry is the objective measurement of IOP, based primarily on the force required to flatten the cornea, or the degree of corneal indentation produced by a fixed force. Goldman tonometry is based on the Imbert-Fick principle. [49]

Tonometry will be performed after instillation of topical anesthetic with fluorescein and the use of a cobalt blue filter (after evaluation of corneal surface staining). Two readings will be taken, which will be recorded in the clinical record, and the average will also be recorded in the eCRF . Tonometry will be performed at 9:00 am and 11:00 am (± 30 minutes). These times were selected to correspond approximately to the minimum (12 hours post-instillation) and maximum (+2 hours post-instillation) IOP-lowering effects of the treatment used. During treatment, the researcher will ensure that the research subject applies the treatment after the 9:00 am IOP check.

9.1.8 Gonioscopy

This is the assessment of the iridotrabecular angle by attaching a gonioscopy lens to the patient's cornea. In some cases, the lens will be filled with a gel to improve its fit with the patient's cornea.

The Shaffer system will be used for angle classification.

*Table 11*Shaffer classification system

Degree	Angular opening	Description	Risk of occlusion
4	45°-35°	Open	Impossible

3	35°-20°	Open	Impossible
2	20°	Narrow	Possible
1	≤ 10°	Extremely narrow	Likely
0	0°	Closed	Occluded

9.1.9 Fundoscopy

Also called ophthalmoscopy, this is an examination performed with a light and magnifying glass to observe the fundus (optic nerve and retina) through the pupil. Sometimes, the pupil will need to be dilated to allow a better evaluation of the fundus.

9.1.10 Cup/disc ratio

It will be performed by indirect slit-lamp ophthalmoscopy; the lens will be chosen at the discretion of the PI. To adequately assess the optic disc, this will be performed under pharmacological mydriasis (tropicamide 0.8% / phenylephrine 5%), which is mandatory at the eligibility, baseline, and final visits.

The cup/disc ratio will also be measured by OCT of the optic nerve.

Cup-to-disc ratio assessments made by OCT and by the investigator may differ between the methods used and be considered normal. However, measurements made over time using the same method should not vary.

9.1.11 Adverse events

An EA is defined as Any adverse medical occurrence in a subject administered an investigational product, regardless of causal attribution. However, Good Clinical Practices, the Mexican Regulation (NOM-220-SSA1-2016), and the need to establish the patient's baseline status, including adverse events caused by treatment prior to the study and disease manifestations, in order to compare adverse events after treatment, require the researcher to collect and report all adverse events and suspected adverse events from the moment informed consent is obtained.

The management of AEs will be carried out in accordance with the provisions of Section 12. Evaluation and management of adverse events.

any AEs that the study subjects present in the corresponding section of the eCRF and will also report them in the clinical record.

For an adequate assessment of AEs, in addition to the targeted questioning, a Comprehensive Ophthalmologic Evaluation must be performed at each visit . This evaluation consists of: an ophthalmologic examination of the eyelids and adnexa, anterior segments, and posterior segments, which are performed during a routine ophthalmologic examination. These procedures are not specifically included in the study variables. The posterior pole evaluation can be performed with or without pharmacological mydriasis (as applicable during the visit). A fundus assessment will be performed to search for abnormalities that could alter the study results. IOP will be measured during this evaluation using a Goldmann tonometer and should be measured after the stain evaluation.

The results of the evaluation will be recorded in the clinical record. Only findings that the PI considers to be AEs will be reported as AEs in the eCRF .

9.1.12 Evaluation of concomitant medications

This question asks about any medications you are currently taking regularly or have used in the past month. If you have required medication therapy injected into the eye, you should be asked about any medications you have injected in the past 6 months.

9.1.13 Urine pregnancy test

For women of reproductive age who do not have a permanent method of contraception, a urine pregnancy test will be performed.

9.1.14 Review of eligibility and continuity criteria

This is a review of the inclusion, exclusion, and elimination criteria. Patients at the eligibility and baseline visits must meet all the inclusion criteria and none of the exclusion or elimination criteria. Subsequently, at the remaining visits, patients cannot meet any elimination criteria.

9.1.15 Visual fields

The visual field refers to the visual cortex's perception of objects and light sources at a particular moment in time with gaze fixation. Perception in the cortex considers that the object or light source was processed by the visual pathway from a stimulus on the retina. The visual field is a three-dimensional cone (Traquair 's island of vision), with its apex at the nodal point of the eye and its base at infinity. [53]The peripheral aspect of the visual field extends approximately 60° superiorly, 60° nasally, 80° inferiorly, and 90° temporally. The blind spot is located temporally between 10° and 20°.

Campimetry is a psychophysical test whose objective is to define the peripheral limits of an individual's visual field.

Humphrey perimetry is an automated test that includes software programming with standardized strategies with a predefined interval (e.g., 30-2, 24-2, 10-2). The full threshold strategy is the reference standard for evaluating glaucoma, however, the SITA (Swedish Interactive Thresholding Algorithm) can replace it as it is faster and more pleasant, as well as having greater sensitivity. [49]

Visual fields will be obtained using a Humphrey automated visual field meter, using a standard SITA 24-2 target-to-target strategy. The results of the visual fields included in the study will be considered reliable if they meet fixation loss, false positives, and false negatives rates of less than 20%. [54]The mean deviation (MD), a measure of overall field loss, and the standard deviation of the model (DSM), a measure of focal loss or within-field variability, will be recorded on the CRF.

9.1.16 Eye comfort index

This questionnaire is designed to measure ocular surface irritation using Rasch analysis to produce estimates on a linear interval scale (scores: 0–100). Similar to the index for ocular surface diseases, the ocular comfort index (OCI) assesses symptoms. The OCI contains eight items (one positive and eight negative) that focus on discomfort associated with ocular surface disorders. Each of these questions has two parts, which separately inquire about the frequency and severity of symptoms. [55] *See Annex 1 8.1 Comfort index ocular.*

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

9.1.17 Corneal pachymetry

Although central corneal thickness (CCT) and IOP have an independent effect on the risk of developing glaucoma, these two factors interact. Since the introduction of Goldman applanation tonometry, it has been recognized that CCT was a potential confounding factor for IOP measurement. CCT will be measured using ultrasound pachymetry. Three measurements will be recorded in the clinical record, and the average will be entered into the CRF. Baseline and final pachymetry should be performed by the same evaluator using the same pachymeter.

9.1.18 Optical coherence tomography (OCT) of the optic nerve and ganglion cells

Optic nerve OCT is a noninvasive fundus examination that allows quantitative analysis of retinal nerve fiber layer thickness and ganglion cell complex thickness. It uses low-coherence light provided by a superluminescent diode coupled to a fiber optic interferometer.

The OCT assessment will be obtained using the Zeiss Cirrus OCT. If the researcher has another OCT, it must be a spectral domain OCT, and its possible use must be validated in advance by the sponsor.

9.1.19 Photograph of the optic nerve

It is performed using a fundus camera that focuses on the optic nerve, magnifying the image. This study will provide a more accurate record of possible changes in the optic nerve head during the examination.

9.1.20 Assignment/randomization and delivery of investigational treatment (concomitant and/or experimental)

It refers to the randomization to the treatment group, and the delivery of the treatment to the subject under investigation.

The concomitant treatment will be the same for all patients (Gaap Ofteno PF®). The experimental treatment (Krytantek Ofteno PF® and Eliptic Ofteno PF®) will be one of the two for each patient, depending on the treatment group.

9.1.21 Assessment of treatment adherence

This refers to indirectly assessing the number of applications during the period between visits. To assess the approximate number of drops, the medication dropper bottle (concomitant or investigational treatment) can be weighed. The Subject Diary is also reviewed to determine the recorded applications.

9.1.22 Delivery of subject material

This refers to the provision of the subject's ID card and the subject's diary. The ID card will serve as identification with the treatment assignment number; this card can also serve as an appointment card. The Subject's Diary is used to record the number of times the treatment is administered.

9.1.23 Return of investigational treatment (concomitant and/or experimental)

It refers to the return that the research subject makes of the treatments provided for the study.

9.1.2 4 Safety call

This refers to a call made by the researcher at the end of the study to check on the health status and inquire about adverse events and the use of medications or other therapies that the research subject may have required after their final visit.

9.2 Study diagram and schedule

The screening visit is conducted 30 ± 3 days before the baseline visit. At this visit, the patient is randomized to concomitant treatment. The baseline visit is conducted approximately 30 days after

the completion of concomitant treatment. At this visit, the patient is randomized to the experimental treatment. Follow-up visit 1 is conducted 14 ± 2 days after the baseline visit. Follow-up visit 2 is conducted 30 ± 2 days after the baseline visit. The final visit is conducted 60 ± 2 days after the baseline visit. The follow-up call is conducted 15 ± 3 days after the final visit. *See Figure 13 Study flowchart* .

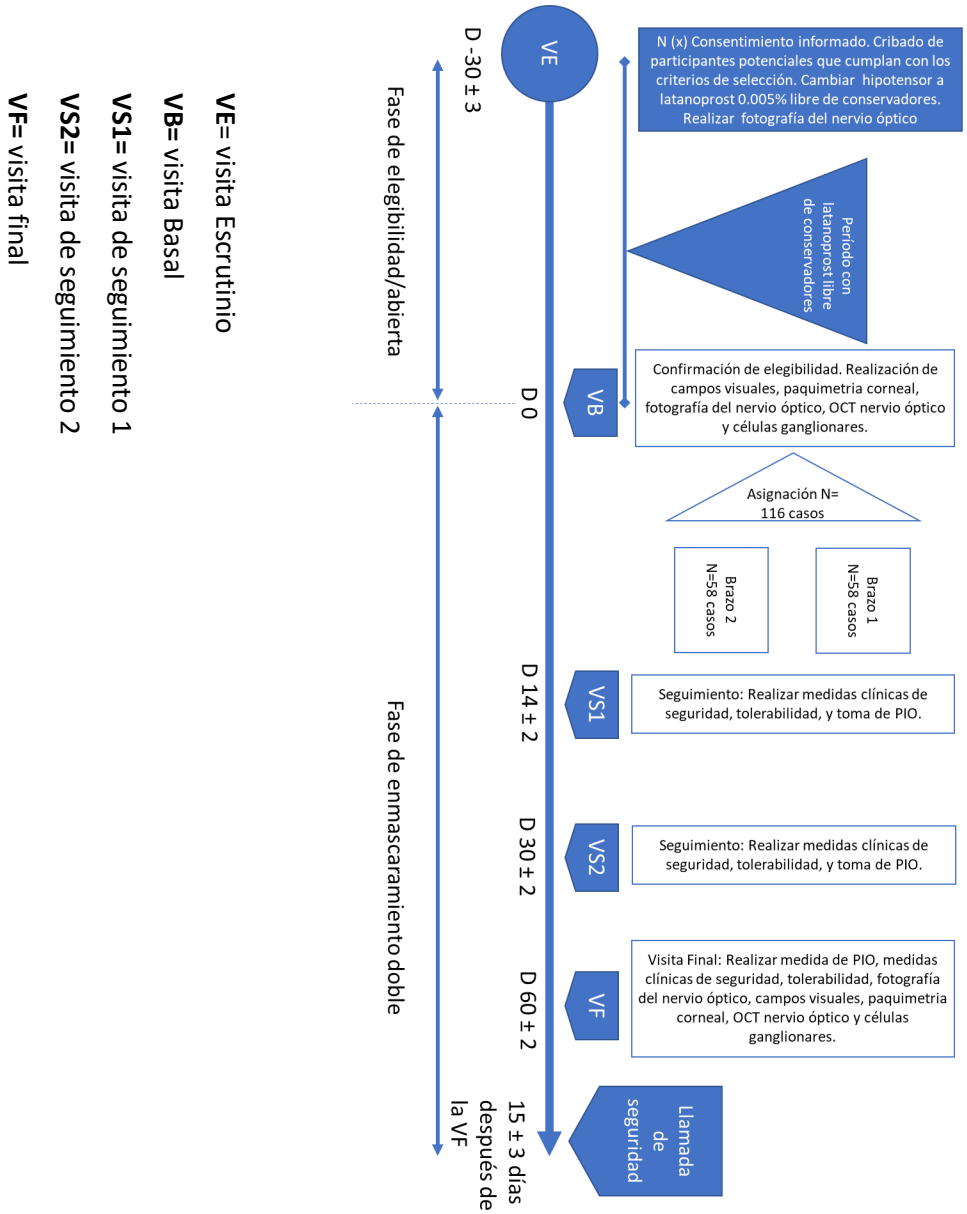


*Figure 13*Diagram of the study

Board12 Schedule of activities

	Eligibility Phase	Double-masking phase	
Procedures	Visit of	Visit of	

	Scrutiny D -30 ± 3	Basal D 0	follow-up 1 D 14 ± 2	follow-up 2 D 30 ± 2	final D 60 ± 2	Safety call D 75 ± 3
Sign informed consent	X					
Complete medical history (general and ophthalmological)	X					
Somatometry (weight and height)	X					
Vital signs	X	X	X	X	X	
Evaluation of concomitant medications	X	X	X	X	X	X
Evaluation of adverse events	X	X	X	X	X	X
Pregnancy test (if applicable)	X				X	
Eye Comfort Index	X	X	X	X	X	
AVMC	X	X	X	X	X	
Assessment of ocular surface integrity (conjunctival hyperemia, chemosis, and corneal fluorescein staining)	X	X	X	X	X	
Goldmann type ocular tonometry	X	X	X	X	X	
Gonioscopy	X	X				
Fundoscopy in mydriasis (evaluation of the optic nerve, its cup, and the retina)	X	X			X	
Evaluation of Eligibility Criteria	X	X				
optic nerve photography	X	X			X	

Subject code assignment	X					
Delivery of the Identification Card	X					
Submission of the subject and training diary	X	X		X		
Delivery of concomitant treatment	X	X		X		
Return of concomitant treatment		X		X	X	
Assessment of treatment adherence (review of subject diary and weight of bottles)		X	X	X	X	
Corneal pachymetry		X			X	
Visual fields		X			X	
oct optic nerve and ganglion cells		X			X	
Randomization to experimental treatment group		X				
Delivery of experimental treatment		X		X		
Fundoscopy without mydriasis, unless the Investigator considers mydriasis necessary (evaluation of the optic nerve, its cup, and the retina)			X	X		
Return of experimental treatment				X	X	
Continuity assessment			X	X		

9.3 Procedures to be carried out per visit

The procedures to be performed at each visit are listed below; these may not be in the most optimal order for the Research Center. The researcher should order them according to their needs, and the needs of the study and sponsor.

In assessing treatment adherence, the subject's diary may be reviewed and/or the dispensed dropper bottles may be weighed.

Adverse events assessment may include those occurring with concomitant treatment, experimental treatment, and/or concomitant medications other than those provided for this study. Because adverse events may in some cases be systemic or present in other extraocular sites, an extraocular examination may be required for their evaluation.

9.3.1 Scrutiny visit

- Signing informed consent
- General and ophthalmological medical history including weight and height
- Measuring vital signs
- Evaluation of concomitant medications
- Assessment of adverse events
- Ophthalmological evaluation
- Measurement of best-corrected visual acuity
- Evaluation of the integrity of the ocular surface
- Measurement of intraocular pressure
- Evaluation of the anterior chamber angle (gonioscopy)
- Urine pregnancy test (if applicable)
- Review of eligibility criteria
- Fundoscopy in mydriasis
- Photograph of the optic nerve.
- Answering the Eye Comfort Index questionnaire
- Assignment and delivery of concomitant treatment
- Delivery of subject material (Identification Card and Subject Diary)

9.3.2 Baseline visit

- Ophthalmological evaluation
- Measuring vital signs
- Measurement of best-corrected visual acuity
- Evaluation of the integrity of the ocular surface
- Measurement of intraocular pressure
- Evaluation of the anterior chamber angle (gonioscopy)
- Evaluation of concomitant medications
- Return of the subject's diary
- Return of concomitant treatment
- Assessment of treatment adherence (review of diary and weighing of bottle)
- Evaluation of adverse events
  Review of eligibility criteria
- Answering the Eye Comfort Index questionnaire
- Visual fields
- Corneal pachymetry

- Fundoscopy in mydriasis
- Photograph of the optic nerve
- OCT optic nerve and ganglion cells
- Assignment and delivery of experimental treatment
- Delivery of concomitant treatment
- Submission of the subject's diary

9.3.3 Follow-up visit 1

- Ophthalmological evaluation
- Measuring vital signs
- Measurement of best-corrected visual acuity
- Evaluation of the integrity of the ocular surface
- Measurement of intraocular pressure
- Fundoscopy
- Evaluation of concomitant medications
- Assessment of treatment adherence (review of subject's diary)
- Assessment of adverse events
- Continuity assessment

9.3.4 Follow-up visit 2

- Ophthalmological evaluation
- Measuring vital signs
- Measurement of best-corrected visual acuity
- Evaluation of the integrity of the ocular surface
- Measurement of intraocular pressure
- Fundoscopy
- Evaluation of concomitant medications
- Return of the Subject's Diary
- Return of concomitant and experimental treatment
- Assessment of treatment adherence (review of subject's diary and weighing of bottles)
- Assessment of adverse events
- Answering the Eye Comfort Index questionnaire
- Continuity assessment
- Delivery of concomitant and experimental treatment
- Submission of the Subject's Diary

9.3.5 Final visit

- Ophthalmological evaluation
- Measuring vital signs
- Measurement of best-corrected visual acuity
- Evaluation of the integrity of the ocular surface
- Measurement of intraocular pressure
- Evaluation of concomitant medications
- Return of the Subject's Diary
- Return of concomitant and experimental treatment
- Assessment of treatment adherence (review of subject's diary and weighing of bottles)
- Assessment of adverse events
- Answering the Eye Comfort Index questionnaire
- Urine pregnancy test (if applicable)

- Pachymetry
- Visual fields
- Fundoscopy in mydriasis
- Photograph of the optic nerve
- OCT optic nerve and ganglion cells

9.3.6 Safety call

- Evaluation of concomitant medications
- Evaluation of adverse events

10. Collection and administration of study data

10.1 Data collection methods

Each research center will be assigned a clinical monitor, who will be authorized to monitor, review, procure, and ensure that the quality of the information obtained from participants is reliable and trustworthy. Each monitor will schedule periodic visits to the research centers to review source documents and corroborate the information captured in the CRF. All clinical monitors will be trained on the study protocol information (objective, visits, procedures, accepted range of values, etc.). If the data is not identical between the two records, the clinical monitor will generate a discrepancy, which must be resolved by the research center within the timeframe the sponsor deems reasonable to meet the objectives of the clinical study. Discrepancies will be corrected in accordance with Good Documentation Practices.

The data recorded in the CRF will be reviewed by Laboratorios Sophia, SA de CV personnel trained in ophthalmology, clinical, and pharmacology. They will have the authority to raise discrepancies if the data do not adhere to the research protocol or pose a risk to participants.

Once all discrepancies generated by the monitoring team and clinical staff have been resolved, the data will be downloaded into an electronic database (Excel spreadsheet) by personnel designated by the sponsor. A new review of the data will be conducted to verify its accuracy, and new discrepancies may be generated if deemed necessary.

The generated database will be safeguarded by the sponsor and will only be accessible to designated personnel.

Strategies to complete the follow-up

- You will be clearly informed about the importance of the study and the benefits the population will gain from its results.
- If deemed necessary, travel assistance will be provided to enable participants to attend their visits.
- If deemed necessary, calls, messages, or a printed calendar will be made to remind participants of their appointments and the activities to be held, along with their estimated duration. A card will also be given at each appointment reminding them of the next appointment date.
- If the participating subject does not attend their appointment, the research center will call to determine the reason and will attempt to schedule a new appointment within the established window or an unscheduled appointment.
- If an appointment cannot be scheduled, the presence of adverse events and the reason for discontinuing the study will be asked as minimum information.

10.2 Data Management

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

The PI or their designated team member will complete the Case Report Form (CRF) as well as all other documents provided by the sponsor (e.g., treatment management documents).

An electronic CRF was designed to record the data required by the protocol and collected by the researcher at each visit.

In the case of self-assessment questionnaires, the principal investigator or the person responsible for completing them is not permitted to modify what was written by the study subject.

Data entry at the investigator's site will be performed by the investigator or a designated person from their team after completing the Medical Record. The investigator or a designated person from their team will be trained in completing the CRF.

All corrections to the CRF data must be made by the researcher or a designated person on his or her team according to the instructions provided.

To ensure data confidentiality and security, usernames and passwords will be used to restrict system access to authorized personnel only.

The monitor must ensure that all information on the CRF has been completed. After comparing the data with the source documents, the monitor will ask the researcher to make corrections/clarifications using clarifications, so that they can be answered and closed as quickly as possible.

The Scientific Committee of Laboratorios Sophia SA de CV will provide the final medical-scientific review and will set the guidelines for freezing the database.

11. Statistical methodology and data analysis

11.1 Statistical analysis

Statistical analysis will be performed by staff of Laboratorios Sophia, SA de CV. The statistical package SPSS version 19.0 for Windows (IBM Corporation , Armonk , NY, USA) will be used.

The personnel assigned to statistical data management will be blinded to the intervention groups. Coding will be performed using consecutive numbers for each intervention group. Data will be collected and organized in an Excel spreadsheet (Microsoft® Office). The data will then be exported to the SPSS software platform. Variables will be categorized according to their nature; *see Table 13 in section 11.6.1 Definition of variables, methods, and scales to be used for their measurement* .

11.2 Data interpretation

The results of continuous quantitative variables will be presented in measures of central tendency: mean, standard deviation and ranges.

Wilk (SW) tests will be performed , as applicable, to determine whether the distribution presents normality in the results obtained in each study group. [56]

The statistical analysis of continuous quantitative variables to find significant differences (p) will be as follows:

- Intra-group analysis : Student's t-test.
- Between-group analysis : Differences between groups will be analyzed using the Student t-test for independent groups or the Mann-Whitney U test when appropriate.

The level of difference considered significant will be an alpha (α) of 0.05 or less. A 95% confidence interval (95% CI) will be used for the noninferiority criteria. [57]

The analysis of nominal and ordinal qualitative variables will be presented in frequencies, proportions and/or percentages.

Statistical analysis to identify significant differences in qualitative variables will be performed by creating 2x2 contingency tables as follows:

- Intra-group differences : will be determined using the McNemar test [58]. Which is applied to 2x2 contingency tables with a dichotomous trait, with pairs of matched subjects, to determine whether the marginal frequencies of row and column are equal (marginal homogeneity).
- Difference between groups : differences between groups will be analyzed using Pearson's Chi-square (X^2) test or Fisher's exact test for expected values less than 5.

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

For the reporting of adverse events, participants who were randomly assigned to an intervention group after application of the investigational product will be considered.

The final results report will be displayed in tables or graphs, as appropriate.

The investigational product will be considered effective when there are no clinical and statistical differences in all primary outcome variables, with respect to its comparator (GOF + EOF).

11.3 Procedure for handling missing data

The safety assessment will include in the analysis all subjects who have been exposed to any of the interventions, regardless of the visit at which they were eliminated from the study (intention-to-treat (ITT) population).

11.4 Deviations from the statistical analysis plan

According to the sample size calculation to meet the study objective, 116 evaluable cases (58 cases per arm) are required. If this number is not met due to a loss of subjects exceeding the 30% threshold considered in the sample size calculation for this protocol (loss to follow-up or withdrawal from ICF), the sponsor may substitute these subjects to balance the treatment groups.

The results obtained from the replaced subjects will continue to be used for safety analysis and will be part of the ITT.

11.5 Subjects included in the analysis

Those subjects who complete all their visits and have adherence to treatment by weight and diary ≥ 90% will be included in the statistical analysis to meet the objective of the study (protocol population, PP).

The variables, method and scales for their measurement are described in detail below.

11.6 Outcome variables

Effectiveness:

- Intraocular pressure

Security:

- Best corrected visual acuity (BCVA).
- Cup/disc ratio measured by the researcher and by OCT.
- Nerve fiber layer and ganglion cell thickness measured by OCT.
- Evaluation of the optic nerve by optic nerve photography.
- Central corneal thickness determined by pachymetry.
- Visual fields determined by computerized campimetry.
- Integrity of the ocular surface:
  - Conjunctival hyperemia
  - Chemosis
  - Corneal staining with fluorescein
- Adverse events.

Tolerability:

Eye comfort index.

11.6.1 Definition of variables, methods and scales to be used for measurement

*Table 13*Method of measurement of variables and reference values

Variable	Guy	Unit	Measurement method	Normal value	Evaluation time	Statistical test
Primary outcome						
Intraocular Pressure (IOP)	Continuous quantitative	mmHg	Goldmann tonometry	≥ 10 and ≤ 21	VE, VB, V1, V2 and VF	Student's paired t-test

						Mann-Whitney U*
Exploratory						
Proportion achieving IOP ≤12, ≤13, ≤14, ≤15, and ≤18	Nominal categorical	But	Observation	Yeah	V1, V2 and VF	χ^2 or Fisher's exact test McNemar test *
Proportion that decreased IOP ≥ 20%, ≥ 25%, ≥ 30%, and ≥ 35%	Nominal categorical	But	Observation	Yeah	V1, V2 and VF	χ^2 or Fisher's exact test McNemar test *
Security						
Adverse events	Discreet	Number of cases (n)	Counting	0	VE, V1, V2 and VF	Student's t test
Adverse events (Bis)	Nominal categorical	Present / Absent	Observation	Absent	VE, V1, V2 and VF	χ^2 or Fisher's exact test
AVMC	Discreet	Fraction (-)	Snellen chart	0.1 – 2.0	VE, V1, V2 and VF	Student's t test Mann-Whitney U*
Retina and optic nerve evaluation and cup/disc ratio	Nominal categorical	Normal / Abnormal	Direct observation (biomicroscopy)	Normal	VB and VF	χ^2 or Fisher's exact test
Evaluation of retina and macular area	Nominal categorical	Normal / Abnormal	Direct observation (biomicroscopy)	Normal	VB and VF	χ^2 or Fisher's exact test
Central corneal thickness	Continuous quantitative	µm	Pachymetry	500	VB and VF	Student's t test Mann-Whitney U*
Nerve fiber layer thickness	Continuous quantitative	µm	OCT	≥ 80 and 95% CI	VB and VF	Student's t test Mann-Whitney U *
Ganglion cell thickness	Continuous quantitative	µm	OCT	≥ 70 and 95% CI	VB and VF	Student's t test

						Mann-Whitney U*
Visual fields	Continuous quantitative	dB	Computerized campimetry	VFI ≥ 80%; DM ≤ -3dB; TSM < P=5%; PHG outside normal limits	VB and VF	Student's t test Mann-Whitney U*
Shaffer	Ordinal	Grades (0 – 4)	Direct observation with Goldman gonioscopy	≥ 2	VB, V1, V2 and VF	χ^2 or Fisher's exact test
Corneal and conjunctival staining with fluorescein	Ordinal	Degrees (0 – V)	Direct observation with a slit lamp, Oxford scale	0	VB, V1, V2 and VF	χ^2 or Fisher's exact test
Conjunctival Hyperemia	Ordinal	Degrees (Efron)	Direct observation with a slit lamp, Efron scale.	0	VB, V1, V2 and VF	χ^2 or Fisher's exact test
Chemosis	Nominal categorical	Present/absent	Direct observation.	Absent	VB, V1, V2 and VF	χ^2 or Fisher's exact test McNemar test *
Tolerability						
ICO	Discreet	Points	Questionnaire	Not applicable	VE, V2 and VF	Student's t test Mann-Whitney U*
BCVA, best-corrected visual acuity; VE, screening visit; VB, baseline visit; V1-2, follow-up visits; VF, final visit; χ^2, Chi-square; *When I applied						

11.7 Preliminary analyses and early termination of the study

Partial analysis will allow the sponsor to make a decision about early termination of the study if participant safety is compromised.

Early termination of the study will be considered in the following cases:

1. Presence of serious adverse events in more than 5% of participants in each intervention group.
2. The competent authority (e.g. COFEPRIS) considers it as security alerts.
3. The Sponsor determines this for its convenience or eventualities such as: financial support, manufacturing errors, etc.

4. Lack of recruitment as expected.

If the decision is to terminate the clinical study early, all research centers will be notified within the first 24 hours, using available communication channels. The corresponding authority in each country (if applicable) and the Ethics Committees involved will also be notified.

Each research center is required to inform subjects participating in the clinical study within 24 hours of receiving the information from the sponsor. All subjects involved in any phase of the study must be informed.

The outcome of the preliminary evaluation will be the responsibility of the Regional Clinical Research Management and the Medical Directorate of Laboratorios Sophia, SA de CV, which will have the authority to determine the fate of this protocol as they deem appropriate.

12. Evaluation and management of adverse events

The registration and reporting of adverse events will be carried out in accordance with the guidelines established in NOM-220-SSA1-2016, which is in accordance with the international ICH E6 guidelines.

12.1 Definition of adverse event

According to the ICH, an AE is any adverse medical occurrence in a patient undergoing clinical research who is administered a pharmaceutical product, regardless of causal attribution.
Therefore, an AE may be any of the following: any undesirable medical event that is temporally related to the use of a medical product, whether or not considered to be related to that product; any new disease or exacerbation of an existing disease (worsening of the nature, frequency, or severity of a known condition); relapse of an intermittent medical condition (e.g., headache) not present at baseline; any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is related to symptoms or that results in a change in study or concomitant treatment or discontinuation of study drug.

12.2 Classification of adverse events

Severity (serious/non-serious), also called seriousness (serious/non-serious). A serious event is defined as any event that: results in death, threatens life, requires hospitalization or prolongs hospitalization, causes permanent or significant disability or incapacity, causes abnormalities or malformations in the newborn, or other medically significant conditions.
Severity (mild, moderate, or severe). Mild symptoms occur with minimal symptoms and do not require treatment or discontinuation of medication. Moderate symptoms interfere with normal activities without threatening the patient's life, require treatment, and may or may not be life-threatening. requiring discontinuation of the medication; severe, those that interfere with normal activities and require pharmacological treatment and discontinuation of the medication.

Causality. This is the relationship assigned between the drug and the AE: certainly caused by the drug, there is clear evidence of causality, i.e. the AE reappears with the administration of the drug; probably caused by the drug, there is a high suspicion of causality but no direct evidence is available or it is considered unnecessary or dangerous, i.e. the reaction disappears when the drug is discontinued; possibly caused by the drug, there is additional information suggesting that the cause may be due to another drug or disease; unlikely to be caused by the drug, there is a clear explanation for the origin due to the underlying disease or the use of another drug; conditional, there is a lack of data to issue a clear causality; not classifiable, those for which, once all possible information on the AE has been obtained, it remains unclassifiable.

12.3 Responsibility of the researcher

Conduct adverse event verification through questioning, a relevant physical examination, assessment of progress, as well as appropriate medical and pharmacological management, resolution or outcome, and final discharge following the definitions established in national and international regulations. [59] [60] [61]

In the event of adverse events or any occurrence that could put the health and well-being of patients at risk, appropriate medical care will be provided, either at the research site or by referring the patient to the Hospital Center with the highest resolution capacity with which the research site and/or researcher have a medical care agreement. The researcher will notify the sponsor's clinical monitor, in accordance with the times established in national and international regulations. In the

case of serious adverse events, the sponsor will be notified and the corresponding information will be recorded in the case report form, and in turn, the Research Ethics Committee and the Research Committee will be informed.

The care of adverse events will be carried out according to the event care diagram (*see Figure* 14. *Care of the adverse event* **,** in section *12.5*)

The final report prepared by the Scientific Committee of the Regional Clinical Research Management of Laboratorios Sophia, SA de CV, will include adverse event reporting in compliance with current national and international regulations.[59] [60] [61]

If the patient under investigation develops a chronic AE, such as diabetes or arterial hypertension, during their participation in the study, they will be referred to a healthcare professional responsible for chronic treatment. Follow-up and completion of their participation will be in accordance with the ICH guidelines.

12.4 Recording of adverse events in the electronic case report form

The adverse event registry considers information concerning the participating patient's identification data such as code, age, sex, left eye, right eye.

Information about the type of adverse event, adverse reaction, or suspected adverse reaction to concomitant treatment, experimental treatment, or concomitant medications, as applicable. The date on which the adverse event occurred is reported, as well as the date on which the Investigator became aware of it, and the date of resolution or outcome, as applicable. The clinical diagnosis is indicated. If a lack of therapeutic response to the investigational product and/or investigational medicinal product is detected, this should be reported as an adverse reaction. Include the therapy used for the pharmacological management of the adverse event, suspected adverse reaction, or adverse reaction under concomitant medications. Record the outcome or resolution of the event: patient recovered without sequelae, with sequelae, or not recovered. Patient who died due to the adverse reaction/adverse event; patient who died and it is judged that the drug may have contributed; patient who died and this death is not related to the investigational product or medicinal product; or indicate that the consequence of the event is unknown.

Record information about the investigational product or drug or the drug associated with the adverse event, adverse reaction or suspected adverse reaction. As applicable, information concerning the generic name, distinctive name or code of the investigational product and/or investigational drug must be recorded, as appropriate according to the methodological design of the study. This is relevant in the case of blinded studies or those where placebo is used as comparators, since there are circumstances that justify opening the blind to determine whether the adverse event, adverse reaction or suspected adverse reaction may be attributable to the active agent, the combination of active agents, or to the pharmacologically inert substance(s), such as the vehicle or additives, as appropriate to the clinical research phase in which the development of the drug is located.

It will also be necessary to record the data concerning a) batch number, b) manufacturing laboratory, c) expiration date, d) dose, e) route of administration, f) start and g) end dates of administration and/or consumption, reason for the prescription; according to whether it is an investigational product or medication (protocol in which the patient is currently participating) or is a medication that the research subject is taking for the treatment of underlying concomitant diseases or uses to manage some transient sign or symptom that does not correspond to the Natural History of the pathology that motivated their entry into the research protocol.

Record the withdrawal or discontinuation of the drug, investigational product, or investigational drug, as appropriate. Indicate whether the adverse event disappears upon withdrawal of the investigational product, investigational drug, or suspected drug (of causing the event). Also indicate whether a dose adjustment is made, if the event changes in intensity or severity, and if the reaction persists. It is important to note that in patients who are re-exposed to the investigational product, investigational drug, or drug, which had previously been discontinued, the adverse reaction or event should reappear.

Regarding concomitant pharmacotherapy, indicate the generic name, dose, route of administration, start and end dates, and the reason for the prescription, regardless of whether it is in accordance with the prescribing information or the data sheet or if it is used outside the regulations or as authorized by the local, national, or international regulatory body.

Regarding relevant clinical history. The analysis of the adverse event, adverse reaction, or suspected adverse reaction takes into account the previously described information. However, the clinical context in which the adverse event occurs in the participants of the clinical research protocol is of special interest. Therefore, information about previous conditions, hypersensitivity or allergy symptoms, previous surgical procedures, laboratory tests or examinations performed on the participant, etc., that the researcher deems appropriate may be mentioned. If there is sufficient space in the case report form, the information in the clinical note may be supplemented in the clinical record.

12.5 Monitoring of adverse events

The IP will provide care and guidance to the participant's EA until its outcome, in accordance with the following section.

12.6 Procedure for handling a serious adverse event

The adverse event handling process considers the following stages:

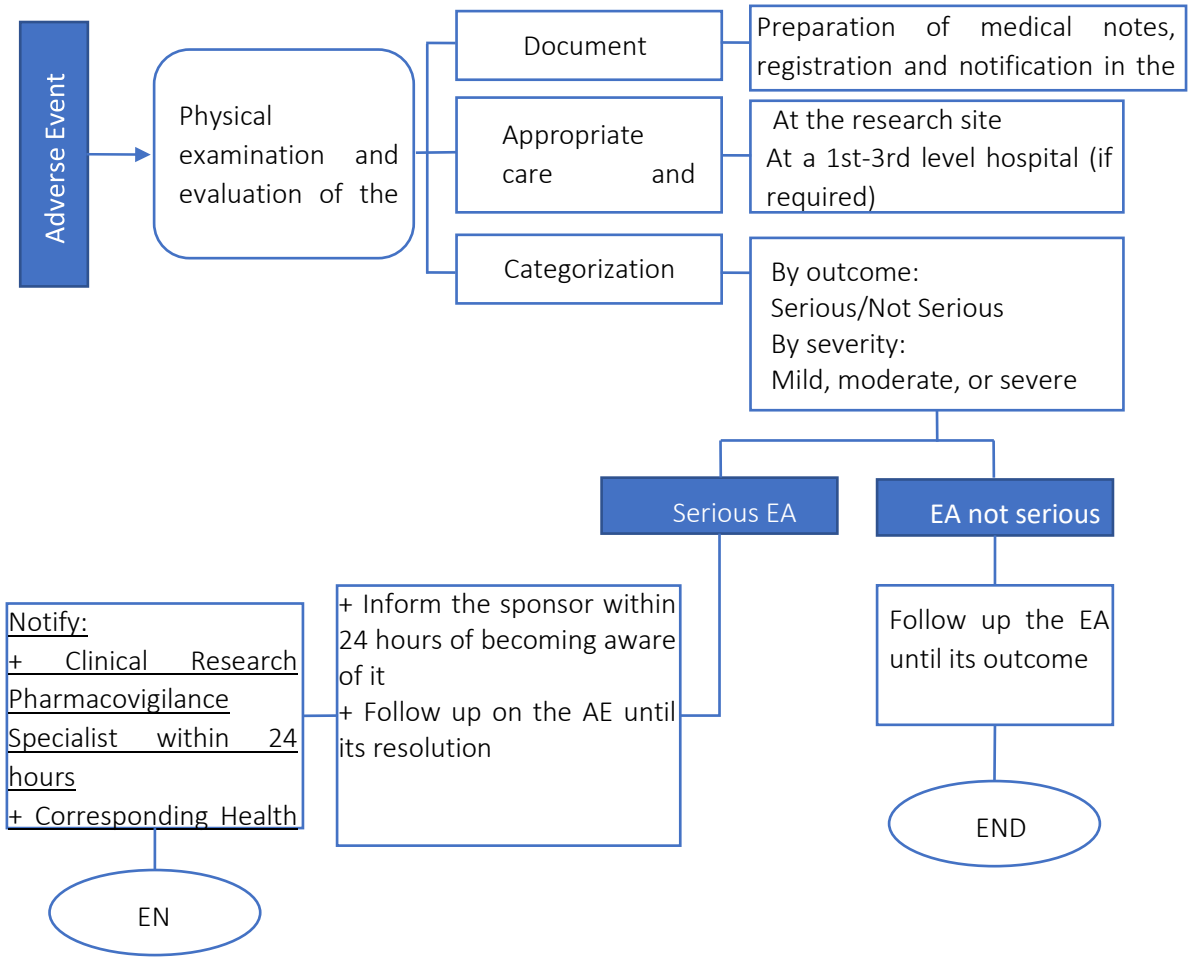


*Figure: 14*Adverse event care

During the development and conduct of this study, undesirable adverse events or adverse reactions of medical significance may occur in the research patient, which are not necessarily causally related to the PI or investigational medicinal product. These adverse events may occur during the use of investigational medicinal products at doses authorized for human use by a local, national, or international regulatory body. However, it may be suspected that the PI or investigational medicinal product may cause some undesirable clinical manifestation. AEs, ADRs, or SRAMs related to one or more medicinal products may occur during the systematic evaluation of participants (on the days when clinical reviews are scheduled, according to the activity schedule) or suddenly, such that:

1. The investigator should be the first person to whom the subject notifies that he or she has developed or experienced any clinically harmful phenomena during his or her participation in this study.

2. Based on their clinical judgment, the principal investigator will determine the appropriate treatment for the adverse event/reaction based on the relevant physical examination, history, etc., as well as the analysis of information available in the medical literature and the information contained in the investigator's manual, Prescribing Information, or the comparator drug's data sheet.

3. This care may be provided at the research center or at the hospital with the highest capacity for treatment. Thus, if the subject is referred by the PI to a hospital, they will

be provided care through a referral system. The referral may be through a card identifying the subject as a study participant and linking them to the pre-established agreement with the institution, or through a referral medical note issued by the PI. Laboratorios Sophia, SA de CV, will pay the costs for the participating subject's medical care when the adverse event is associated with or related to the PI or investigational drug.

4. Taking into account the clinical information collected, either during the care provided at the research center or provided by the treating physician(s) at the hospital, the IP will record the AE in his/her clinical note, stating the seriousness, intensity (mild, moderate, or severe), and relationship with the product or drug under investigation.

5. The PI must migrate the relevant data to the eCRF and its respective adverse event section. Serious adverse events must be reported to the study's clinical monitor within 24 hours of becoming aware of them, so that they can then inform the Clinical Team and the UTFLS, and subsequently notify the IEC/CI. Non-serious adverse events will be recorded and appropriately addressed, and the corresponding regulatory body will be informed about the safety profile of the PI or investigational drug in the final clinical trial report.

Recording the outcome of an adverse event depends substantially on the PI's follow-up of the subject, as most adverse events (see the safety profile section in the investigator's manual) are expected to be ophthalmic in nature; however, systemic changes may occur. Therefore, at the investigator's discretion, the participant's withdrawal or continuation will be considered.

12.7 Causality Assessment

Causality assessment is the methodology used to estimate the probability of attributing an observed adverse event to a medication. It considers probabilistic categories according to the available evidence and the quality of the information, based on national pharmacovigilance and technovigilance regulations. [59]

The Pharmacovigilance and Technovigilance Unit of Laboratorios Sophia (UFTLS) can use the Karch and Lasagna algorithm , modified by Naranjo and referred to by Aramendi I, as a tool to facilitate the probabilistic categorization of causality. This algorithm scores various items, which allow a value to be assigned to the cause-effect relationship between the administration of the medication and the adverse reaction. [62] *See Table 14. Karch and Lasagna algorithm modified by Naranjo.*

Table: 14Karch and Lasagna algorithm modified by Naranjo

No	Reagent	Yeah	No
1.	There are conclusive previous reports on adverse drug reaction, adverse event or suspected adverse drug reaction	+1	0
2.	The adverse event occurred when the suspected drug was administered	+2	-1
3.	The adverse drug reaction, adverse event, or suspected adverse drug reaction improved upon discontinuation or administration of a specific antagonist	+1	0
4.	The adverse drug reaction/adverse event/suspected adverse drug reaction recurred upon administration of the investigational drug/investigational product/investigational drug	+2	-1

5.	There are alternative causes that can provoke this reaction.	-1	+2
6.	The adverse reaction/adverse event/suspected adverse drug reaction occurred after placebo administration	-1	+1
7.	The drug was determined in blood or other fluids in toxic concentrations	+1	0
8.	The intensity of the adverse reaction/adverse event/suspected adverse drug reaction was greater with higher doses or less with lower doses	+1	0
9.	The subject has had similar reactions to the investigational drug/product or investigational drug in the past	+1	0
10.	The adverse reaction/adverse event/suspected adverse drug reaction was confirmed with some objective evidence	+1	0
	Total score	summation	
Probabilistic category based on the score obtained			
Yo	The causal relationship is verified	≥,9	
II	The ADR is likely due to the investigational drug or product	5 to 8	
III	The ADR may be due to the investigational drug or product	1 to 4	
IV	The causal relationship is doubtful	0	

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

Thus, the degree of certainty required to establish the PI as the causal agent of the harmful phenomenon occurring to the subject of the clinical study is essential. This can also be indicated directly by the PI based on their clinical experience or through the voluntary application of the aforementioned tool. However, it is important that the researcher and the UFTLS consider the following arguments in favor of a causal relationship:

a) Strength of association, which refers to the number of cases in relation to those exposed.

b) The consistency of the data, that is, the presence of a common characteristic or pattern.

c) The exposure-effect pattern, which determines the relationship with the site of onset, time, dose and reversibility after suppression.

d) Biological plausibility, which refers to the possible pharmacological or pathophysiological mechanisms involved in the development or presentation of the adverse event.

e) Experimental findings, for example, the appearance of anomalous metabolites or high levels of drug or its biotransformation product.

f) Analogy, which refers to the experience acquired with other related drugs, adverse reactions frequently produced by the same family of pharmacological agents.

Nature and characteristics of the data, i.e. objectivity, accuracy and validity of the relevant documentation. [63]

12.8 Unanticipated Problems

Unanticipated problems (ANP) are considered situations that pose risks to the participating subjects, generally any incident, experience or result that meets all of the following criteria:

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

12.9 Reporting unanticipated problems

The PI will be responsible for reporting PNAs to the sponsor, the IC, and the IEC. The report should contain the following information:

- Study identification: protocol title and number, name of the PI and, where applicable, the center.
- Detailed description of the event, incident, experience or outcome.
- Explanation, justification of the reasons why the incident represents a PNA.
- Description of changes to the protocol or corrective actions taken or proposed in response to the NAP.

PNAs that are EAS must be reported to the IEC/ CI and the sponsor within the first 24 hours of the IP becoming aware of it.

Any other PNA will be reported to the IEC/CI and the sponsor within the first 5 business days after the IP becomes aware of it.

Study monitoring

The study sponsor is responsible for monitoring the study. Monitoring activities include, but are not limited to: general safety monitoring, general study quality monitoring, study site monitoring, adverse event detection monitoring, reporting and follow-up, monitoring to resolve data entry discrepancies, etc.

Responsibility for monitoring activities and ultimate responsibility for monitoring rests with the sponsor.

The details of the monitoring activities are specified in a separate document from this protocol in a Monitoring Plan.

13. Research Centers

13.1 From the research center

This study will be conducted in properly equipped and registered ophthalmology offices. Depending on the sponsor's needs, these offices may be private or public, attached to a hospital or clinic, or independent.

13.2 Number of research centers

Six research centers are considered for the study, although this number is not limited to this. Depending on the needs of the study, additional research centers could be considered to supplement the sample size.

13.3 Recruitment and selection metrics

The recommendation is that research centers recruit a minimum of three cases per month who can continue from the baseline visit and complete the study.

13.4 Organization of the research center

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

The PI is responsible for forming a multidisciplinary research team to execute the clinical study according to the protocol, under his or her scientific guidance. The PI is responsible for designing the organization of his or her center and selecting the personnel who will perform these functions. However, the minimum organization of the research team requested by the sponsor requires the following: a sub-investigator , study coordinator, and pharmacist. *See Figure 15 Organization of the Research Center* .

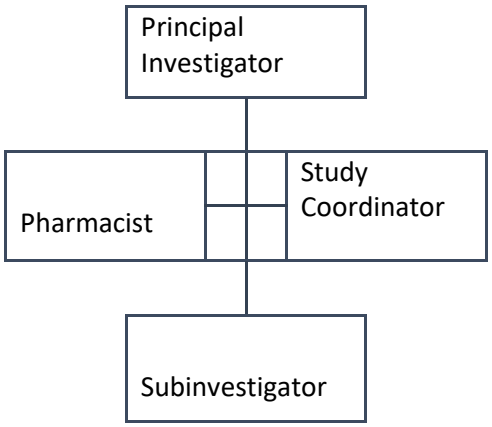


Figure 15Organization of the research center

Any person designated by the PI as responsible for monitoring the study (coinvestigator, sub-investigator, nurse, etc.) or for a specific role in the study (pharmacist, administrative assistant, study coordinator, etc.) must be listed on the "Delegation of Responsibilities" form.

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

13.5 Documents to be submitted to the sponsor by the principal investigator

The IP must submit to the sponsor, before the start of the study:

- *curriculum vitae* , in Spanish, dated and signed (maximum 10 pages), of the IP and the staff that make up the center's organizational chart.
- Copy of academic certifications from the IP (degree and specialty diploma in ophthalmology; federal professional certificates or similar corresponding to the country)
- Copy of academic certifications of the highest degree obtained by each member of your research team, which support their ability to perform the delegated functions.
- Copy of notice of operation or similar issued by the corresponding regulatory entity (When applicable)
- Valid certificate of good clinical practice. If the issuing institution does not specify the validity period in the certificate, the certificate issue date must not exceed one year.

13.6 Closure of the research center

The center will close after the last visit of the last enrolled subject, as previously agreed upon by the sponsor and the IP, has been completed. The closure process will be in accordance with the sponsor's internal operating procedures.

It is the sponsor's prerogative to inform the PI of the reasons for the premature closure of a study center.

14. Monitoring

14.1 Data Monitoring

Monitoring visits by a Laboratorios Sophia, SA de CV site monitor are intended to confirm that studies sponsored by Laboratorios Sophia, SA de CV are conducted in accordance with the ethical principles originating in the Declaration of Helsinki and are consistent with Good Clinical Practices and applicable regulatory requirements (by verifying continued compliance with the protocol, amendment(s), reviewing investigational product accounting records, verifying that site personnel and facilities remain suitable for conducting the study).

The researcher must ensure that sufficient time, space, and qualified personnel are available for monitoring visits.

In order to conduct the monitoring review, it is mandatory to provide direct access to all source data and data related to the study site. The monitor will conduct a review of the CRF and a Source Document Verification (SDV). SDV refers to the verification of records in the CRF by comparing them with the source data that the researcher will make available for this purpose.

Regarding the CRF, the monitor will mark the completed and approved screens on each visit.

In accordance with applicable regulations, Good Clinical Practices, and the procedures of Laboratorios Sophia, SA de CV, Laboratorios Sophia, SA de CV monitors will contact the site prior to the start of the study to review the protocol, regulatory, ethical, and Laboratorios Sophia, SA de CV requirements with site personnel. When reviewing procedures for data collection, the discussion will also include the identification, agreement, and documentation of individual data for which the records in the CRF will serve as source documents.

Laboratorios Sophia, SA de CV will monitor the study to verify, among other things, that:

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

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

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

Upon premature completion or discontinuation of the study, the monitor will conduct site closure activities with the investigator or site personnel, as appropriate, in accordance with applicable regulations, Good Clinical Practices, and Laboratorios Sophia, SA de CV procedures.

After the study is closed, the researcher must keep all study records on-site in a secure location. Records must be maintained to allow for easy and timely retrieval when necessary (e.g., during an audit or inspection). Sophia Laboratories,

SA de CV will inform the researcher/institution of the length of time they will need to retain these records in order to comply with all applicable regulatory requirements. However, the

researcher/institution must seek written approval from the sponsor before disposing of these records. The minimum retention period will satisfy the most stringent standard applicable to that study site, in accordance with GCP, any institutional requirements, or applicable laws or regulations, or the standards/procedures of Laboratorios Sophia, SA de CV.

The researcher/institution must notify Laboratorios Sophia, SA de CV of any changes in archiving arrangements, including, but not limited to, the following: archiving in an off-site facility, transfer of ownership of records in the event the researcher leaves the site.

14.2 Monitoring of research centers

The research centers participating in the study will be monitored. At least one initial visit and one closing visit must be conducted for each center, although one or more follow-up visits may be required between these two mandatory visits.

The initial visit must be conducted before the first participant is enrolled at that center. During this visit, the monitor will verify that the materials to be used during the study have been received and that the personnel involved in study activities have been trained in the study. The monitor will also verify compliance with applicable regulatory requirements and standard operating procedures.

At the follow-up visit(s), the monitor will review the study documents to confirm that the research protocol and applicable standard operating procedures are being followed, that data entry is complete and timely, and that adverse event reporting is being conducted appropriately. At each visit, the monitor will discuss the findings with the investigator and determine the appropriate actions to be taken.

The closing visit will take place at the end of the study, once the last participant at the site has been discharged from follow-up. During this visit, the monitor will verify that the site has all necessary documentation for archiving, that all biological samples have been analyzed, that all PI (used and unused) has been returned to the sponsor, and that all unused materials have been recovered.

Details of monitoring are set out in the relevant plan.

14.3 Audit and quality control

To ensure compliance with GCPs and all applicable regulatory requirements, Laboratorios Sophia, SA de CV may conduct quality assurance audits. Regulatory agencies may also conduct a regulatory inspection of this study.

Details of the audit process are set out separately in an Audit Plan.

14.3.1 Pre-study audit

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

14.3.2 Audit during the conduct of the study

They may take place at any time before, during, or after the conclusion of the study. If an audit or inspection is conducted, the investigator and the institution must agree to allow the auditor/inspector direct access to all relevant documents and must allocate their time and staff time to the auditor/inspector to discuss the findings and any pertinent issues. If the audit has not been scheduled by the sponsor, the center must notify Laboratorios Sophia, SA de CV immediately.

15. Ethical considerations

15.1 Approval of committees

This study will be conducted in accordance with the standards of the Declaration of Helsinki, World Medical Association 2013. Nuremberg Code ; Nuremberg Judgment by the International Tribunal at Nuremberg , 1947. Belmont Report, National Commission for the Protection of Subjects of Biomedical and Conduct Research, 1979. It will be conducted in accordance with the scientific and technical requirements necessary for the registration of medicines for human use of the International Conference on Harmonization (The International Council for Harmonisation (ICH) Guideline for Good Clinical Practice. International Ethical Guidelines for Biomedical Research Involving Human Subjects of the Council for International Organizations of Medical Sciences of Medical Sciences , CIOMS, 2002). International Ethical Guidelines for Epidemiological Studies of the Council for International Organizations of Medical Sciences of Medical Sciences , CIOMS, 2008). The Research Ethics Committee and the Research Committee will evaluate the protocol before conducting the study and will issue their approval or any possible modifications for its implementation. These Committees must be notified of any significant changes to the protocol. In addition to the above, the current regulations of the regulatory authority must also be complied with.

The sponsor's authorized personnel will submit the essential documentation of the research project for evaluation by the Research Ethics Committees, Research Committees, and when applicable, to the Biosafety Committee: research protocol, informed consent form, researcher's manual, subject material, as well as other additionally requested documents, in accordance with the local, national or international requirements applicable by regulatory entities.

The study will not be initiated at the research center without the confidentiality agreements and financial proposals from each of the principal investigators, duly signed, and without having previously obtained the favorable opinion and/or approval of the corresponding Research Ethics Committees, Research Committees, and, where applicable, the Biosafety Committee.

The study will not begin without meeting the relevant local, national, or international regulatory requirements and obtaining the appropriate health authorization.

The study is considered to be research with greater than minimum risk, in accordance with the Regulations of the General Health Law on Health Research, Title Two, Chapter I, Article 17, Section III, published in the Official Gazette on January 6, 1987.

15.2 Amendments to the protocol

The amendment process will be relevant when there is a need to make any changes to a document that is part of the research project or protocol, due to changes in the methodological structure, replacement of the principal investigator, or the identification of risks to the research subjects. Documents that may be amended include: the protocol, informed consent letter, researcher's manual, subject documents, measurement scales, and activity schedule.

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

Amendments that substantially modify the protocol or impose additional or different risks to research subjects must be approved by the aforementioned Committees. It is the investigator's

responsibility to take measures in situations requiring immediate action to prevent unnecessary harm to study participants.

The principal investigator is responsible for communicating to the Research Ethics Committee any amendments to the protocol that could affect the rights, safety, or well-being of the research participants. They must also report any situation or new knowledge that indicates an increased risk to the participants, the premature termination or suspension of the study, the reasons for this, and the results obtained to that point. They must also report the conclusion of the study upon completion of the research protocol.

15.3 Early termination of the study

The study may be temporarily suspended or terminated prematurely if there is sufficiently reasonable cause. Written notification documenting the reason for the suspension or early termination must be provided by the party executing the suspension. The PI must promptly inform the study participants, the IC, and the IRB, providing the reasons.

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

1. The presence of serious adverse events in more than 10% of participants in a study group.
2. The regulatory authority (COFEPRIS) considered it due to security alerts.
3. The Sponsor determines this for its convenience or eventualities such as: financial support, manufacturing errors, etc.
4. The determination of unexpected risks to participants that are significant or unacceptable.
5. Obtaining new relevant safety information.
6. Insufficient adherence to protocol requirements.
7. The data obtained are not evaluable or are not sufficiently complete.
8. The determination that the primary objective has been achieved.
9. The determination of futility.

In the event of suspension, the study may be resumed once the situations that led to the suspension have been resolved, provided this justification is sufficient for the sponsor, IC, IEC, and regulatory authorities.

15.4 Informed consent

The FCI contains complete and understandable information about the study and the investigational product, in accordance with current applicable regulations and Good Clinical Practices.

The FCI will be considered a source document and will be filed as such. The site's principal investigator is responsible for ensuring that all new versions of the informed consent form undergo the appropriate approvals (the same ones that the original informed consent form underwent) and that the most current approved version is presented to the study subjects.

Obtaining informed consent

Informed consent must be obtained before the subject undergoes any procedure indicated in the protocol. For this purpose, the informed consent form must be signed.

Written consent documents will incorporate the elements of informed consent described in the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice and will be in compliance with all applicable laws and regulations.

The PI, or the study staff delegated by him or her, will provide the potential participant with all information regarding the characteristics of the study, its potential benefits, risks, objectives, and procedures.

This information will be provided in a language understandable to the subject. The subject will be explained that they have the right to discontinue their participation in the study at any stage, without affecting their relationship with the researcher and/or their future participation. Informed consent will be presented to the potential participant; they must have sufficient time to review each and every aspect mentioned above. Any questions they may have will be clarified by the person responsible for obtaining informed consent.

Once the participant agrees to participate in the study, he or she must sign and date the informed consent letter in the presence of two witnesses, whether or not related to the study subject. These witnesses will participate in the informed consent process and sign, confirming that the process was carried out prior to any study procedure, that the study information was clearly explained, and that any questions were clarified.

In the event that a subject is illiterate, acceptance will be with his or her fingerprint, and in the event that the subject is not capable of providing adequate written informed consent, a “legally authorized” representative of the subject may provide such consent for the subject in accordance with applicable laws and regulations.

Likewise, the PI, or the study staff delegated by him, must sign and date this consent.

The FCI must be signed in duplicate by all involved; one copy will be filed in the researcher's folder and the other will be given to the participant. The PI or designated staff member must document the process of obtaining Informed Consent through a detailed, accurate, and contemporaneous medical note, specifying the signed version, the date the document was signed, and how the process was carried out.

15.5 Special Considerations

The procedures that will be performed during the conduct of the study do not pose any additional risk that should be considered apart from the procedures listed in the informed consent.

15.6 Modifications to informed consent

Any change to the FCI constitutes an amendment to this document and must be submitted for approval to the Research Ethics Committees and COFEPRIS.

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

re-consent process must be conducted for each subject affected by the amendment under the same conditions as those described above, in order to promptly communicate the new information contained in the document. The subject will be given a signed original of the amendment, and the researcher will retain the second original.

15.7 Confidentiality

All documents and information provided to the research center by the sponsor are strictly confidential. The PI expressly agrees that the data regarding his or her professional and clinical experience, provided to the sponsor in paper form and stored electronically, are solely for use in connection with his or her activities with the clinical study sponsor, in accordance with Good Clinical Practice.

The PI agrees that he and his team members will use the information only within the scope of this study, to carry out the protocol. This agreement is binding as long as the confidential information has not been publicly disclosed by the sponsor.

The clinical study protocol provided to the PI may be used by the PI and his or her team to obtain informed consent from the subjects for the study. The clinical study protocol, as well as any information derived from it, must not be disclosed to other parties without the sponsor's written authorization.

The PI will not disclose any information without the prior written consent of Laboratorios Sophia, SA de CV, except to representatives of the Competent Authorities, and only at their request. In the latter case, the researcher is obligated to inform Laboratorios Sophia, SA de CV before disclosing the information to these authorities.

The PI will complete and maintain a subject selection log, as well as the identification and enrollment list of each subject participating in the study. The researcher agrees to grant on-site access to the auditor and/or representatives of the Competent Authorities. The information will be treated in compliance with professional secrecy.

In the eCRF and all communications related to study subjects, they will be identified only by their study subject identification number, either the screening number or the randomization number. The information collected in this study will be exchanged between the sponsor and the research site and must be treated confidentially. The Health Authority, the IRB, the IC, the sponsor, the monitors/auditors, and third-party auditors will be the only bodies authorized to review the study documentation. If publications arise from this research project, under no circumstances will they contain information about the identification of the study subjects. If the study results are published, no personal information about the study subjects will be disclosed.

The protection of personal data will be in accordance with the corresponding current regulations.

15.8 Conflict of interest

The independence of the study's conduct and results from any actual or perceived external influences is critical. Therefore, any current conflict of interest of any person playing a role in the design, conduct, analysis, publication, or any other aspect of this study will be declared. Furthermore, those with a perceived conflict of interest will be asked to manage it in a manner appropriate to their participation in the study.

15.9 Declaration of interests

The PI agrees to declare his or her financial interests and conflicts of interest prior to the start of the study.

15.10 Access to information

The final study database will be the property of Laboratorios Sophia, SA de CV, and access to it will be restricted. The PI will not have access to it except with prior written authorization from the sponsor.

Any information obtained that is relevant to the safety of the subjects participating in the study must be immediately shared with the research center, so that the study subjects can be notified.

15.11 Ancillary and post-study care

Once the study is completed and adverse events are closed in accordance with *section 12. Evaluation and management of adverse events* , the sponsor will not extend care to the research subject.

16. Publication and funding policies for the study

16.1 Final report

Once the statistical analysis is completed, the final report will be written with the results obtained, by the Medical Management Department Team of Laboratorios Sophia, SA de CV. This report will be prepared following the recommendations of the ICH E3 *Step 4 Guide.*

16.2 Communication of results

Regardless of the results of the study, Laboratorios Sophia, SA de CV, is committed to communicating the final study report to the principal investigators and COFEPRIS. These results will also be shared with the research committee and the IEC. The PI will be responsible for communicating the results to the research subjects.

Laboratorios Sophia, SA de CV will retain at all times the rights to the publication and dissemination of the information contained herein.

16.3 Publication of results

Laboratorios Sophia, SA de CV, acting as the sponsor of the study, assumes full responsibility for its role and retains exclusive ownership rights to the study results, which it may use as it sees fit.

The PI agrees not to publish or communicate data collected from the study, unless prior written agreement is obtained from Laboratorios Sophia, SA de CV. Any manuscript derived from the data obtained with this protocol must be submitted for review by the sponsor before any attempt to submit it for publication in any journal or scientific conference.

However, if the sponsor is in the process of filing a patent application on the results of the study, the sponsor may delay publication or communication of the results of the study until the date of registration or when it deems appropriate.

Authorship assignments for publications are the sponsor's responsibility. However, express authorization from those invited to participate as authors is required. Authors have the right to review the manuscript prior to publication, as well as to provide comments and suggestions. Such comments must be submitted within the first 15 calendar days of receipt of the project.

16.4 Financing and insurance

16.4.1 Compensation to study participants

Subjects participating in the study will not receive financial compensation for their participation.

16.4.2 Insurance for study participants

Subjects participating in the study will sign the informed consent form, which specifies that Laboratorios Sophia, SA de CV agrees to pay for immediate treatment resulting from injuries or illnesses caused by the investigational products until resolved, in accordance with medical judgment.

All study participants will be covered by a liability insurance policy contracted by Laboratorios Sophia, SA de CV. Information on the policy will be available at the research centers. In the event of a medical emergency, the research center must have the personnel, materials, equipment, and procedures for immediate management .

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18. Annexes

18.1 Eye comfort index

No de estudio: SOPH122-0420/IV	Fecha: _____/_____/_____
Iniciales del sujeto: _____	No. De sujeto: _____

Directions:

This questionnaire was designed to rate the degree of comfort of your eyes.

For each question, circle your answer.

Example: In the past week, how often were your eyes red?

Never Always

0 1 2 3 4 5 6

There are no right or wrong answers. Try not to spend too much time on each question.

1. In the past week, how often did your eyes feel dry?

Never Always

0 1 2 3 4 5 6

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

I have not felt it Serious or very intense

0 1 2 3 4 5 6

2. In the past week, how often did your eyes feel gritty?

Never Always

0 1 2 3 4 5 6

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

I have not felt it Serious or very intense

0 1 2 3 4 5 6

3. In the past week, how often did your eyes feel stinging?

Never Always

0 1 2 3 4 5 6

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

I have not felt it Serious or very intense

0 1 2 3 4 5 6

4. In the past week, how often did your eyes feel tired?

Never Always

0 1 2 3 4 5 6

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

I have not felt it Serious or very intense

0 1 2 3 4 5 6

5. In the past week, how often did your eyes feel sore?

Never Always

0 1 2 3 4 5 6

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

I have not felt it Serious or very intense

0 1 2 3 4 5 6

6. In the past week, how often did your eyes feel itchy?

Never Always

0 1 2 3 4 5 6

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

I have not felt it Serious or very intense

0 1 2 3 4 5 6

18.2 Efron scale for conjunctival hyperemia

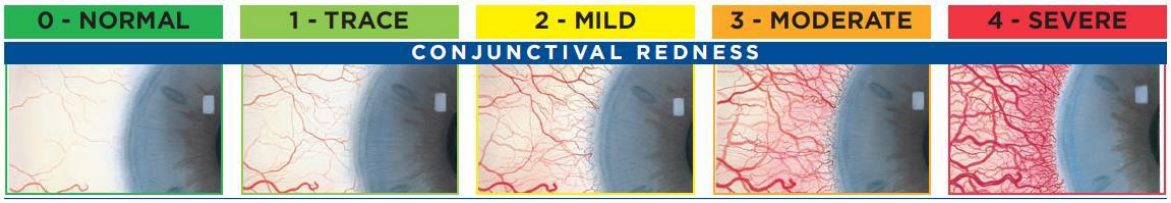
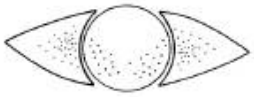
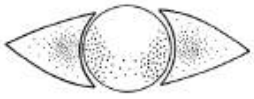
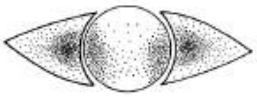


Figura 16 Escala de Efron

18.3 Oxford Scale

Tabla 15 Escala de Oxford

PANEL	Grado	Criterios
A 	0	Igual a o menor que panel A
B 	I	Igual a o menor que panel B, mayor que A
C 	II	Igual a o menor que panel C, mayor que B
D 	III	Igual a o menor que panel D, mayor que C
E 	IV	Igual a o menor que panel E, mayor que D
>E	V	Mayor que panel E