A Multicentric, Prospective, Crossover, Double-Blind Clinical Study, to Evaluate the Non-inferiority of the PRO-067 ophthalmic solution, Manufactured by Laboratorios Sophia, S.A. de C.V., Previous Treatment with GAAP Ofteno ®, In Subjects With Primary Open-angle Glaucoma (POAG) or Ocular Hypertension (OHT): "COMPLIANCE" Study.

- Drug under study: Latanoprost 0.005%
- Indication: Antiglaucomatous
- Development phase: Phase 3
- Protocol code: SOPH067-0914 / III
- Sponsor: Laboratorios Sophia, S.A. of C.V.
- Version: 3
- Date: February 2016

2. STUDY SHEET SUMMARY

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

Active Ingredient Name: Latanoprost 0.005%

Study title: A Multicentric, Prospective, Crossover, Double-Blind Clinical Study, to Evaluate the Non-inferiority of the PRO-067 ophthalmic solution, Manufactured by Laboratorios Sophia, S.A. de C.V., Previous Treatment with GAAP Ofteno ®, In Subjects with Primary Open-angle Glaucoma (POAG) or Ocular Hypertension (OHT): ("COMPLIANCE" Study) Protocol No.: SOPH067-0914 / III

Study period: **Study development phase**

Duration of the study for the participant: 75 days. Phase: 3

Goals:

Aim: To demonstrate the non-inferiority of the PRO 067 ophthalmic solution manufactured by Laboratorios Sophia, S.A. de C.V., versus GAAP Ofteno ® ophthalmic solution like hypotensive therapy in subjects with a diagnosis of POAG or OHP.

Primary Outcome Measures: To evaluate the efficacy of the PRO-067 ophthalmic solution elaborated by Laboratorios Sophia, S.A. of C.V. versus the GAAP Ofteno® ophthalmic solution applied on the ocular surface in subjects with a diagnosis of POAG or OHT by control and maintenance of a Target Intraocular Pressure (TIOP).

Secondary Outcome Measures: To assess the tolerability of the PRO-067 ophthalmic solution elaborated Laboratorios Sophia, S.A. of C.V. versus the GAAP Ofteno® ophthalmic solution in subjects with a diagnosis of POAG or OHT through the evaluation of ocular symptoms such as burning, hyperemia, lacrimation, foreign body sensation; fluorescein staining, the Visual Function Index (VF-14) questionnaire score and ocular comfort index.

Primary security objective: To evaluate the safety of the PRO-067 ophthalmic solution elaborated by Laboratorios Sophia, S.A. of C.V. versus GAAP Ofteno® ophthalmic solution in subjects with a diagnosis of POAG or OHT through visual capacity, anterior segment biomicroscopy, fundus examination and frequency of adverse events.

Work hypothesis / Ho: The proportion of subjects with open-angle primary glaucoma and / or intraocular hypertension exposed to GAAP Ofteno ® who maintained the TIOP values during the study is greater than or equal to the proportion of subjects with primary open-angle glaucoma and / or intraocular hypertension exposed to PRO-067 who maintained the TIOP values plus 2mmHg during the study.

Ha: The proportion of subjects with primary open-angle glaucoma and / or intraocular hypertension exposed to GAAP Ofteno® who maintained the TIOP values during the study is lower than the proportion of subjects with primary open-angle glaucoma and / or intraocular hypertension exposed to PRO-067 who maintained the TIOP values plus 2mmHg during the study.

Methodology

A national, multicenter, prospective, crossover, longitudinal, double-blind study, with fixed dose. Number of participants: 120 subjects.

Diagnosis and main inclusion criteria: Female or male, age ≥18 years, with primary open-angle glaucoma with or without pseudoexfoliation or pigmentary dispersion previously treated with GAAP Ofteno® at least for two months before inclusion and under TIOP corresponding to their condition in at least 2 previous visits without concomitant eye surface diseases and an informed consent signature.

Study medication:

The PRO-067 Ophthalmic drops. They will be applied with the following posology:

1 drop every 24 hours for 30 days, alternating therapy with 30 more days of GAAP Ofteno® with the same frequency.

Comparator: GAAP Ofteno®

Treatment duration:

- Inclusion period: 3 months

- Period of treatment: 60 days

- Follow-up period: 75 days.

Evaluation criteria:

Efficacy measurements:

Main efficacy criteria:

Efficacy will be determined by maintaining the TIOP throughout the study.

Secondary efficacy criteria:

Specific signs and symptoms such as burning, hyperemia, lacrimation, foreign body sensation, measurements with fluorescein staining, the VF-14 questionnaire score and ocular comfort index will be evaluated.

Primary security criteria

Visual capacity, anterior segment biomicroscopy, fundus examination and frequency of adverse events.

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4. GLOSSARY AND DEFINITIONS

- AE Adverse Event
- VA Visual acuity
- VC Visual Capacity
- CRF Case Report Form
- GCP Good Clinical Practices
- ICH International Conference on Harmonization
- IC Informed Consent
- RM Researcher's Manual
- ERC Ethics and Research Committee
- ICL Informed Consent Letter
- EPIT Estimated Population by Intent to Treat
- IOP Intraocular Pressure
- EPPP Estimated Population by Proper Protocol
- SAE Serious Adverse Event
- RC Rear Camera
- SM Study Medication
- Cr Committee of the researcher
- OHT Intraocular hypertension
- POAG Primary Open-angle Glaucoma
- mmHg Mercury milimiters

5. ADMINISTRATIVE STRUCTURE OF THE STUDY

5.1. Sponsoring parties

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

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6. BACKGROUND

Most drugs for the management of intraocular pressure were introduced before having reports in the literature about their ocular effects. In contrast, hundreds of publications on the ocular effects of prostaglandins can be found.i

Prostaglandins are normally present in ocular tissues, and are known to modulate a broad spectrum of biological processes and responses, either alone or in combination with other autacoids. Although prostaglandins can reduce intraocular pressure (IOP) sufficiently, they have considerable adverse effects on human eyes, in some cases including the rupture of the blood-aqueous barrier and an initial hypertensive phase. The esterification of the carboxylic acid of PGF2α reduces the amount of drug needed to decrease intraocular pressure, thereby minimizing its side effects.ii

Glaucoma is a progressive optic neuropathy, characterized by structural alterations, which result in functional anomalies. These alterations are manifested by: specific changes in the optic disc, defects in the nerve fiber layer, visual field alterations and other signs usually related to the difficulty of outflow of aqueous humor and a constant or intermittent abnormal intraocular pressure.iii

Ocular hypertension is currently considered the main risk factor in the pathophysiology of damage to the head of the optic nerve; the ischemia of the optic nerve, at the level of the lamina cribosa, is also important. Three variables determine the average level of intraocular pressure: (1) production of aqueous humor by the non-pigmented epithelium of the ciliary body; (2) outflow of aqueous humor; (3) pressure of the episcleral veins. In this way, medical treatment should be aimed at modifying these variables.

 Agents that modify the rate of formation of aqueous humor:

1. Beta-adrenergic antagonists.

2. Alpha adrenergic agonists.

3. Carbonic anhydrase inhibitors.

 Agents that alter the outflow of aqueous humor:

1. Cholinergic agents.

2. Alpha adrenergic agonists (non-conventional route).

3. Prostaglandin analogues.

 Agents that modify the episcleral venous pressure.iii

Sophia Laboratories, S.A. of C.V. has developed a formula of Latanoprost at 0.005% which remains stable at different temperatures and at different periods of time, thus showing advantages over Xalatan®, which is unstable under certain environmental conditions. iv

Glaucoma is a silent disease, being the second cause of legal blindness worldwide and the first cause of irreversible blindness in the adult population.v.

Among the ocular hypotensive drugs currently used for the treatment of primary open-angle glaucoma (POAG) and ocular hypertension, prostaglandin analogs are considered to be the most potent. Although the mechanism of action of these drugs is yet not fully understood, it is believed that these act by increasing the drainage of the aqueous humor by both conventional and non-conventional routes. In a study carried out by Dr. Masanobu and Col. in the Department of Ophthalmology at the University of Hiroshima, in Japan, a total of 124 Japanese subjects diagnosed with primary open-angle glaucoma were included, showing that the intraocular pressure was decreased with Latanoprost, maintaining its reducing effect for 1 year, the duration of the study. In addition, in this same study Latanoprost demonstrated good tolerance. Vi

Jean Philippe Nordmann et al. developed a clinical study comparing the effect of Latanoprost in monotherapy versus the effect of the combination of timolol maleate plus pilocarpine in subjects with glaucoma or ocular hypertension, with a poor response and lack of control of IOP with the use of β-adrenergic antagonists. We included 237 subjects who were assigned the randomized study article, those who were administered Latanoprost at 0.005% once a day and those whom the combination was administered twice a day, evaluating its intraocular pressure reducing effect, reaching the conclusion that a single application of Latanoprost a day is as effective as two daily applications of the combination of timolol maleate with pilocarpine to reduce intraocular pressure in those subject's refractory to treatment with β-adrenergic alone.vii

JUSTIFICATION

Recently, an increase in the prevalence of ocular surface disease in glaucoma subjects has been reported in approximately 48.4% compared to 15% in the 1990s. It is believed that this increase in dry eye symptoms is due in part to the chronic use of medications and to the preservatives they contain, with benzalkonium chloride as the most widely used in ophthalmic preparations.

Due to its efficacy, prostaglandin analogs have been positioned as first-line drugs for the treatment of primary open-angle glaucoma, its application once a day has also favored compliance by subjects.

It has been reported that Latanoprost is the best tolerated analog of prostaglandin in the market, although there is controversy in the different references with respect to other prostaglandins. Regarding this, Laboratorios Sophia S.A. of C.V. developed a new formulation in the search to provide subjects with greater comfort, compliance, and effectiveness.

Starting from the conclusions enunciated by Dr. Boudinxii and collaborators in studies of the effects of the conservators on the ocular surface in which the inflammation factors that lead to histological changes were measured, it is logical to propose a formula with the same effectiveness. In these studies, first performed on the conjunctiva of healthy patients, then in patients diagnosed with primary glaucoma it was concluded that the following differences existed:

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

 The tear rupture time is altered after 7 days of exposure and reaches abnormal times after 3 weeks.xi.

Also, the migration of pro-inflammatory cells from the innate response promotes secondary immunological reactions,

such as:

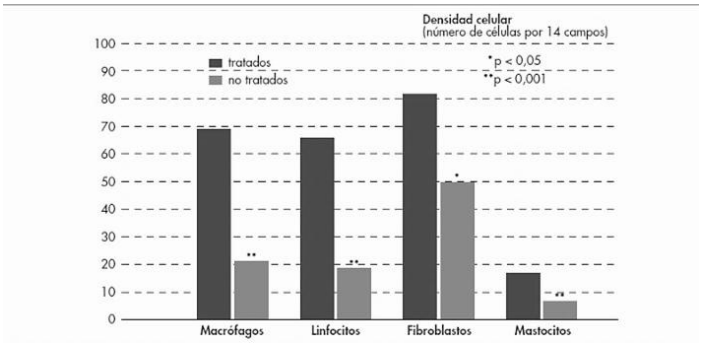
- HLA-DR antigens and pro-kinetic molecules I-cam – 3 are the main molecules found in the conjunctival proper substantia and tenon. xiii.
- As a result, there is a significant increase of CD 20/22/23 as well as CD 4 (Th2) xii, xiii.

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

- Corneal de-epithelization.
- Loss of epithelial microvilli.
- Subconjunctival fibrosis.
- Reduction of the number of goblet cells.
- Epithelial keratinization.
- Squamous metaplasia.
- Increase in the number of desmosomes.
- Bullous epithelium dystrophy.
- Subepithelial fibrosis.
- Increase in subepithelial lymphocytes and plasma cells
- Thickening of the basement membrane.

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

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



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

	No users	Monotherapy	Multi-therapy
Nomal	**80%**	**59%**	**12%**
Immunohistochemical markers	**20%**	**27.3%**	**42%**
fibrosis	**0%**	**12.7%**	**46%**

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

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

Hypothesis

Ha: πs <πe + $^{\delta}$

Ha: The proportion of subjects with primary open-angle glaucoma and / or intraocular hypertension exposed to GAAP Ofteno® who maintain the TIOP values during the study is lower than the proportion of subjects with primary open-angle glaucoma and / or intraocular hypertension exposed to PRO-067 who maintain TIOP values plus 2mmHg during the study.

H0: πs ≥ πe + $^{\delta}$

Ho: The proportion of subjects with primary open-angle glaucoma and / or intraocular hypertension exposed to GAAP Ofteno ® who maintain the TIOP values during the study is greater than or equal to the proportion of subjects with primary open-angle glaucoma and / or intraocular hypertension exposed to PRO-067 who maintain the TIOP values plus 2mmHg during the study.

Where:

H0: Null hypothesis

Ha: Alternative hypothesis

πs: Proportion of subjects with primary open-angle glaucoma and / or intraocular hypertension exposed to GAAP Ofteno ® who maintained the TIOP values during the study

πe: Proportion of subjects with primary open-angle glaucoma and / or intraocular hypertension exposed to PRO-067 who maintained the TIOP values during the study

$^{\delta}$ Noninferiority limit determined at +2 mmHg. That is, the study subjects should not exceed the values of their TIOP by more than 2mmHg with respect to the baseline value during their participation in the present study. VIII

Therefore, the evaluation of efficacy in the present clinical trial focuses on the maintenance of the TIOP, which was previously achieved with the antiglaucomatous stablished treatment, VIII, IX when receiving for 75 days the formulation PRO-067 or GAAP ofteno® (as active control). XI

NON-CLINICAL PHARMACOLOGY

Laboratorios Sophia S.A. of C.V. studied the bioavailability of Latanoprost® from 3 products containing its prodrug Latanoprost, which were GAAP Ofteno, PRO 067 ophthalmic solution elaborated by Laboratorios Sophia S.A. of C.V and Xalatan®. The study times were 30, 60, 120, 180 minutes, using two rabbits in both eyes with an n = 4. Table 4 (curve from 10 to 40 ng / mL) and table 6 (curve from 40 to 300 ng / mL) show the calibration curves used for the quantification of Latanoprost Acid in aqueous humor, it should be noted that two curves were used since a single curve of 10 to 300 ng does not present a good linearity contrary to what was presented when using two of them.

Figures 1 and 2 show the individual bioavailability of Latanoprost® from PRO-067 ophthalmic solution developed by Laboratorios Sophia S.A. of C.V and GAAP Ofteno® respectively, where a vertical line marks the minimum, average value and the maximum value obtained, plotting in the tempo using only the average.

Tables 8, 10 show the 4 values obtained for each study time, in the last column, the average of them is shown in bold. Viii

7. Tabla 1.- Curva calibración en Diluyente				
ng/mL	INY1	INY2	PROM	DE%
8	174	136	155	24.5
10	213	207	210	2.9
20	520	507	513.5	2.5
30	551	521	536	5.6
40	725	739	732	-1.9
50	966	920	943	4.9
70	1297	1168	1232.5	10.5
100	1863	1852	1857.5	0.6

Tabla 2.- Linealidad de la curva en diluyente	
r^2	0.991
a	-2.026
m	0.056

Table showing the standard recoverability loaded in aqueous humor.

8. Tabla 3.- Evaluación HA cargado							
ng/mL	INY1	INY2	PROM	DE%	ng/mL recuperados	% recuperado	% Exacta
10	95	105	100	-10.0	3.574	35.74	104.6
20	190	216	203	-12.8	9.342	46.71	80.1
30	231	221	226	4.4	10.63	35.43	105.6
40	383	406	394.5	-5.8	20.066	50.17	74.6
50	351	368	359.5	-4.7	18.106	36.21	103.3
70	724	642	683	12.0	36.222	51.75	72.3
100	715	629	672	12.8	35.606	35.61	105.0
200	921	879	900	4.7	48.374	24.19	154.6
300	1267	1066	1166.5	17.2	63.298	21.10	177.3
					promedio	37.43	

Curva de calibración en humor acuoso de 10 a 70 ng/mL

9. Tabla 4.- Primer curva de calibración HA cargado				
ng/mL	Iny 1	Iny 2	Promedio	DE%
10	95	105	100	-10.0
20	190	216	203	-12.8
30	231	221	226	4.4
40	383	406	394.5	-5.8
70	724	642	683	12.0

Tabla 5.- Linealidad de primer curva de HA	
r^2	0.981
a	38.515
m	0.100

10. Tabla 6.- Segunda curva de calibración HA cargado				
ng/mL	Iny 1	Iny 2	Promedio	DE%
40	383	406	394.5	-5.8
50	351	368	359.5	-4.7
100	715	629	672	12.8
200	921	879	900	4.7
300	1267	1066	1166.5	17.2

Tabla 7.- Linealidad de segunda curva de HA	
r^2	0.970
a	-84.455
m	0.318

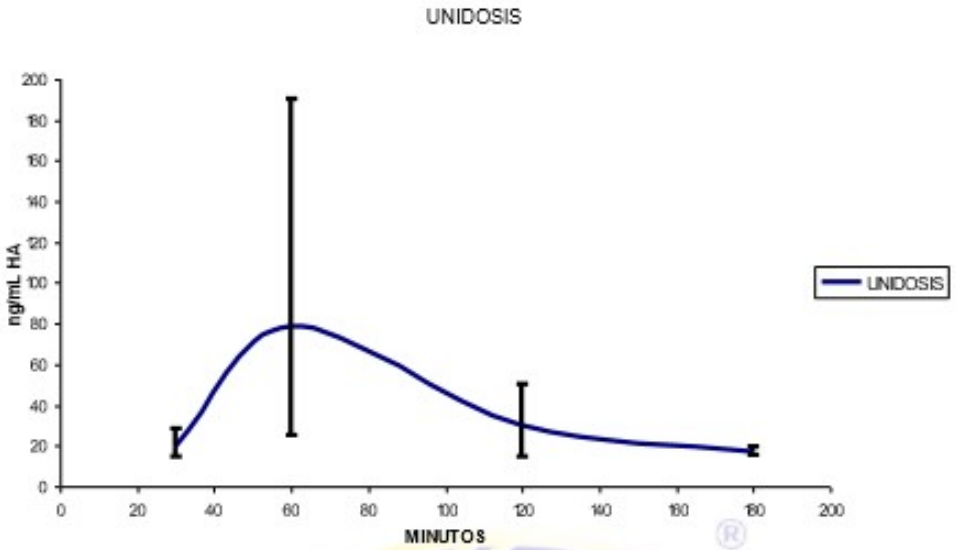


Figura No. 1 Biodisponibilidad de Ácido Latanoprost a partir de GAAP libre de conservador.

Tabla 8.- ng Acido Latanoprost / mL HA en GAAP libre de conservador			
30 min	**60 min**	**120 min**	**180 min**
15	25	14	16
17	46	24	17
18	51	32	18
28	190	50	20
19	**78**	**30**	**17**

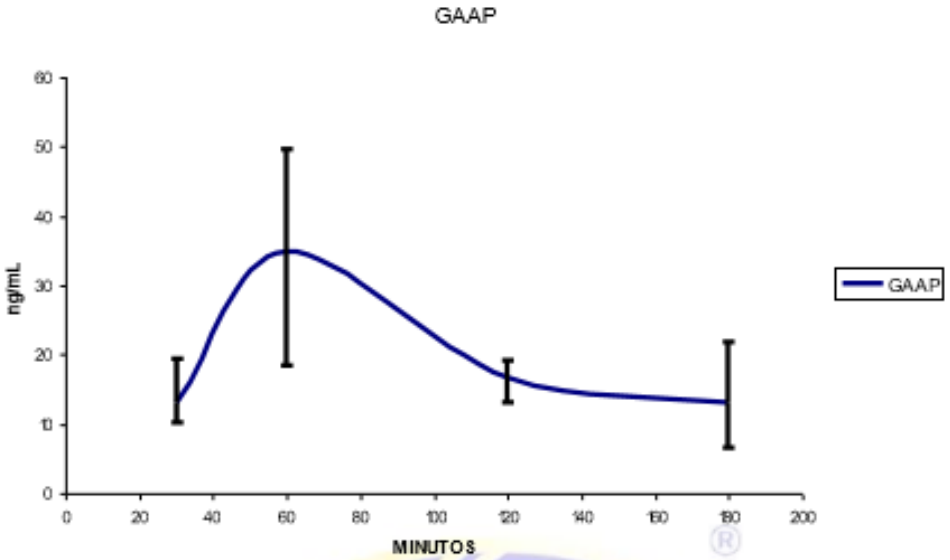


Tabla No. 4 Biodisponibilidad de Ácido Latanoprost a partir de GAAP Ofteno.

Tabla No. 10 ng Acido Latanoprost / mL HA en GAAP Ofteno			
30 min	**60 min**	**120 min**	**180 min**
10	18	13	6
10	31	17	10
12	41	17	14
19	50	19	22
13	**35**	**17**	**13**

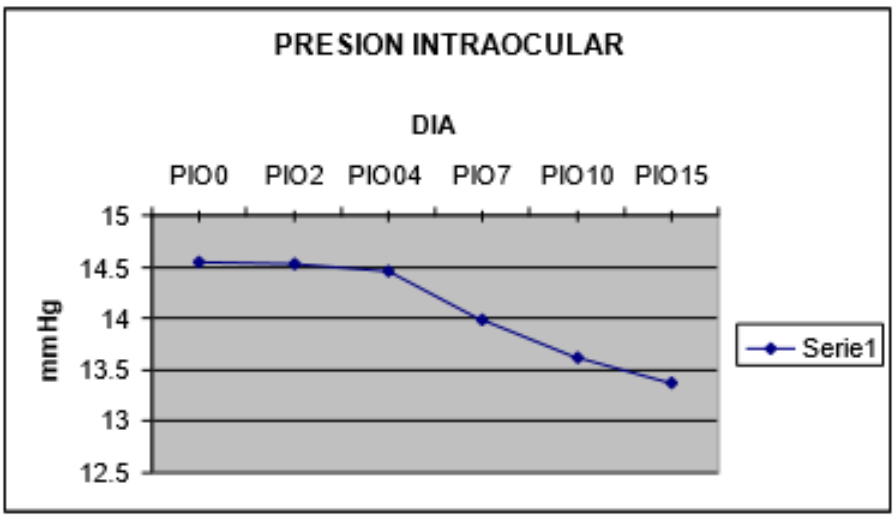
CLINICAL DATA FROM PHASE I

An unicentric, prospective and open study was carried out to evaluate the safety and the tolerance of the PRO-067 ophthalmic solution elaborated by Laboratorios Sophia S.A. of C.V applied on the ocular surface of ophthalmologically healthy human volunteers.

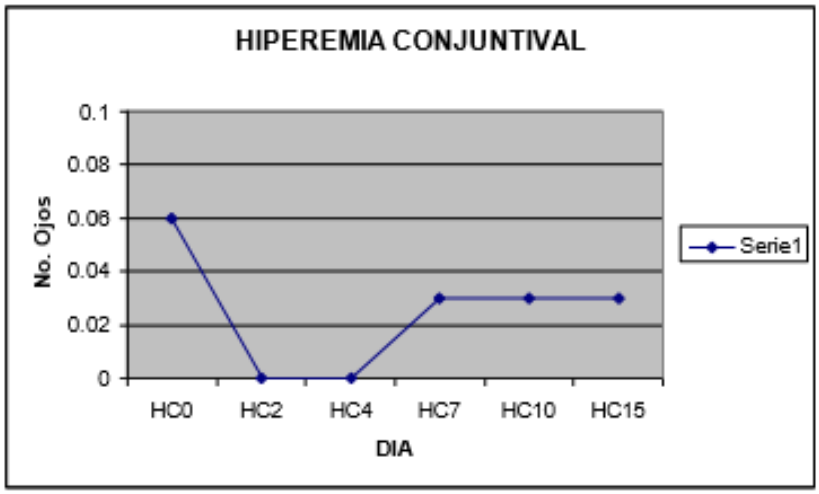
We studied 30 subjects in total (60 eyes) who met the eligibility criteria of the study, and received a drop of Latanoprost ophthalmic solution developed by Laboratorios Sophia S.A. of C.V in each eye. The Principal Investigator only made the clinical assessment. The study article was applied once a day, at night (22:00 hrs.), during a period of 15 days.

On day 0 of the study, the researcher confirmed that each subject met the essential requirements for participation in the protocol, in the same way he asked each subject to sign the informed consent. As part of the direct questioning of the subject, demographic information, reason for consultation, background, evolution, and current status were obtained and recorded, as well as investigation of specific symptoms. Evaluations were conducted on days 2, 4, 7, 10 and 15 of the study. At each visit, a physical examination was performed, and the findings were recorded in the following order: 1) Visual capacity 2) Review of the anterior segment with slit lamp 3) Investigation of specific signs 4) Tonometry and 5) Indirect ophthalmoscopy under pharmacologic mydriasis.

Each subject was assigned and delivered his study article, and they were instructed to apply it once a day, at 22:00 hrs., for 15 days. The results were the following:



Graph 1. Behavior of the IOP, in which a reduction of 1 mmHg is observed in the study group.

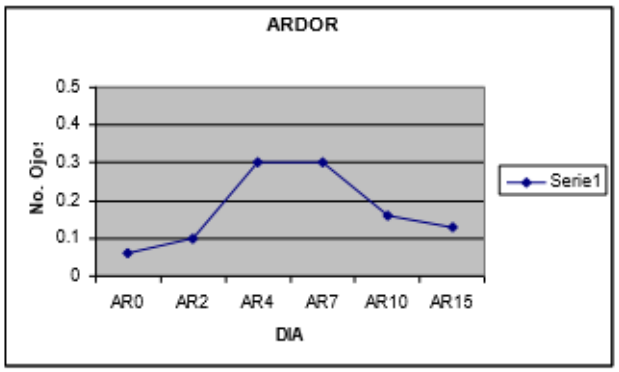


Graph 2. Conjunctival Hyperemia. The graph shows an insignificant degree of hyperemia during the entire study period.

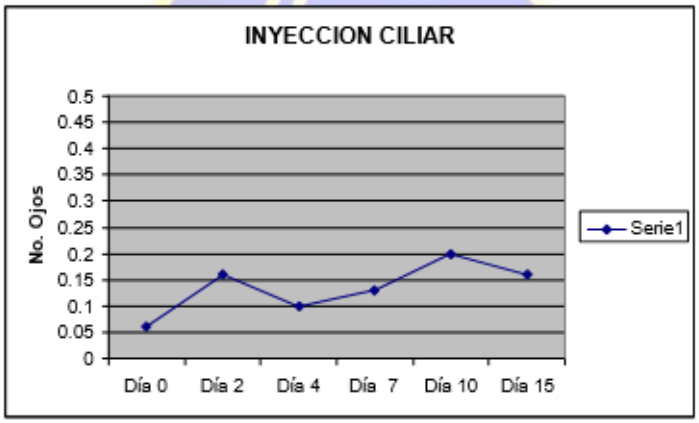
Regarding intraocular pressure, the results show an average reduction of 1 mmHg below the baseline (graph 1).

Continuing with the safety data, conjunctival hyperemia (graph 2) did not show a significant increase during the 15 days of treatment.

As to the tolerance data, the degree of burning (graph 3) increased in day 2 of treatment, but gradually decreased in subsequent visits. Finally, in terms of ciliary injection (graph 4), and hyperemia (graph 5) both parameters showed no appreciable changes during the study.



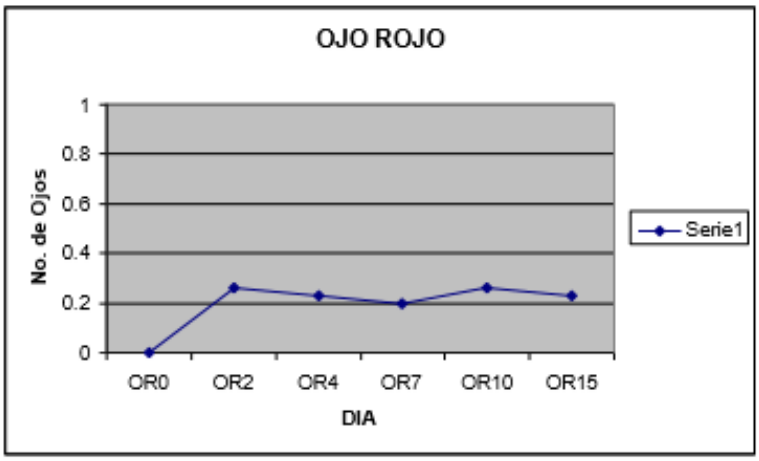
Gráfica 3. Ardor referido por los participantes el estudio durante el periodo del mismo. Aunque se aprecia un aumento entre el día 4 y 7 de tratamiento, en realidad la intensidad del ardor no resultó significativa.



Gráfica 4. Inyección ciliar durante el periodo de tratamiento. No se aprecian cambios significativos.

Graph 3. Referred burning sensation by the participants during the study period. Although an increase was observed between day 4 and day 7 of treatment, in reality the intensity of the burning was not significant.

Graph 4. Ciliary injection during the treatment period. No significant changes are appreciated.



Graph 5. Hyperemia during the treatment period. No significant changes are appreciated.

There were no changes in the ocular surface of any eye after the application of the study article for 10 days, in the same way there were no changes regarding ocular surface stains in any day of study.

Therefore, it was concluded that Latanoprost elaborated by Laboratorios Sophia S.A. C.V is safe and well tolerated when administered topically ophthalmic at the indicated dosage in ophthalmologically healthy volunteers.

7. STUDY DESIGN

7.1. Point or limit points

Main efficacy criterion

The effectiveness of the GAAP Ofteno® ophthalmic solution versus PRO-067 ophthalmic solution elaborated by Laboratorios Sophia S.A. will be evaluated. of C.V applied on the ocular surface in subjects with a diagnosis of POAG and / or OHT by controlling the target IOP.

Tolerability criteria

Ocular symptoms such as burning, hyperemia, lacrimation, foreign body sensation, fluorescein stain, VF-14 questionnaire score and ocular comfort index will be evaluated.

Security criteria

Visual capacity, anterior segment biomicroscopy, fundus examination and frequency of adverse events.

7.2 Study plan

A national, multicenter, prospective, crossover, longitudinal, doble-blind study, with fixed dose. This study will be conducted with 120 subjects from the ophthalmologic consultation who were using GAAP Ofteno® for at least two months prior to the study and are under control of the TIOP for glaucoma with mild or moderate damage.

Subjects that meet all the inclusion criteria and none of exclusion can be included in the study. At the same time, a study group with a predetermined sequence will be assigned randomly, respecting the double-blind system, in the sequence "A" the therapy with GAAP Ofteno® will continue for 30 days, in which will evaluate the subject again and then change the therapy to the PRO-067 ophthalmic solution elaborated by Laboratorios Sophia SA of C.V which will be used for 30 days until the 60th day, date of the final visit.

Those assigned to sequence B on day 1, the change to PRO-067 ophthalmic solution prepared by Laboratorios Sophia S.A. of C.V will be for 30 continuous days until the date of revision on day 30, day in which the treatment with GAAP Ofteno® will be restored to continue until the 60th day, for the final evaluation.

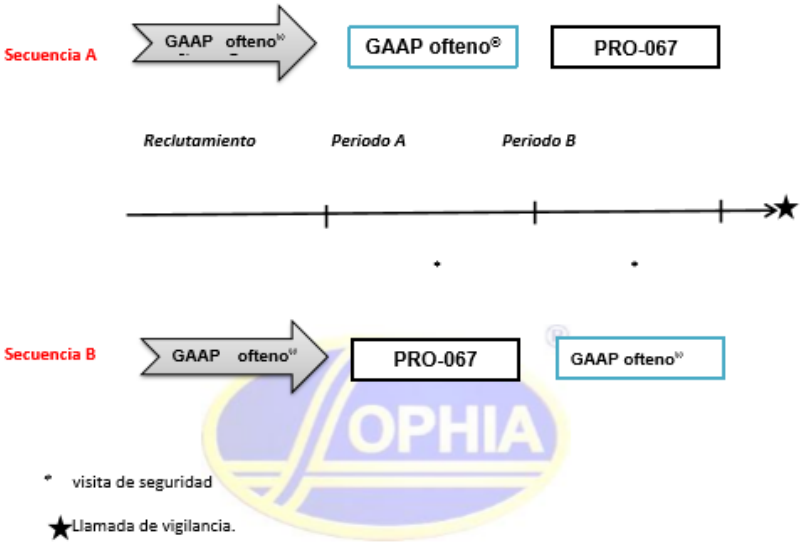
The selected subjects will be observed for 75 days, 60 days under treatment and 15 days later a telephone interview will be conducted to monitor adverse events.

All subjects in both groups should go on the 15th and 45th day of the study to a safety evaluation to monitor that there are no adverse events resulting from the change of medication.

No subject may use the mentioned treatment for more than the established time.

El plan del estudio se muestra en la Figura 1

Figura 1 – Plan del Estudio



* security visit

Surveillance call.

7.2.1 Study Schedule

Table 2 - Study Schedule

Cuadro 2 – Cronograma de estudio

*en caso de contar con campos visuales Humphrey de <6 meses de realizado estos pueden ser tomados en cuenta.

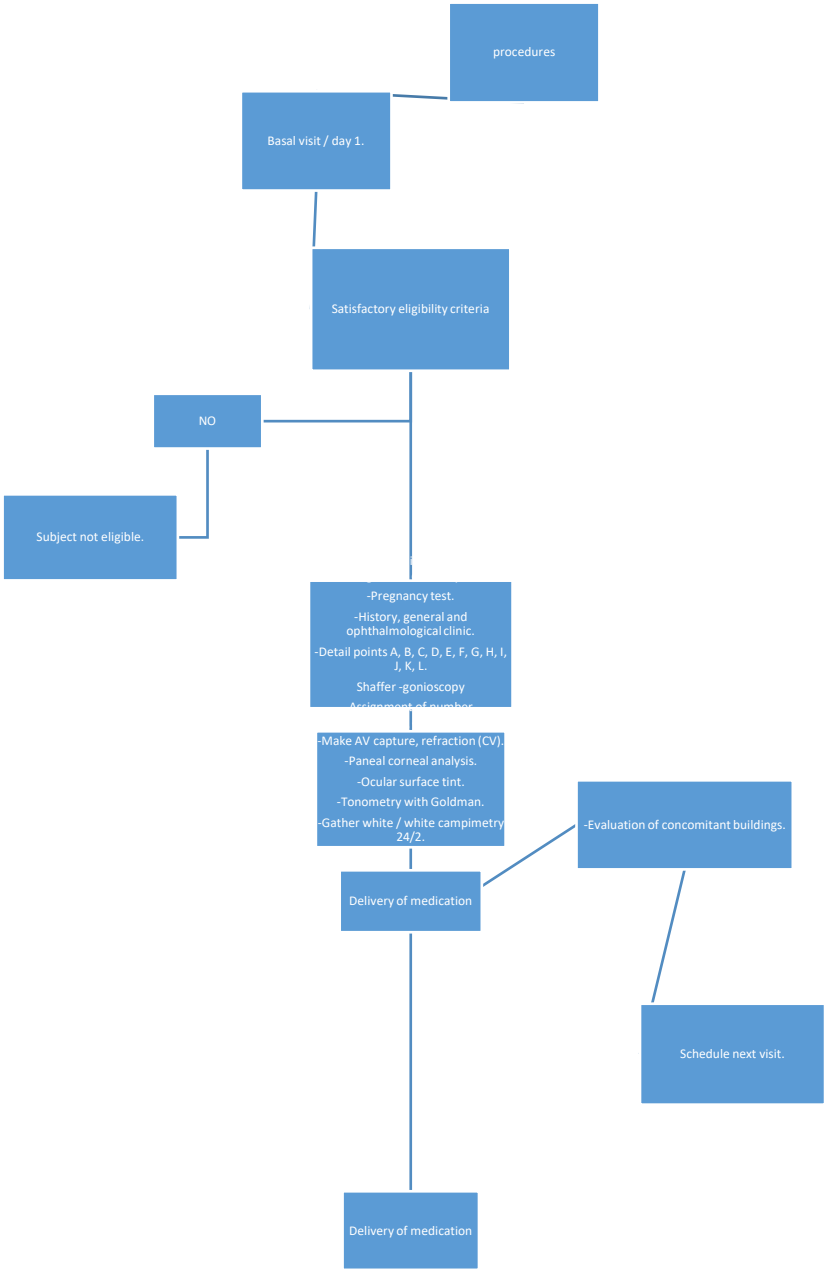
Procedimiento	SEGUIMIENTO						
	Visita de selección	Visita Basal	Visita seguridad 1	Visita 1 Cross over.	Visita seguridad 2	Visita Final	Llamada de vigilancia
		Día 1	Día 15	Día 30	Día 45	Día 61	Día 75
Criterios de elegibilidad (inclusión y exclusión).		X					
Prueba de embarazo (si aplica).		X				X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

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

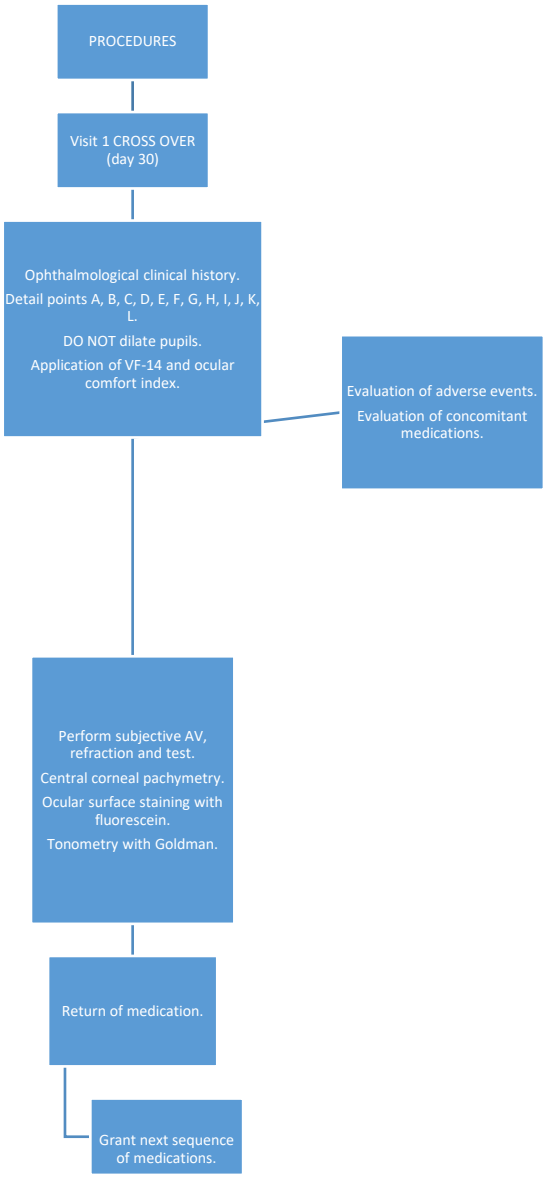
* if you have Humphrey visual fields of <6 months of completion these can be considered.

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

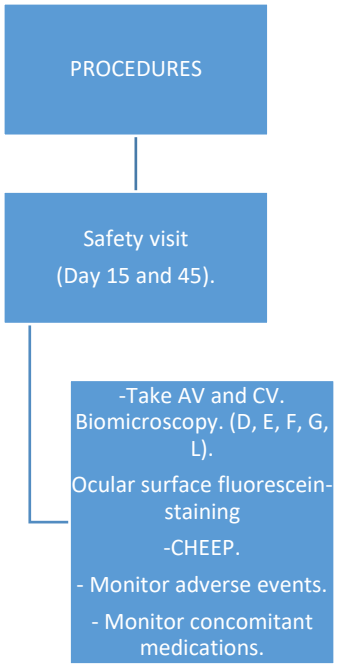
Fig. 2



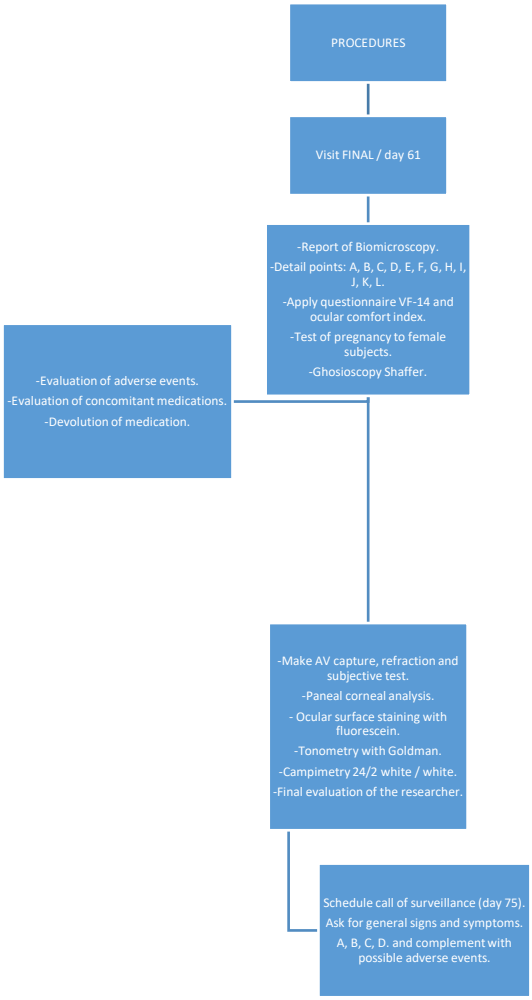
A) **A)** Burning B) Foreign body sensation C) Lachrymation D) Conjunctival hyperemia E) Chemosis F) Crystalline G) Iris H) Retina I) Macula J) Vitreous K) optic nerve excavation in decimals L) TRL * ICO = index of eye comfort.



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



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



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

7.3 Measures to minimize deviations

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

- With the accounting of the medicine returned.

- The subjects will have a "diary of the subject" where they will have to write down the time of application of the drop and any incident or setback at the time of the application of the drop, e.g. forgetting the application of the drop, application of extra drops, etc.

The adherence to treatment must be greater than 80%.

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

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

7.4 Managed products

Table 3 gives a description of the study's products.

Table 3 - Description of study drugs

Ophthalmic drops PRO-067 Latanoprost 0.005% free of preservative - Chemical Name: (13,14-dihydro-17-phenyl-18,19,20 trinor-prostaglandin F2α- isopropyl ester) - Molecular weight: 432.593 g / mol - Molecular formula: C26H40O5 - Chemical structure:

Gotas oftálmicas PRO-067
Latanoprost 0.005% libre de conservador

- **Nombre Químico**: (13,14-dihidro-17-fenil-18,19,20-trinor-prostaglandina F2α-isopropil éster)
- **Peso molecular:** 432.593 g/mol
- **Fórmula molecular:** $C_{26}H_{40}O_5$
- **Estructura química:**

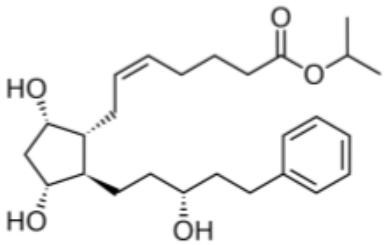


Table 4 - Packaging description

Primary packaging:

PRO-067 Ophthalmic solution developed by Laboratorios Sophia S.A. of C.V. will have a primary label with the protocol code to which it belongs, but not the name of the content, to respect the double blind.

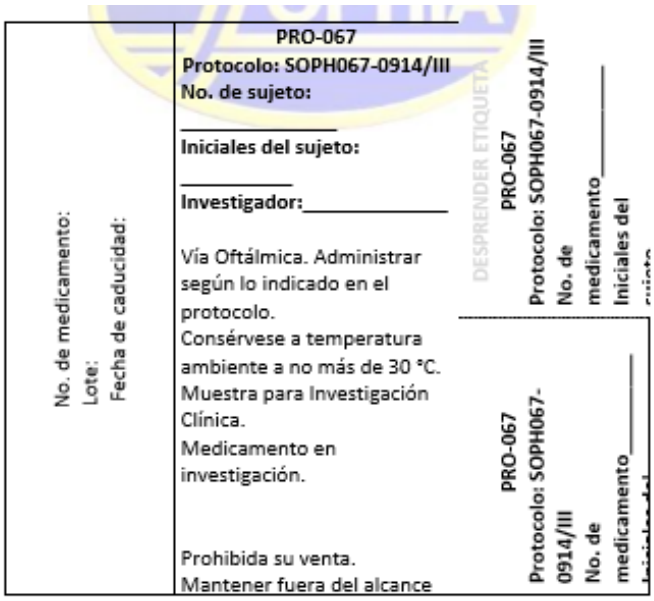
Example: (subject to changes).

Ejemplo: (sujeto a cambios).

Secondary package

PRO-067 Ophthalmic solution developed by Laboratorios Sophia S.A. of C.V. will be delivered in its box and also, the primary packaging will be there without labeling. The specifications of the study will be described in the box and envelope as shown in the example.

Example:



7.4.1 Treatment management

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

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

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

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

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

- The delivery of the treatments will be in accordance with the study plan and following the delivery methods that are described in the section. The researcher and / or pharmacist of the healthcare establishment should use the treatment delivered only for the subjects participating in the study.

- The study medication count.

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

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

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

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

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

7.5 Discontinuation of the study

7.5.1 Premature discontinuation of the study

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

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

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

7.5.2 Closure of the center

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

7.6 Source data

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

- The subject's medical record

- Journal of the subject

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

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

8 SELECTION AND REMOVAL OF STUDY SUBJECTS.

8.5 Selection criteria

All selected subjects:

- Age from ≥ 18 years to ≤ 90 years.

- Male or female.

- Obtained in the external consultation.

- Diagnosis of primary open-angle glaucoma and / or chronic intraocular hypertension, classified as mild to moderate or severe, previously treated with GAAP Ofteno® at least two months before inclusion and while under control of their TIOP.

Physical examination of the subjects

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

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

8.5.1 Informed consent

Obtained as described in section 15.3 of the protocol.

8.6 Exclusion criteria

8.6.1 General criteria

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

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

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

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

5. Positive substance abuse (illegal drugs).

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

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

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

8.6.2 Medical and therapeutic criteria

Related to ophthalmological criteria

1. Subjects with only one eye with vision.

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

3. Subjects with another etiology of glaucoma different from primary open-angle.

4. Subjects with intraocular hypertension secondary to a different etiology at open-angle or linked to another ocular condition.

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

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

7. Uncontrolled or progressive retinal diseases that threaten vision.

8. Chronic ocular surface diseases not controlled or recently diagnosed (last 3 months).

Related to various conditions

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

Related to a therapy of previous and / or concomitant treatments

Previous therapy

 Subjects cannot be treated at the time of inclusion with any other type of antiglaucomatous drug other than GAAP Ofteno ®.

To know the other prohibited treatments and their rest period, please refer to section 10.3 (Table 5) "Main prohibited treatments - Rest period to be respected".

8.7 Criteria for non-inclusion

- Any exclusion criteria that may appear after the screening visit.

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

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

8.8 Criteria for participant discontinuation

8.8.1 Criteria for exclusion

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

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

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

 Document the subject's decision in clinical notes.

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

 Evaluate the clinical status of the subject.

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

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

- Decision of the investigator.

 Especially if an adverse event occurs.

 If the researcher considers that this can threaten the health of the subject.

 If an important disease occurs that requires the prescription of a medication incompatible with the objective of the study.

 If the progression or deterioration of the basal disease occurs as well as non-compliance with the TIOP according to its classification.

- Need for another treatment according to the criteria of the medical investigator.

- Pregnancy.

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

8.8.2 Procedure

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

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

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

In case of discontinuation of the study treatment as a result of an event that requires immediate notification, the corresponding monitor, or the drug-surveillance contact (11.3.2) 1 will be contacted.

9 TREATMENT OF STUDY SUBJECTS

9.1 Managed treatments

Pre-treated with GAAP Ofteno® for at least 2 months prior and under control of TIOP, they will begin to apply PRO-067 or GAAP Ofteno® without leaving the washing period as follows: Sequence A: 1 drop of PRO-067 ophthalmic solution prepared by Laboratorios Sophia S.A. of C.V. every 24 hours for 30 days at the end of which GAAP Ofteno® will be given, administered for an additional 30 days. Sequence B: 1 drop of GAAP Ofteno® every 24 hours for 30 days at the end of which PRO-067 ophthalmic solution elaborated by Laboratorios Sophia S.A. of C.V. will be administered equally for 30 more days.

9.2 Treatment delivery

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

9.3 Previous and concomitant treatments

Prohibited treatments

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

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

Table 5: Main prohibited treatments - Rest periods to be respected

medicine			
Group	Prototype	Route of administration	Rest periods
Artificial tears with conservative.		Ophthalmic	2 weeks
Carbonic anhydrase inhibitor	Acetazolamide Dorzolamide	Oral, I.V, ophthalmic	1 month
Parasympathetic-mimetic	Pilocarpine	Ophthalmic	1 month
Selective alpha agonists	Brimonidine	Ophthalmic	1 month
Beta-Non-selective blocker	Timolol	Ophthalmic	2 weeks

9.4 Authorized treatments before and during the study

- Tretacaine Hydrochloride
- Tropicamide / Phenylephrine Hydrochloride
- Artificial tear without conservator

9.5 Treatment compliance

- Quantification of the weight of the bottle that has been returned.

- The subjects will have a "subject's diary" where they will have to write down the time of application of the drop and any incident or setback at the time of the application of the drop, e.g., forgetfulness in the application of the drop, application of extra drops, etc.

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

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

10 VALUATION OF EFFECTIVENESS

10.1 Efficiency measurements

In the research schedule, the effectiveness measurements made in each visit or treatment period are indicated.

Primary efficacy parameters are:

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

Secondary efficacy parameters:

Fluorescein staining, VF-14 questionnaire score and ocular comfort index evaluation.

Primary security parameters:

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

10.2 Measurement methods and times

Scales to fill out by the researcher:

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

A guide will be made available for the interview to be carried out in each of the visits.

The subject must complete self-score questionnaires:

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

Visual acuity

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

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

Standardization of the visual examination:

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

- This exam will be held at the research center

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

- The research subject will keep both eyes open.

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

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

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

Equivalence between the different AV scales

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

Previous Biomicroscopy

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

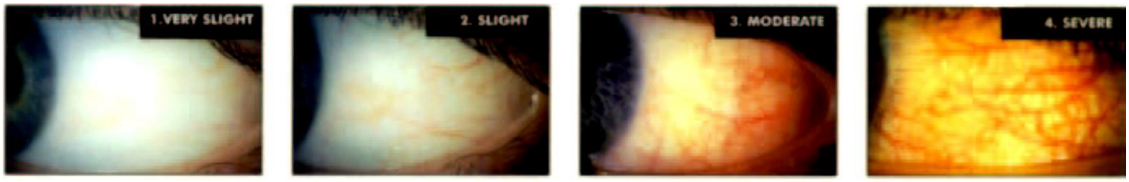
It will be qualified as follows:

Normal.

Abnormal.

Abnormality that does not affect the result of the study:

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



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

-Foreign body sensation

-Burning

-Lachrymation

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

Fluorescein stain

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

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

2.- The subject's lower eyelid will be gently grabbed, first on the right side and then on the left side asking the subject to look upwards so that with this maneuver a greater area of the lower bulbar conjunctiva is exposed, then the fluorescent filter paper moistened with a drop of anesthetic will be placed in the surface of the area previously mentioned, subsequently the subject will be asked to blink several times and proceed to examine it.

Defects of the corneal and conjunctival epithelium will be reported.

Central corneal pachymetry

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

Applanation tonometry

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

The methodology for taking the pressure will be as follows:

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

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

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

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

Gonioscopy with Shaffer classification:

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

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

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

Normal.

Abnormal.

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

Optic Nerve Excavation

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

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

11 EVALUATIONS OF SECURITY

11.1 Safety measurements

Table 2 shows the safety measures that are carried out in each visit or treatment period.

The safety measurements are the following:

- Adverse events.

- Visual acuity and visual ability.

- Previous biomicroscopy data.

- Concomitant medications.

- Fluorescein staining.

- Taking IOP with Goldman.

11.2 Specific procedures by type of visit.

Clinical examination

Basal visit (day 1)

The principal investigator or the head of the research team of the site must obtain the letter of informed consent of each of the subjects, before carrying out any procedure of the study. When the informed consent is obtained, a unique identification number of the subject will be assigned, this will be used throughout the study for its identification.

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

The following evaluations will be made to ALL enrolled subjects:

1. Complete general and ophthalmological clinical history.

2. VF-14 questionnaire and ocular comfort index.

3. Visual Acuity and Visual Ability

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

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

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

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

8. Vertical excavation of the optic nerve.

9. Fluorescein staining.

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

11. Corneal pachymetry.

12. IOP adjustment with corneal thickness.

13. Subject number assignment

14. Evaluation of concomitant medications.

15. Evaluation of acute adverse events.

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

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

Safety visit 1: (day 15).

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

In this visit, the following will be evaluated:

1. Visual acuity and visual capacity.

2. Anterior segment biomicroscopy.

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

4. Fluorescein staining of the ocular surface.

5. Evaluate concomitant medications and adverse events.

Visit crossover 1 (Day 30)

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

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

1. Visual acuity and visual capacity.

2. VF-14 questionnaire and ocular comfort index.

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

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

5. Ultrasonic pachymetry

6. Fluorescein staining

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

8. Evaluation of concomitant medications.

9. Evaluation of adverse events

10. Delivery of new treatment.

11. Return of medication granted as first treatment.

Safety visit 2 (day 45) The subject will go to review 15 days after the start of the new treatment (day 45), a window period of +/- 1 day will be allowed for the visit.

In this visit, the following will be evaluated:

1. Visual acuity and visual capacity.

2. Anterior segment biomicroscopy.

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

4. Fluorescein staining of the ocular surface.

5. Evaluate adverse events and concomitant medications.

Final visit (Day 60) In this the following parameters will be evaluated:

1. Acuity and visual ability.

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

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

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

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

6. Ultrasonic corneal pachymetry.

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

8. Vertical excavation of the optic nerve.

9. Fluorescein staining.

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

11 Urine pregnancy test (if applicable).

12. Evaluation of concomitant medications.

13. Evaluation of adverse events.

14. Return of the second treatment.

15. Final evaluation by the researcher.

11.2.1 Laboratory tests

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

11.3 Adverse events

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

11.3.1 Responsibilities of the researcher

11.3.2 Record of adverse events in the Case Report Form

-Events to register

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

Therefore, the investigator will document as an adverse event:

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

 Any intercurrent symptoms or illness,

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

 Detected during a study visit or in an additional examination,

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

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

 Results in the death of the subject

 Represents a threat to life

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

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

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

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

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

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

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

 In these specific cases, the investigator must immediately report by telephone or fax, or in non-working hours to the 24-hour telephone line (see Table 6). These cases must be reported on separate "Adverse Event" paper pages that will be provided to the centers, and should be sent immediately by fax to the responsible person (see Table 6)

 A pregnancy that occurs during the study.

11.3.2.1 Methods for registration

Adverse events must be documented in an "Adverse Event" form. Some sections of the page must always be filled out in full, whether the event is serious or not serious. The other sections will be filled only when the event requires immediate notification.

In case of progression of the disease by episodes (chronic disease):

If the disease was already known when the subject entered the study, only be documented as an adverse event when there is a worsening (increase in frequency and / or intensity of episodes / attacks),

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

11.3.2.2 Adverse events follow-up

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

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

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

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

11.3.2.3 Procedure for a serious adverse event

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

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

The researcher must:

Write down the date in the participant's medical record on which the event was made known (in a follow-up visit or through telephone contact with the participant or with a third party, ...), **immediately** after being informed about this event, filling out a "Serious Adverse Event" form, and without waiting for the clinical results or the results of additional investigations, the sponsor will be informed (Clinical Research Department and Pharmacovigilance Department) by telephone or fax, or after business hours to the 24 hour telephone line.

Provide to the people designated below, as they are available, anonymous copies of documents that offer useful additional information, such as admission hospital reports, consultation reports, laboratory tests reports or other exam reports that help the diagnosis (when possible, pre-treatment assessments must be attached to compare them against the results obtained with the treatment), or the autopsy report, if it has been done.

- Comply with their regulatory obligations before the Competent Authorities and / or before the Ethics Committee, in compliance with local regulatory requirements.

Table 6 - Structures of the contacts in case of a serious or not serious Adverse Event.

Responsible for Pharmacovigilance:

Dr. Alicia Paulina Melgarejo

Sophia Laboratories, S.A. of C.V.

Av. Paseo del Norte, 5255

Col. Guadalajara Technology Park.

C.P. 45010 Zapopan, Jalisco. Mexico.

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01 33 3001 4200 Ext. 1029

Cell phone. 044 33 1043 1474

Direct helpline, toll free: 01 800 7102 254

E-mail: farmatec@sophia.com.mx

If an initially non-serious adverse event worsens and becomes serious, this should be reported **immediately** in the "Serious Adverse Event" form. If a woman subject in the study becomes pregnant, the researcher should: - Suspend the study treatment for the subject.

- Communicate with the assigned monitor to receive details for the report.

11.3.2.4 Causality assessment

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

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

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

11.3.3 Responsibilities of the sponsor

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

11.4 Biosecurity aspects

The research protocol does not contemplate the performance of any procedure that involves the use of ionizing radiation or genetic engineering techniques. It also does not involve the use or transport of infectious materials or dangerous chemicals.

12 Statistics

Statistical analysis

The analysis of the study will be carried out using the statistical software SPSS version 19 as soon as all the efficacy and safety data of the study are available, and the obligatory steps defined in section 15.2 "Data Management" have been carried out.

Evaluation criteria

Efficacy criteria

The main criterion will be the maintenance of the TIOP throughout the study.

The secondary criteria will be: burning, hyperemia, lacrimation, foreign body sensation, fluorescein staining, ocular comfort index score and VF 14 questionnaire evaluation.

The analytical approach is the change from the initial value to the last value in the final visit after the application of the test treatment.

Security criteria

Visual capacity, anterior segment biomicroscopy, fundus examination and frequency of adverse events.

The analytical approach is the change from the initial value to the last value in the final visit after the application of the test treatment.

Statistical elements

The type I error of the statistical tests will be set at 5% (unilateral situation), which is consistent with the objective of demonstrating the non-inferiority in terms of maintaining the TIOP + 2mmHg than the comparator study.

The following descriptive statistics will be provided, depending on the nature of the variables:

Quantitative variant: Before normal distribution: they will be expressed as mean ± standard deviation, minimum and maximum values and if the variable does not have a normal distribution: they will be expressed in median, minimum, and maximum range

Qualitative variable: will be expressed as categories, frequencies, and proportions

Analysis sets

The Randomized Set (RS) will be defined as all the subjects included and assigned randomly (according to the subject selection procedure).

The Complete Set of Analysis (CSA) will be defined according to the intention to treat principle and section 5.2.1 of the ICH-E9 guidelines, as the subjects of the RS who were given at least one dose of the medication under study and that have a value at the beginning of at least one of the values after the initial in the main criterion throughout the period of pharmacological intervention.

The Safety Set will be defined as all included subjects who were given at least one dose of the study medication.

Statistical methodology

A treatment group will be considered: PRO-067

Result of the Study

The evaluated variables will be described by treatment group and in general in the RS and the CSA.

The treatment length, compliance, and in case of early withdrawal of a volunteer, the reasons for withdrawal, deviations from the protocol and concomitant treatments will also be described in the RS.

Effectiveness

Main analysis

To identify differences in the study group, considering ordinal and nominal variables, the following statistical test will be used:

 Chi square test with Pearson's exact, assuming normal distribution, otherwise the Chi square test with Fisher's exact test will be applied.

To identify differences in the study group, considering continuous quantitative variables, the following statistical test will be used:

 Test t with paired samples, assuming normal distribution, otherwise the Mann-Whitney U test will be applied.

Security

All safety analyzes will be done by treatment group in the Safety Set in the periods from day 0 to day 60.

Adverse events

The number of adverse events emerging under treatment (until the last date of application of the study drug + 1 day), number and percentage of subjects reporting at least one adverse event emerging under treatment will be described by system organ class and / or preferred term

The same analysis will be performed for serious adverse events (emergent or not).

Adverse events reported after the treatment period will also be described.

13 DIRECT ACCESS TO DATA / DOCUMENTS SOURCE

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

14 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Supervision of the study

14.1.1 Before the study

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

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

The researcher will allow the monitor:

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

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

- See all documents related to the study,

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

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

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

If electronic medical records are used, the investigator should:

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

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

The researcher will personally put the signature and date on the first page of the printout and indicate the number of pages.

If the computer system allows tracking of changes made to medical records, the investigator will give the monitor an impression of the medical records of the participants and the records of the changes made at each visit.

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

14.2 Electronic medical record

If medical files are used, the researcher must guarantee the safety of the study data in the medical files by implementing security measures to prevent unauthorized access to the data and the computer system.

The researcher undertakes to maintain:

- All the impressions of the medical record signed and dated by him (principal investigator) in the record of the study,

- If the computer system allows it, the changes made in the medical records of the file during the study

- All original source documents (originals of specific exams, informed consent forms).

14.3 Audit - Inspection

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

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

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

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

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

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

- See all documents related to the study.

15 ETHICS

15.1 Ethics Committee

The investigators, or the coordinators, or the sponsor will deliver to the Ethics Committees the study protocol, the informed consent, the researcher's manual, and the required documents in accordance with the local requirements.

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

15.2 Conducting the study

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

15.3 Information for the subject and informed consent form

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

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

The principal investigator will provide the potential participant with all the information regarding the characteristics of the study, its potential benefits, risks, objectives, and procedures. This information will be with a language understandable to the subject, the right to interrupt their participation in the study at any stage will be explained to the subject, this, without affecting the relationship with the researcher and / or their future assistance. The informed consent will be put to the consideration of the possible participant; and must have enough time to analyze each and every one of the aspects mentioned above and if there is any doubt, this will be clarified by the person in charge of obtaining the informed consent. Once the participant agrees to participate in the study, he / she must sign and date the letter of informed consent in the presence of two witnesses who have or are not related to the subject of study, who will participate during the informed consent process and will sign endorse that the process was carried out prior to any study procedure, that the study information was clearly explained, and, if present, doubts were clarified.

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

The principal investigator must also sign and date this consent.

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

Investigator must document the date on which the informed consent was signed in the subject's medical history.

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

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

15.4 Modification to "informed consent"

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

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

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

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

16 DATA MANAGEMENT AND CONSERVATION OF RECORDS

16.1 Study data

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

FRC

A CRF was designed to record the data that are required in the protocol and that the researcher collects in each of the visits. In the case of self-assessment questionnaires, it is not allowed for the principal investigator or person responsible for filling in or modify what was written by the subject of the study.

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

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

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

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

16.2 Data management

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

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

16.3 File

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

17 OWNERSHIP OF THE RESULTS -POLICY OF PUBLICATION

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

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

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

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

18 ADMINISTRATIVE CLAUSES

18.1 Related to the sponsor and the researcher

18.1.1 People to inform

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

18.1.2 Substantial amendment to the protocol

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

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

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

18.1.3 Final report of the study

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

18.2 Related to the sponsor

The sponsor agrees to:

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

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

18.3 Related to the researcher

18.3.1 Confidentiality - Use of information

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

The researcher expressly agrees that the data on their professional and clinical experience, provided to the sponsor in paper and stored on the computer, are solely for use related to their activities as the sponsor of clinical studies, in accordance with Good Clinical Practices. The

researcher accepts that he / she and the members of his team will use the information only within the framework of this study, to carry out the protocol. This agreement is mandatory as long as the confidential information has not been disclosed to the public by the sponsor. The protocol of the clinical study provided to the researcher may be used by him and his colleagues to obtain the informed consent of the study subjects. The clinical trial protocol, like any information taken from it, should not be disclosed to other parties without the sponsor's written authorization.

The researcher will not disclose any information without the prior written consent of Laboratorios Sophia SA. of C.V., except to the representatives of the Competent Authorities, and only by request. In the latter case, the researcher undertakes to inform Laboratorios Sophia S.A. of C.V. before revealing the information to these authorities. The researcher will fill out and maintain a binnacle of selection of the subjects as well as the identification and list of enrollment of each of the subjects. The researcher agrees to give on-site access to the auditor and / or the representatives of the Competent Authorities. The information will be treated in compliance with professional secrecy.

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

18.3.2 Organization of the center

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

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

18.3.3 Documentation to be delivered to the sponsor

The researcher undertakes, before the start of the study:

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

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

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

9 APPENDICES

Appendix 1: Declaration of Helsinki of the World Medical Association

DECLARATION OF HELSINKI WORLD MEDICAL ASSOCIATION

Ethical Principles for Medical Research in Human Beings

Adopted by the 18th General Assembly of the AMM, Helsinki, Finland, June 1964, and amended by:

29th General Assembly of the AMM, Tokyo, Japan, October 1975

35th General Assembly of the AMM, Venice, Italy, October 1983

41st General Assembly of the AMM, Hong Kong, September 1989

48th General Assembly of the AMM, Somerset West, Republic of South Africa, October 1996

52nd General Assembly of the AMM, Edinburgh, Scotland, October 2000

53rd General Assembly of the AMM, Washington 2002 (Explanatory note added in paragraph 29)

55th General Assembly of the AMM, Tokyo 2004 (Explanatory note added in paragraph 30)

General Assembly 59th of the AMM, Seoul, October 2008.

A. INTRODUCTION

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

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

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

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

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

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

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

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

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

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

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

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

B. PRINCIPLES FOR ALL MEDICAL INVESTIGATIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL ATTENTION

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

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

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

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

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

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

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

Appendix 2: questionnaire VF14

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

Firma del sujeto: _____

Para uso exclusivo del aplicante:

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

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

V= ☐

Firma del médico aplicante: _____.

VF-14 Rating:

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

It will be done like this with each column.

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

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

Appendix 3: Eye comfort index questionnaire.

Version 1.0

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

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

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

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

0____ 1____2____3____4____5____6____7____8____9____10

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

0____ 1____2____3____4____5____6____7____8____9____10

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

0____ 1____2____3____4____5____6____7____8____9____10

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

0____ 1____2____3____4____5____6____7____8____9____10

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

0____ 1____2____3____4____5____6____7____8____9____10

Nombre del médico que aplicó:_____.

Firma:_____.

Appendix No. 4: calculation of sample size

Sample size Protocol PRO-067

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

$$n=2[(\underline{Z\alpha-Z1-\beta)(\delta}\text{)d}]2$$

d

With a statistical confidence of 95% that corresponds to the type I error, and is equal to 1.96, with a power of 80% that corresponds to the type II error, and is equal to 0.84. A standard deviation for the decrease in intraocular pressure of 2.5 mmHg1 was considered, with an expected difference of at least 0.417 mmHg.

Based on the above, the result was 41 patients, which increased 20% due to the loss, with a total of 50 patients per group.

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