STUDY TITLE:
The Effects of Mirtogenol® with Bimatoprost on Intraocular Pressure in Hispanics with Open-Angle Glaucoma: A Double-Blind, Randomized Controlled Trial

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STUDY TITLE

The Effects of Mirtogenol® with Bimatoprost on Intraocular Pressure in Hispanics with Open-Angle Glaucoma: A Double-Blind, Randomized Controlled Trial

RESEARCH QUESTION

Can Mirtogenol® have an additive effect on the reduction of intraocular pressure when combined with bimatoprost in the Hispanic population with primary open-angle glaucoma?

HYPOTHESIS & SPECIFIC AIM

The combination of Mirtogenol® and bimatoprost will have a superior reduction on intraocular pressure than bimatoprost with a placebo in Hispanic patients with primary open-angle glaucoma. Null hypothesis: The combination of Mirtogenol® and bimatoprost will have no difference on the reduction of intraocular pressure when compared to bimatoprost with a placebo in the Hispanic population with primary open-angle glaucoma (POAG). The specific aim of the study is to determine if the addition of Mirtogenol® to the bimatoprost 0.01% for open-angle glaucoma will have an additive effect on the intraocular pressure in the Hispanic population as compared to bimatoprost plus placebo. The continuous variable of intraocular pressure (IOP) will be compared

using a t-test to determine statistical significance. In addition, the safety of the combination of Mirtogenol® with bimatoprost will be evaluated, but no statistical analysis will be performed.

BACKGROUND/SIGNIFICANCE

Glaucoma is a progressive condition caused by the degeneration and death of retinal ganglion cells and their axons that form the optic nerve, resulting in irreversible visual field reduction and blindness. Glaucoma is the second cause of legal blindness in the United States[1] and consists of several eye disorders, the most common being open-angle glaucoma. In primary open-angle glaucoma (POAG), there is a malfunction in the ocular drainage system resulting in the accumulation of aqueous fluid that exerts pressure and may damage the optic nerves. [3] It affects up to 4 million individuals in the United States, up to 70 million individuals worldwide and is found primarily in patients older than 50 years of age. [2,3] Symptoms are not present until 25 to 35% of the nerve fibers are damaged. [3] The American Academy of Ophthalmology states that the prevalence of POAG in Hispanics is thought to be between that of African-Caribbean and Caucasian populations. The risk of developing glaucoma increases with older age, female gender, family history of glaucoma, lower ocular perfusion pressure, lower blood pressure, thinner central cornea, optic disk hemorrhage, larger cup-to-disk ratio, and specific visual fields findings.[3] Glaucoma is multifactorial and is affected by both intraocular pressure (IOP) dependent and non-dependent factors such as vascular damage, ocular blood flow and free radicals.[4] Intraocular pressure can be controlled with glaucoma medications such as bimatoprost, with a successful rate between 60% to 80% of patients over a 5-year period. Progression of visual field loss still occurs in 8% to 20% of patients despite reaching standard therapy IOP goals.[3]

Elevated intraocular pressure is considered the most significant modifiable risk factor for the development of glaucoma and ocular hypertension. [3] The normal IOP is below 21 mmHG and the mean is around 15.5 mmHg, but POAG patients may have normal or elevated IOP reaching more than 30 mmHg.[3] The increased IOP in all types of glaucoma may result from the decreased facility for aqueous humor outflow.[3] The reduction of IOP at any point along the spectrum of the disease severity may reduce progression. [3,10] Each 1 mm Hg in IOP reduction reduces risk of disease progression by at least 10%.[3] The American Academy of Ophthalmology recommends the target IOP should be a 25% reduction and states that reduced risk of progression was noted with IOP consistently below 18 mmHg or largely below 14 mmHg. Prostaglandin analogs, including bimatoprost, are often recommended as first-line therapy and are considered the most potent

topical medications for reducing IOP. They works to lowering intraocular pressure by increasing both uveoscleral and trabecular aqueous humor outflow.[2] Mirtogenol® is a potent antioxidant and free radical scavenger supplement, which has been shown to lower intraocular pressure and improve blood flow with minimal side effects. [6,7,8] Mirtogenol® once daily oral capsule contain a synergistic combination formula of 80 mg of standardized bilberry extract, Mirtoselect® and 40 mg of the French maritime pine bark extract, Pycnogenol®.[4]

New strategies to prevent retinal ganglion cell death are necessary, since current medications are not completely effective in halting the progression of the condition. Mirtogenol® is a supplement with antioxidant properties and free radical scavenger, which has shown to lower intraocular pressure with minimal side effects.[6,7,8] The purpose of the study is to evaluate the efficacy and safety of the combination of Mirtogenol® and bimatoprost on intraocular pressure in POAG. Since prostaglandin analogs decrease IOP by increasing the drainage of aqueous humor, while Mirtogenol® is assumed to act on humor secretion, the combination of both may have an additive response.[7] The objective of this study is to determine if Mirtogenol® has an additive effect on the reduction of IOP when combined with bimatoprost in the Hispanic population with primary open-angle glaucoma. To date, there have been no studies identified by the researchers in the literature review conducted, that evaluate the effect of Mirtogenol® with bimatoprost in the reduction of intraocular pressure with POAG patients in the Hispanic population. Due to current medication not being able to cure or detain POAG progression, this study may advance our knowledge on new complementary alternatives and pave the way for more studies to halt the progress of the condition in order to preserve the patient's visual function and improve quality of life.[9]

LITERATURE REVIEW

Both constituents of Mirtogenol®, Bilberry[11,12,13] and Pycnogenol, [14,15,16] are powerful antioxidants. The active components of Bilberry (Mirtoselect®) are flavonoid anthocyanosides (anthocyanins). Anthocyanosides are the only flavonoids able to reach the eye as a target organ in experimental animals. Unchanged anthocyanosides demonstrated after oral administration that it is absorbed and distributed into ocular tissues, showing its ability to pass through the blood-aqueous and blood retinal barriers.[6] A meta-analysis of preliminary clinical research shows that taking bilberry anthocyanin 60 mg twice daily for at least 12 months improves visual function in patients with normal tension glaucoma when compared to pretreatment.[11] Anthocyanins are

involved in the stabilization of collagen fibers, promotion of collagen biosynthesis, decrease capillary permeability and fragility.[12]

Pycnogenol® major actions include antioxidant as radical scavenger, anti-inflammatory effects, and stimulation of eNOS synthesis.[13] It has shown to improve pathologic permeability of blood vessels and has been extensively studied for enhancing capillary resistance and integrity in retinopathy.[6] Pycnogenol® has also been found to significantly lower plasma endothelin-1, a vasoconstrictor peptide that affects the trabecular meshwork contractility, which allows for regulatory mechanisms controlling fluid outflow.[6] Pycnogenol® has previously been shown to significantly enhance the generation of endothelial nitric oxide, involved pulsatile choroidal and total choroidal blood flow.[6] Bilberry and Pycnogenol® may interact with immunosuppressant therapy and anticoagulant drugs. Pycnogenol® and bilberry may cause minor side effects that include gastrointestinal discomfort, dizziness, headache and nausea.[11] Serious side-effects have never been reported for Mirtoselect® and Pycnogenol®, despite their long use in ophthalmology, predominantly for diabetic retinopathy.[7]

Previous studies on human subjects found that Mirtogenol® alone or in combination with prostaglandin analogues can reducing IOP. [6,7] A six-month study titled "Effects of Mirtogenol® on ocular blood flow and intraocular hypertension in asymptomatic subjects", used 38 asymptomatic nonglaucoma participants with high intraocular pressure ranging from 22 to 26 mmHg. It concluded that Mirtogenol® decreased intraocular pressure from 25.2 to 22.2 mmHg and no side effects were observed. Another six-month study titled, "Mirtogenol® potentiates latanoprost in lowering intraocular pressure and improves ocular blood flow in asymptomatic subjects" evaluated the effects in three groups using Mirtogenol®, latanoprost or both with 79 asymptomatic participants with high intraocular pressure ranging from $\geq$ 35 to $\leq$ 40 mmHg without glaucoma. It concluded that the combination of both, Mirtogenol® and latanoprost, was more effective for lowering IOP from 38.0 to 24.2 mmHg and no serious side effects occurred during the study, apart from standard side effects in patients related to latanoprost. In 2017, a 12 week study titled "Mirtogenol® supplementation in association with dorzolamide-timolol or latanoprost improves the retinal microcirculation in asymptomatic patients with increased ocular pressure", used three group with dorzolamide-timolol plus Mirtogenol®, latanoprost drops plus Mirtogenol® or latanoprost with 88 asymptomatic participants with high intraocular pressure > 28 mmHg without glaucoma. It concluded that supplementation with Mirtogenol® in addition to local ophthalmic

treatments was safe and may lower IOP to normal levels and was well-tolerated without side effects.

In conclusion, we know that no data exist using Mirtogenol® on the Hispanic population, which has a high prevalence for glaucoma. No studies on the effect on stable IOP glaucoma patients and no studies have been done on a population that were already using antiglaucoma medication. Furthermore, there exist the need for data on new alternatives that may detain the progression of glaucoma. We do know that Mirtogenol® may lower intraocular pressure alone or in combination and has minimal side effects. [6,7] That each 1 mm Hg in IOP reduction reduces risk of disease progression by at least 10% [3] and progression of visual field loss still occurs in 8% to 20% of patients despite reaching standard therapy IOP goals. Our study will provide data on Hispanic population and an insight on the effects of Mirtogenol® on stable IOP in glaucoma patients. Furthermore, it will evaluate efficacy and safety of Mirtogenol® with bimatoprost 0.01% and may pave the way for more studies om new alternatives to reduce intraocular pressure and detain the progression of glaucoma.

METHODOLOGY AND STUDY DESIGN

A prospective, parallel-group, double-blind, randomized placebo-controlled clinical trial will be conducted with an estimated 72 primary open-angle glaucoma patients. A double blind RCT was chosen to minimize bias and yield similar groups with the same prognostic at baseline to avoid compromising the validity of the study results. The primary efficacy endpoint of the study will be IOP and the secondary endpoint will be the safety analysis. Qualifying participants will be evaluated for inclusion and exclusion criteria by their ophthalmologist (Dr. Marino Blasini) and informed about the study objectives. If they agree to participate, relevant baseline clinical data will be collected for each participant and they will be assigned to a treatment or a control group by stratified randomization based on their age, intraocular pressure and cup-to-disk ratio. This stratified randomization will allow comparability of randomized study groups at baseline. Participants will be randomized in a 1:1 ratio to treatment group (bimatoprost 0.01% and Mirtogenol®) or control group (bimatoprost 0.01% and placebo) and be assigned a participant ID number. Once the randomization process has concluded, participants will be notified to pass by the office to receive the product and to start using the Mirtogenol® or placebo the next day. Both Mirtogenol® and placebo bottles will label drug of study and be registered with a number identification for each patient. Mirtogenol and the placebo will be stored in a destinated area in the

primary investigator's pharmacy under a cool, dry environment that protects them from extreme temperature changes and light. Oral and written instructions on drug regimen, including route of administration, frequency, proper storage and mode of administer will be provided. The groups will self-instill one drop of bimatoprost 0.01% in the affected eye(s) once daily as instructed by the ophthalmologist. In addition, participants will use one (1) capsule of Mirtogenol® or one (1) placebo capsule orally daily in the morning with food. Mirtogenol® will be funded by Life Extension Clinical Research, Inc. Placebo capsules will be similar in appearance, size, and route of administration to Mirtogenol®.

The study will have five visits: screening and baseline, week 4, week 8, week 12 and week 24 of approximate 30-60 minutes of duration and an addition visit for pickup of the product after the randomization process. An ophthalmological evaluation will be conducted by a glaucoma specialist at each visit. At the baseline visit, the following tests will be performed: visual acuity, visual field evaluation, applanation tonometry, optical coherence tomography (OCT), and pachymetry. At week 4, and week 8 the following tests will be performed: visual acuity and applanation tonometry. At week 12, the following tests will be performed: visual acuity, visual field evaluation and applanation tonometry. At week 24, assessments will include the following: visual acuity, visual field evaluation, applanation tonometry, optical coherence tomography and pachymetry.

The same equipment will be used throughout the study for measurement consistency. Each test will be measured in the morning and the patient will be resting, sitting for at least 10 minutes before measurement. The tests will always be performed by the same person to rule out variations. At each visit, the IOP will be measured twice, with 10-minute intermissions between measurements, and mean values will be recorded. If only one eye is determined eligible as trial eye (meeting the diagnostic criteria for glaucoma), then all assessments will be performed only for the trial eye. If both eyes are eligible, only the eye with highest baseline mean IOP will be included in the statistical analysis. Patients will be instructed not to take any medications within two hours before measurements. Any therapy considered necessary for the patient's welfare will be given at the discretion of the treating physician and will be documented.

Safety measures include non-invasive techniques, standard of care treatment during the duration of the study, ophthalmological evaluations and assessment tests. Side effects or adverse effects will be reported and evaluated by the ophthalmologist at each visit and if deemed necessary the trial medication (Mirtogenol® or matching placebo) will be discontinued and therapy adjusted as

appropriate by the clinician. Adverse effects will be recorded at each study visit as well as the probability of possible association of the adverse effects to the treatment. Compliance will be reinforced with daily reminder for a month by email or text messages and then weekly reminders until the termination of the study. A monthly calendar will be provided to keep track of doses and possible miss doses. Patient must bring their supplement or placebo bottles and monthly track calendar to each visit and a pill count will be performed. Participants will be contacted one month after discontinuing the trial medication to assess for any prior changes or side effects.

The expected duration of the subject's participation shall be 24 weeks. The duration of the study will be one year. **Timeline**: Study January 2020- January 2021

- IRB Submission in December 2019- January 2020
- Project approval in January – January - February 2020
- Subjects recruitment process in February 2020- March 2020
- Study and data collection begin in April 2020- December 2020
- Data analysis in December 2020 – April 2021
- Final report and presentation in May 2021

STUDY SUBJECTS

The data selection will be using a non-probabilistic sample with convenience sampling, preferably with a consecutive design. The individuals recruited will be Hispanic who receive services in a private ophthalmology glaucoma specialist office in San Juan, Puerto Rico.
Inclusion criteria include patients with:

1. Diagnosed with primary open-angle glaucoma (POAG)
2. $\geq$ 21 years old
3. Patient must be Hispanics (self-identified)
4. Current glaucoma treatment regimen of monotherapy with bimatoprost 0.01% administered into affected eye(s) once daily with stable IOP $\leq$ of 21 mmHG

Exclusion criteria include patients with:

1. < 21 year old,
2. Pregnant women or those who are planning to become pregnant in the next six (6) months,

3. Women who are breastfeeding,

4. Individuals with cardiovascular diseases that have required medical intervention in the past three (3) months,

5. Patients that required any kind of surgery, radiotherapy or chemotherapy in the past three (3) months,

6. Patients with advanced glaucoma with a cup to disk ratio > 0.9, previous glaucoma surgeries or other abnormalities of the eye that affect the visual pathway,

7. Patients with uveitis, diabetic retinopathy, macular edema or degenerative eye,

8. Patients with a history of adverse side effects of prostaglandin inhibitors,

9. Patients planning to undergo trabeculectomy or cataract surgery during the next six (6) months,

10. Patients using immunosuppressant therapy and anticoagulant,

11. Patients currently using Mirtogenol®.

Both bimatoprost 0.01% and Mirtogenol® have been shown to have a good tolerability profile and a low incidence of side effects in previous studies. [6,7,8] The risks and discomfort that may result because of this study are mild and minimal. Mirtogenol® contains bilberry and Pycnogenol® which may theoretically interact with immunosuppressive therapies and anticoagulant. [52] Mirtogenol® may cause gastrointestinal discomfort, dizziness, headache and nausea. The ophthalmic solution of bimatoprost can cause an increase in the pigmentation of the iris, periorbital tissue (eyelid) and eyelashes, conjunctival hyperemia, conjunctival edema, conjunctival hemorrhage, eye irritation, eye pain, eye itching, eyelid sprain, pruritus eyelids, blurred vision and reduced visual acuity. All visual tests will be noninvasive, but some may cause discomfort and a small chance of cornea abrasion, which usually heals in a few days.

Benefits of the study may include intraocular pressure improvement, visual examinations and tests at no cost and the results of each test performed will be provided at the end of the study. The information in this research study may lead to better treatments in the future for people with glaucoma. Safety measures include non-invasive techniques, standard of care treatment during the duration of the study, ophthalmological evaluations, and assessment tests. Side effects or adverse effects will be reported and evaluated by a specialist and discontinuation of the trial medication will occur if deemed necessary by the treating ophthalmologist. Adverse effects will be documented at each study visit and the treating ophthalmologist will assess possible association of all adverse effects to the trial

medication. A visual acuity score indicating a loss of two or more lines or a cup to disk ratio from mild (<0.65) to moderate (0.7-0.85) or moderate to severe (>0.9) will be considered relevant and a possible discontinuation of the study of participant from the study. Any changes in visual field, central corneal thickness or increase in IOP will be considered relevant and will be evaluated for a possible discontinuation of the participant.

To ensure confidentiality, all information will be coded so that it cannot be associated with any individual. A separate document (code sheet) will have the participant full name and the code assigned and will be destroyed as soon as data collection has completed. The data collection form will only have the code number to avoid direct connection with the participant's personal information. All data entered into the computerized database will be identifiable by subject code number only. The individuals recruited for this study will be informed of the purpose of the investigation and treatment procedure in accordance with the Declaration of Helsinki and asked to provide written consent for their participation. All participants are required to read and sign detailed consent forms before participating in the study. Participants are advised of the voluntary nature of participation and of their right to withdraw from the project at any time and to require that information about them be removed from data analysis. Each study participant will receive a verbal and written description of the study. Contact information will include name, phone number, address, and email address of the patient and one emergency contact. All information will be kept confidential and protected under the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). The experimental design will be submitted to the Institutional Review Board (IRB) of the Medical Sciences Campus of the School of Medicine of Puerto Rico for approval.

VARIABLES

Variable	**Type**	**Description**	**Measurement**
Treatment Groups: (Bimatoprost 0.01% with Mirtogenol® or Bimatoprost 0.01% with Placebo)	Independent variable (Dichotomus)	Bimatoprost is a prostaglandin inhibitor used to lower IOP. Mirtogenol®, a potent antioxidant and free radical scavenger supplement, or matching placebo to take daily in addition to bimatoprost.	Mirtogenol® or Matching Placebo One capsule orally, once daily in the morning

Intraocular pressure	Dependent variable (Quantitative - Continuous)	The fluid pressure inside the eye created by the continual renewal within the eye.	Goldmann Applanation Tonometry
Visual acuity	Dependent variable (ordinal)	Measures the clarity of vision.	Snellen chart
Cup-to-disc ratio	Dependent variable (ordinal)	Measures the progression of glaucoma. Staging glaucomatous damage: Mild: <0.65 Moderate: 0.7-0.85 Severe: >0.9	OCT
Central Corneal Thickness	Dependent variable (Quantitative - Continuous)	Is the thickness of the cornea of the eye.	Pachymetry
Visual field changes	Dependent variable (Dichotomus)	Any type of visual field changes in the participants.	Perimetry
Adverse effects	Dependent variable (Dichotomus)	Adverse effects include: ● Conjunctival hyperemia ● Periocular skin pigmentation ● Itching ● Eye irritation ● Foreign body sensation ● Growth of lashes ● Skin rash ● Headache ● Nausea ● Vomiting ● Diarrhea ● Dizziness (vertigo) ● Hyperglycemic episode ● Hypoglycemic episodes	Patients will be questioned on the presence or absence of adverse effects.

		• Bleeding • Other	

ANALYTIC PLAN

A minimum sample of 72 participants will be used based on the primary efficacy endpoint of intraocular pressure to have an 80% probability to detect a difference between treatments at a two-sided 0.05 significance level. This is based on the assumption that the within-patient standard deviation of the response variable is 3.9 mmHg. Approximately 72 patients will be randomized in a 1:1 ratio to bimatoprost with Mirtogenol® or bimatoprost with placebo (intent-to-treat [ITT] population). There will be 36 patients enrolled in each population. Data will be presented as mean values with standard deviation to describe the population. The 95% confidence intervals assessments will be provided for descriptive purposes. The inferential statistical analysis to be conducted for the primary efficacy endpoint of IOP will be a t-test. All statistical tests will be performed with a significance level set at $P<0.05$. The statistical software to be use will be Minitab. The safety analysis includes presence of adverse effects, changes in visual acuity, visual field, central corneal thickness and cup-to-disk ratio, but no correlation for multiple comparisons will be performed. The intention-to-treat method will be used where all participants who were randomized are included in the data analysis regardless of whether they received their assigned treatment for the entire study. Missing data will not be replaced, instead the last observation or value will be carried forward to account for patients who dropped out and for the statistical analysis.

Sample Size: We used the standardized effect size to estimate the sample size needed for the primary efficacy endpoint of IOP. The standardized effect size is the effect size divided by the standardized deviation of the variable. A previous study has reported that the mean on intraocular pressure in treated glaucoma patients is 15.1 mmHg, with a standard deviation of 3.9 mmHg.[20] We would like to be able to detect a difference of 15% or more in the mean intraocular pressure between the two treatment groups. The effect size was calculated to be 0.39 and the standardized effect size is 0.60. Using a two-sided α of 0.05 and power of 80%, the estimated sample size needed was 36 patients for each group, and 72 patients in total.[21]

LIMITATIONS

The limitations that may affect the internal validity may be malfunction in equipment, misinterpretation of the data, or errors in the input of the data. Factors that may affect the external validity are use of other drugs that may affect the IOP, nonadherence, or discontinuation of the

participant in the study. There may be relevant confounding elements that remain unidentified and the potential confounding impact of both ocular and systemic medications warrants further investigation. A longer duration of study is required to determine long term effects and the effects on the progression in glaucoma patients.

APPENDIX

Table 1: Assessment Template

Assessment Template for Study Inclusion	
Patients Name:	
Check ☐ with an X	
A. **Inclusion criteria** ☐ Diagnosed with primary open-angle glaucoma (POAG) ☐ Patient over 21 years old ☐ Hispanic ☐ Using only bimatoprost 0.01% ☐ Consent from patient	B. **Exclusion criteria include patients with**: ☐ Patient under 21 years old ☐ Pregnant women or those who are planning to become pregnant in the next six (6) months ☐ Women who are breastfeeding, ☐ Cardiovascular diseases that have required medical intervention in the past three (3) months, ☐ Patients that required any kind of surgery, radiotherapy or chemotherapy in the past three (3) months ☐ Patients with advanced glaucoma with a cup to disk ratio > 0.9, previous glaucoma surgeries or other abnormalities of the eye that affect the visual pathway

	☐ Patients with uveitis, diabetic retinopathy, macular edema or degenerative eye ☐ Patients with a history of adverse side effects of prostaglandin inhibitors ☐ Patients planning to undergo trabeculectomy or cataract surgery during the next 6 months. ☐ Patients using immunosuppressant therapy, and anticoagulant. ☐ Patients who are currently using Mirtogenol®.

Table 2: Data Collection Form

Data Collection Form					
Code number: _____					
Gender	[ ] Male [ ] Female				
Age	_____ years				
	Baseline	Week 4	Week 8	Week 12	Week 24
IOP Mean (two takes 10 min. apart)	1) _____ 2)	1) _____ 2)	1) _____ 2)	1) _____ 2)	1) _____ 2)

Cup to disk ratio		N/A	N/A	N/A	
Central Corneal Thickness (CCT)		N/A	N/A	N/A	
Visual acuity	____/____	____/____	____/____	____/____	____/____
Visual field changes	[ ] Yes [ ] No	N/A	N/A	[ ] Yes [ ] No	[ ] Yes [ ] No
Adverse Effects					
-Conjunctival hyperemia	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N
-Periocular skin pigmentation	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N
-Itching	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N
-Eye irritation	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N
-Foreign body sensation	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N
-Growth of lashes	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N
-Skin rash	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N
-Headache	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N

-Nausea	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N
-Vomiting	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N
-Diarrhea	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N
-Dizziness (vertigo)	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N
-Hyperglyce-mic episode	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N
-Hypoglyce-mic episode	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N
-Bleeding	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N	[ ] Y [ ] N
-Other	_____	_____	_____	_____	_____

Table 3: Code Sheet

Code Sheet	
First and last names	Code number:
1.	
2.	
3.	
4.	
5.	
6.	
7.	

8.	
9.	
10.	
11.	
12.	
13.	
14.	
15.	
16. …72	

Table 3: Baseline Characteristics

Baseline Characteristics		
Description	Bimatoprost with Mirtogenol® (n=36)	Bimatoprost with Placebo (n=36)
Age, mean (SD), yrs		
Gender, No. (%)		
IOP, mean (SD), mmHg		
Cup to disk ratio, mean (SD)		
CCT, mean (SD) mm		
Visual acuity, mean (SD)		

Table 4: Primary Efficacy Endpoint

Primary Efficacy Endpoint

Time of Assessment and End Point (Week 12)	Bimatoprost with Mirtogenol® (n=36)	Bimatoprost with Placebo (n=36)	Difference [95% CI]	P-value
IOP				

Table 5: Safety Analysis

Table 3. Safety Analysis		
Variable	Bimatoprost with Mirtogenol® (n=36)	Bimatoprost with Placebo (n=36)
Changes in Vision and progression of glaucoma -no (%)		
Cup to disk ratio		
Central Corneal Thickness		
Visual acuity		
Visual field changes		
Adverse Effects Reported- no. (%)		
Conjunctival hyperemia		
Periocular skin pigmentation		
Itching		
Eye Irritation		
Foreign Body Sensation		
Growth of lashes		
Skin Rash		
Headache		

Nausea		
Vomiting		
Diarrhea		
Dizziness (vertigo)		
Hyperglycemic episode		
Hypoglycemic episode		
Bleeding		
Other		

Consent form: Spanish and English (See separate attachment)

Calendar for Monthly Compliance Assessment:

March 2020						
Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
1 ☐ Used ☐ Miss	**2** ☐ Used ☐ Miss	**3** ☐ Used ☐ Miss	**4** ☐ Used ☐ Miss	**5** ☐ Used ☐ Miss	**6** ☐ Used ☐ Miss	**7** ☐ Used ☐ Miss

8 ☐ Used ☐ Miss	**9** ☐ Used ☐ Miss	**10** ☐ Used ☐ Miss	**11** ☐ Used ☐ Miss	**12** ☐ Used ☐ Miss	**13** ☐ Used ☐ Miss	**14** ☐ Used ☐ Miss
15 ☐ Used ☐ Miss	**16** ☐ Used ☐ Miss	**17** ☐ Used ☐ Miss	**18** ☐ Used ☐ Miss	**19** ☐ Used ☐ Miss	**20** ☐ Used ☐ Miss	**21** ☐ Used ☐ Miss
22 ☐ Used ☐ Miss	**23** ☐ Used ☐ Miss	**24** ☐ Used ☐ Miss	**25** ☐ Used ☐ Miss	**26** ☐ Used ☐ Miss	**27** ☐ Used ☐ Miss	**28** ☐ Used ☐ Miss
29 ☐ Used ☐ Miss	**30** ☐ Used ☐ Miss	**Instructions:** **Mark** ☐ Used- If drug of study was used **Mark** ☐ Miss- If drug of study was Not used **Use one (1) capsule of drug of study capsule orally daily in the morning with food.**				

Reference:

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