COMPARISON OF THE EFFICACY AND SAFTEY OF PRESERVATIVE FREE TRAVOPROST 0.004% WITH TRAVOPROST 0.004% WITH POLYQUATERNIUM-1 AS PRESERVATIVE IN PATIENTS WITH PRIMARY OPEN ANGLE GLAUCOMA AND OCULAR HYPERTENSION -A RANDOMIZED CONTROLLED TRIAL.

DISSERTATION SUBMITTED TOWARDS FULFILLMENT OF THE RULES AND REGULATIONS FOR THE M.S. BRANCH III OPHTHALMOLOGY EXAMINATION OF THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY TO BE HELD IN MAY 2022

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BONAFIDE CERTIFICATE

This is to certify, this dissertation entitled '**A Randomized controlled trial to compare the efficacy and safety of preservative free Travoprost 0.004% with Travoprost 0.004% with polyquarternium-1 as preservative in patients with primary open angle glaucoma and ocular hypertension**' done towards fulfillment of the requirements of the Tamil Nadu Dr. MGR Medical University, Chennai, for the MS Branch III (Ophthalmology) examination to be conducted in May 2022, is the bona fide work of Dr. Malini.D, postgraduate student in the Department of Ophthalmology, Christian Medical College, Vellore.

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Table of Contents

ABBREVIATIONS

IOP	-	Intra ocular pressure
POAG	-	Primary open angle glaucoma
PG	-	Prostaglandin
OSD	-	Ocular surface disease
OHT	-	Ocular hypertension
RNFL	-	Retinal nerve fibre layer.
RGC-	-	Retinal ganglion cell
ONH	-	Optic nerve head
AGM	-	Antiglaucoma medication
BAK	-	Benzalkonium chloride
NRR-	-	Neuroretinal rim
VF-	-	Visual field
OCT	-	Optical coherence tomography
BCVA	-	Best corrected visual acuity
GAT	-	Goldmann applanation tonometry
TBUT	-	Tear film breakup time
SPK	-	Superficial punctate keratopathy
NEI	-	National eye institute

ACES	-	Aravind comprehensive eye survey
VES	-	Vellore eye study
CCT	-	Central corneal thickness
EGS	-	European glaucoma society
AAO	-	American academy of ophthalmology
C amp	-	Cyclic adenosine monophosphate
CME	-	Cystoid macular oedema
ECM	-	Extracellular matrix
MMP	-	Matrix metalloprotease
LHON	-	Leber's hereditary optic neuropathy
CORE	-	Centre for ocular research and education
TFOS DEWS	-	Tear film ocular surface society dry eye work shop.
DED	-	dry eye disease
OSDI	-	Ocular surface disease index
SD	-	standard deviation
IOR	-	Interquartile range
ITT	-	Intention to treat
COPD	-	Chronic obstructive pulmonary disease

LG - Lissamine green

PCTF - Precorneal tear film

DM - Diabetes mellitus

SHT - Systemic hypertension

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INTRODUCTION

Globally, glaucoma is one of the leading causes of irreversible blindness. Primary open angle glaucoma (POAG) is a chronic progressive optic neuropathy characterised by degeneration of retinal ganglion cells (RGC) resulting in changes in the optic nerve head (ONH) and corresponding changes in the visual field, with a multifactorial pathogenesis, in which the only recognised and modifiable risk factor is raised intraocular pressure (IOP) (1).

Despite recent advances, it is estimated that the global glaucoma population will reach 111.8 million by 2040(2).These estimates clearly show the need for newer glaucoma screening and management strategies, particularly in Asian countries, which are the single largest contributors to global glaucoma prevalence.

Since POAG progresses asymptomatically, the majority of patients present very late. Early diagnosis and appropriate management can delay or even prevent the progression of the disease by reducing IOP which is the only modifiable risk factor. IOP is maintained by the equilibrium between aqueous secretion and drainage. Aqueous which is produced by the ciliary body after nourishing the lens and cornea drains through the anterior chamber angle via the trabecular meshwork and uveoscleral pathway. Increased in IOP in POAG is due to the increased resistance to this outflow. The first line of management in POAG is topical antiglaucoma medications (AGM). In the last 3 decades, prostaglandin analogues (PG) have become the first line AGM even in developing countries. (3)

PGs reduce IOP by increasing both uveoscleral and trabecular outflow resulting in 25-35% reduction of IOP. They also have the advantage of once daily dosing with improved

compliance, prolonged IOP lowering effect of up to 48 hours and extremely short systemic half-life, with minimal systemic side effects.(4) Local side effects of PGs include conjunctival hyperaemia, dry eye, increase in iris pigmentation, eyelash lengthening and rare adverse reactions like periocular pigmentation and cystoid macular oedema.(5)

It is established that preservatives used in AGMs, though important in maintaining the stability of the drug molecule can have dose-dependent toxic effects on the ocular surface. The commonly used preservatives in PGs are Polyquaternium 1 and Benzalkonium chloride (BAK). Of these, Polyquaternium 1 causes fewer ocular side effects than BAK. The development of preservative-free preparations may reduce such adverse effects and therefore improve patient compliance.

Our study was done to compare the safety and efficacy of Awarene PF® (preservative free Travaprost 0.004%) to TRAVATAN* (Travaprost 0.004% with polyquaternium 1 as preservative) and also to compare the ocular surface changes between these medications.

AIM

To compare the efficacy and safety of preservative free Travoprost 0.004% (AWARENE PF®) with polyquarternium-1 preserved Travoprost 0.004% (TRAVATAN*) in patients with primary open angle glaucoma (POAG) and ocular hypertension (OHT).

OBJECTIVES

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Primary objectives:

- To assess IOP reduction 6 weeks after starting Travoprost 0.004% preserved with polyquarternium-1 (TRAVATAN*) in POAG and OHT
- To assess IOP reduction 6 weeks after starting preservative free Travoprost 0.004% (AWARENE PF®) in POAG and OHT
- To compare the IOP reduction at 6 weeks between those on Travoprost 0.004% preserved with polyquarternium-1 (TRAVATAN*) versus preservative free Travoprost 0.004% (AWARENE PF®) in POAG and OHT

Secondary objectives:

- To assess the ocular side effects and surface changes caused by to Travoprost 0.004% preserved with polyquarternium-1(TRAVATAN*) in POAG and OHT.
- To assess the ocular side effects and surface changes caused by preservative free Travoprost 0.004% (AWARENE PF®) in POAG and OHT.
- To compare the ocular side effects and surface changes caused by polyquarternium-1 preserved Travoprost 0.004%(TRAVATAN*) versus preservative free Travoprost 0.004% (AWARENE PF®) in POAG and OHT

REVIEW OF LITERATURE

Glaucoma is a neurodegenerative disease and the most common cause of irreversible blindness worldwide with an estimated prevalence of 60 million people(6). Glaucoma is estimated to affect 3.5% of people aged 40 to 80 worldwide. The prevalence rises from 0.7% in the 40-49 age group to 7.7% in those over 80 (2). POAG estimated to affect 4.2% of the population, while primary angle closure glaucoma (PACG) is estimated to affect 1.09%. Over a period of 15-20 years, the estimated risk of blindness from POAG ranges from 14.5% to 27% (unilateral) and from 6.4% to 9% (bilateral) (2).

POAG is the most common form of glaucoma in European and African populations.(2) On the basis of the available data from India, there are approximately 11.2 million persons aged 40 years and older with glaucoma in the country(7). Of these POAG is estimated to affect 6.48 million. Angle closure disease, though more prevalent with an estimate of 27.6 million, the estimated number with PACG is 2.54 million. Most of those with POAG are undetected and there exist major challenges in detecting and treating those with disease (7)

According to the Aravind Comprehensive Eye Survey (ACES), the prevalence of glaucoma in South India is 2.6 percent, with POAG being 1.7%. According to the results of the above survey, one-fifth of the patients were blind in one or both eyes due to glaucoma (8). According to the Vellore Eye Study (VES), the prevalence of POAG was 0.41 percent (9)According to the above studies, the estimated population with glaucoma in India is around 11.2 million, with POAG accounting for 6.48 million, majority of whom go undetected or are diagnosed at an advanced stage.(7)

Definition:

POAG is defined as a chronic progressive anterior optic neuropathy with characteristic changes in the optic nerve head(ONH) and corresponding visual field defects, in which intraocular pressure (IOP) is the only modifiable risk factor.(3) Individuals IOP more than 21 mm Hg, open angles, normal ONH, normal visual fields and absence of any ocular or systemic disorders contributing to the elevated IOP are classified as ocular hypertension (OHT)

Pathogenesis:

The pathogenesis of POAG is still unclear. There are numerous risk factors that have been identified. IOP, Hispanic or Black race, older age, positive family history of glaucoma, decreased central corneal thickness and possibly myopia and diabetes mellitus are among these risk factors. Because there is no clearly defined disease mechanism to target, glaucoma treatment focuses on risk factor modification. IOP is the only modifiable risk factor and hence IOP reduction is the only therapy proven to be effective in controlling the disease**.**(10)IOP reduction has been shown to prevent or delay the development of glaucoma in eyes with OHT, and delay progression of POAG.(11)(12)

Pathophysiology:

Pathophysiology of glaucoma is directly related to aqueous humor dynamics. Aqueous humor is produced in the pars plicata of the ciliary body. The ciliary body is attached anteriorly to the scleral spur, creating a potential space (supraciliary space) between itself and the sclera. The iris inserts into the short anterior side of the ciliary body, leaving a narrow width of ciliary face visible on gonioscopy posterior to the scleral spur.

The ciliary processes are finger like projections in the pars plicata of the ciliary body. Each process is lined by 2 layers of epithelial cells. The core of the ciliary process contains blood vessels and loose connective tissue. The plasma within the capillary network of ciliary processes produce aqueous humor.(13) The equilibrium between production and drainage of aqueous humor helps in the maintenance of IOP. The normal aqueous production rate is 2.3 μl/min. The three mechanisms involved in production of aqueous are diffusion, ultrafiltration and secretion (active transport) (14)

The aqueous humor enters the posterior chamber, between the iris and the lens, passes through the pupil against a physiologic resistance and enters the anterior chamber. It drains through the trabecular meshwork in the angle of the anterior chamber to the Schlemm's canal and collector channels into the episcleral veins. Trabecular out flow contributes up to 70-80% of aqueous drainage. 20-30 % of the outflow is through uveoscleral pathway (3).The aqueous drains by passing across the bundles of ciliary muscle into suprachoroidal space and into the venous circulation.

Target IOP:

Although there is no absolute 'safe' pressure that guarantees progression delay, lowering IOP to the low-normal range usually stops or slows the progression of glaucoma.(3)Medical and surgical management are the two main treatment modalities. The treatment goal is 25% - 30% reduction from baseline IOP or achievement of target IOP for that eye based on the severity of the disease, i.e., the more advanced the glaucoma, the less the target IOP.(12)

Target IOP is that IOP at which further damage to the optic nerve for that individual is unlikely (15). The European Glaucoma Society(EGS) guidelines define target IOP as "an estimate of the mean IOP obtained with treatment that is expected to prevent further glaucomatous damage" (16)According to the American Academy of Ophthalmology(AAO), target IOP is a range of IOP adequate to stop progressive pressure-induced injury. (17)

The World Glaucoma Association(WGA) defines it as an estimate of the mean IOP at which the risk of decreased vision-related quality of life due to glaucoma exceeds the risk of the treatment.(18) The progression of glaucomatous visual field (VF) loss also has a significant and permanent impact on quality of life, so stabilisation of the VF is equally important. To summarise target IOP refers to an IOP that prevents further progression of without compromising a patient's quality of life.(19)(20)

EGS recommends a stepwise treatment algorithm that begins with pharmacological IOP reduction, followed by laser treatment of the trabecular meshwork and then filtering glaucoma surgery(4). According to the EGS, target IOP should be calculated based on the amount optic nerve damage, the patient's life expectancy, the rate of progression, and the baseline IOP(21) .A large reduction of IOP by 30% to 50% is more likely to be needed in patients with severe disease.(4)

Role of central corneal thickness in IOP:

With the rapid advancement of refractive surgery, central corneal thickness (CCT) has emerged as an important parameter for selecting surgery modality and determining prognosis. Meanwhile CCT in the diagnosis of glaucoma field also has an important role.

CCT measured by pachymetry has a significant impact on the clinical management of glaucoma patients and glaucoma suspects.(22)Several studies have found an association between CCT and IOP in adults. Every 10 m increase in CCT causes an increase in IOP of 0.15–1.0 mmHg. According to the Ocular Hypertension Treatment Study, CCT was a strong predictor for the development of POAG in patients with OHT. This study found that subjects with lower CCT measurements had a higher risk of developing POAG (relative risk:1.71 per 40-µm decrease in CCT). Furthermore, individuals with CCTs of 555µ m or less had a threefold increased risk of developing glaucoma compared to patients with CCTs greater than 588 µm. (22) The CCT and IOP are important in glaucoma management because low CCT will lead to an underestimation of IOP.(23)A thin cornea is a significant risk factor for the development of glaucoma, and it is unclear whether this is an independent effect or the result of the influence of CCT on IOP measurements.(24)

Medical management of POAG:

This is first line of management in POAG. Medical management consists of topical administration of various classes of anti-glaucoma medications (AGM) in the form of eye drops. AGMs reduce IOP either by reducing aqueous production or by increasing aqueous drainage. The topical AGMs include β blockers, alpha adrenergic agonists, para-sympathomimetics, prostaglandin analogues (PGs) and carbonic anhydrase inhibitors.

Those that reduce aqueous production include beta-blockers which inhibit beta-mediated Na+/K+-ATPase stimulation, carbonic anhydrase inhibitors and

sympathomimetic drugs that act by activation of alpha-mediated inhibition of Na+/K+-ATPase.(4) Those that increase the drainage of aqueous are cholinergic or parasympathomimetic drugs, prostaglandin derivatives and sympathomimetic drugs (4)

Reducing IOP by increasing aqueous drainage has potential benefits as compared to decreasing aqueous secretion. One of these is correction of outflow deficit, which is the main cause of high IOP. Moreover, increasing drainage prevents IOP fluctuations and dangerous spikes. Additionally, it maintains the physiological production of aqueous humor, which is important for the nutrition of the lens and cornea and removal of metabolic waste products (25).

Prostaglandin analogues PGs, beta-blockers, alpha-2 agonists, and topical carbonic anhydrase inhibitors are the agents of first choice, according to the EGS guidelines.(21)The goal of medical treatment is to achieve ″24-h″ IOP control with the lesser number and minimum concentration of medications, as well as with the lesser local and systemic side effects. The initiation of treatment depends on the target IOP. The factors that should be considered when prescribing a drug are its efficacy, compliance, safety, persistence and most important of all, its affordability. Compliance is expected to improve if the drug is inexpensive and the dosage is simple.

The introduction of fixed combination drugs has aided in improving compliance and lowering costs. If the drug fails to reduce IOP by at least 15% from baseline or causes severe side effects, the second option is to conduct a unilateral drug trial. In an ideal world (without considering costs), prostaglandin analogues would be the first-line drugs for most glaucoma patients.

If we want to reduce our IOP by around 20% from the baseline, beta-blockers could be the first line of treatment. If the goal is to reduce IOP by 30-35 percent from baseline, prostaglandin analogues (PG) such as Latanoprost (0.005%), Bimatoprost (0.03%), or Travatoprost (0.004%) are preferred.

Picture 1 Antiglaucoma medications (3)

Drug classification	Mechanism of Action	IOP reduction
Prostaglandin analogue	Increased uveoscleral and trabecular outflow	25-33%
Alpha adrenergic agonists	Non-selective: improve aqueous outflow Selective: Decrease aqueous outflow, decrease episcleral venous pressure, increase uveoscleral outflow	20-25%
Beta adrenergic antagonists	Decrease aqueous production	20-25%
Parasympathomimetic agents	Increase trabecular outflow	20-25%
Topical CAIs	Decrease aqueous production	15-20%
Oral CAIs	Decrease aqueous production	20-30%
Hyperosmotic agents	Dehydration of vitreous	

Prostaglandin analogues:

PGF2-tromethamine salt was the first prostaglandin analogue tested in humans. Despite the fact that this agent reduced IOP, more than one-third of patients experienced significant conjunctival hyperemia, stinging, foreign body sensation, and headache.

Isopropyl unoprostone (Rescula) is a prodrug derived from a pulmonary PGF2 metabolite that lowers IOP in a dose-dependent manner with twice daily dosing and is

well tolerated. Latanoprost, Bimatoprost, Travoprost, Isopropyl Unoprostone and Tafluprost are the different PGs available.

Mechanism of action: The outflow through the uveoscleral pathway is increased by PGs. They appear to alter not only the function but also the structure of the uveoscleral pathway. Extracellular matrix (ECM) remodelling, widening of intermuscular spaces along the longitudinal ciliary muscle bundles, and collagen type I and III dissolution are all caused by PGs. This effect could be attributed to an increase in the production of metalloproteinases (MMPs). Latanoprost stimulates MMP-I activity in the non-pigmented epithelium of the ciliary body. It increases cellular metalloproteinases and improves uveoscleral outflow through extracellular, interciliary body muscular bundles. Thus, prostaglandin analogues lower intraocular pressure (IOP) by activating matrix metalloproteinase (MMP) enzymes and increasing uveoscleral outflow. MMPs have been discovered in the cornea, and their activation has the potential to alter the central corneal thickness (CCT).(26)But this change occurs only if administered for an extended period > 2 years (27).

Latanoprost: With a single daily dose of 0.005% latanoprost, IOP is reduced by 25–35%. The once-daily dosage appears to be superior to the twice-daily dosage, and its efficacy is maintained throughout the day. Over the first 6 months of treatment, an evening dose appears to be slightly superior to a morning dose in terms of lowering morning IOP. It deteriorates, when exposed to heat above 100°F for more than 8 days and hence has to be refrigerated.

Bimatoprost: Bimatoprost, when compared to latanoprost, has been shown in studies to provide slightly better pressure control. A meta-analysis of four controlled comparative

studies found that bimatoprost has improved pressure control by about 1–1.5 mmHg when compared to latanoprost. It is more effective than timolol and dorzolamide in lowering IOP and maintaining 24-hour control.

Travoprost: Travoprost is an isopropyl ester of a highly active prostaglandin F2 agonist. It is an FP receptor agonist with a high degree of specificity. When used once daily, it is a highly effective agent for lowering IOP. It is also slightly more effective at controlling daytime IOP and limiting IOP fluctuation when administered at night.

It lowers IOP levels over a 24-hour period but may have a longer duration of action more than 40 hours from a single dose. If a dose is missed, the effect on IOP is reduced during the day but appears to be maintained during the nocturnal period, when the pressure may be at its highest. Travoprost may be the best agent if adherence to the treatment regimen is an issue, as it appears to be more forgiving of occasional missed doses.

PGs are the most potent ocular hypotensive medications used in the treatment of POAG and OHT (28). They reduce IOP by up to 33%.(29)PGs are thus recommended as first-line topical agents because of their IOP-lowering ability, safety profile, and once-daily dosing (30). The pressure reduction lasts up to 48 hours with • a very short systemic half-life, resulting in a very low rate of systemic side effects.(4)

The various topical PG analogues available are Latanoprost (0.005%), Travoprost (0.004%), Bimatoprost (0.03%) and Tafluprost (0.0015%). The only limitation for prescribing PG analogues as first line drug of choice in our population is the increased cost of these medications as compared to others. Travoprost 0.004% is a prostaglandin

F2α analogue, which is widely used in the treatment of POAG and OHT. The initial formulation, TRAVATAN (Travoprost 0.004% ophthalmic solution; Alcon Laboratories, Inc, Fort Worth, Texas, USA), like many other topical ophthalmic medications, which contained benzalkonium chloride, a commonly used preservative. This was found to cause conjunctival inflammation(31), tear film disruption(32) and symptoms of ocular surface disease and decreased ocular surface health following chronic exposure(33).

PGs are also known to produce eyelid skin hyperpigmentation, which almost completely resolves in around 4 months after stopping the medication. Conjunctival hyperaemia, the most common ocular adverse effect, occurs in up to 31% of patients, a greater frequency than found with timolol (34) Decrease in goblet-cell density, conjunctival epithelial size, abnormal Schirmer's test TBUT after treatment have been reported with PG (35). Animal studies have shown that prostaglandin analogues affect conjunctival fibroblasts (36).

Benzalkonium chloride (BAK): BAK is a quaternary ammonium compound. It is used in different concentrations varying from 0.004% to 0.02%. Because these compounds contain both hydrophilic and hydrophobic elements, and have surfactant and detergent properties(36)(37). As a result, it causes bacterial cell death by interacting with lipid components in the cell membrane, causing the membrane to become unstable and allowing the contents of the cell to be released.(38)

Toxic effects of benzalkonium chloride include "dry eye" and trabecular meshwork degeneration. BAK's ocular toxicity is caused by its inhibition of mitochondria in human

corneal epithelial cells and cells with LHON mutations. As a result, prescribing BAK-containing eye drops should be avoided in patients with mitochondrial deficiency, such as LHON patients, LHON carriers (39).

The most common ocular symptoms are discomfort upon instillation, burning and stinging sensations, foreign body sensation, dry eyes, tearing, and itchy eyelids.(40)

According to Walsh and Jones, Centre for Ocular Research & Education (CORE) Canada, the prevalence of ocular surface symptoms in a large pooled data of glaucomatous patients using preserved eye drops was as high as 30 to 50%.(36) Superficial punctate keratitis, conjunctival hyperaemia, staining, follicles, and blepharitis are seen associated with the use of BAK-preserved drops (41)(40). Other side effects include increased osmolarity(42)(43), reduced tear production and reduced tear film break up time (TBUT). BAK-induced tear film instability has been observed even in healthy subjects.(36)

Histopathological studies show an increase in inflammatory cells in the conjunctival epithelium,(40)(44)(45) and a significant reduction in the number of goblet cells.(46)(44) Even in asymptomatic patients, flow cytometry revealed an increase in inflammatory markers in ocular surface cells(47)(48)(49)(50). BAK has also been shown to affect corneal nerves, with in vivo confocal microscopy revealing reduced number of sub-basal nerves compared to preservative-free formulations in glaucoma patients.(51) BAK disturbs tear stability, causes cellular injury to the epithelium of cornea and conjunctiva and also induces inflammatory changes. Besides, in patients who have associated dry eye, BAK, will possibly worsen the disease. (36)

There have been many clinical studies where patients were substituted from BAK-preserved to preservative-free drops. These so-called "switch" studies, showed improvement in symptoms.(41)(40)(52)(53)(54). Preservative-free drops reduced the incidence of pain and discomfort from 52.4% to 7.8% when compared to drops with BAK as preservative(41).

Since its introduction in 2001, efforts have been made to improve the safety profile of Travoprost 0.004%. Two formulations preserved without BAK are currently marketed. Travoprost 0.004% preserved with SofZia (Travatan Z; Alcon Laboratories, Inc) is available in the United States, Canada, and Japan; Travoprost 0.004% preserved with polyquaternium-1 (TRAVATAN*; Alcon Laboratories, Inc) is marketed throughout the world, including Europe, South America and Asia.

Non inferiority of the IOP-lowering efficacy of polyquaternium-1preserved Travoprost 0.004% compared with BAK preserved Travoprost 0.004% was demonstrated in a randomized, double-masked study of 371 patients with POAG and OHT (55).Safety profiles were also similar; however, incidence of hyperaemia was noticed to be less with the polyquaternium-1preserved formulation(55). Another double blinded randomized trial comparing polyquaternium- 1 preserved Travoprost 0.003% and BAK preserved Travoprost 0.004%, showed that, in patients with POAG and OHT, polyquaternium-1-preserved Travoprost 0.003% provided comparable IOP lowering effect as well as safety to that of BAK preserved Travoprost 0.004%(56).

A prospective randomized multicentre single-masked study was done on patients with POAG and OHT who had been on BAK-preserved Latanoprost 0.005% (Xalatan (®) monotherapy for 3 months and subsequently switched to SofZia-preserved Travoprost

0.004% (Travatan Z) for 3 months. The study revealed a lower incidence of keratoconjunctival epitheliopathy, with no clinically relevant difference in hyperaemia and IOP (57).

Polyquaternium -1:

Polyquaternium (POLYQUAD®, Alcon Inc., Fort Worth, TX) (PQ-1) is a hydrophilic cationic polymer.(58)(59)(60) Since the mid-1980s, it has been used as a disinfectant in contact lens solutions, and then as a preservative in both dry eye preparations and glaucoma medications.(61)(60)(62)(63)(64). It is a polymeric quaternary ammonium molecule with its size approximately 27 times bigger than that of BAK.(65)(66).

How a molecule interacts with cells is dependent on its size. PQ-1 disrupts microbial cell membranes, though too large to enter mammalian cells.(67)(68)This, theoretically reduces its toxic effects on ocular surface cells as compared to BAK.

Confocal microscopic studies were done on corneal epithelial and Langerhans cells in travoprost-treated eyes preserved with either BAK or PQ-1. When compared to healthy controls, the BAK-preserved formulation significantly reduced tear breakup time and epithelial cell density.(69)Changes with PQ-1-preserved drops were not as significant, showing a limited response of the corneal immune system to travoprost with PQ-1. This could be interpreted as an indicator of better controlled corneal homeostasis and a less disturbed ocular surface when compared to the BAK-preserved drop.(69)The safety profiles were also similar; however, the PQ-1 preserved formulation had a lower incidence of hyperemia.(55)

Another double-blind randomized trial comparing PQ-1preserved Travoprost 0.003% solution to BAK preserved Travoprost0.004 % found that PQ-1preserved Travoprost 0.003% solution provided equivalent IOP-lowering efficacy and safety to BAK preserved Travoprost0.004 %.(56)

Ocular surface disease (OSD): OSD includes a group of ocular disorders that affects several components of the ocular surface. OSD affects 15% of all individuals over the age of 65.(70). Tang et al., found that the prevalence of OSD (48-59%) in glaucoma patients on long-term topical medications.(70).

The TFOS DEWS II (Tear Film Ocular surface Society Dry Eye Work Shop) defines DED as a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles. (71)

OSD is clinically diagnosed by measuring the tear film break up time (TBUT), performing Schirmer's test, and observing the staining pattern of the cornea and conjunctiva. OSD has been shown to be more prevalent in POAG patients using anti-glaucoma medications. The exposure to the preservative, rather than the active ingredient of the drug, probably has a more significant role to play in causing ocular surface disorders in these patients(72).

The effect of preservative-free lubricant drops on patients with DED has been studied in a large switch study which enrolled 1249 dry eye patients, of whom (81%) had severe DED.(54) All patients regularly used preserved artificial tears, with roughly half (46%)

of the cohort using BAK and 54% using PQ. After a minimum 3-week switch to preservative-free artificial tears, Ocular Surface Disease Index (OSDI) scores and superficial punctate keratitis was significantly reduced in 97 % of patients.(36)

The use of preservatives significantly increases the shelf-life of medications. This allows patients to administer medications in a more convenient and cost-effective manner than preservative-free medications over a longer period of time. Preservative-free eye drops are usually single-use vials that are costly and have strict storage and usage requirements. Many regulatory authorities have also made the use of preservatives in multi-dose containers as requirement(73).

Nenciu et al., observed that the severity of conjunctival inflammation and metaplasia varies between different topical anti glaucoma medications, all containing BAK as preservative.(74). This study also that reported the DED is due to loss of goblet cells leading to mucin deficiency in these patients. (74) The safer preservatives like PQ-1, oxychloro complex and SofZia® have shown to cause less OSD(75)(67)(76).

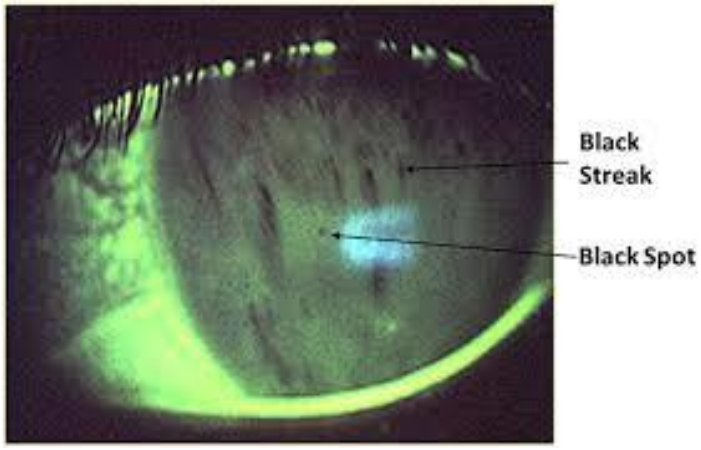
DRY EYE DISEASE

International Dry Eye Workshop (DEWS) in 2007: dry eye is defined as a "multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface." Evaluation of the dry involves measuring the following parameters

Tear break up time (TBUT) :(described by Norn)

It is a measurement of tear film stability & is the amount of time it takes fora dry spot to appear in the tear film after a complete blink.

Technique: A drop of fluorescein is instilled in the eye (ideal concentration of the dye is 0.05%) and asked to blink 2 to 3 times so that the dye is well distributed in the eye The patient examined at the slit lamp and asked to stare straight ahead without blinking. Cornea is examined with cobalt blue filter & the appearance of the 1st black spot is noted.



Picture 2: Tear film break up time showing black spots

TBUT is measured in seconds between the last blink & the appearance of the 1st black spot. A normal TBUT is > 10 sec. The areas of breakup must appear in a random pattern. Repeated drying of the same area suggests a localized corneal abnormality like a dellen. Other techniques to measure TBUT includes Xeroscope, Tandem scanning confocal microscopy, high-speed, high-resolution thermograph

Schirmer Test: This is used to measure aqueous tear deficiency.

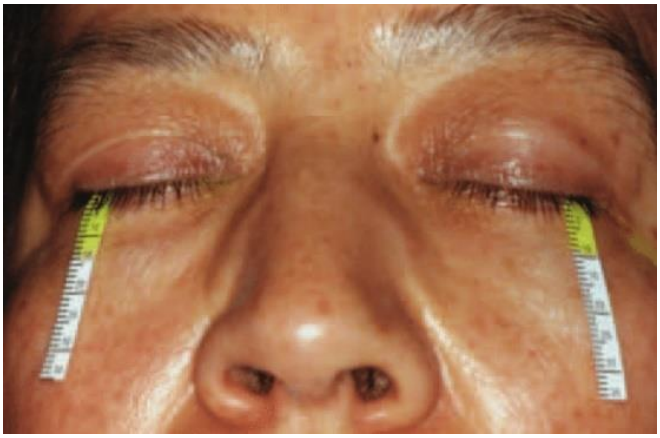
Technique: 5*35mm strip of No: 41 Whatman filter paper is used. A notch is present 5mm from one end of the strip. The strip is bend at the notch & inserted into the lower

fornix at the junction of middle and lateral one third. Filter paper shouldn't touch the cornea while placing the strip in the eye. Strips are noted for wettability after 5 min.(g)

Schirmer1 A: measure total reflex & basic tear secretion. Normal value is 10-30mm. If >30mm - reflex is not controlled or there is insufficient drainage. A value of < 5mm indicates hyposecretion.

Schirmer 1B: Measures only basic secretion. Topical anesthesia is instilled prior to the test. Basic secretion of 3mm or less in 5 mins is abnormal.

Schirmer 2: It is a test for reflex tearing. Instill topical anesthetic drops into the eye and irritate ipsilateral unanesthetized nasal mucosal with cotton swab. Measure wetting after 2 min: --<15mm suggestive of decrease in reflex secretion.



Picture 3 Schirmer's test

Rose Bengal staining: is a vital dye that stains for devitalized or abraded epithelial cells, mucus & filaments. Determines secondary damage of superficial epithelium of the

cornea &conjunctiva in patients with keratoconjunctivitis sicca. Best seen using red free filter.

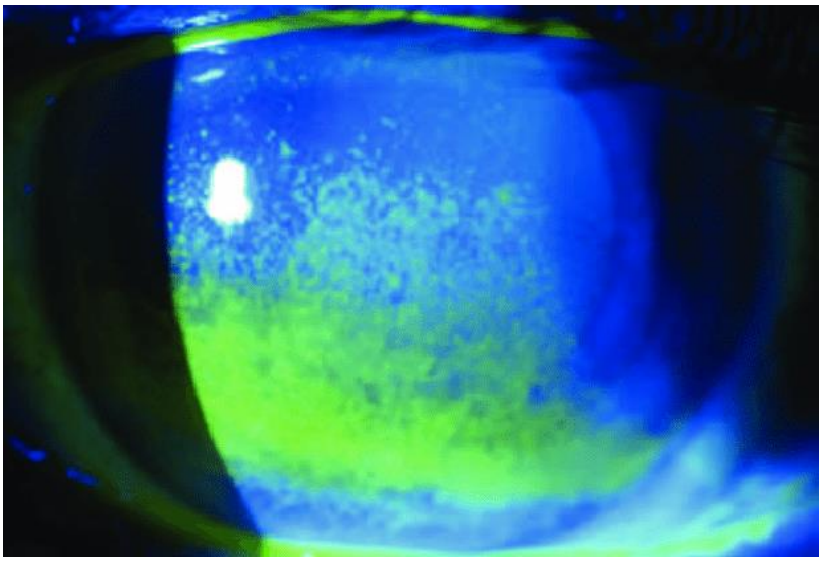
Lissamine Green:

Lissamine green stains ocular surface epithelial cells that are not protected by mucin or glycocalyx, as well as damaged cells. Staining with Lissamine green (LG) has been comparable to that of rose Bengal. However, it is less irritating and better tolerated by patients.

Picture 4 Lissamine green staining

Fluorescein stain: dye penetrates intercellular spaces &staining indicates epithelial permeability. Fluorescein stains the cornea more than the conjunctiva and is used to detect superficial punctate keratitis.

Fluorescein staining cornea showing SPKs



Picture 5 Fluorescein staining showing SPK s in the cornea

The first comprehensive definition of DED was published in 1995 on the basis of consensus from the National Eye Institute (NEI) Industry Working Group on Clinical Trials in DED. In the report, DED is defined as follows:

“Dry eye is a disorder of the tear film due to tear deficiency or excessive evaporation, which causes damage to the interpalpebral ocular surface and is associated with symptoms of ocular discomfort.”

The definition states unequivocally that DED is caused by changes in the tear film, which result in irritating symptoms and epithelial abnormalities. It also implies that the main causes of DED are a lack of tears and excessive evaporation. (77) DED was classified into two major categories: tear deficient and evaporative, and then subclassified into a variety of intrinsic and extrinsic causes. It is critical that the definition uses the term "disorder" rather than "disease." This definition and

classification scheme influenced subsequent DED studies and clinical approaches, including the American Academy of Ophthalmology's Preferred Practice Pattern reported in 2013 and others.

The following definition of DED is provided in a recent revision, published in 2017, dealing with the DED definition and classification in the DEWS II report:

"A multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles

DEWS II listed a variety of diagnostic tests in the diagnosis report, including questionnaires, tear film tests, epithelial abnormalities, and others. The test begins with DED screening questions, followed by a series of examinations such as slit-lamp bio microscopy, osmolarity, BUT measurement, and staining tests. Then, additional tests for subtype classification such as meibomian gland/lid margin changes and tear volume examinations.

In addition, a European group proposed diagnostic criteria for severe DED. In this study, Baudouin and colleagues proposed that patients with a high ocular surface disease index (OSDI; >33) and increased corneal fluorescein score (≥3) were considered to have severe DED, whereas an OSDI score (≥3) with a fluorescein score 3, an OSDI score (≥3) with a fluorescein score = 2, or an OSDI score (≥3) with a fluorescein score <2 were considered to have severe DED if there were other DED findings, such as as impaired corneal sensitivity, a breakup time (BUT) <5 seconds.(77)

Symptomatic evaluation of DED:

The Ocular Surface Disease Index (OSDI), developed by Allergan Inc's Outcomes Research Group in Irvine, California, is a 12-item questionnaire designed to provide a rapid assessment of the symptoms of ocular irritation consistent with dry eye disease and their impact on vision-related functioning. The initial OSDI items were developed based on patient feedback from several years of clinical studies conducted by Allergan Inc, several quality-of-life instruments, and clinical investigator suggestions. The initial questionnaire contained 40 items, which were later reduced to the final 12 questions based on validity and reliability data from three groups (2 small groups of patients with dry eye and one phase II clinical trial group)(78).

OSDI Scoring Algorithm

The 12 items of the OSDI questionnaire were graded on a scale of 0 to 4, with 0 indicating none of the time, 1 indicating some of the time, 2 indicating half of the time, 3 indicating most of the time, and 4 indicating all of the time. The total OSDI score was then computed using the formula below.:

$$\text{OSDI} = \frac{(\text{Sum of scores for all questions answered}) \times 100}{(\text{Total number of questions answered}) \times 4}$$

. As a result, the OSDI is graded on a scale of 0 to 100, with higher scores indicating greater disability. In a large sample of patients with dry eye disease and normal controls, the OSDI demonstrated both high internal consistency (the Cronbach for the overall instrument and each of the subscales ranged from good to excellent) and good to excellent test-retest reliability. The OSDI also demonstrated excellent validity, effectively distinguishing between normal, mild to moderate, and severe dry eye disease as defined by a physician's assessment of severity and a composite disease severity score. Furthermore, the OSDI showed good sensitivity and specificity in differentiating between normal subjects and patients with dry eye disease. The OSDI is a valid and reliable instrument for measuring the severity of dry eye disease, according to a study conducted by Schiffman RM, and it possesses the necessary psychometric properties to be used as an end point in clinical trials.(78).

We aim to compare the IOP reduction with preservative free Travoprost 0.004% (Awarene PF®) eye drops with the commonly used polyquaternium -1 preserved Travoprost 0.004% (TRAVATAN*) in patients with POAG and OHT.Till date there are no studies comparing the safety and efficacy of this formulation of Travoprost with other formulations containing other preservatives. We also looked at any significant difference in side effects and ocular surface changes between the two formulations.

MATERIALS AND METHODS

Study Design: Randomized controlled trial

Place of Study: Department of Ophthalmology, Christian Medical College, Vellore.

After institutional review board clearance, newly diagnosed patients with POAG and OHT who satisfy the inclusion and exclusion criteria were prospectively included in the study after informed written consent.

Inclusion Criteria for POAG:

1. Age ≥ 40 years

2. IOP > 21 mmHg

3. Open angles on gonioscopy

4. Retinal nerve fibre layer defects or glaucomatous optic nerve head (ONH) changes like neuroretinal rim (NRR) thinning, disc excavation or disc hemorrhage

5. Corresponding visual field (VF) defects confirmed by reliable visual field examination. (i.e., false-positive errors <15%, false negative errors <15%, and fixation loss <20%) A glaucomatous VF defect was defined as presence of two out of the three Hodapp-Anderson-Parrish's criteria: 1) the presence of a cluster of 3 non edge contiguous points on a pattern deviation plot with P < 5% (1 of which had a P < 1%) 2) Pattern standard deviation with P < 5%; 3) glaucoma hemifield test result- outside normal limits.

6. OCT RNFL showing glaucomatous changes

7. Willing to give informed consent

Inclusion Criteria for OHT:

1. Age ≥ 40 years

2. IOP > 21 mmHg

3. Open angles on gonioscopy

4. Normal ONH

5. Normal visual fields using Humphrey's Field Analyzer

6. Normal RNFL thickness on OCT- RNFL

7. Willing to give informed consent

Exclusion criteria

1. History of allergic conjunctivitis

2. Known hypersensitivity to any topical or systemic medication

3. History of dry eye or any autoimmune disease, causing dry eye and /or on lubricants or any other topical medications within the last 3 months.

4. Previous intraocular surgery in the last 6 months.

5. Non glaucomatous disc pathologies that cause VF defects like optic disc pit, coloboma, optic neuritis, anterior ischemic optic neuropathy, retinitis pigmentosa, optic pathway lesions.

6. Inability to perform a reliable VF evaluation using HFA.

7. Media not clear enough to obtain OCT images with an image quality < 40.

8. Advanced glaucomatous disc and field changes.

9. Lid abnormalities and corneal pathology which could alter ocular surface.

10. Use of Contact lens.

11.Patients on systemic Beta blocker will be excluded from the study.

Method of Randomization: Participants eligible for inclusion in the study were randomly allocated in a 1:1 ratio to one of the two treatment groups using a computer-generated block randomization with block size 2, 4 and 6.

Method of Allocation concealment:

The randomisation code was computer-generated, and treatment assignments were unavailable to the principal investigator till the completion of the study. The randomization sequence remained with the biostatistician, and thesis guide. Upon study entry, patients were assigned numbers of 01 to 62 by designated personnel, a social worker. The list of patient numbers was generated by biostatistician, not involved in the conduct of the study. Sequentially numbered, sealed, opaque envelopes prepared by biostatistician was given to thesis guide who assigned patients in sequential order to one of the treatment arms as decided before the start of the study.

All patients who fulfill the inclusion and exclusion criteria underwent a routine ophthalmic examination which consists of best corrected visual acuity (BCVA), a detailed torchlight and slit lamp examination including IOP with Goldmann Applanation Tonometry (GAT), gonioscopy and a stereo-biomicroscopic examination of the optic nerve head. In addition, these patients underwent a detailed ocular surface examination including dry eye evaluation which includes tear film breakup time (TBUT), superficial

punctuate keratopathy (SPK) assessment, Schirmer's 1a test and Lissamine green test. The examination was done in both eyes. However, eye with higher IOP for OHT and the eye with more advanced glaucomatous disc changes and visual field changes in POAG were chosen as the study eye. In some cases, where disease severity was same in both eyes, the right eye has been chosen as the study eye.

After BCVA and torch light examination, the dry eye evaluation was done. TBUT test was performed by applying fluorescein into the inferior conjunctival cul de sac using a fluorescein strip which is a filter paper impregnated with 1 mg fluorescein sodium. The tear film was examined using a slit lamp with cobalt blue light. The time interval between the last blink and the appearance of a first hypo fluorescent spot or streak was recorded as the TBUT. 3 such readings were taken and the average of the 3 readings were recorded as the final TBUT. The severity designations used for TBUT are the following: (79)

- >10 seconds- normal
- 5 to 9 seconds-mild to moderate
- <5 seconds- severe

Then, superficial punctate keratitis (SPK) was assessed according to NEI (National Eye Institute) classification, where the area of SPK will be divided into five areas: center, superior, nasal, temporal and inferior(80). The density of SPK was graded as given below

:

- No SPK is present: 0
- SPK is sparse: 1
- SPK moderately dense: 2
- SPK is dense and the lesions overlap: 3

For Schirmer's-1a test (without anesthesia), the patient was asked to look up and the lower eyelid is gently retracted. The rounded bent end of the sterile Schirmer's strip made of Whatmann 41 filter paper with gradations, was inserted into the lower conjunctival cul de-sac over the junction of the lateral and middle one-third of the lower eyelid. The strip was removed after 5 minutes and the amount of wetting was recorded. The severity designations used for the Schirmers-1 test are as follows(81):

- >10 mm: normal
- 6 to 10 mm: mild to moderate
- 0 to 5 mm: severe

Next, a 1.5 mg Lissamine green strip (LG), wetted with a drop of artificial tear solution was applied to the lower tarsal conjunctiva. After a few blinks, conjunctival staining were scored using the standard NEI classification.(80) The area of conjunctiva was divided into six areas: medial canthus, nasal superior, nasal inferior, temporal inferior, temporal superior and lateral canthus. The density of LG staining was graded as given below.

- 0: no staining present
- 1: staining sparse
- 2: moderately dense staining
- 3: severe staining with overlapping lesions

After completing dry eye evaluation, IOP was checked using the Goldmann Applanation Tonometer (GAT) attached to a Haag Striet slit lamp (HAAG-STREIT BERN model BM 900). IOP was measured at 09:00 Hours (±30min), 13:00 Hours (±30min), and 17:00 Hours (±30min) on the same day. The average of the 3 readings were noted. IOP, after correction for central corneal thickness using the normogram proposed by Ehlers etal.,(82) was considered as the final IOP.

The technique of Goldmann tonometry is as follows: One drop of 0.5% proparacaine hydrochloride was instilled in both eyes. After 30 seconds, the tip of a moistened fluorescein strip is inserted into the inner surface of each lower lid and the patient is asked to blink a few times to stain the ocular surface with fluorescein. Excess tears are wiped with cotton. The tonometer tip is sterilised, dried and the prism is properly positioned on the applanation attachment on the slit lamp.(83)

The tension knob has been set to 1 which corresponds to 10 mm Hg. When the knob is set to 0, the prism head may vibrate and damage the corneal epithelium when it comes into contact with the eye. The prism's 0 graduation mark is set at the white line on the prism holder.(83)The cobalt filter is used with the slit beam as wide as possible. The

angle between the lighting and the microscope should be around 60°. The patient is seated on an adjustable stool in a comfortable position. The patient is asked to blink a few times to spread the fluorescein-stained tear film across the cornea, then keep the eyes open wide.

The biprism should not come into contact with the lids or lashes because this causes blinking and squeezing. If the tonometer tip comes into contact with the lids, the fluorescein rings thicken, resulting in an overestimation of IOP. It is critical not to put any pressure on the globe because this raises IOP.(83)Using the control stick, the observer raises, lowers, and centres the assembly until two equal semicircles are visible in the centre of the field of view. IOP is overestimated if the two semicircles are not the same size. The fluorescein rings should be 0.25–0.3mm thick, or about one-tenth the diameter of the flattened area. If the rings are too narrow, the patient should blink two or three times to replenish the fluorescein. IOP is underestimated if the fluorescein rings are too narrow. If the fluorescein rings are too wide, the patient's eyelids should be carefully blotted with a tissue, and the front surface of the prism should be dried with lint-free material. An excessively wide fluorescein ring cause overestimation of IOP. IOP is recorded along with the date, time of day.

Gonioscopy was performed using a 2 mirror non-indentation indirect gonioscope (Goldmann 905 2- Mirror Lens) by a glaucoma specialist with more than 8 years' experience in a dimly lit room. Patient was positioned on slit lamp and after topical anaesthesia, the two mirror gonioscope was placed over the cornea using lubricants as bridging agent and rotated to see angles using slit-lamp illumination and magnification. In situ gonioscopy was performed without indentation or manipulation. The examination

was performed in primary gaze with the height of the slit beam decreased to 1-2 mm so that it does not impinge on the pupil and cause pupillary constriction (with attendant artefactual opening of the angle).

The two mirror gonioscope was used so as not to cause inadvertent indentation. If the posterior trabecular mesh work is not visible on in situ gonioscopy, “over the hill” view where the patient is asked to look towards the mirror in order to view the angle above the ‘hill’ of the iris in the corresponding quadrant was performed. All patients had open angles on gonioscopy.We followed Modified Madhan Mohan grading in our study and all patients had a gonioscopy grading of 4 or more over 360 degrees with no evidence of peripheral anterior synechiae (83).

Central corneal thickness (CCT) measurements were taken in the undilated eye using a hand-held ultrasonic pachymeter probe (PachmateTM DGH 55, DGH Technology Inc, PA, USA) gently placed in the mid-pupillary axis of the cornea. The IOP was adjusted using the manufacturer's logarithm, which is based on Ehlers et al (84)

PICTURE 6 CENTRAL CORNEAL THICKNESS AND ADJUSTMENT IN IOP

Central Corneal Thickness (Microns)	Adjustment in IOP (mm Hg)
445	+7
455	+6
465	+6
475	+5
485	+4
495	+4
505	+3
515	+2
525	+1
535	+1
545	0
555	-1
565	-1
575	-2
585	-3
595	-4
605	-4
615	-5
625	-6
635	-6
645	-7

The Humphrey Field Analyzer II (ZIESS 750I, Carl Zeiss Meditec, Inc) was used for visual field assessment. Optical Coherence Tomography (OCT) scans for retinal nerve fiber layer thickness and macular thickness using as per standard protocol were performed on all patients using the swept source optical coherence tomography (TOPCON DRI TRITON PLUS SS OCT) which uses the wavelength of 1050 nm light source and scanning speed of 100,000 A scans

On day 1 of the study, eligible patients will be randomized in a 1:1 ratio by assigned number to either preservative free Travoprost 0.004% (ARM-A) or polyquaternium-1–preserved Travoprost 0.004% (ARM-B). The drugs were kept in the pharmacy**.** After a written informed consent by the PI, patients were sent to Guide who opened the envelopes in sequential order and dispensed the medicines as randomized.

Designated social worker was in charge of patient education, consenting and dispensing medications. She was also the 1st point of contact when the patient came for 2 week and 6 week follow up. At each visit, she would take the medication bottles from the patient, till the examination by principal investigator was over. Since the bottles are of different shapes, patients were instructed not to disclose the study medication to principal investigator. Individual patient files with all study data were kept locked but accessible till the end of study.

Those in Arm A, were started on Awarene PF eye drops and those in Arm B were started on Travatan eye drops. Patients were advised to keep the allotted medication in the refrigerator to ensure that the temperature is below 30^{0}C and instill the drops at the same time every day (9:00 pm +/- 30 minutes) for 6 weeks. Patients in both the groups were followed up after 2 weeks, during which time, IOP was measured. At this visit patient were questioned about the presence of any side effects. Those patients with inadequate reduction in IOP during this time were taken out of the study.

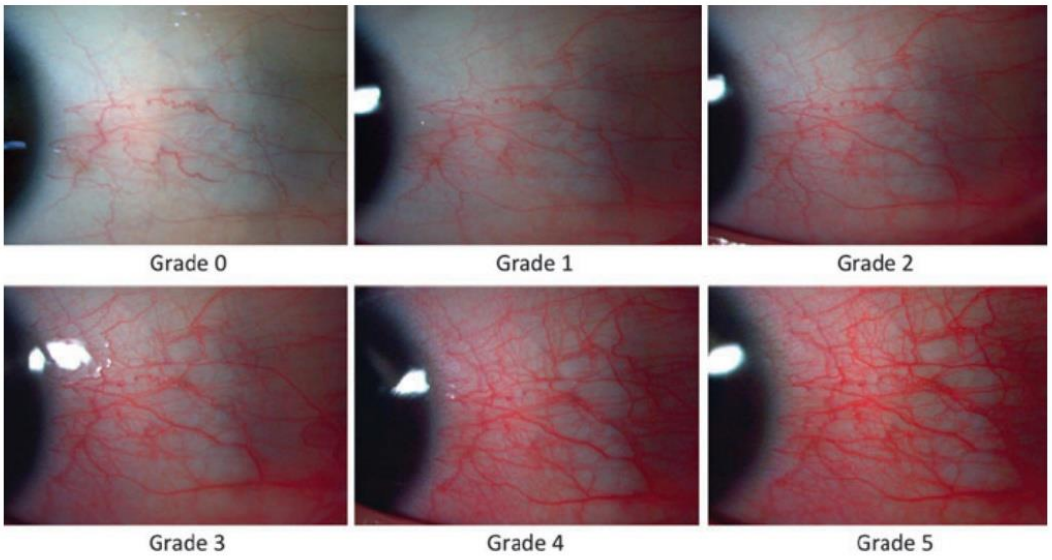
All patients were again followed up at 6 weeks. During this visit, a slit lamp photograph of conjunctival hyperemia, IOP measurement [at 09:00 Hours (±30min), 13:00 Hours (±30min), and 17:00 Hours (±30min)] and ocular surface evaluation including TBUT,

corneal staining fluorescein strip, Schirmer's 1a and conjunctival staining with Lissamine Green strip were performed similar to Day 1.

In addition, details of ocular adverse effects were noted as follows:

1. Conjunctival hyperemia grading done using standard clinical photograph as shown in figure below (85)

Picture 7 : Conjunctival hyperemia



2. Burning: Mild / Moderate / Severe
3. Watering: Mild / Moderate / Severe
4. Pain: Mild / Moderate / Severe
5. Pricking/foreign body sensation/irritation: Mild / Moderate / Severe
6. Sensation of dryness: Mild / Moderate / Severe
7. Itching, Swelling around the eyes: Mild / Moderate / Severe
8. Crusting of the lids: Mild / Moderate / Severe
9. Lengthening of eye lashes: Mild / Moderate / Severe

10. Increase in the number of eye lashes: Mild/ Moderate/ Severe
11. Darkening of eyelashes: Mild/ Moderate/ Severe
12. Darkening of eyelids: Mild/ Moderate/ Severe
13. Photophobia: Mild/ Moderate/ Severe
14. Blurring of vision: Mild/ Moderate/ Severe

With regard to the above symptomatology, the severity was classified based on the following criteria.

Mild: Did not interfere with activities of daily life

Moderate: Interfered with activities of daily life, but not severe enough to discontinue medication

Severe: Interfered significantly, enough to consider discontinuation of the medication by the PI or the patient

An adverse event was defined as any change from baseline in the patient's ophthalmic or medical health during the study. These events were obtained as investigator observations or complaints from the patient at each visit, and patients were removed from the study if the investigator presumed the patient to be at risk or if the patient chose to withdraw for any reason at any time during the study's duration. The patient was informed of the potential side effects and was asked to report to the 24-hour casualty in the Department of Ophthalmology, at which point the PI was notified. If the patient experienced a severe adverse event, the medication was discontinued. Further management was carried out in consultation with specialists. Following the study period, all patients were followed up and managed in the Glaucoma clinic in accordance with the standard operating procedure for glaucoma management.

DETAILED ALGORITHM OF THE STUDY

Patients with POAG and OHT who fulfilled the eligibility criteria were recruited for the study after a written informed consent. Patients were called to report to Principal investigator at 9:00 am on Day 1

↓

Patients were assigned screening numbers of 01 to 62 by a designated social worker. The list of patient numbers were already been generated by Biostastician Slit lamp photo of conjunctiva was taken by designated social worker

↓

IOP at 9:00 am, 1:00 pm amd 5:00 pm, complete ophthalmic evaluation, CCT, HFA 24-2, OCT RNFL, Gonioscopy, TBUT, Schirmer's 1a, Fluorescein and Lissamine green tests were performed by Principal investigator

↓

Sequentially numbered, sealed, opaque envelopes containing the code and protocol corresponding to one of the treatment groups prepared by Biostatistician were opened by the guide (LMA). Eligible patients were randomized in a 1:1 ratio by assigned number

↓

ARM A:-1 bottle of Awarene PF drops and ARM B-:2 bottles of TRAVATAN eye drops. Designated social worker were in charge of patient education, consenting and dispensing medications. Medications were stored in the pharmacy. Patient were advised to meet designated social worker at 2 week follow up .

↓

At 2 week follow up: Designated social worker monitored side effects from patient history, Collected drops and checked for compliance, PI checked IOP and given date for next appointment, Patients were counselled and , returned drops to the patient by designated social worker

↓

At 6 weeks follow up: Designated social worker collected drops and checked for compliance, slit lamp photo of conjunctival hyperemia was taken.
IOP at 9:00 am, 1:00 pm and 5:00 pm, complete ophthalmic evaluation,TBUT, Schirmer's 1a, Fluorescein and Lissamine green tests were performed by principal investigator and checked for adverse events

↓

Data Entry and Analysis
Further followed up of patients in the glaucoma clinic

Sample size calculation and statistical analysis:

This was a phase 3 clinical trial. The sample size was calculated based on the primary outcome measure i.e., the difference in the mean IOP at 6 weeks by treatment groups. Allowing for an estimated dropout rate of 10%, the sample size was planned to include a total of 62 patients in the study with 31 in each arm. This was based on a sample size calculation which suggested that including 31 participants in each of the study groups would give 80% power to detect a mean difference of 3 mm Hg between the two groups with a 5% significance level using a two-sided test and an estimated SD of 4 mmHg.

Given the Covid 19 pandemic and the reduced outpatient numbers during the last one year, we were not able to get adequate numbers for the study. Again, many patients refused to take part in the study due to the follow up that was required and the restrictions due to lockdown and the apprehension relayed to coming to hospitals during the pandemic. Hence for the presentation for thesis we have done statistical analysis with available data. We, however will continue the randomized controlled trial till we get the calculated sample size to get accurate scientific data.

Results are presented as means (SD) for normally distributed variables and as medians (IQR) for non-normally distributed variables. The baseline demographics as well as clinical characteristics of the intervention and the comparator group are presented and compared. The two-sample t-test was done comparing the IOP at 6 weeks between the groups. The average changes between baseline and 6 weeks, in primary and secondary

outcomes were calculated for each of the groups. We had planned to do the Intention-to-treat (ITT) analysis can be performed as the primary analysis on all primary and secondary outcomes. Unfortunately, it can be done after the last participant has ended participation and hence cannot be included in this dissertation.

RESULTS

Given the limitations in patient recruitment and follow up during the Covid 19 pandemic including stringent inclusion and exclusion criteria, we were not able to achieve the calculated sample size. Here we present our preliminary results on true available data. All patients who were willing to take part in the trial till October 2021 were included in the final analysis. We are continuing to recruit patients but their follow-up will not be completed before the final date of submission of this thesis.

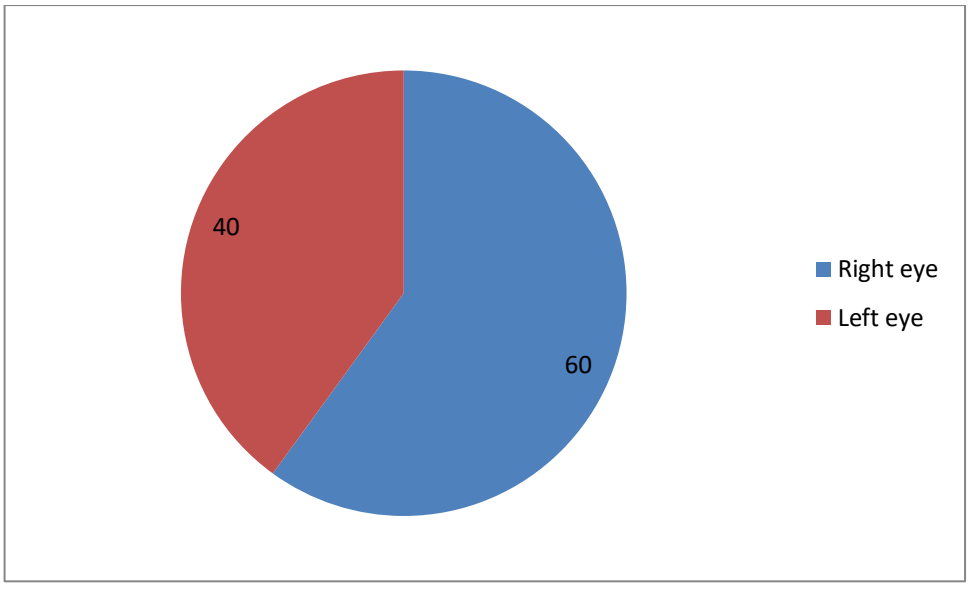
15 patients with POAG and ocular hypertension were randomized to receive either preservative free Travoprost 0.004% (Awarene® PF; Arm A) or polyquarternium-1 preserved Travoprost 0.004% (TRAVATAN*; Arm B). 8 patients were treated with Awarene® PF and 7 patients received TRAVATAN*. All patients were followed up at two and six weeks. Fischer exact test done for comparing categorical variables since more than 20% of the cells had expected count less than 5 and t test was used to compare the means of two arms.

The available results are detailed and also presented graphically as given below. Though the sample size has not been achieved, the number of patients in each group is similar as shown in Table 1.

Table.1: Distribution of patients (n=15)

STUDY ARM	n	%
ARM A: AWARENE®-PF	8	53.3
ARM B: TRAVATAN*	7	46.7

Figure.1: Distribution of study eyes



Left eyes of 6 patients had higher IOP or severe glaucomatous changes and right eyes of 2 patients had higher IOP or severe glaucomatous changes. Of the other 7 patients who

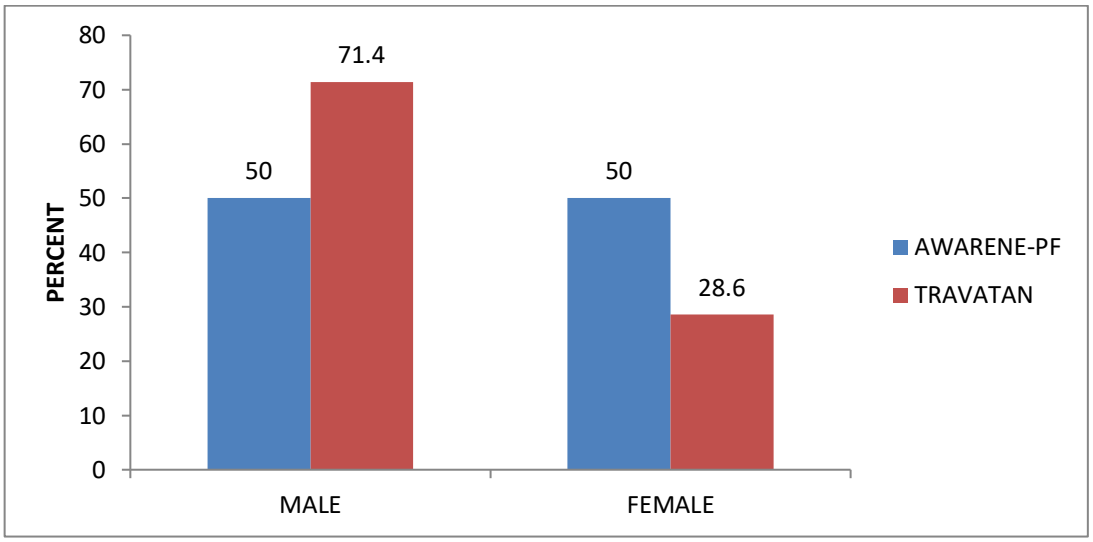
had with similar glaucoma in both eyes, the right eye was chosen as study eye. Thus 60% of the eyes were right eye and the rest were left eyes.

The gender-wise distribution of patients included in our study is given in Table 2. It is depicted graphically in Figure 2. There were equal number of male and female patients Though there were more male patients in Arm B, there is no statistically significant difference between the male and female patient distribution in either group(p=0.398).

Table 2: Gender-wise distribution of patients

GENDER	AWARENE®-PF(n=8)		TRAVATAN* (n=7)	
	n	%	n	%
MALE	4	50	5	71.4
FEMALE	4	50	2	28.6

Figure 2: Gender distribution:



The mean age in Arm A is 59.6 years and that in Arm B is 58.1 years. The age ranged from 44-71years in the AWARENE® group and from 46-65 years in the TRAVATAN* group, which is the age group of patients who develop POAG and OHT. This result also clearly shows that there is no discrepancy in the diagnosis of the patients included in our study. The details are as shown in Table 3.

Table 3: Age distribution among study patients

AGE	AWARENE-PF (In years)	TRAVATAN (In years)	p value
MEAN	59.6	58.1	0.734
S. D	9.25	6.91	
RANGE	44-71	46-65	

We did not exclude patients who had systemic diseases like diabetes, hypertension and chronic obstructive pulmonary disease (COPD) from our study. We ensured that our patients with hypertension were not on systemic beta blockers. Since beta blockers is part of the management protocol for all patients with ischemic heart disease in our institution, those patients with ischemic heart disease were excluded from our study. Table 4 shows the number and percentage of patients with diabetes in our study patients. 50% of patients in Arm A and 71.4% of patients in Arm B had diabetes mellitus. Even the higher percentage in Arm B was not statistically significant (p=0.398)

Table 4: Patients with associated diabetes mellitus

DIABETES MELLITUS		AWARENE®-PF	TRAVATAN	p value
PRESENT	n	4	5	0.398
	%	50.0%	71.4%	
ABSENT	n	4	2	
	%	50.0%	28.6%	

Table 5: Patients with associated systemic hypertension

SYSTEMIC HYPERTENSION		AWARENE® -PF	TRAVATAN*	p value
PRESENT	n	5	4	0.888
	%	62.5	57.1	
ABSENT	n	3	3	
	%	37.5	42.9	

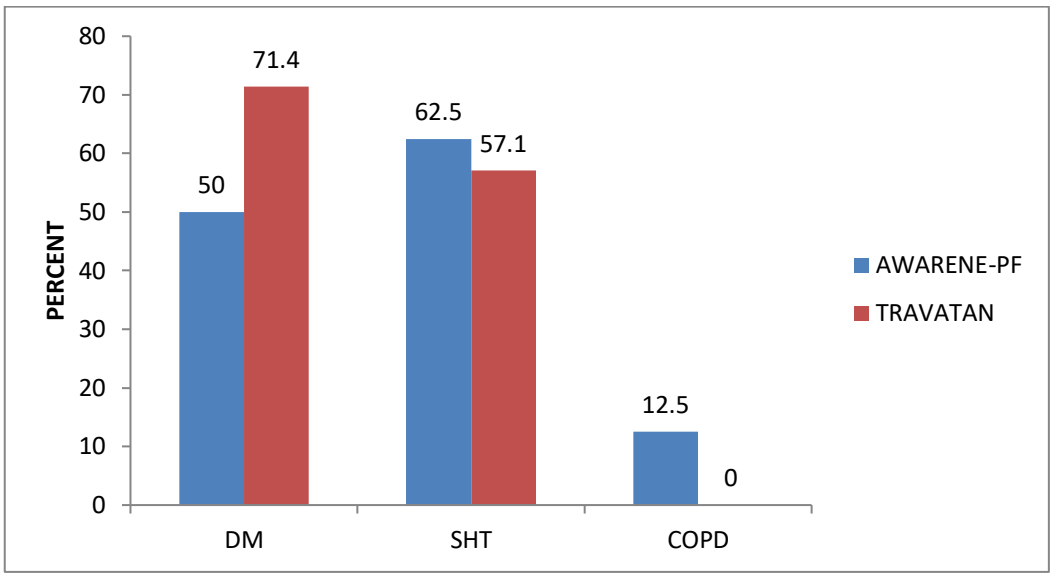
Table 5 shows the distribution of patients with hypertension. Similar number of patients had hypertension in both the arms (p=0.88). One patient in arm A had COPD. This is shown in Table 6.

Table 6: Patients with COPD

COPD		AWARENE®-PF n=8	TRAVATAN* n=7	p value
PRESENT	n	1	0	0.338
	%	12.5	0	
ABSENT	n	7	7	
	%	87.5	100	

Figure 3 presents the bar graph representing the percentage of patients in both arms with systemic comorbidities like diabetes, hypertension and COPD.

Figure 3: Graphic representation of major comorbidities



Other minor comorbidities that we included were dyslipidaemia and anaemia. In arm A, one patient had dyslipidaemia and one had anaemia. Both patients were undergoing treatment from their physicians. None of the patients in the TRAVATAN group had either of these comorbidities.

Table 7: Patients with other comorbidities

OTHER COMORBITIES		AWARENE®-PF n=8	TRAVATAN n=7	p value
PRESENT	n	2	0	0.155
	%	25	0	
ABSENT	n	6	7	
	%	75	100	

Of the 15 patients who were included in our study, 6 patients were diagnosed to have POAG (40%) and 9 patients, OHT (60%). The graphical representation of the same is given in Figure 4.

Figure 4: Clinical Diagnosis

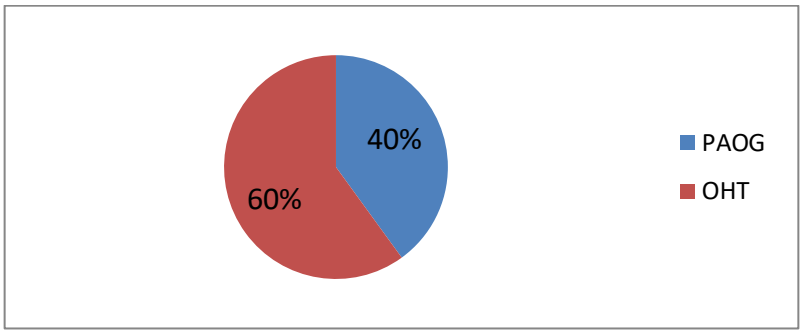


Table 8 shows the distribution of patients according to the clinical diagnosis in both the study arms. In Arm A, there were equal number of patients with POAG and OHT. In Arm B, 29% of patients had POAG. The difference was not statistically significant (p=0.398)

Table 8: Distribution of patients according to diagnosis

DIAGNOSIS		AWARENE®-PF n=8	TRAVATAN* n=7	p value
POAG	n	4	2	0.398
	%	50	28.6	
OHT	n	4	5	
	%	50	71.4	

At base line all patients underwent a complete ophthalmic examination including central corneal thickness (CCT) corrected IOP using Goldmann Applanation Tonometry, gonioscopy, dry eye evaluation and stereoscopic assessment of the optic nerve head using a 78 D condensing lens. All patients included in the study had open angles on gonioscopy. The comparison of all the other parameters in the two groups is given in Table 9.

Table 9: Examination results at baseline

EXAMINATION	AWARENE®-PF mean (SD)	TRAVATAN* mean (SD)	p value
TBUT (sec)	11(3.2)	11.71(2.69)	0.654
SCHIRMER TEST (mm)	23.6(9.1)	18.7(6.9)	0.258
CCT (microns)	499.7(23.3)	537.1(38.4)	0.038
Cup: disc ratio	0.46(0.22)	0.51(0.18)	0.634
Corrected IOP (mm Hg)	29.7(3.05)	29(3.65)	0.672

Table 9 clearly shows that both study groups were very similar in baseline dry eye evaluation parameters including TBUT (p=0.65) and Schirmer 1A (p=0.258). The cup disc ratio was also not statistically significantly different (p=0.63). The central corneal thickness was statistically significantly lower in Arm A as compared to Arm B (p=0.038). However, the corrected IOP was not statistically different (p=0.67).

Tear film break up time (TBUT) grading of DED was done for all patients on Day 1 and at 6 week follow up. On day 1, 75% in Arm A and 85 % in Arm B had normal TBUT. Suggestive of absence of DED. 25% of patients, in Arm A and 15% in Arm B had mild to moderate DED. This is presented in Figure 5 and Table 10.

Figure 5: TBUT grading on Day 1

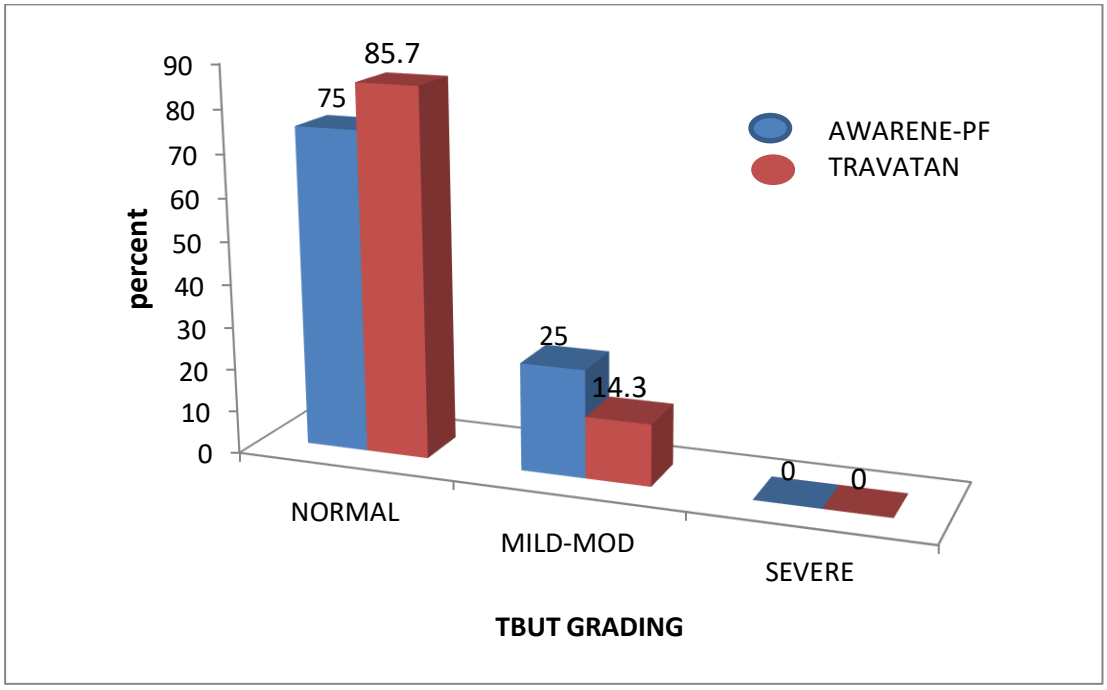


Table 10: TBUT grading on Day 1

Tear Film Break up Time (TBUT)			
GRADES	**AWARENE®-PF (n, %)**	**TRAVATAN* (n, %)**	p value
Normal	6 (75%)	6 (85.7%)	
Mild- Moderate	2 (25%)	1 (14.3%)	
Severe	0	0	0.605

DED was also evaluated using the presence and severity of superficial punctate keratitis (SPKs) in the study eyes on Day 1. Like TBUT 75% of eyes in Arm and 85% in Arm B had no SPKs. The rest had sparse SPKs. No eyes had moderate or severe disease. This is shown in Figure 6 and Table 11.

Figure 6: SPK grading at baseline

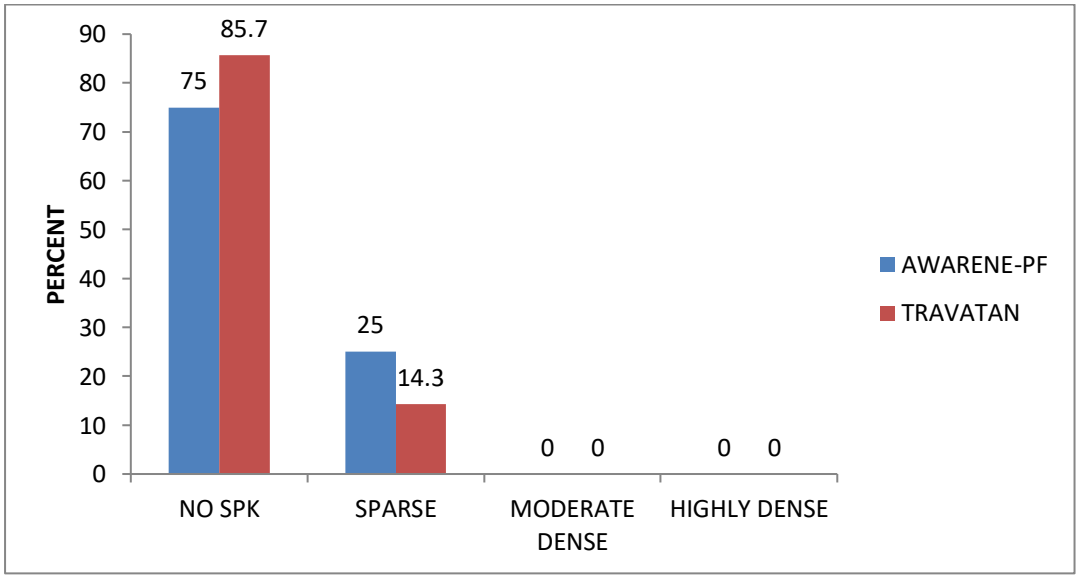


Table 11: SPK Grading at Baseline

Superficial Punctate Keratitis Grading			
GRADES	**AWARENE®-PF**	**TRAVATAN***	p value
No SPK	75	85.7	
Sparse	25	14.3	
Moderate dense	0	0	
Highly dense	0	0	0.605

Schirmer 1A was another test used to assess DED in these patients. On day 1 (Baseline) we have recorded very similar findings as with other tests. 25% of eyes in Arm A and 14.7 % of eye in Arm B showed mild DED according the Schirmer 1A. The rest were normal as shown in Figure 7 and Table 12.

Figure 7: Schirmer 1A at baseline

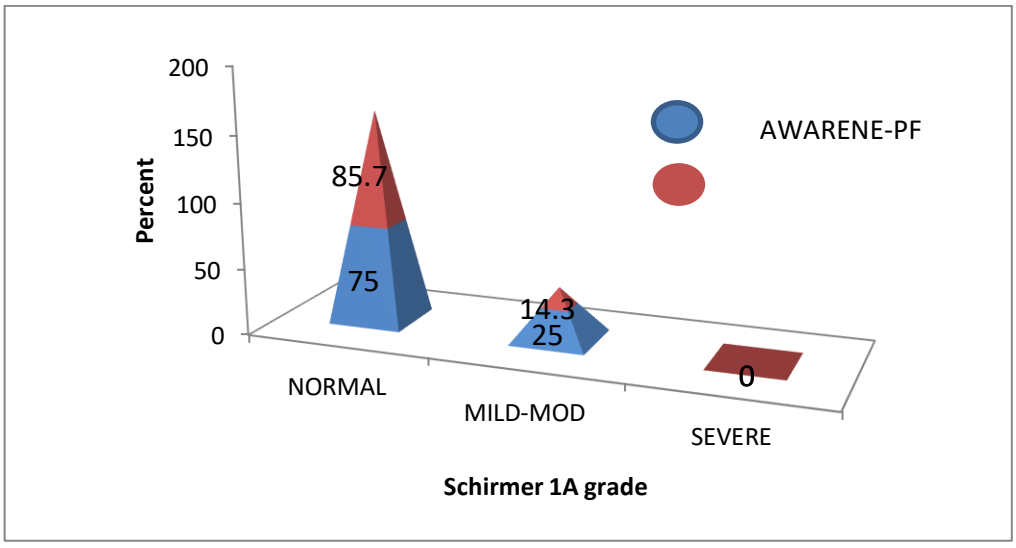


Table 12: Schirmer 1A at baseline

SCHIRMER 1A GRADING			
GRADES	**AWARENE®-PF**	**TRAVATAN***	p value
Normal	7 (87.5%)	7 (100%)	
Mild-Moderate	1 (12.5%)	0	
Severe	0	0	0.333

Figure 8 and Table 13 depict the grading of DED using Lissamine Green conjunctival staining. One out of 8 patients I Arm A had grade 1 or sparse conjunctival staining. None in Arm B had any conjunctival staining.

Figure 8: Grading using Lissamine Green conjunctival staining-Day 1

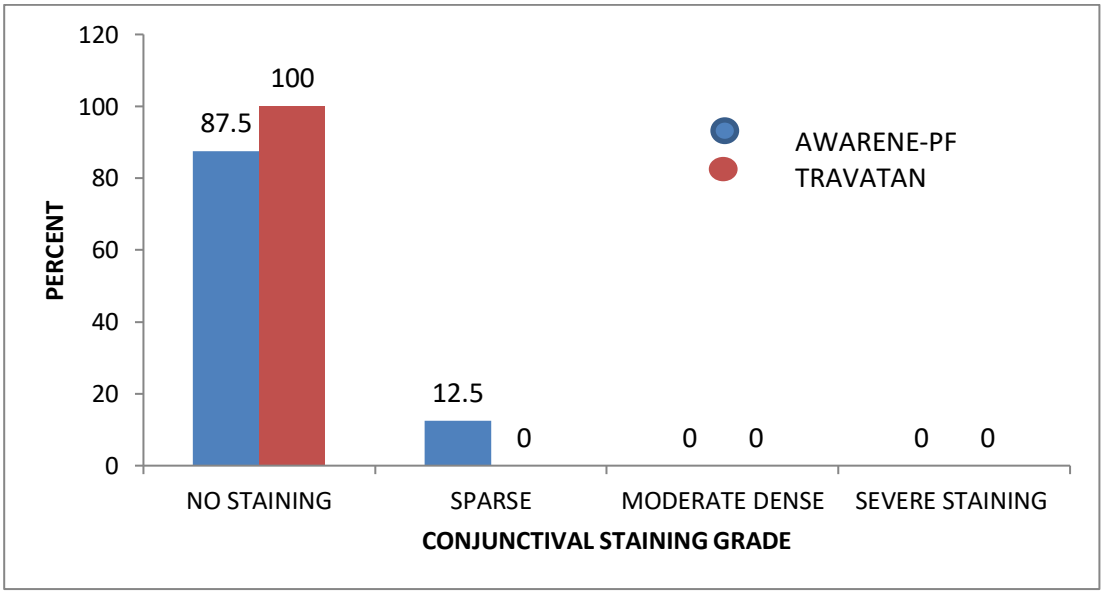


Table 13: Lissamine Green conjunctival staining-Day 1

CONJUNCTIVAL STAINING: LISSAMINE GREEN			
GRADES	**AWARENE®-PF**	**TRAVATAN***	p value
No staining	7 (87.5%)	7 (100%)	
Sparse	1 (12.5%)	0	
Moderate dense	0	0	
Severe staining	0	0	0.333

Of the 4 eyes with POAG in Arm A, one had nasal step defect, two had a superior arcuate scotoma and one had a double arcuate scotoma. In Arm B, one out of two eyes had superior arcuate scotoma and the other had unreliable fields. Table 14 summarises the above details including those with OHT who have normal visual fields.

Table 14: Visual Field Defects

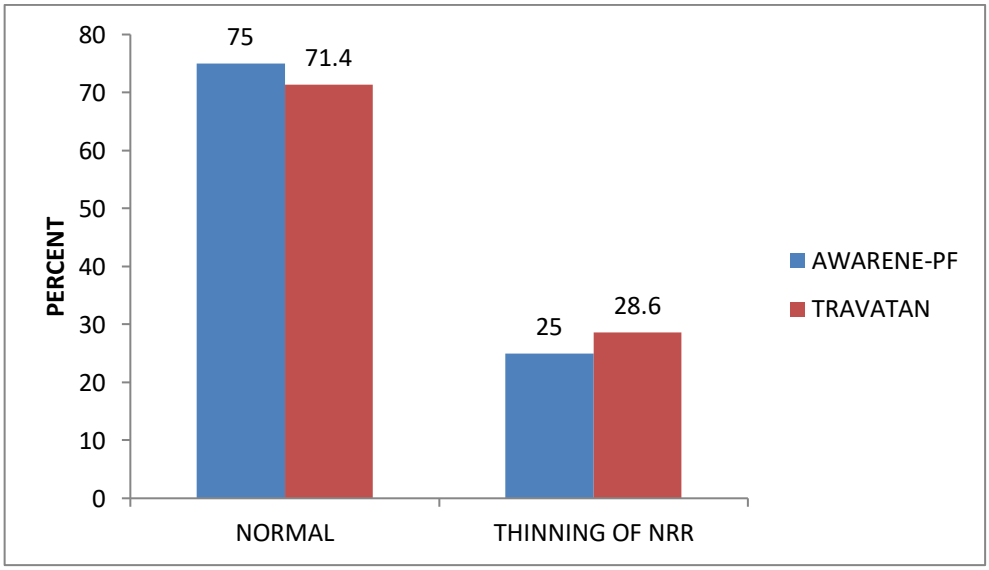
Visual Field Defects		AWARENE®-PF	TRAVATAN*	p value
Superior arcuate	n	2	1	0.494
	%	25%	14.3%	
Double arcuate	n	1	0	
	%	12.5%	0	
Nasal step	n	1	0	
	%	12.5%	0	
Normal	n	4	5	
	%	50%	71.4%	
Unreliable fields	n	0	1	
	%	0	14.3%	

Optical Coherence Tomography (OCT) of the retinal nerve fibre layer around the optic nerve head was performed for all patients. Among those with POAG, 4 out of the 6 patients had thinning of neuroretinal rim. The other 2 patients had normal NRR. Normal NRR was seen in all patients with OHT. This is shown in Table 15 and Figure 9.

Table 15: OCT of the Optic Nerve Head

OCT RNFL		AWARENE®-PF	TRAVATAN *	p value
Normal	n	6	5	0.876
	%	75%	71.4%	
Thinning of NRR	n	2	2	
	%	25%	28.6%	

Figure 9: OCT RNFL among study patients



The primary outcome measure of our study was IOP reduction following treatment for 6 weeks. We did follow up at 2 weeks to make sure that there is some therapeutic effect of the medication that was started and also to assess if there are any major adverse events. Those patients who did not respond to the study drug at 2 weeks would have been taken out of the trial. We compared the IOP at baseline to IOP at 2 weeks and at 6 weeks. The details are given in table 16. There was a significant reduction of IOP by 2 weeks with both AWARENE-PF (32%) and with TRAVATAN (28%). This reduction persisted at 6 weeks. 36% reduction in Arm and 27% IOP reduction in Arm B. However even at 6 weeks there was no statistically significant difference in mean IOP between the two arms.

Table 16: IOP at each follow up

IOP	AWARENE®-PF Mean (SD)	TRAVATAN* Mean (SD)	p value
Baseline	29.7(3.05)	29(3.65)	0.672
2 weeks	20.2(4.2)	20.1(4.1)	0.961
6 weeks	19.1(2.6)	21.2(2.26)	0.156

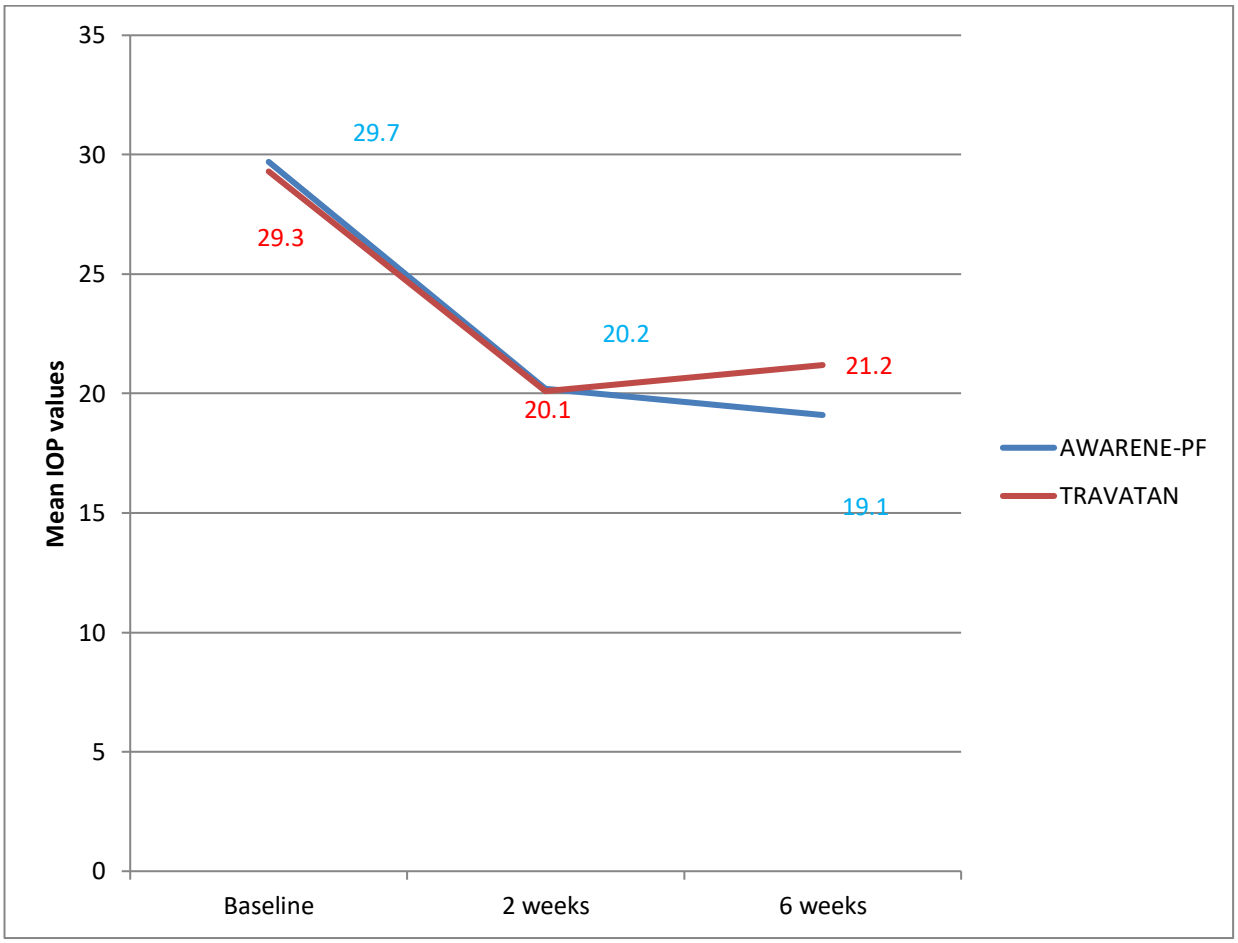
The mean IOP reduction from baseline at 2 weeks and 6 weeks in both arms is given in Table 17. Although the mean IOP reduction in Arm A is 2.7 mm Hg more than that of Arm B at 6 week follow up, the difference is not statistically significant (p=0.155).

Table 17: IOP reduction at each follow up

IOP reduction from baseline	AWARENE®-PF Mean (SD)	TRAVATAN* Mean (SD)	p value
2 weeks	9.5(6.25)	8.85(3.35)	0.813
6 weeks	10.5(3.84)	7.8(2.73)	0.155

We looked at the trend in IOP reduction from baseline to 6 weeks which is shown in Figure 10. Both Arms A and B show a very similar downward trend in mean IOP at 2 weeks follow up. This shows the efficacy of AWARENE® PF which is in comparison with TRAVATAN*. At six weeks, Arm B showed a very slight upward trend, though there was still a significant IOP reduction (27%) from baseline. This slight increase in IOP on TRAVATAN*, however, is not statistically significant. This also shows noninferiority of AWARENE®-PF when compared to the commonly prescribed TRAVATAN*.

Figure 10: Trend in mean IOP reduction



The secondary outcomes that we looked at were ocular surface abnormalities, like dry eye disease. The average changes between baseline and 6 weeks for secondary outcomes like TBUT and Schirmer 1A test were calculated for each of the groups. These are given in Tables 18 and 19.

Table 18: TBUT, Day 1 *vs* 6 weeks

TBUT (sec)	AWARENE®-PF mean (SD)	TRAVATAN* mean (SD)
Baseline	11(3.2)	11.71(2.69)
6 weeks	11.5(3.3)	13(3.1)
p value	0.762	0.411

Table 19: Schirmer 1A, Day 1 *vs* 6 weeks

SCHIRMER 1A (mm)	AWARENE®-PF mean (SD)	TRAVATAN* mean (SD)
Baseline	23.6(9.1)	18.7(6.9)
6 weeks	19.8(6.7)	19.8(9.6)
p value	0.3557	0.809

Using the severity grading for each of the parameters like TBUT, SPK, Schirmer 1A and Lissamine Green conjunctival staining, we looked for any increase ocular surface symptoms at 6 weeks as shown in Table 20. There was no major ocular surface complication in either Arm at 6 weeks when compared to baseline.

Table 20: Ocular surface parameters- Baseline *vs* 6 weeks

PARAMETERS	BASELINE (n, %)		6 WEEKS (n, %)	
TBUT	**AWARENE®-PF**	**TRAVATAN***	**AWARENE®-PF**	**TRAVATAN***
Normal	6, 75	6, 85.7	7, 87.5	7, 100
Mild - Moderate	2, 25	1, 14.3	1, 12.5	0
Severe	0	0	0	0
p value	1.000			
SPK GRADE	**AWARENE®-PF**	**TRAVATAN***	**AWARENE®-PF**	**TRAVATAN***
No SPK	75	85.7	6, 75	5,71.4
Sparse SPK	25	14.3	1,12.5	2, 2.86
Moderate SPK	0	0	1, 12.5	0
Highly dense	0	0	0	0
p value	0.605			
SCHIRMER 1A	**AWARENE®-PF**	**TRAVATAN***	**AWARENE®-PF**	**TRAVATAN***
Normal	7, 87.5	7, 100	7,87.5	7,100
Mild - moderate	0	0	1, 12.5	0,0
Severe	1, 12.5	0	0	0
p value	0.999			
LISSAMINE GREEN	**AWARENE®-PF**	**TRAVATAN***	**AWARENE®-PF**	**TRAVATAN***
NO STAINING	7, 87.5	7, 100	7, 87.5	6, 85.7
SPARSE	1, 12.5	0	0	1,14.3
MODERATE DENSE	0	0	1, 12.5	0
p value	0.999			

Using the OSDI, questionnaire we also looked at symptomatology related to topical AGMs and added preservatives. Table 21 shows that there is no significant difference the presence of any of the possible adverse effects in either group at 6 weeks. In Arm A one patient complained of dryness of the eyes and another had moderate burning sensation.

Table 21: Ocular adverse effects at 6 weeks

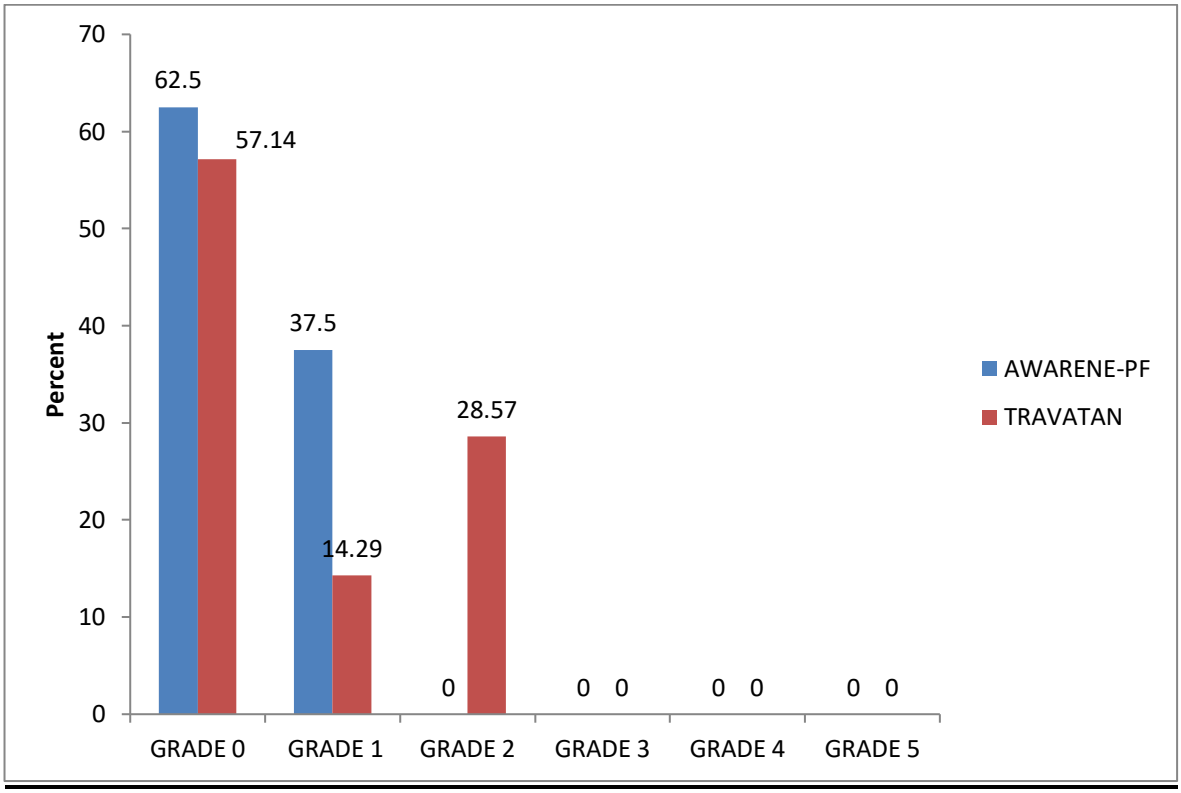
CLINICAL FINDING	AWARENE®-PF	TRAVATAN*	p value
Dryness			
Present	1,12.5	0	0.333
Absent	7,87.5	7,100	
Photophobia			
Present	0	0	-
Absent	8,100	7,100	
Burning sensation			
Present	1,12.5	0	0.333
Absent	7,87.5	7,100	
Watering of eye			
Present	0	0	-
Absent	8,100	7,100	
Pain			
Present	0	0	-
Absent	8,100	7,100	
Crusting of lid			
Present	0	0	-
Absent	8,100	7,100	
Lengthening of Lashes			
Present	0	0	-
Absent	8,100	7,100	
Increase in number of lashes			-
Present	0	0	
Absent	8,100	7,100	
Darkening of Lashes			-
Present	0	0	
Absent	8,100	7,100	
Swelling around the eye			-
Present	0	0	
Absent	8,100	7,100	

Table22: Conjunctival hyperaemia at 6 weeks

Conjunctival hyperemia	Awarene®-PF	TRAVATAN*	p value
Grade	n.%	n, %	
0	5,62.5	4.57.12	
1	3,37.5	1,14.29	0.384
2	0	2,28.59	
3	0	0	
4	0	0	
5	0	0	

Table 22 and figure 11 shows that none of the patients had conjunctival hyperaemia of ≥ grade 3 in both arms. 5 patients in arm A and 4 patients in arm B were normal with no conjunctival hyperaemia. 3 patients in Awarene® -PF arm and one patient in Travatan* group had grade one hyperaemia. None in Awarene® -PF arm and two patients in Travatan* arm had grade 2 hyperaemia. There was no significant difference in incidence of adverse effect of conjunctival hyperaemia in between the two arms. The images demonstrating conjunctival hyperaemia of patients belonging to both arms are given in appendix.

Figure 11: Distribution of conjunctival hyperemia among study patients



DISCUSSION

Prostaglandin analogues (PGs) have revolutionised the medical management of glaucoma and has been widely used more than 2 decades. Latanoprost 0.005% was the first prostaglandin analogue approved by the US FDA and subsequently by our authorities for topical use. Multicentric 3 phase trials in Indian eyes also proved improved efficacy of Latanoprost 0.005% in the late nineties and was approved for use in India. The main advantage of PGs over other available AGMs at that time like beta blockers (Timolol 0.5%) and pilocarpine 0.2% was the improved efficacy with more than 30% IOP reduction and improved compliance due to once daily dosing. Moreover, local and systemic side effects associated with the available medications were significant enough to affect the patients' quality of life. Given the inability to reach target IOP in advanced glaucoma and the difficulty in using systemic medications like acetazolamide and oral glycerol, long term, in the age group of patients with POAG, most patients with POAG underwent primary trabeculectomy.

The main disadvantages of latanoprost 0.005% were the high cost and stringent storage conditions as compared to cheaper available alternatives in developing countries. With improved economy and the availability of other PGs like Bimatoprost 0.03%, Travoprost 0.004% and Tafluprost 0.0015%, PGs have become the first line of management in POAG in our glaucoma practice.

Given the ease of storage as compared to Latanoprost and lesser side effects as compared to Bimatoprost, Travoprost is the preferred PG in our institution. The cost of all these three PGs is comparable. Decrease in goblet-cell density, conjunctival epithelial size, abnormal Schirmer's test TBUT after treatment have been reported with PG use.(86). Preservatives continue to be in extensive use in topical AGMs due to the convenience

they provide, regulatory requirements and the higher cost of alternatives. Preservatives provide stability of the molecule.(37). Initial preservative-free AGMs, were very expensive. Recent noninferiority studies demonstrated efficacy of these medications in randomized trials.(87)

This double-blind randomised control trial was designed to compare the efficacy and safety of preservative free Travoprost (AWARENE-PF) when compared to time tested Travoprost with polyquaternium -1 as preservative (TRAVATAN). Given the Covid 19 pandemic and its restrictions, we were unable to recruit patients who would fulfil the inclusion and exclusion criteria and follow up. So, our sample was only one fourth of calculated sample size. Thus, we had 8 patients randomised to receive AWARENE- PF arm A and 7 patients received TRAVATAN in ARM B.

The age and gender distribution in both arms were not statistically different which implies that both groups were comparable. Similarly, presence of systemic comorbidities like diabetes mellitus, systemic hypertension and COPD were similar in both groups. Hence these parameters also would not have had any effect on the final outcome of the study. Though the corneal thickness was statistically significantly different between the groups, with thinner CCT in Arm A, corrected IOP at baseline was not different. These findings confirm the similarity between the groups before starting treatment.

Our primary objectives were to determine the reduction in IOP after using either treatment at 6 weeks and to see if there is any difference between the two medications in terms of efficacy. Arm B, using TRAVATAN, at 6 week follow up demonstrated a 27% IOP reduction in this group of patients as was expected. The IOP reduction at 6 weeks

after starting AWARENE -PF was 36%, which was much more than that of TRAVATAN. This clearly shows the significant efficacy of both these preparations of travoprost. This reduction was, however not statistically significant. Whether this difference actually exists or not can be confirmed only if our sample size has the power to determine it. Our current sample is grossly inadequate to detect the presence or absence of any difference between the two groups.

Our secondary objectives focused on safety of the medications used in the study under the assumption that AWARENE -PF is superior to TRAVATAN because of the effect that preservatives may have on the ocular surface. Preservatives are essential to keep topical drugs sterile and hence they can't be avoided. All preservatives have been shown to impact both the structure and function of the ocular surface. Piscella et al., have shown that preservatives like BAK and polyquaternium, that serve as detergents, reduce the surface tension of the pre-corneal tear film by acting on the superficial lipid layer. This in turn permits aqueous layer to evaporate and mucin layer components to precipitate. Additionally, the toxic effect on the conjunctiva affects the number and function of conjunctival goblet cells, causing reduction in mucin production and reduce TBUT (88). Hence, we used tests to detect dry eye disease like TBUT and Schirmer test and also graded these and other ocular surface parameters like SPK and Lissamine Green (LG) conjunctival staining for both study arms at baseline. There was no clinically or statistically significant difference between the groups and hence were comparable.

Table 18 and 19 illustrates the mean TBUT and Schirmer 1A at baseline and 6 weeks. There is no statistically significant difference in both these parameters. Table 20 shows in detail that there is no significant difference in severity grading of TBUT, Schirmer

1A, SPK grading and LG conjunctival staining between two study arms at 6 weeks. Beneficial effects on tear production with less severe corneal staining and reduced inflammation were noticed following 7 days of therapy with preservative-free travoprost in a mouse model.(89)

In a large study on 4000 glaucoma patients in France, it was found that those on preservative-free drops had much reduced symptoms and indicators of ocular side effects compared to those on preserved drops. They also showed that reducing the number of preservatives or switching to preservative-free eye drops resulted in a significant reduction in symptoms (36). Our study showed no such difference in TBUT and Schirmer 1A, as well as conjunctival and corneal staining between two groups showing that preservative free eye drops are not superior to those with polyquaternium as preservative. The lack of adequate numbers obviously has a role to play in this outcome.

On comparing the ocular side effects like dryness, burning, photophobia, lengthening of lashes, crusting of lids, conjunctival hyperaemia, there was no significant difference between the two arms at 6 weeks after intervention. Uusitalo et al., presented the findings of two separate clinical phase III b investigations. Patients who had side effects while using latanoprost with preservative were switched to the drug without preservatives and monitored for 12 weeks. After six weeks of switching to preservative-free eye drops, there was a statistically significant decrease in symptoms like burning, stinging, foreign body sensation, itching, and dry eye sensation with a steady improvement. At 12-weeks, only 33% of preservative-free group had any ocular symptoms. The severity of conjunctival hyperemia reduced to half over 12-weeks of treatment. (90)

Shedden et al., in their RCT enrolled 261 patients with either POAG or OHT who were randomly assigned to receive either a dorzolamide/timolol without preservatives or with preservative. Both formulations were well tolerated, with no significant difference in side effects (91). There is hardly any data comparing polyquaternium preserved and preservative free AGMs unlike those with BAK as preservative. Polyquaternium is a BAK derivative which is considerably less harmful to the ocular tear film.

The pharmacodynamics and safety of preserved versus preservative-free AGMs were studied by Hamacher et al., in a randomized trial. Both medications well tolerated, with minor ocular side effects. (92) Gandolfi et al., studied 371 patients who were randomly assigned to receive either travoprost without preservatives (n=185) or travoprost with a preservative (n=186) once daily in the evening for three months. This study demonstrated non inferiority in the IOP lowering effect of preservative free travoprost(93).

One of the main disadvantages of preservative free medications is the higher cost due to stringent storage and use criteria. The cost price of 2.5 ml of TRAVATAN* is Rs. 689/- and that of 5 ml of Awarene PF® is Rs.590/- with no stringent storage criteria. Given the long duration of treatment, Awarene PF® is more economically viable for a patient with POAG in a country like ours.

LIMITATIONS

- Due to Covid 19 pandemic and government restrictions and lock down, we were unable to recruit all patients who would fulfil all the inclusion and exclusion criteria. Moreover, we were not able to recruit those who had trouble in coming for follow-up. Hence the number of patients that we could recruit till October 2021 was far below the calculated sample size. This small sample size would have altered the significance of the results of our study.

- From available data we feel that a longer follow up of at least 6 months would be required to detect any difference in ocular surface symptoms and signs if any. 6 weeks may be too short a time to demonstrate preservative induced damage in patients who do not have any ocular surface disease at baseline.

- This randomized controlled trial will need to be continued to achieve adequate sample size and then analyzed for definitive results

CONCLUSION

- Travoprost 0.004% preserved with polyquarternium-1 (TRAVATAN*) produced adequate IOP reduction in patients with POAG and OHT from 2 weeks to 6 weeks follow up
- Preservative free Travoprost 0.004% (Awarene PF®) caused more than 30% IOP reduction in patients with POAG and OHT from 2 weeks to 6 weeks follow up
- There was no statistically significant difference in IOP reduction at 2-6 weeks follow up between both medications
- There were no significant ocular side effects and surface changes in eyes with TRAVATAN* even up to 6 weeks.
- There were no significant ocular side effects and surface changes in eyes with Awarene PF® up to 6 weeks.
- There was no statistically significant difference in ocular side effects and surface changes at 6 weeks follow up between eyes on either medication.

BIBLIOGRAPHY

1. Glaucoma Blindness at a Tertiary Eye Care Center - PubMed [Internet]. [cited 2021 Dec 2]. Available from: https://pubmed.ncbi.nlm.nih.gov/26509509/

2. Tham Y-C, Li X, Wong TY, Quigley HA, Aung T, Cheng C-Y. Global Prevalence of Glaucoma and Projections of Glaucoma Burden through 2040. Ophthalmology. 2014 Nov;121(11):2081–90.

3. Krieglstein GK. Becker–Shaffer's Diagnosis and Therapy of the Glaucomas (8th Edition) Eds: Robert L Stamper, Marc F Lieberman and Michael V Drake 2009 568pp., Hardcover ISBN: 9780323023948 Mosby Elsevier. Graefes Arch Clin Exp Ophthalmol. 2011 Aug 1;249(8):1271–2.

4. Dietlein TS, Hermann MM, Jordan JF. The Medical and Surgical Treatment of Glaucoma. Dtsch Arztebl Int. 2009 Sep;106(37):597–606.

5. Holló G. The side effects of the prostaglandin analogues. Expert Opin Drug Saf. 2007 Jan;6(1):45–52.

6. Jutley G, Luk SM, Dehabadi MH, Cordeiro MF. Management of glaucoma as a neurodegenerative disease. Neurodegener Dis Manag. 2017 Apr;7(2):157–72.

7. George R, Ve RS, Vijaya L. Glaucoma in India: Estimated Burden of Disease. Journal of Glaucoma. 2010 Aug;19(6):391–7.

8. Ramakrishnan R, Nirmalan PK, Krishnadas R, Thulasiraj RD, Tielsch JM, Katz J, et al. Glaucoma in a rural population of southern India: the Aravind comprehensive eye survey. Ophthalmology. 2003 Aug;110(8):1484–90.

9. Jacob A, Thomas R, Koshi SP, Braganza A, Muliyil J. Prevalence of primary glaucoma in an urban South Indian population. Indian Journal of Ophthalmology. 1998 Jun 1;46(2):81.

10. Denis P, Covert D, Realini A. Travoprost in the management of open-angle glaucoma and ocular hypertension. Clin Ophthalmol. 2007 Mar;1(1):11–24.

11. Kass MA. The Ocular Hypertension Treatment Study: A Randomized Trial Determines That Topical Ocular Hypotensive Medication Delays or Prevents the Onset of Primary Open-Angle Glaucoma. Arch Ophthalmol. 2002 Jun 1;120(6):701.

12. Heijl A, Leske MC, Bengtsson B, Hyman L, Bengtsson B, Hussein M, et al. Reduction of intraocular pressure and glaucoma progression: results from the Early Manifest Glaucoma Trial. Arch Ophthalmol. 2002 Oct;120(10):1268–79.

13. Wybar K. Wolff's Anatomy of the Eye and Orbit. Br J Ophthalmol. 1977 Apr;61(4):302.

14. Cole DF. Adler's Physiology of the Eye: Clinical Application. Br J Ophthalmol. 1982 Nov;66(11):743.

15. Sihota R, Angmo D, Ramaswamy D, Dada T. Simplifying "target" intraocular pressure for different stages of primary open-angle glaucoma and primary angle-closure glaucoma. Indian Journal of Ophthalmology. 2018 Apr;66(4):495–505.

16. European Glaucoma Society, editor. Terminology and guidelines for glaucoma. 4th ed. Savona: PubliComm; 2014. 195 p.

17. Primary Open-Angle Glaucoma PPP 2020 - American Academy of Ophthalmology [Internet]. [cited 2021 Dec 10]. Available from: https://www.aao.org/preferred-practice-pattern/primary-open-angle-glaucoma-ppp

18. 4th Consensus Meeting: Intraocular Pressure [Internet]. World Glaucoma Association. [cited 2021 Dec 10]. Available from: https://wga.one/wga/consensus-4/

19. Grant WM, Burke JF. Why do some people go blind from glaucoma? Ophthalmology. 1982 Sep;89(9):991–8.

20. Odberg T. Visual field prognosis in advanced glaucoma. Acta Ophthalmologica. 2009 May 28;65:27–9.

21. European Glaucoma Society Terminology and Guidelines for Glaucoma, 4th Edition - Chapter 2: Classification and terminologySupported by the EGS Foundation. Br J Ophthalmol. 2017 May;101(5):73–127.

22. Shih CY, Zivin JSG, Trokel SL, Tsai JC. Clinical Significance of Central Corneal Thickness in the Managementof Glaucoma. Archives of Ophthalmology. 2004 Sep 1;122(9):1270–5.

23. Wei W, Fan Z, Wang L, Li Z, Jiao W, Li Y. Correlation Analysis between Central Corneal Thickness and Intraocular Pressure in Juveniles in Northern China: The Jinan City Eye Study. PLoS One. 2014 Aug 22;9(8):e104842.

24. Tonnu P-A, Ho T, Newson T, Sheikh AE, Sharma K, White E, et al. The influence of central corneal thickness and age on intraocular pressure measured by pneumotonometry, non-contact tonometry, the Tono-Pen XL, and Goldmann applanation tonometry. British Journal of Ophthalmology. 2005 Jul 1;89(7):851–4.

25. Goel M, Picciani RG, Lee RK, Bhattacharya SK. Aqueous Humor Dynamics: A Review. Open Ophthalmol J. 2010 Sep 3;4:52–9.

26. Stefan C, Dumitrica DM, Tebeanu E, Nae I, Sapundgieva A, Dragomir L. [Prostaglandin analogues and central corneal thickness]. Oftalmologia. 2007;51(4):95–9.

27. Bafa M, Georgopoulos G, Mihas C, Stavrakas P, Papaconstantinou D, Vergados I. The effect of prostaglandin analogues on central corneal thickness of patients with chronic open-angle glaucoma: a 2-year study on 129 eyes. Acta Ophthalmol. 2011 Aug;89(5):448–51.

28. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between control of intraocular pressure and visual field deterioration.The AGIS Investigators. Am J Ophthalmol. 2000 Oct;130(4):429–40.

29. van der Valk R, Webers CAB, Schouten JSAG, Zeegers MP, Hendrikse F, Prins MH. Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials. Ophthalmology. 2005 Jul;112(7):1177–85.

30. Prum BE, Rosenberg LF, Gedde SJ, Mansberger SL, Stein JD, Moroi SE, et al. Primary Open-Angle Glaucoma Preferred Practice Pattern(®) Guidelines. Ophthalmology. 2016 Jan;123(1):P41–111.

31. Broadway DC. Adverse Effects of Topical Antiglaucoma Medication: I. The Conjunctival Cell Profile. Arch Ophthalmol. 1994 Nov 1;112(11):1437.

32. Goto Y. Human Lens Epithelial Cell Damage and Stimulation of Their Secretion of Chemical Mediators by Benzalkonium Chloride Rather Than Latanoprost and Timolol. Arch Ophthalmol. 2003 Jun 1;121(6):835.

33. Mundorf T, Wilcox KA, Ousler GW, Welch D, Abelson MB. Evaluation of the comfort of Alphagan® P compared with Alphagan® in irritated eyes. Adv Therapy. 2003 Nov;20(6):329–36.

34. Servat JJ, Bernardino CR. Effects of common topical antiglaucoma medications on the ocular surface, eyelids and periorbital tissue. Drugs Aging. 2011 Apr 1;28(4):267–82.

35. Moreno M, Villena A, Cabarga C, Sanchez-Font E, Garcia-Campos J. Impression cytology of the conjunctival epithelium after antiglaucomatous treatment with latanoprost. Eur J Ophthalmol. 2003 Jul;13(6):553–9.

36. Walsh K, Jones L. The use of preservatives in dry eye drops. Clin Ophthalmol. 2019 Aug 1;13:1409–25.

37. Steven DW, Alaghband P, Lim KS. Preservatives in glaucoma medication. Br J Ophthalmol. 2018 Nov;102(11):1497–503.

38. Freeman PD, Kahook MY. Preservatives in topical ophthalmic medications: historical and clinical perspectives. Expert Review of Ophthalmology. 2009 Feb 1;4(1):59–64.

39. Datta S, Baudouin C, Brignole-Baudouin F, Denoyer A, Cortopassi GA. The Eye Drop Preservative Benzalkonium Chloride Potently Induces Mitochondrial Dysfunction and Preferentially Affects LHON Mutant Cells. Invest Ophthalmol Vis Sci. 2017 Apr;58(4):2406–12.

40. Pisella PJ, Pouliquen P, Baudouin C. Prevalence of ocular symptoms and signs with preserved and preservative free glaucoma medication. Br J Ophthalmol. 2002 Apr;86(4):418–23.

41. Jaenen N, Baudouin C, Pouliquen P, Manni G, Figueiredo A, Zeyen T. Ocular symptoms and signs with preserved and preservative-free glaucoma medications. Eur J Ophthalmol. 2007 Jun;17(3):341–9.

42. Janulevičienė I, Derkač I, Grybauskiene L, Paulauskaitė R, Gromnickaite R, Kuzmienė L. Effects of preservative-free tafluprost on tear film osmolarity, tolerability, and intraocular pressure in previously treated patients with open-angle glaucoma. Clin Ophthalmol. 2012;6:103–9.

43. Clouzeau C, Godefroy D, Riancho L, Rostène W, Baudouin C, Brignole-Baudouin F. Hyperosmolarity potentiates toxic effects of benzalkonium chloride on conjunctival epithelial cells in vitro. Mol Vis. 2012;18:851–63.

44. Sherwood MB, Grierson I, Millar L, Hitchings RA. Long-term morphologic effects of antiglaucoma drugs on the conjunctiva and Tenon's capsule in glaucomatous patients. Ophthalmology. 1989 Mar;96(3):327–35.

45. Broadway DC, Grierson I, O'Brien C, Hitchings RA. Adverse effects of topical antiglaucoma medication. I. The conjunctival cell profile. Arch Ophthalmol. 1994 Nov;112(11):1437–45.

46. Herreras JM, Pastor JC, Calonge M, Asensio VM. Ocular surface alteration after long-term treatment with an antiglaucomatous drug. Ophthalmology. 1992 Jul;99(7):1082–8.

47. Baudouin C, Hamard P, Liang H, Creuzot-Garcher C, Bensoussan L, Brignole F. Conjunctival epithelial cell expression of interleukins and inflammatory markers in glaucoma patients treated over the long term. Ophthalmology. 2004 Dec 1;111(12):2186–92.

48. Baudouin C, Liang H, Bremond-Gignac D, Hamard P, Hreiche R, Creuzot-Garcher C, et al. CCR 4 and CCR 5 expression in conjunctival specimens as differential markers of T(H)1/ T(H)2 in ocular surface disorders. J Allergy Clin Immunol. 2005 Sep;116(3):614–9.

49. Baudouin C. Detrimental effect of preservatives in eyedrops: implications for the treatment of glaucoma. Acta Ophthalmol. 2008 Nov;86(7):716–26.

50. Pisella P-J, Debbasch C, Hamard P, Creuzot-Garcher C, Rat P, Brignole F, et al. Conjunctival proinflammatory and proapoptotic effects of latanoprost and preserved and unpreserved timolol: an ex vivo and in vitro study. Invest Ophthalmol Vis Sci. 2004 May;45(5):1360–8.

51. Martone G, Frezzotti P, Tosi GM, Traversi C, Mittica V, Malandrini A, et al. An in vivo confocal microscopy analysis of effects of topical antiglaucoma therapy with preservative on corneal innervation and morphology. Am J Ophthalmol. 2009 Apr;147(4):725-735.e1.

52. Iester M, Telani S, Frezzotti P, Motolese I, Figus M, Fogagnolo P, et al. Ocular surface changes in glaucomatous patients treated with and without preservatives beta-blockers. J Ocul Pharmacol Ther. 2014 Aug;30(6):476–81.

53. Uusitalo H, Chen E, Pfeiffer N, Brignole-Baudouin F, Kaarniranta K, Leino M, et al. Switching from a preserved to a preservative-free prostaglandin preparation in topical glaucoma medication. Acta Ophthalmol. 2010 May;88(3):329–36.

54. Nasser L, Rozycka M, Gomez Rendon G, Navas A. Real-life results of switching from preserved to preservative-free artificial tears containing hyaluronate in patients with dry eye disease. Clin Ophthalmol. 2018;12:1519–25.

55. Gandolfi S, Paredes T, Goldberg I, Coote M, Wells A, Volksone L, et al. Comparison of a travoprost BAK-free formulation preserved with polyquaternium-1 with BAK-preserved travoprost in ocular hypertension or open-angle glaucoma. Eur J Ophthalmol. 2012 Feb;22(1):34–44.

56. Peace JH, Ahlberg P, Wagner M, Lim JM, Wirta D, Branch JD. Polyquaternium-1–Preserved Travoprost 0.003% or Benzalkonium Chloride–Preserved Travoprost 0.004% for Glaucoma and Ocular Hypertension. American Journal of Ophthalmology. 2015 Aug;160(2):266-274.e1.

57. Aihara M, Ikeda Y, Mizoue S, Arakaki Y, Kita N, Kobayashi S, et al. Effect of Switching to Travoprost Preserved With SofZia in Glaucoma Patients With Chronic Superficial Punctate Keratitis While Receiving BAK-preserved Latanoprost. J Glaucoma. 2016 Jun;25(6):e610-614.

58. Codling CE, Maillard J-Y, Russell AD. Aspects of the antimicrobial mechanisms of action of a polyquaternium and an amidoamine. J Antimicrob Chemother. 2003 May;51(5):1153–8.

59. Good RM, Liao JC, Hook MJ, Punko CL. Colorimetric determination of a polymeric quaternary ammonium antimicrobial preservative in an ophthalmic solution. J Assoc Off Anal Chem. 1987 Dec;70(6):979–80.

60. Gibbs DE, Stein JM, Rockett J, Nicovich-Cushing G, Anderson M, Carmichael C. Opti-Free chemical disinfectant: a safety study with various soft contact lenses. CLAO J. 1989 Mar;15(1):57–60.

61. Baudouin C, Labbé A, Liang H, Pauly A, Brignole-Baudouin F. Preservatives in eyedrops: the good, the bad and the ugly. Prog Retin Eye Res. 2010 Jul;29(4):312–34.

62. López Bernal D, Ubels JL. Quantitative evaluation of the corneal epithelial barrier: effect of artificial tears and preservatives. Curr Eye Res. 1991 Jul;10(7):645–56.

63. Kahook MY, Ammar DA. In vitro toxicity of topical ocular prostaglandin analogs and preservatives on corneal epithelial cells. J Ocul Pharmacol Ther. 2010 Jun;26(3):259–63.

64. Whitson JT, Ochsner KI, Moster MR, Sullivan EK, Andrew RM, Silver LH, et al. The safety and intraocular pressure-lowering efficacy of brimonidine tartrate 0.15% preserved with polyquaternium-1. Ophthalmology. 2006 Aug;113(8):1333–9.

65. Brignole-Baudouin F, Riancho L, Liang H, Baudouin C. Comparative in vitro toxicology study of travoprost polyquad-preserved, travoprost BAK-preserved, and latanoprost BAK-preserved ophthalmic solutions on human conjunctival epithelial cells. Curr Eye Res. 2011 Nov;36(11):979–88.

66. Rolando M, Crider JY, Kahook MY. Ophthalmic preservatives: focus on polyquaternium-1. Expert Opin Drug Deliv. 2011 Nov;8(11):1425–38.

67. Ammar DA, Noecker RJ, Kahook MY. Effects of benzalkonium chloride-preserved, polyquad-preserved, and sofZia-preserved topical glaucoma medications on human ocular epithelial cells. Adv Therapy. 2010 Nov;27(11):837–45.

68. Kaur IP, Kanwar M. Ocular preparations: the formulation approach. Drug Dev Ind Pharm. 2002 May;28(5):473–93.

69. Marsovszky L, Resch MD, Visontai Z, Németh J. Confocal microscopy of epithelial and langerhans cells of the cornea in patients using travoprost drops containing two different preservatives. Pathol Oncol Res. 2014 Jul;20(3):741–6.

70. Tang W, Zhang F, Liu K, Duan X. Efficacy and safety of prostaglandin analogues in primary open-angle glaucoma or ocular hypertension patients: A meta-analysis. Medicine. 2019 Jul;98(30):e16597.

71. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo C-K, et al. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017 Jul;15(3):276–83.

72. Rossi GCM, Scudeller L, Rolle T, Pasinetti GM, Bianchi PE. From benzalkonium chloride-preserved Latanoprost to Polyquad-preserved Travoprost: a 6-month study on ocular surface safety and tolerability. Expert Opinion on Drug Safety. 2015 May 4;14(5):619–23.

73. Garcia-Feijoo J, Sampaolesi JR. A multicenter evaluation of ocular surface disease prevalence in patients with glaucoma. Clin Ophthalmol. 2012;6:441–6.

74. Nenciu A, Stefan C, Ardelean C. [Structural and immunohistochemical changes of conjunctiva induced by topical glaucoma medication]. Oftalmologia. 2004 Jan 1;48(1):35–42.

75. Bell N, Rosin L. Preservative toxicity in glaucoma medication: clinical evaluation of benzalkonium chloride-free 0.5% timolol eye drops. OPTH. 2013 Oct;2131.

76. Katz, Springs C, Craven, Montecchi-Palmer. Ocular surface disease in patients with glaucoma or ocular hypertension treated with either BAK-preserved latanoprost or BAK-free travoprost. OPTH. 2010 Nov;1253.

77. Shimazaki J. Definition and Diagnostic Criteria of Dry Eye Disease: Historical Overview and Future Directions. Investigative Ophthalmology & Visual Science. 2018 Nov 27;59(14):DES7–12.

78. Schiffman RM, Christianson MD, Jacobsen G, Hirsch JD, Reis BL. Reliability and Validity of the Ocular Surface Disease Index. Archives of Ophthalmology. 2000 May 1;118(5):615–21.

79. Leung EW, Medeiros FA, Weinreb RN. Prevalence of Ocular Surface Disease in Glaucoma Patients. Journal of Glaucoma. 2008 Aug;17(5):350–5.

80. Lemp MA. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes. CLAO J. 1995 Oct;21(4):221–32.

81. Baudouin C, de Lunardo C. Short term comparative study of topical 2% carteolol with and without benzalkonium chloride in healthy volunteers. British Journal of Ophthalmology. 1998 Jan 1;82(1):39–42.

82. Ehlers N, Bramsen T, Sperling S. APPLANATION TONOMETRY AND CENTRAL CORNEAL THICKNESS. Acta Ophthalmologica. 2009 May 27;53(1):34–43.

83. Krieglstein GK. Becker–Shaffer's Diagnosis and Therapy of the Glaucomas (8th Edition) Eds: Robert L Stamper, Marc F Lieberman and Michael V Drake 2009 568pp., Hardcover ISBN: 9780323023948 Mosby Elsevier. Graefes Arch Clin Exp Ophthalmol. 2011 Aug 1;249(8):1271–2.

84. Wells M, Wu N, Kokkinakis J, Sutton G. Correlation of central corneal thickness measurements using Topcon TRK-1P, Zeiss Visante AS-OCT and DGH Pachmate 55 handheld ultrasonic pachymeter. Clin Exp Optom. 2013 Jul;96(4):385–7.

85. Aihara M, Ikeda Y, Mizoue S, Arakaki Y, Kita N, Kobayashi S. Effect of Switching to Travoprost Preserved With SofZia in Glaucoma Patients With Chronic Superficial Punctate Keratitis While Receiving BAK-preserved Latanoprost: Journal of Glaucoma. 2016 Jun;25(6):e610–4.

86. Russ HH, Nogueira-Filho PA, de Nadai Barros J, de Faria NVL, Montiani-Ferreira F, Gomes JÁP, et al. Ocular surface evaluation in patients treated with a fixed combination of prostaglandin analogues with 0.5% timolol maleate topical monotherapy: a randomized clinical trial. Clinics (Sao Paulo). 2013 Oct;68(10):1318–24.

87. Hahn S. Understanding noninferiority trials. Korean J Pediatr. 2012 Nov;55(11):403–7.

88. Zhang X, Jeyalatha M V, Qu Y, He X, Ou S, Bu J, et al. Dry Eye Management: Targeting the Ocular Surface Microenvironment. Int J Mol Sci. 2017 Jun 29;18(7):1398.

89. Barabino S, Antonelli S, Cimbolini N, Mauro V, Bouzin M. The Effect of Preservatives and Antiglaucoma Treatments on the Ocular Surface of Mice With Dry Eye. Investigative Ophthalmology & Visual Science. 2014 Oct 14;55(10):6499–504.

90. Pflugfelder SC, Baudouin C. Challenges in the clinical measurement of ocular surface disease in glaucoma patients. Clin Ophthalmol. 2011;5:1575–83.

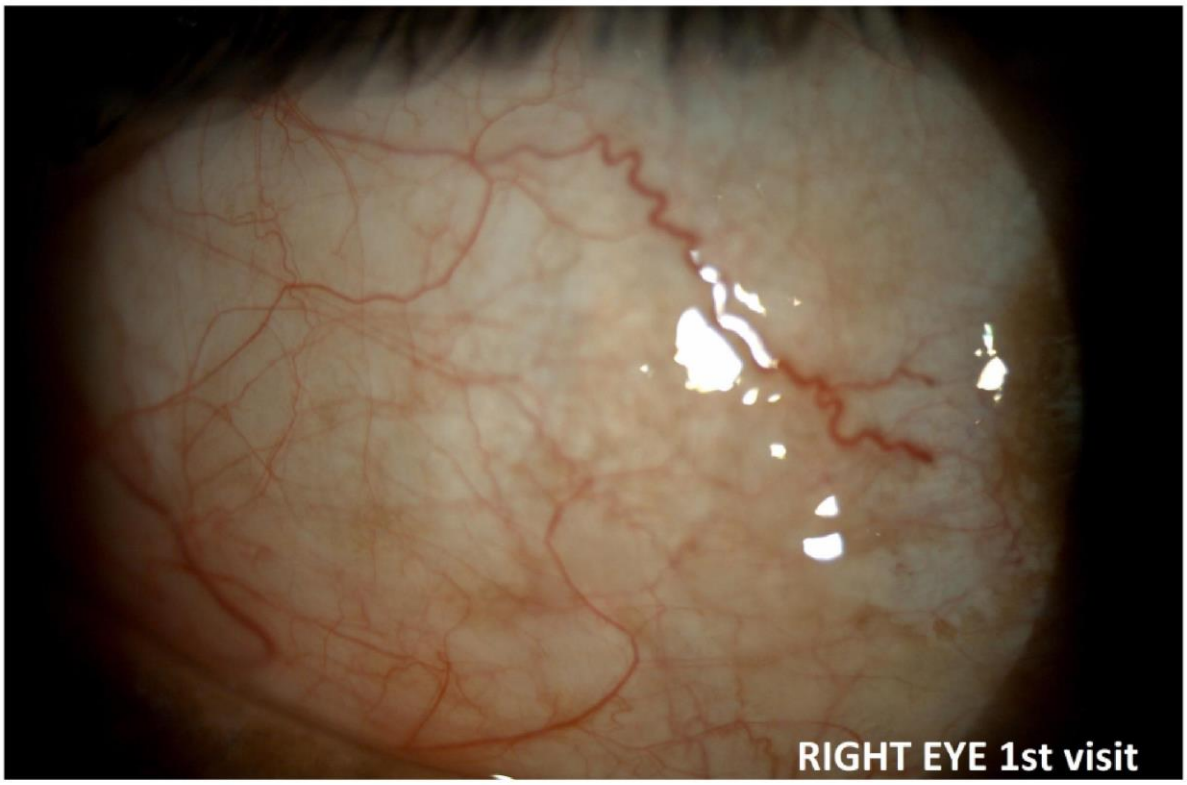
91. Shedden A, Adamsons IA, Getson AJ, Laurence JK, Lines CR, Hewitt DJ, et al. Comparison of the efficacy and tolerability of preservative-free and preservative-containing formulations of the dorzolamide/timolol fixed combination (COSOPT™) in patients with elevated intraocular pressure in a randomized clinical trial. Graefes Arch Clin Exp Ophthalmol. 2010 Dec;248(12):1757–64.

92. Hamacher T, Airaksinen J, Saarela V, Liinamaa MJ, Richter U, Ropo A. Efficacy and safety levels of preserved and preservative-free tafluprost are equivalent in patients with glaucoma or ocular hypertension: results from a pharmacodynamics analysis. Acta Ophthalmol Suppl (Oxf). 2008;242:14–9.

93. Aptel F, Pfeiffer N, Schmickler S, Clarke J, Lavín-Dapena C, Moreno-Montañés J, et al. Noninferiority of Preservative-free Versus BAK-preserved Latanoprost-timolol Fixed Combination Eye Drops in Patients With Open-angle Glaucoma or Ocular Hypertension. Journal of Glaucoma. 2019 Jun;28(6):498–506.

ANNEXURE

ARM A SLITLAMP PHOTOGRAPHS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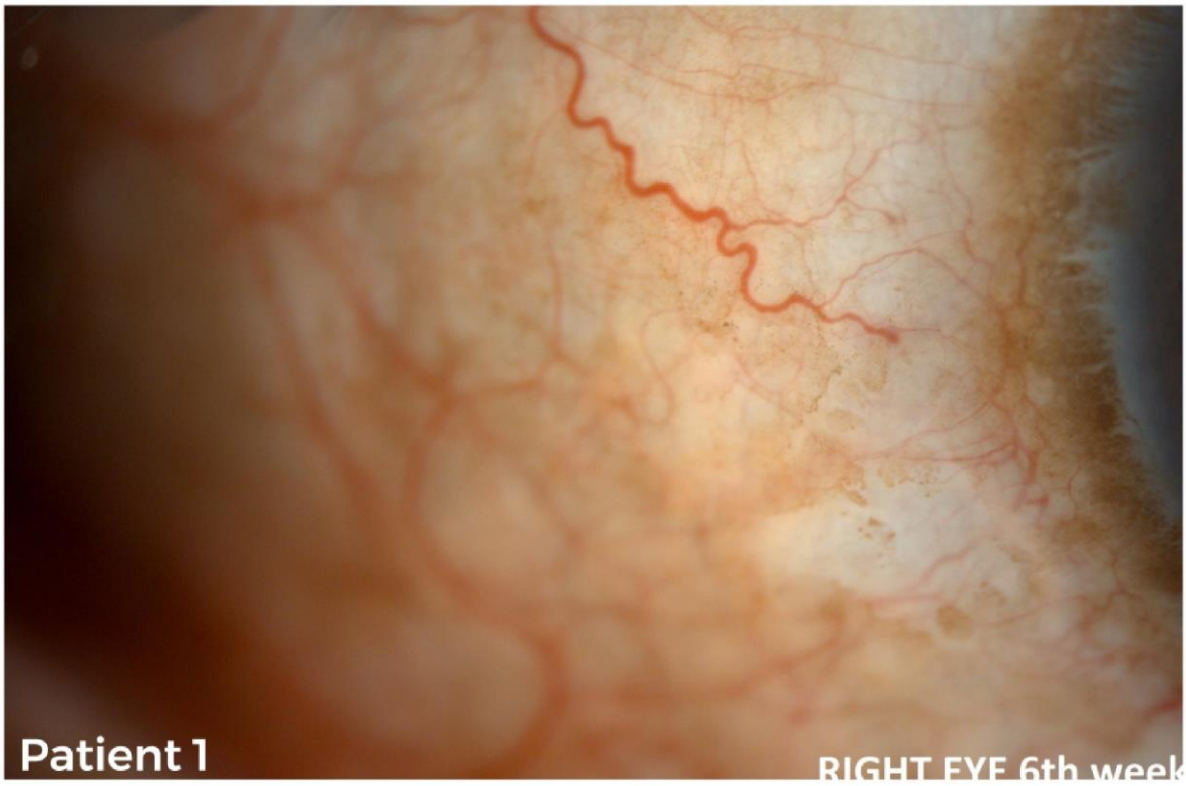
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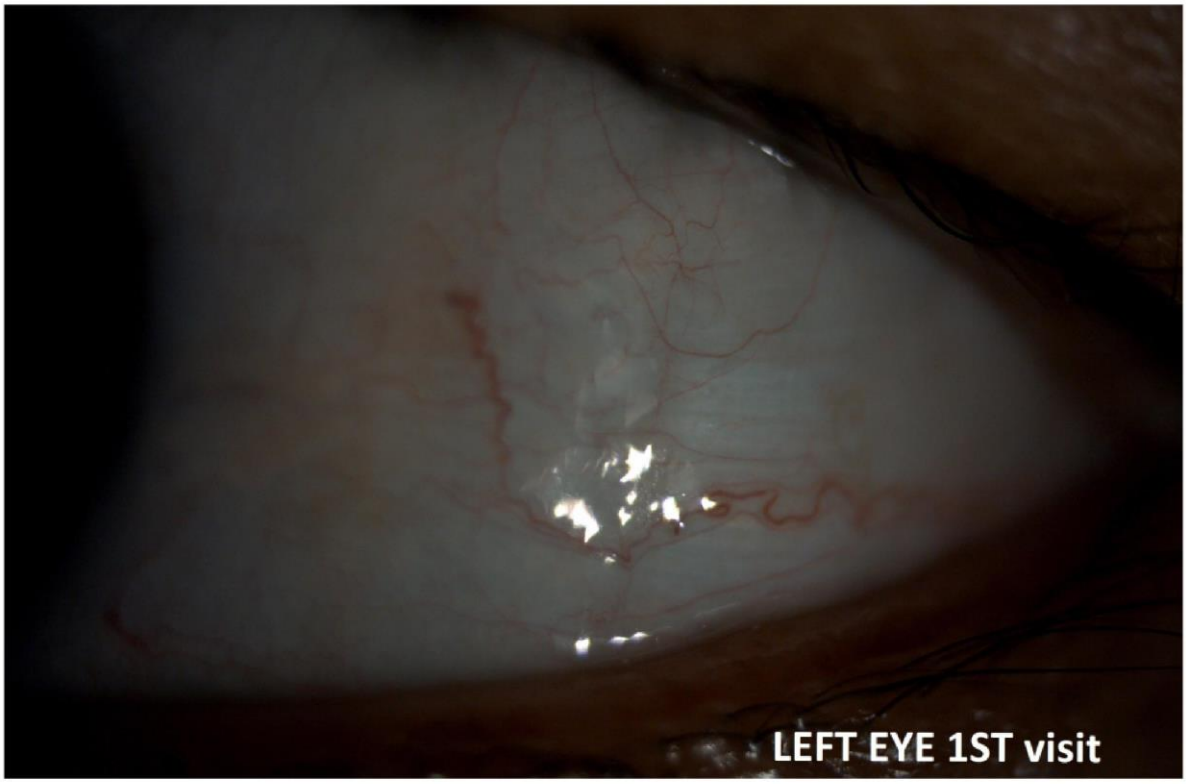
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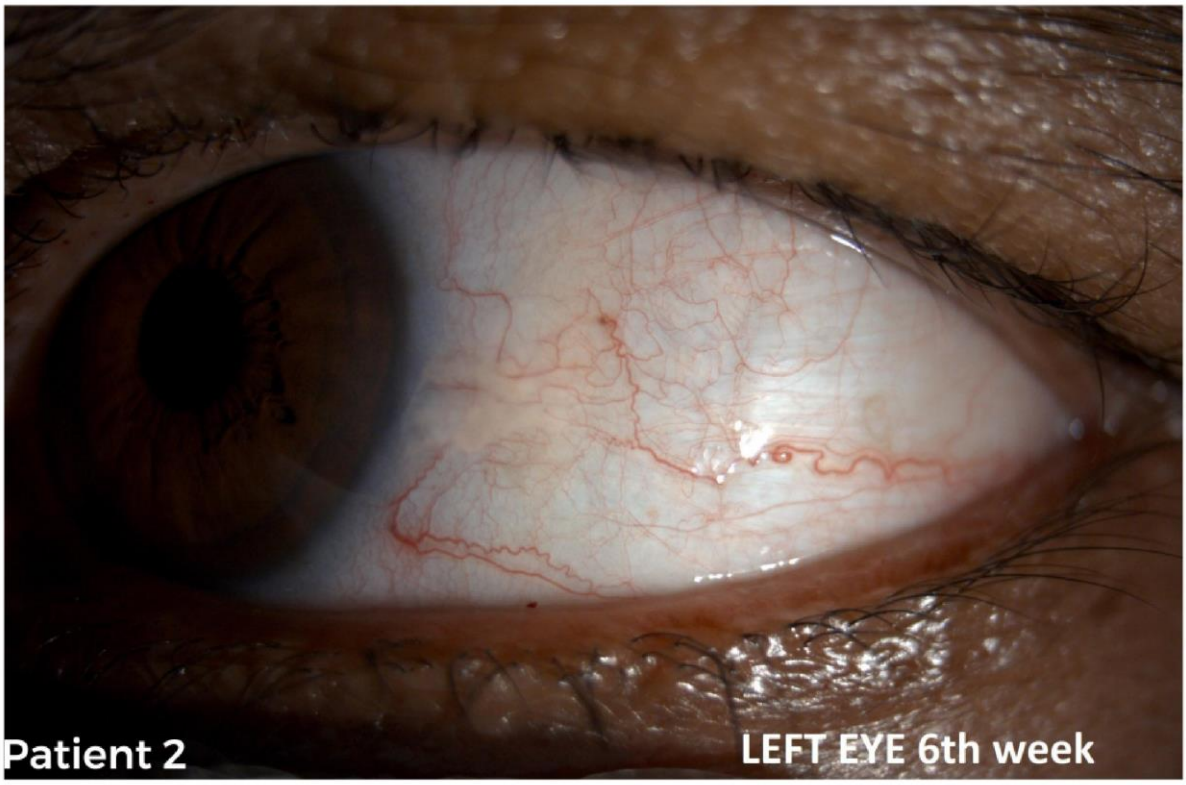
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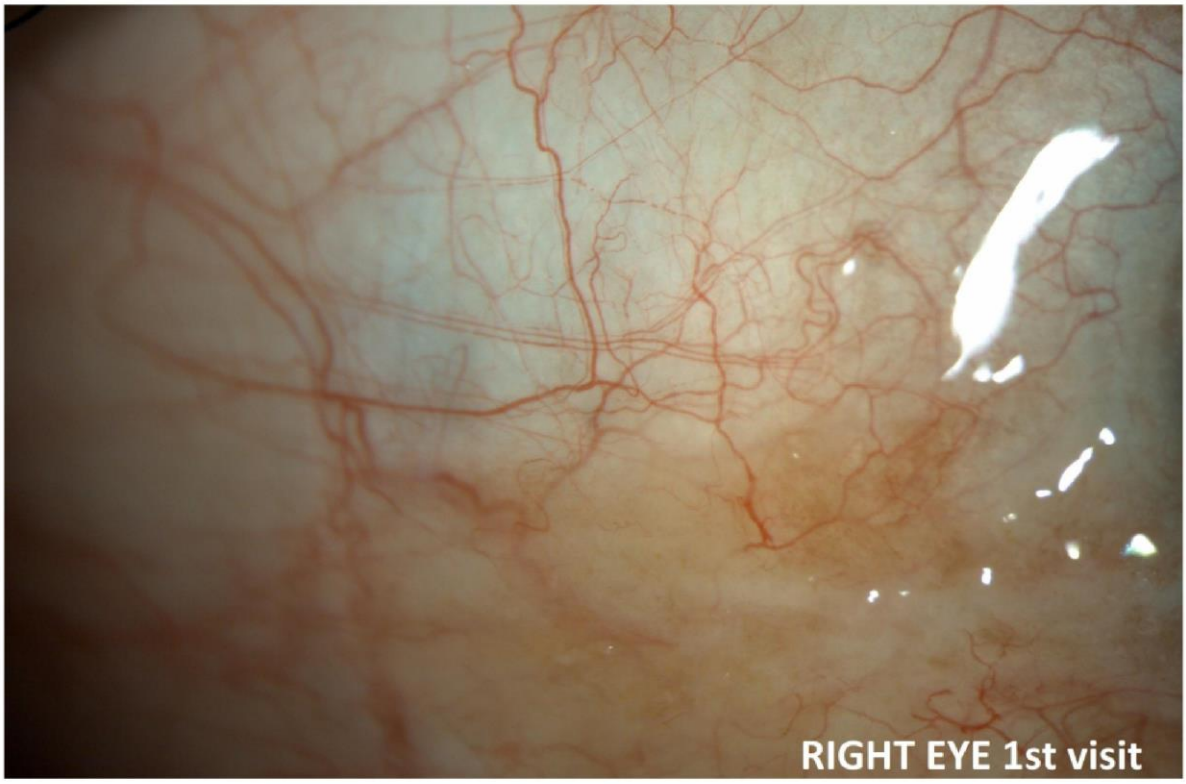
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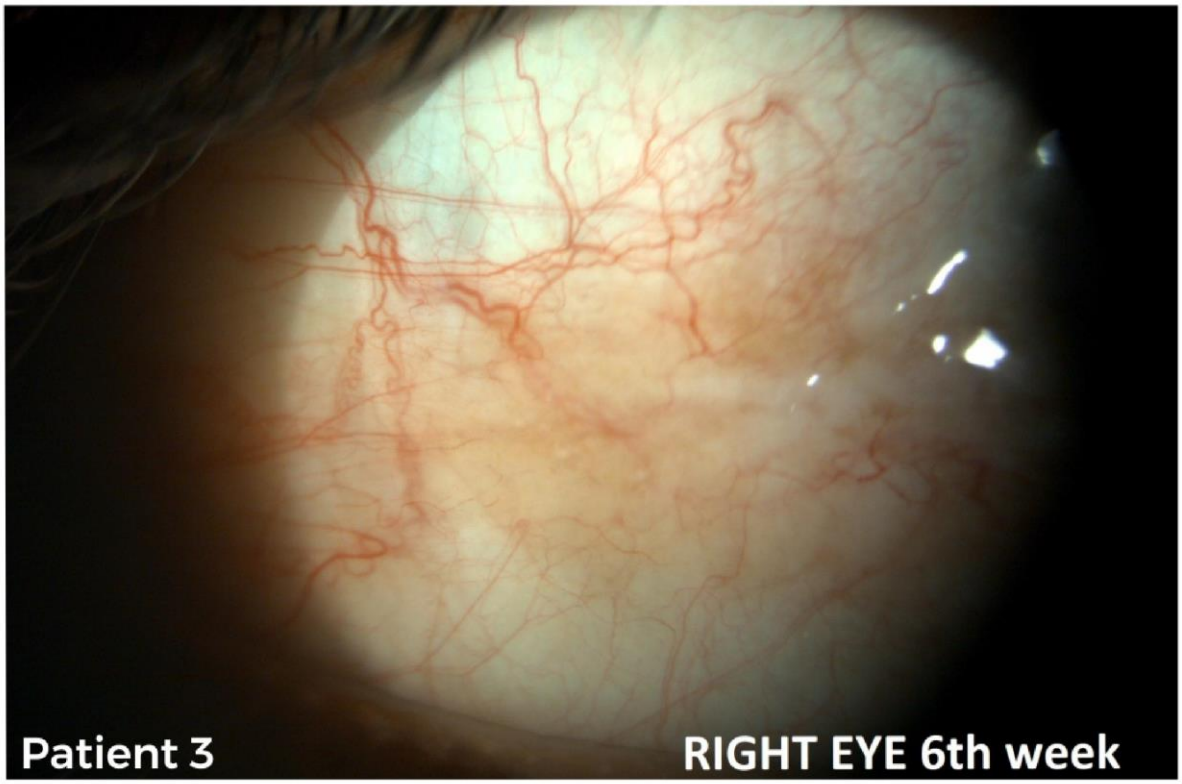
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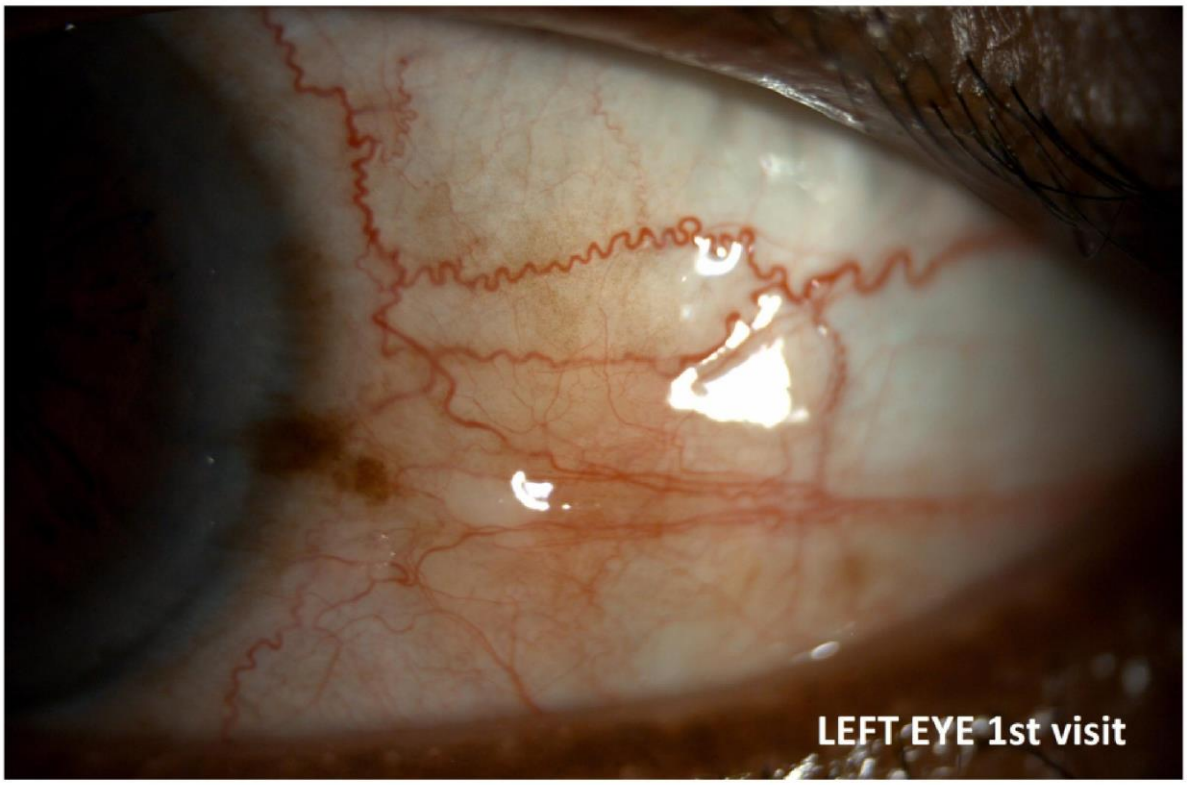
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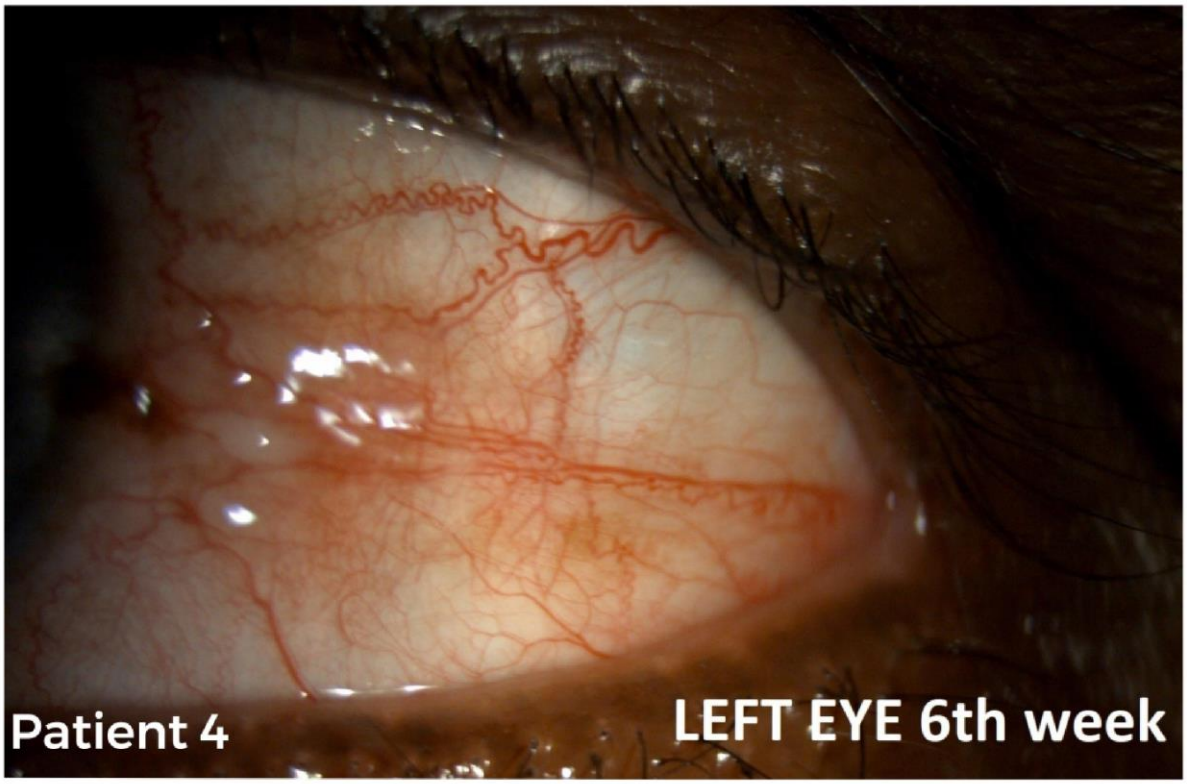
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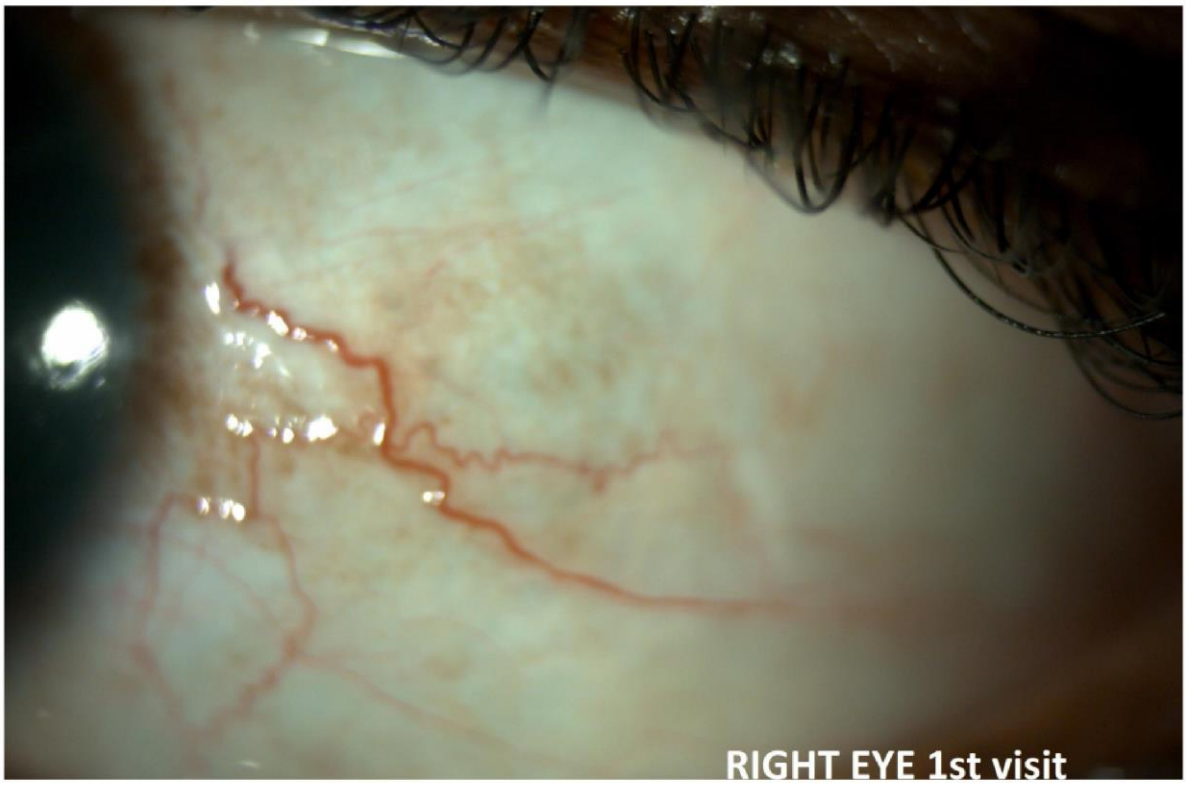
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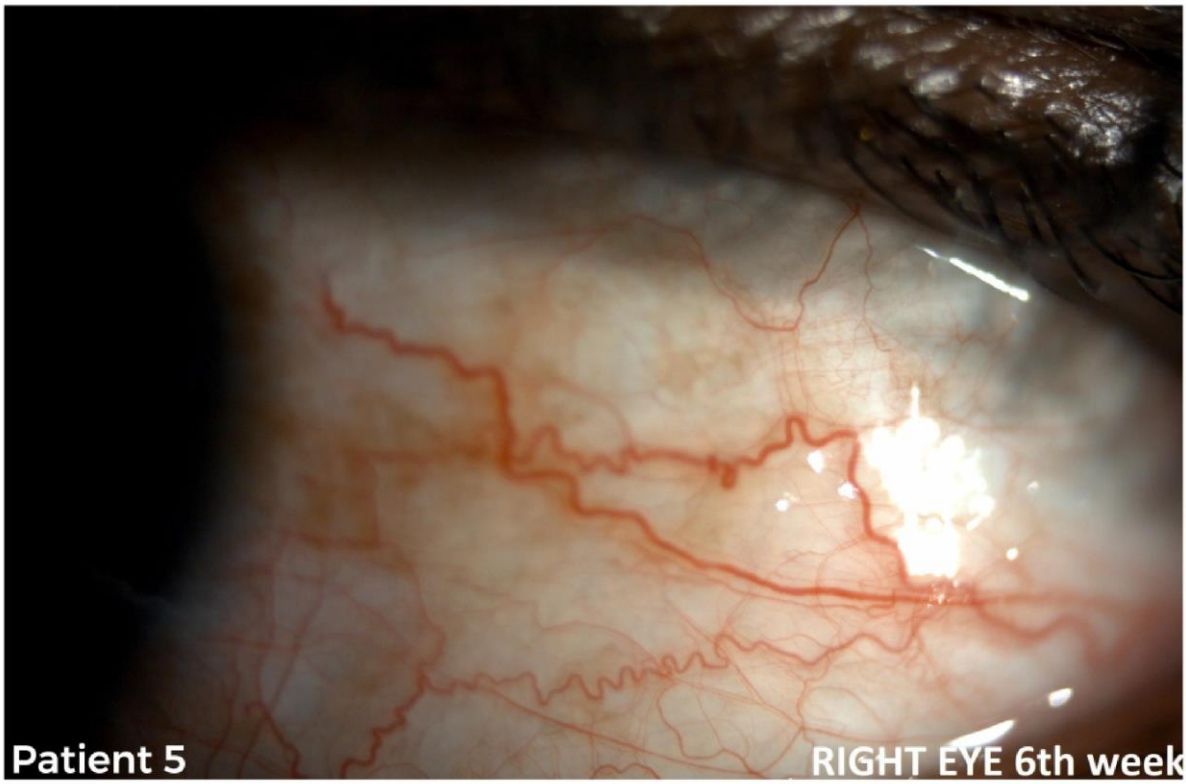
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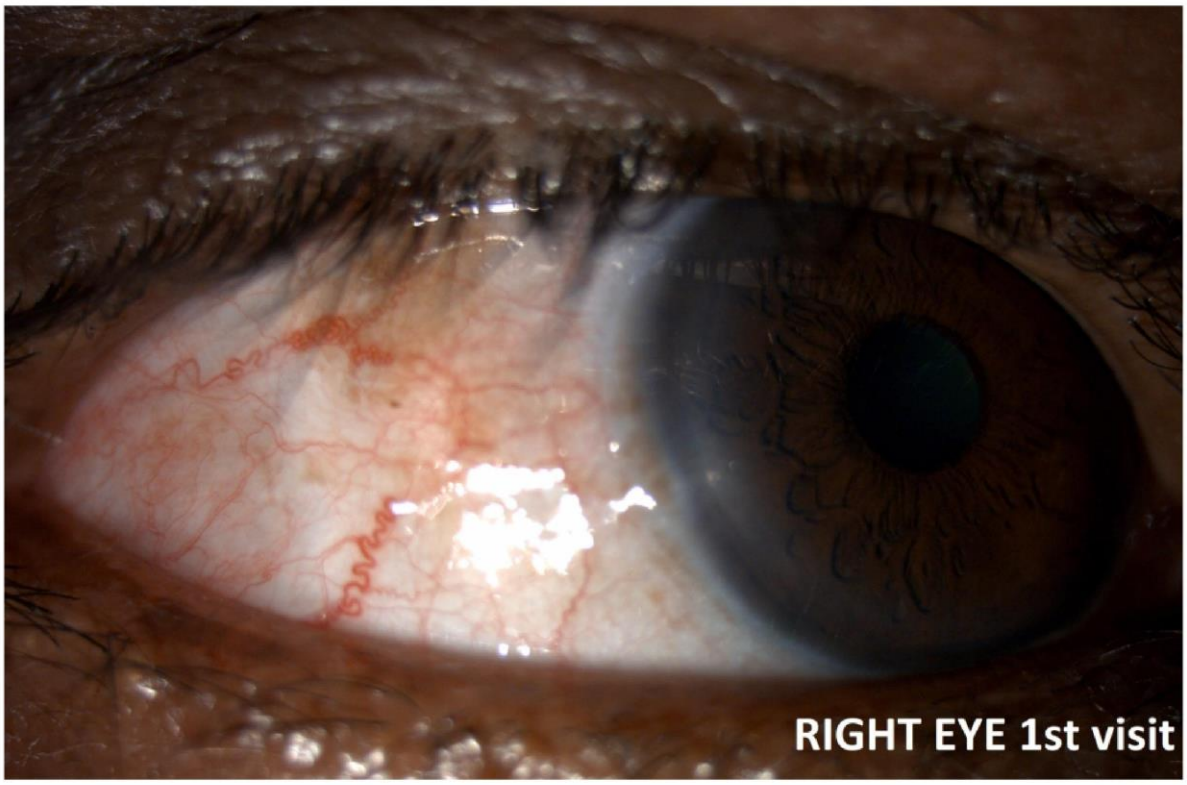
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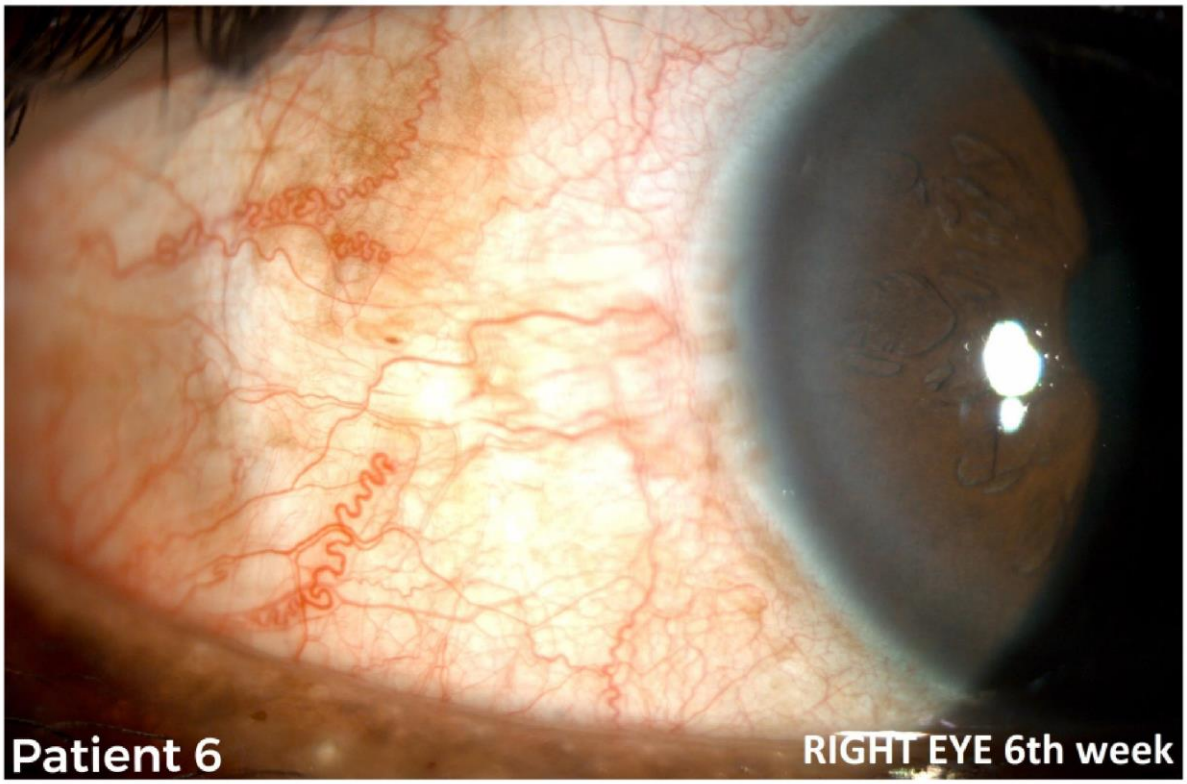
Patient 6
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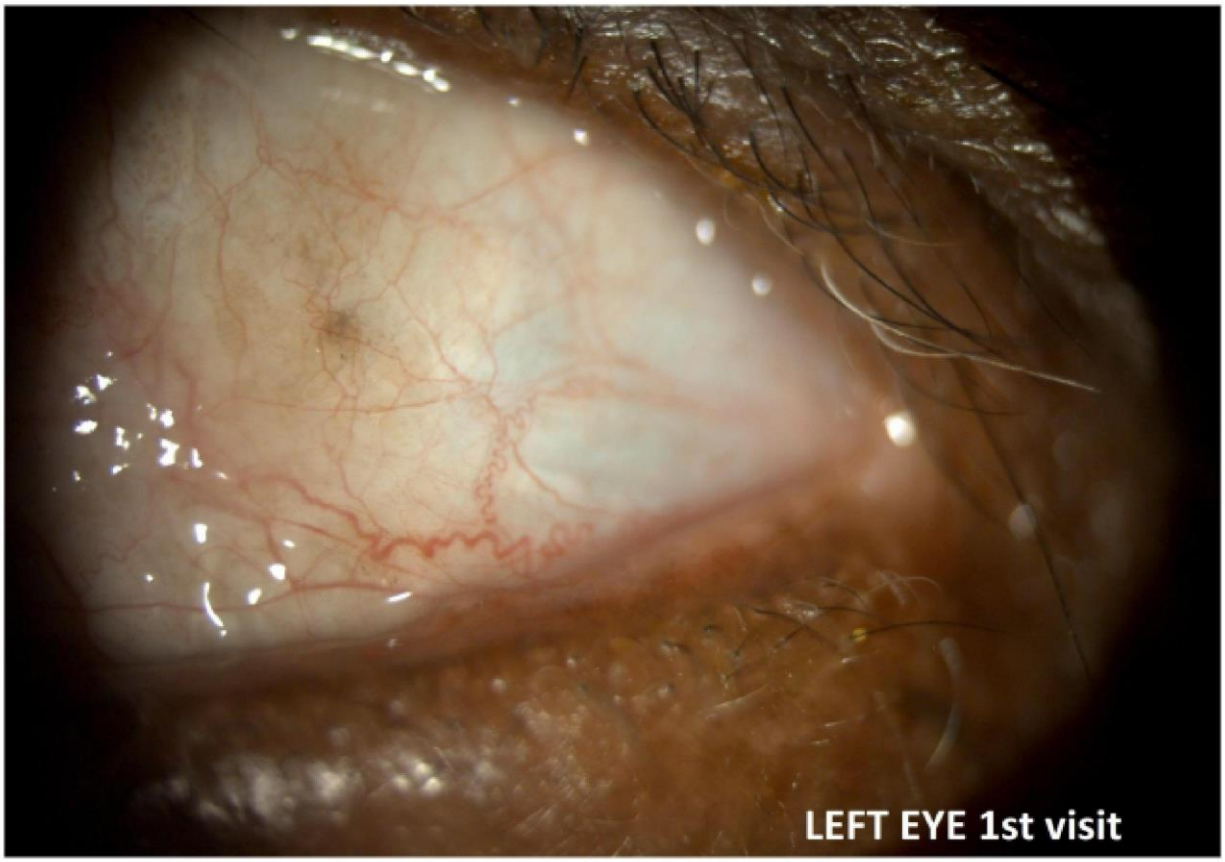
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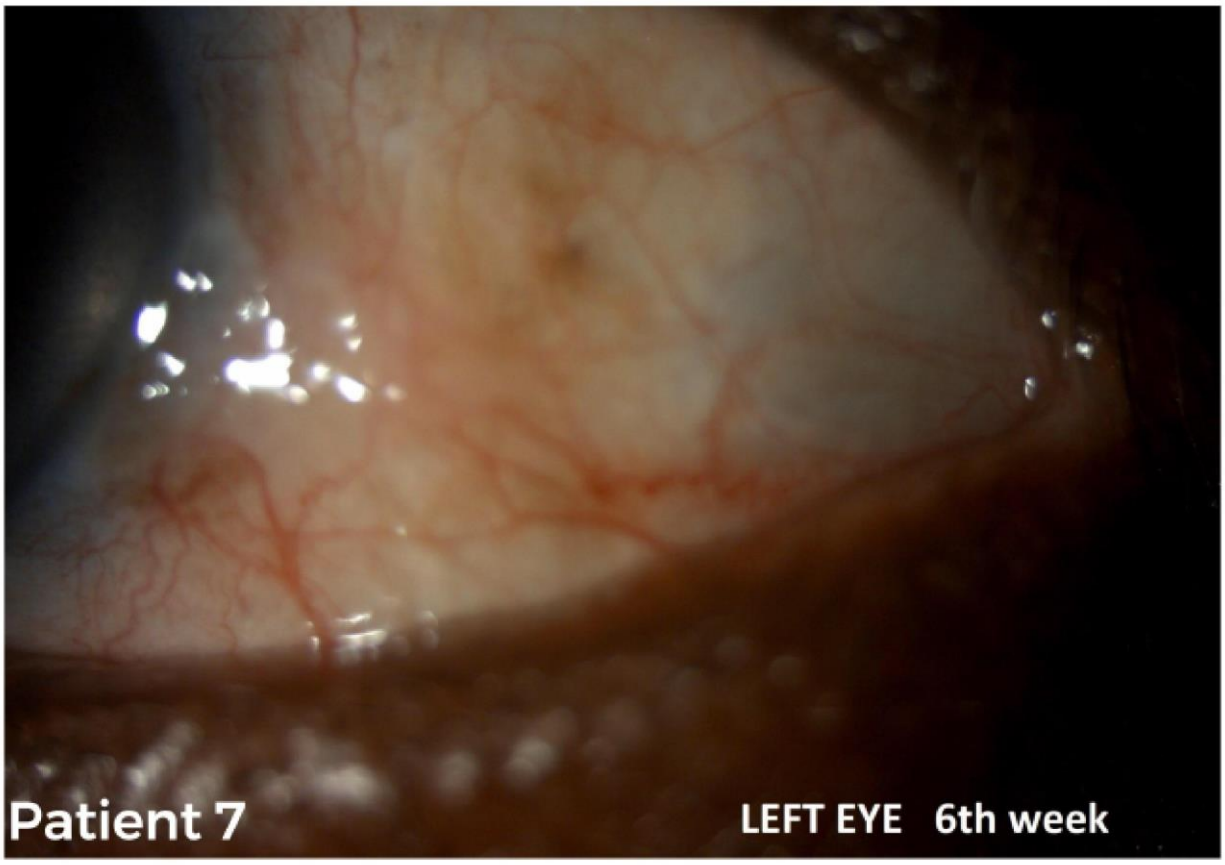
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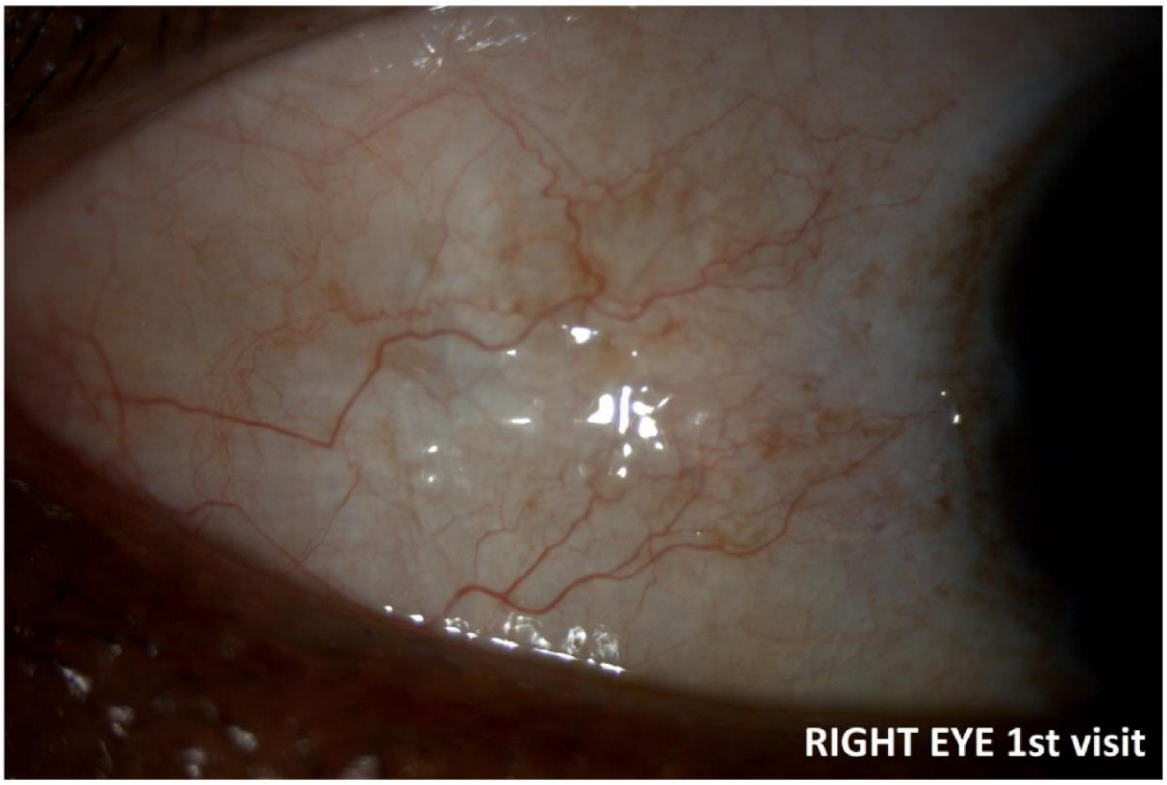
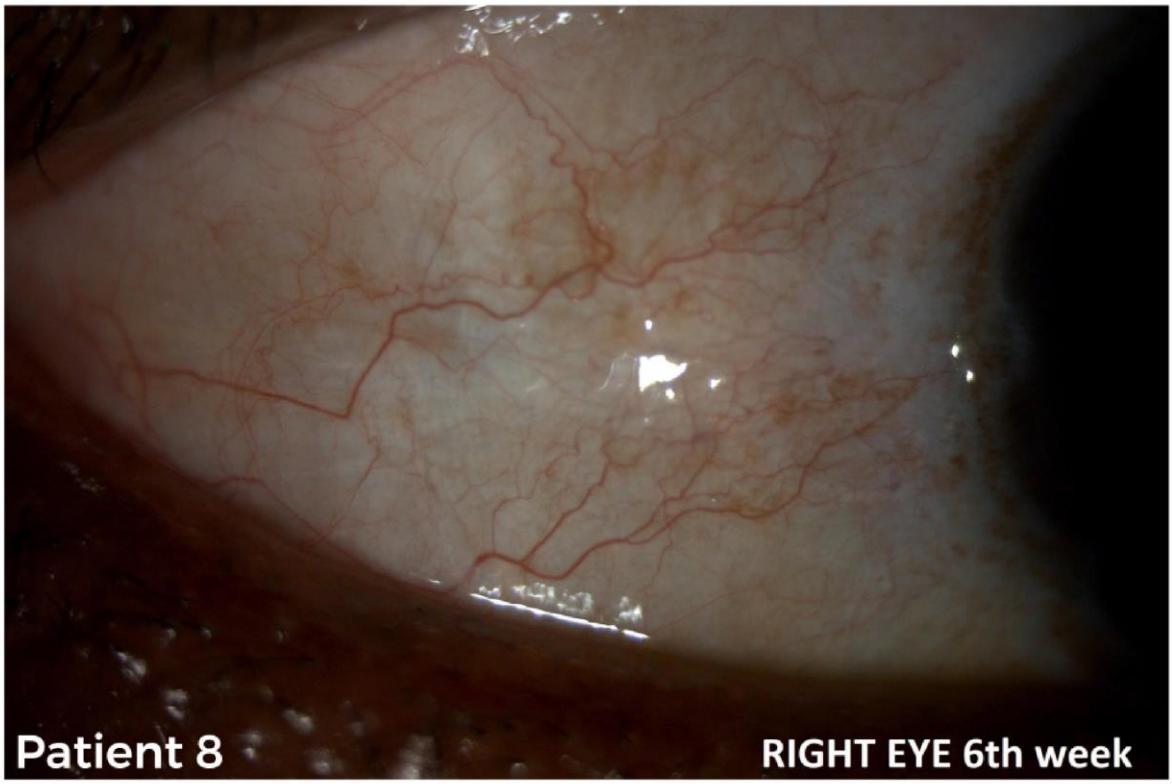
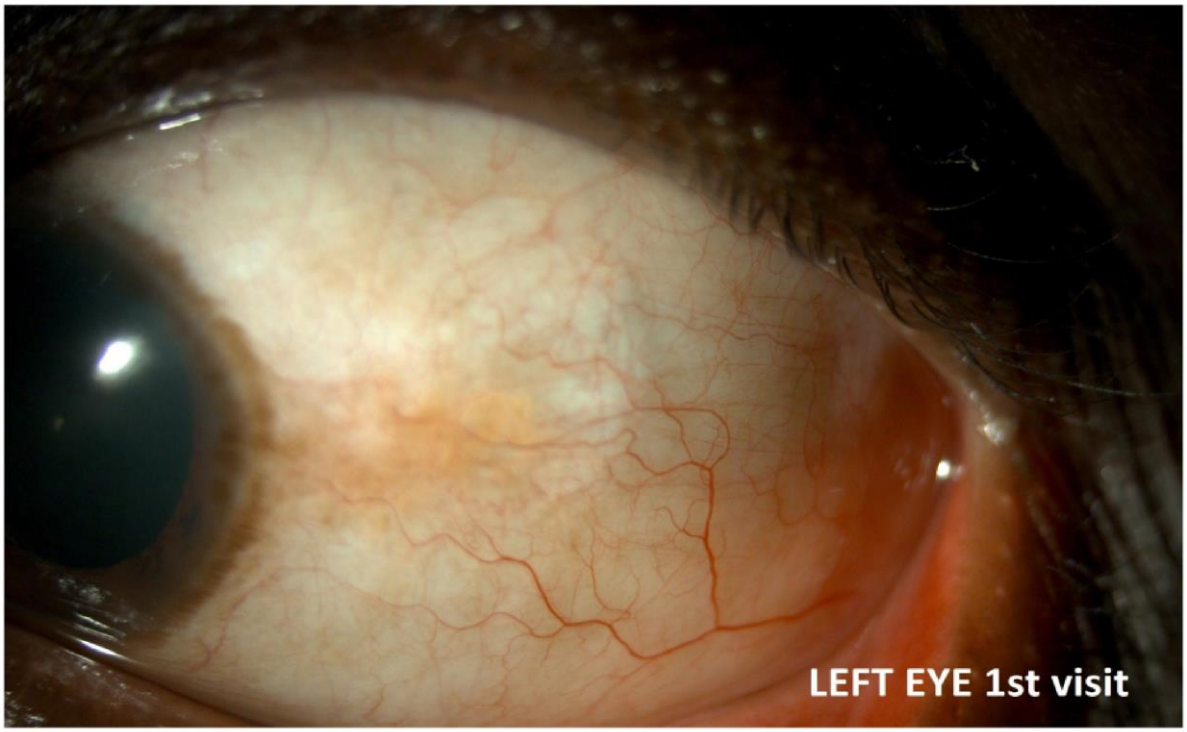
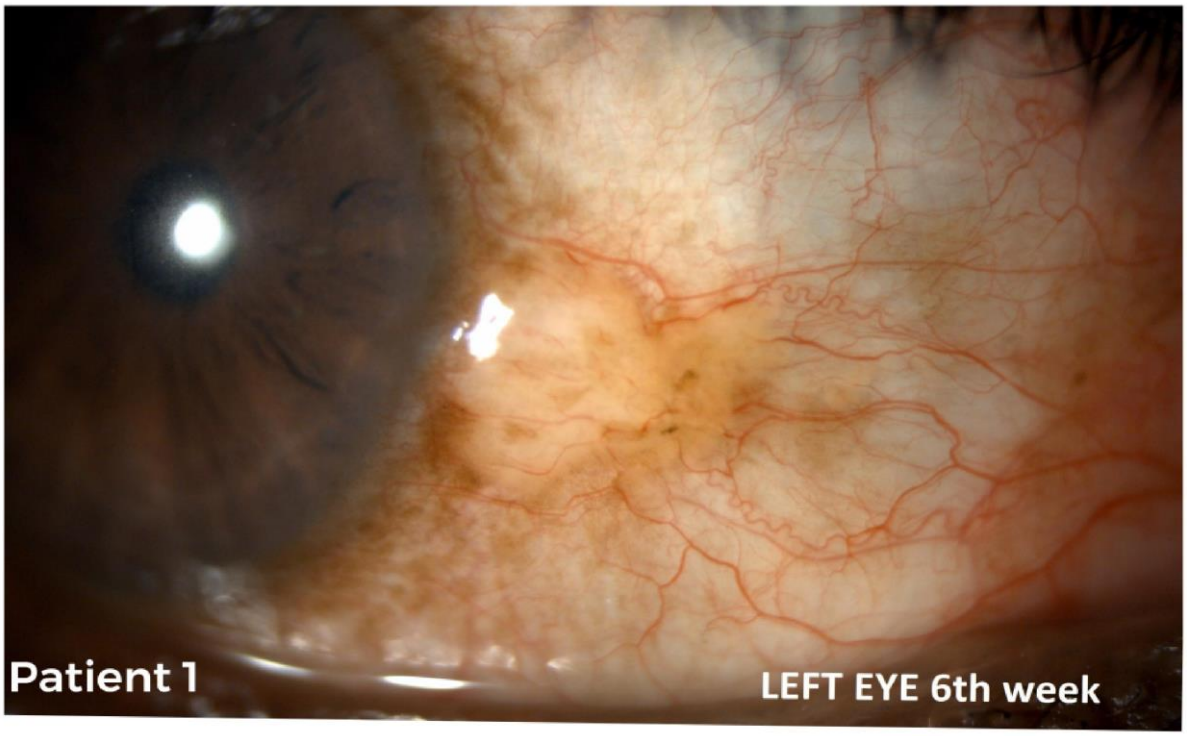
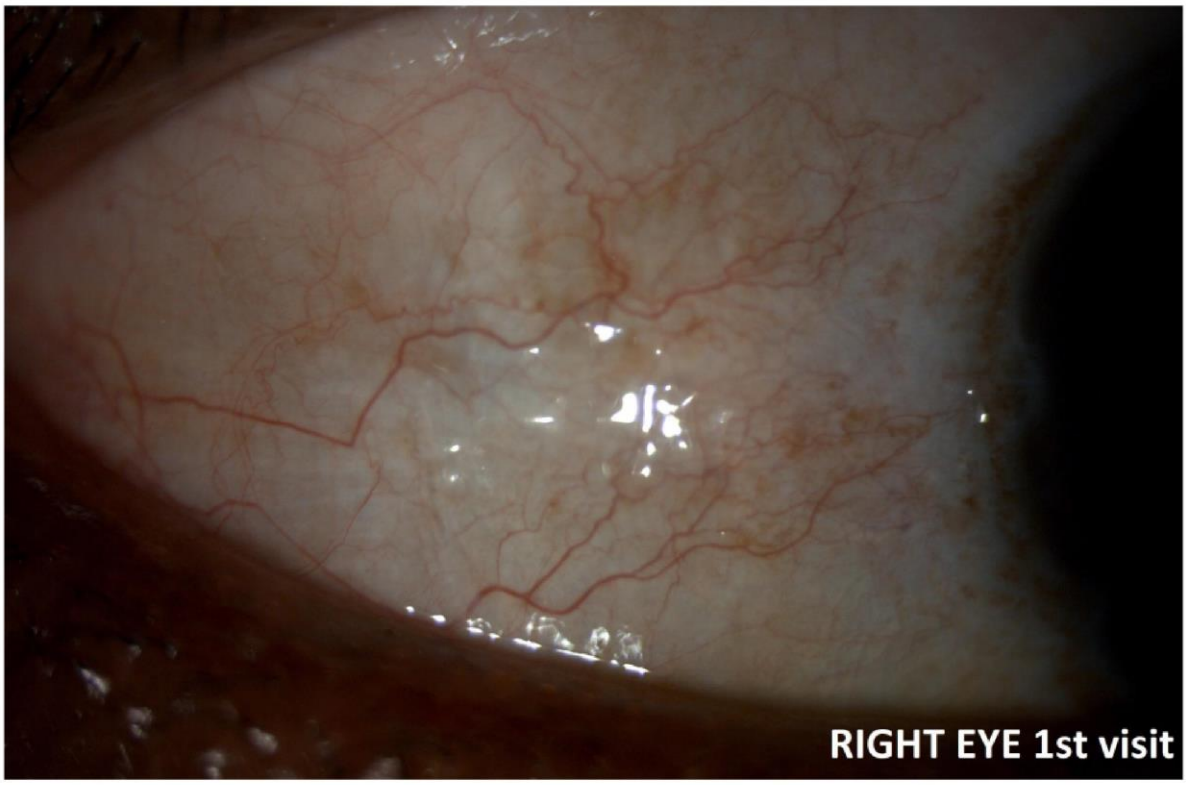

RIGHT EYE 1st visit

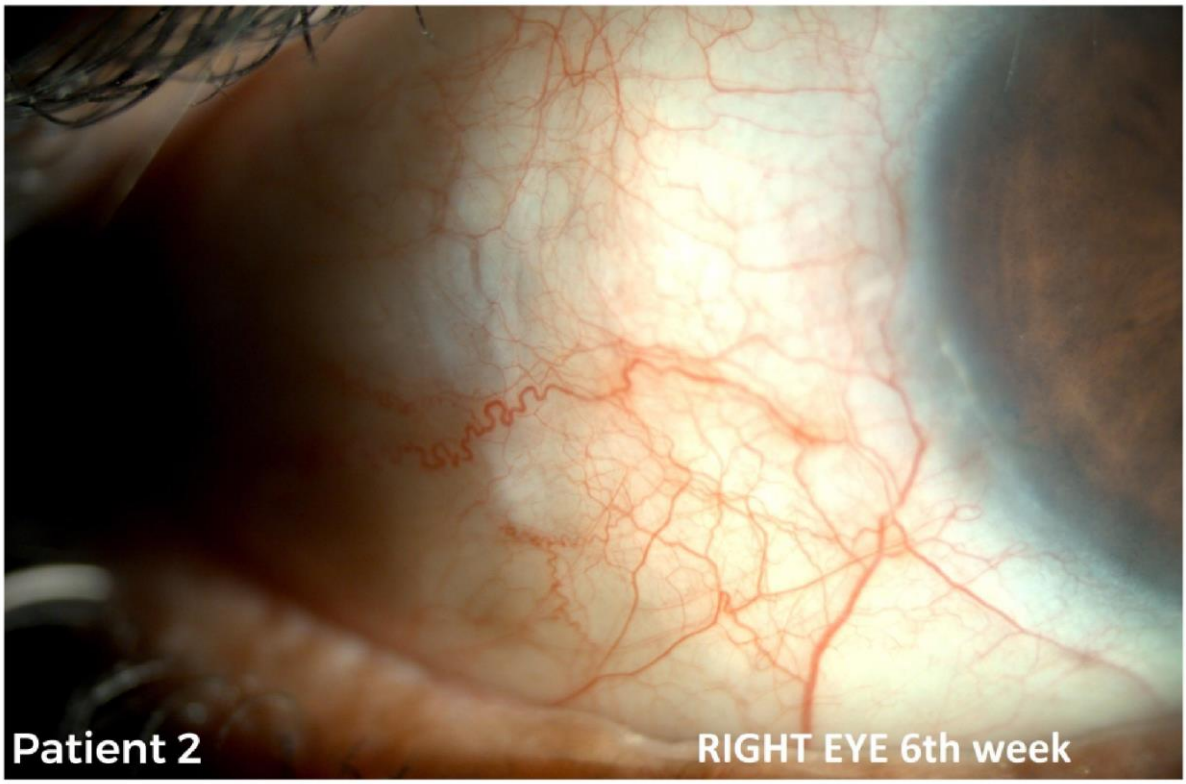

Patient 8
RIGHT EYE 6th week

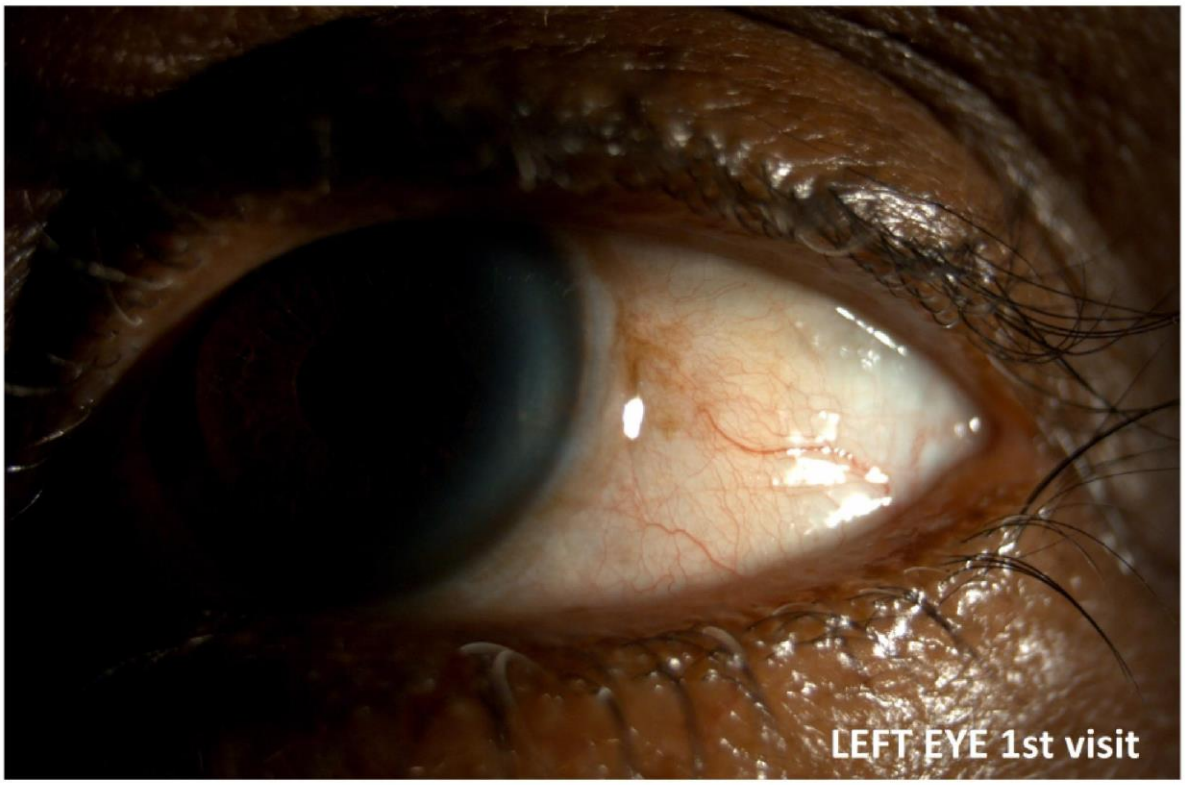
ARM B SLIT LAMP PHOTOGRAPHS

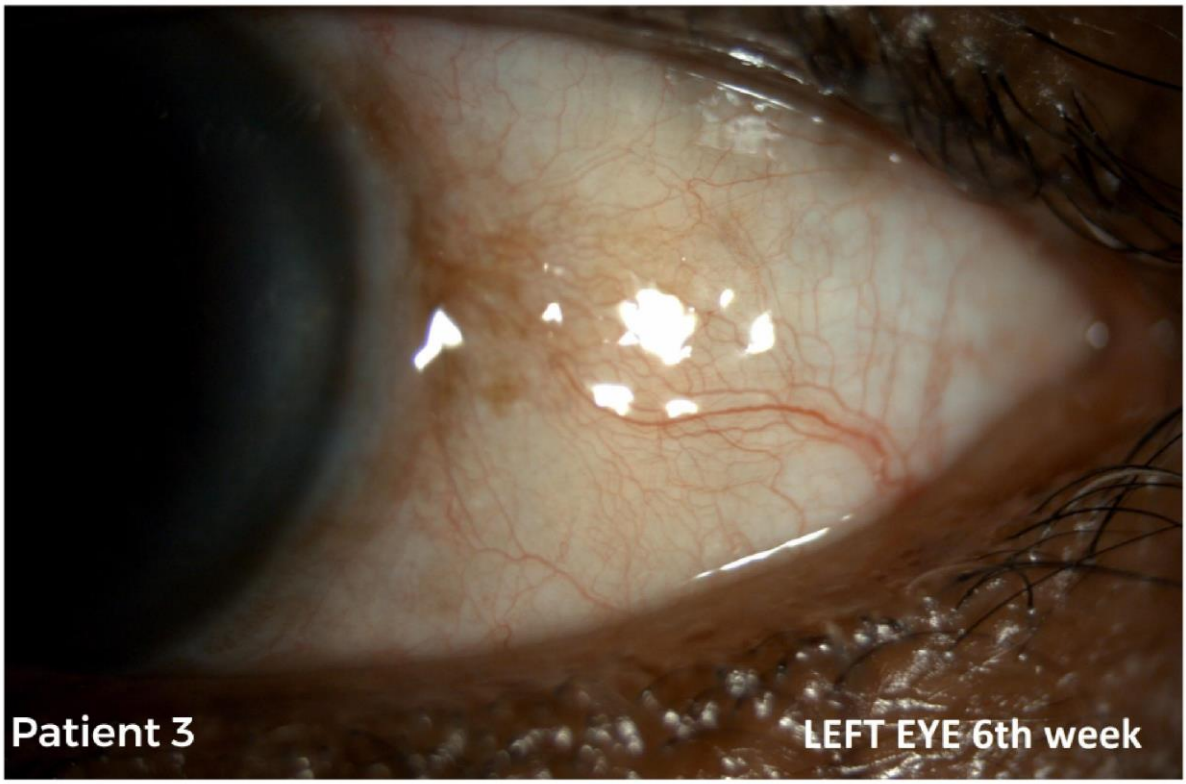

LEFT EYE 1st visit

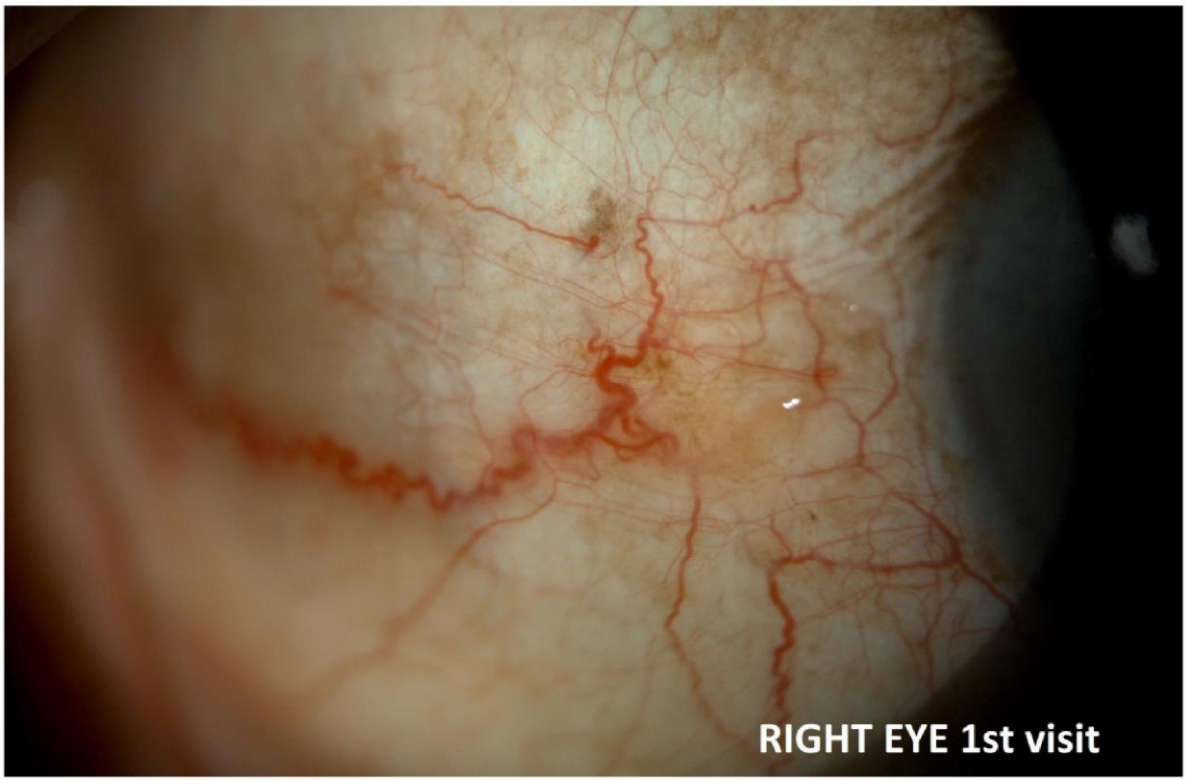

Patient 1
LEFT EYE 6th week

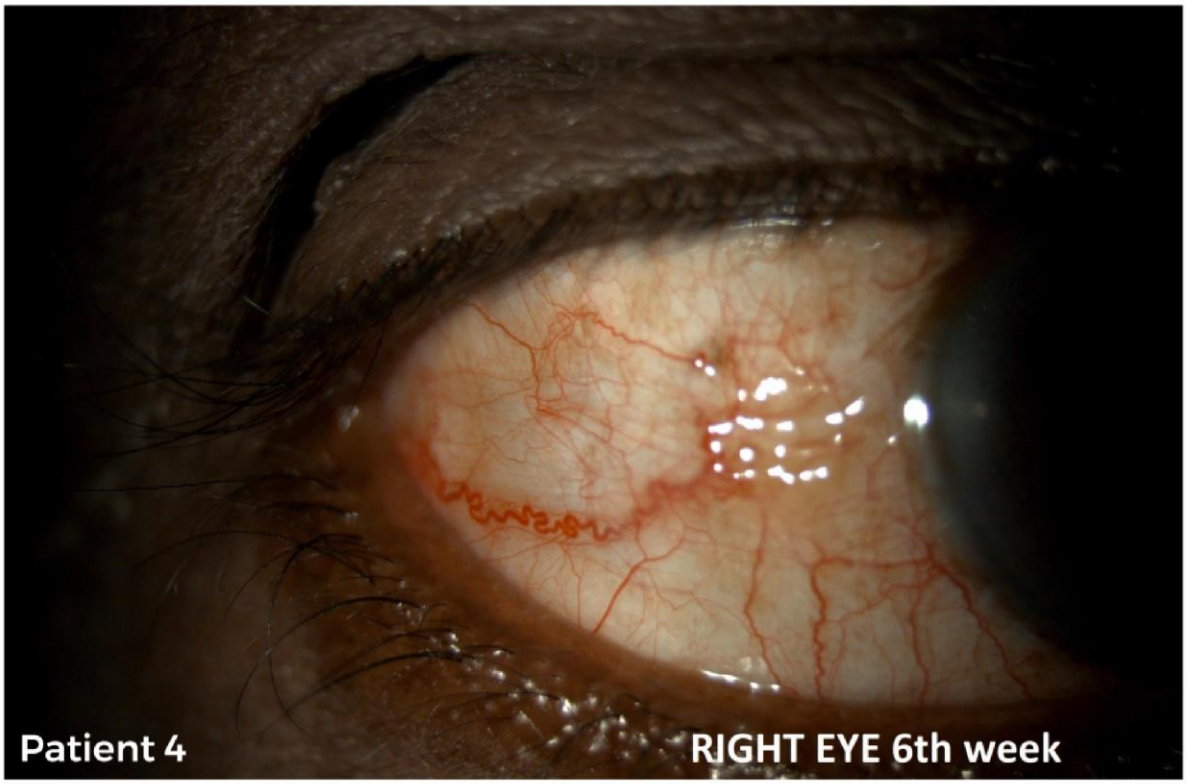

RIGHT EYE 1st visit

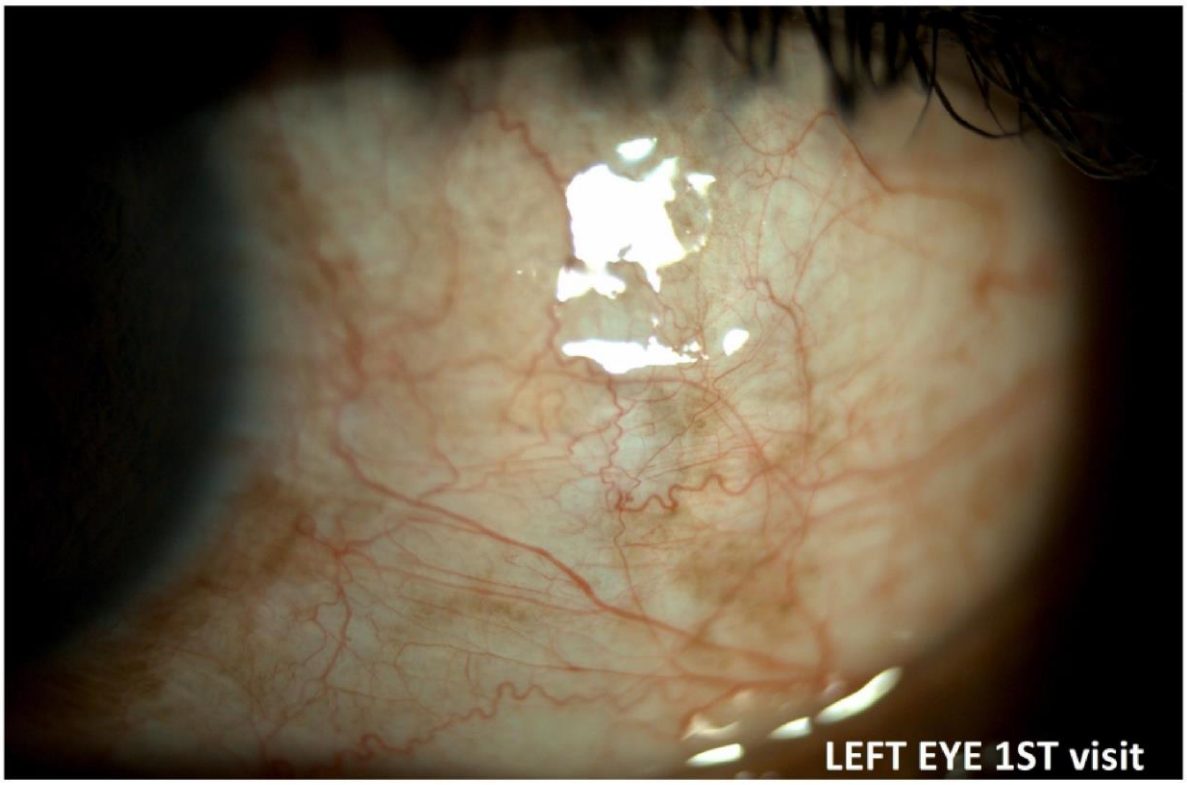

Patient 2
RIGHT EYE 6th week

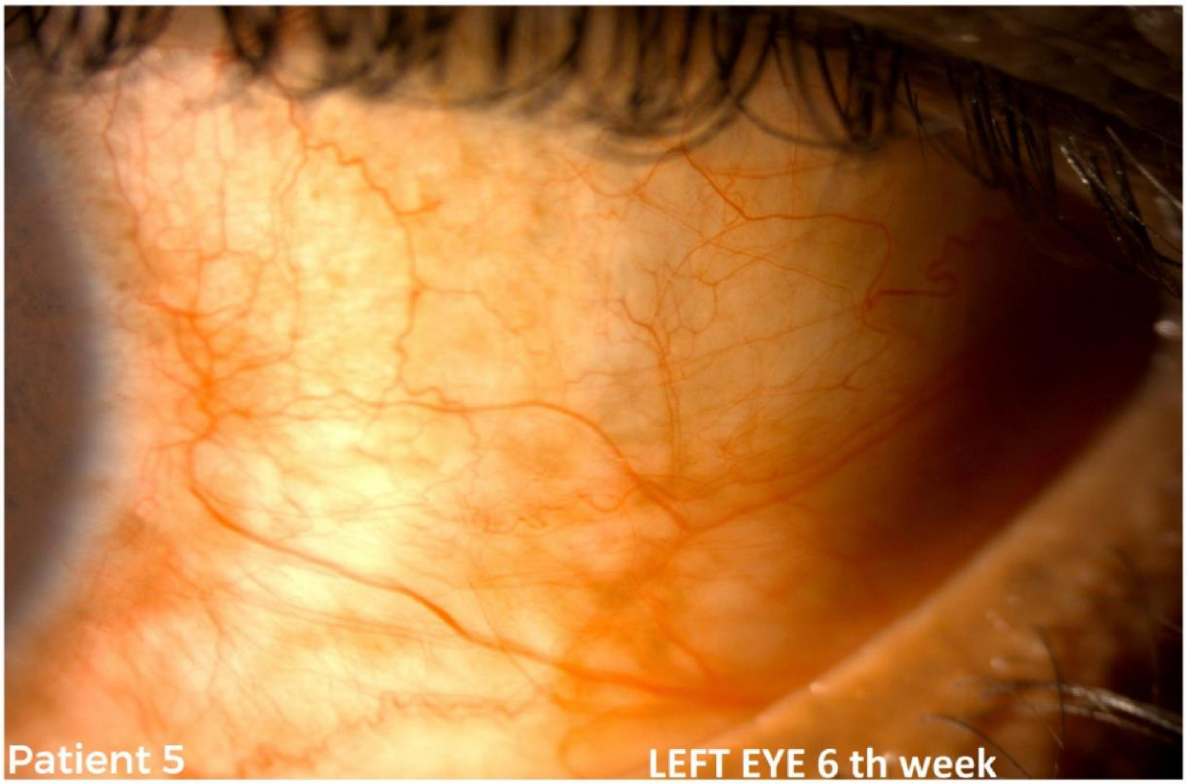

LEFT EYE 1st visit

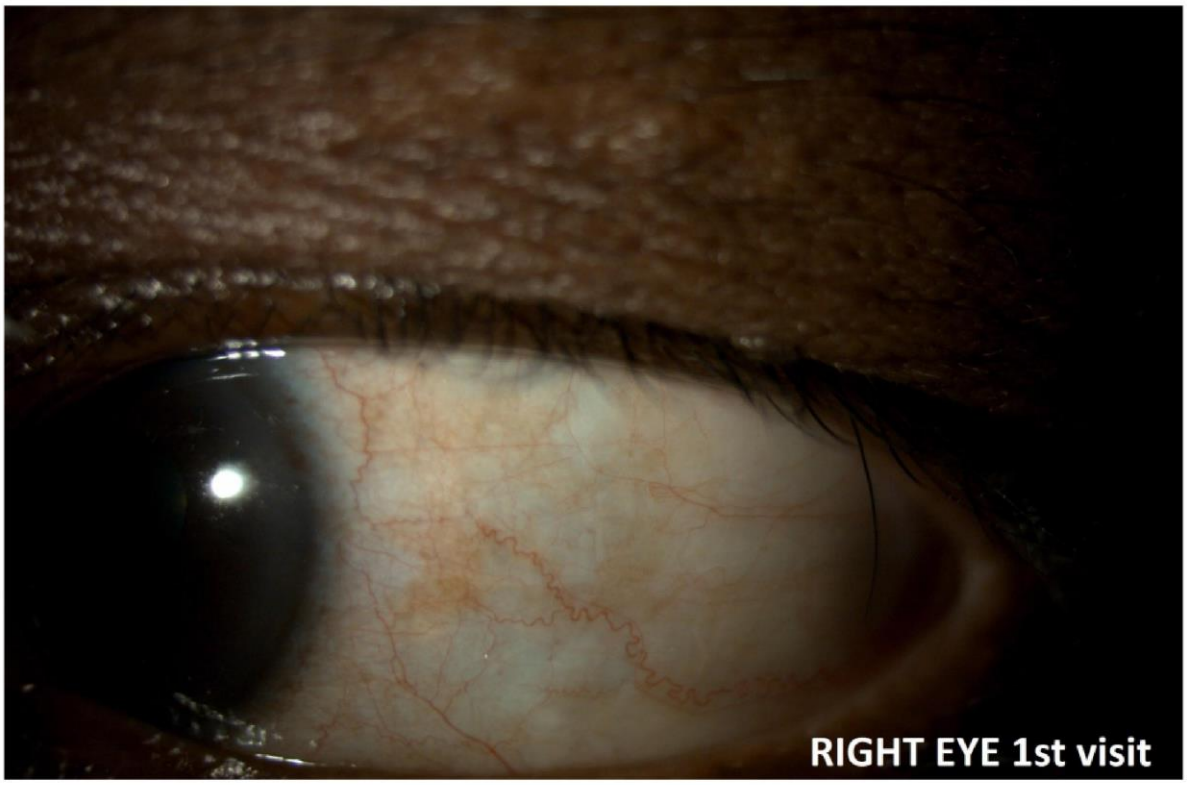

Patient 3
LEFT EYE 6th week

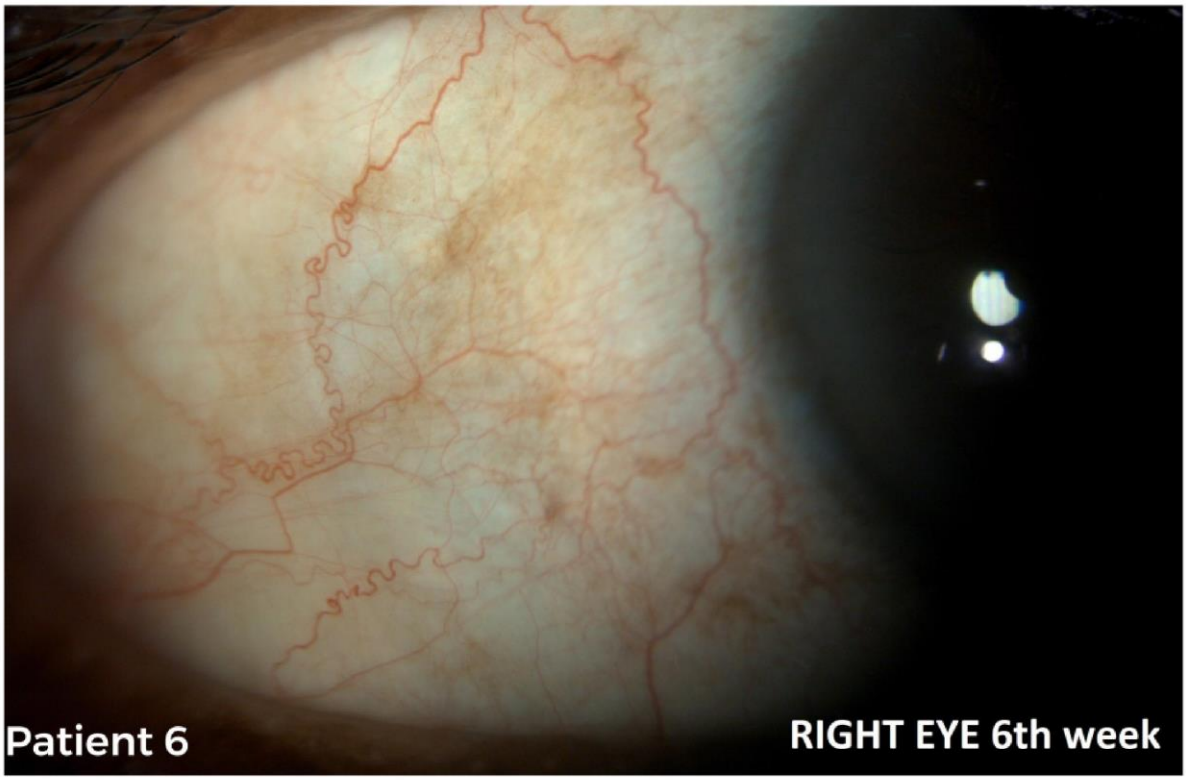

RIGHT EYE 1st visit

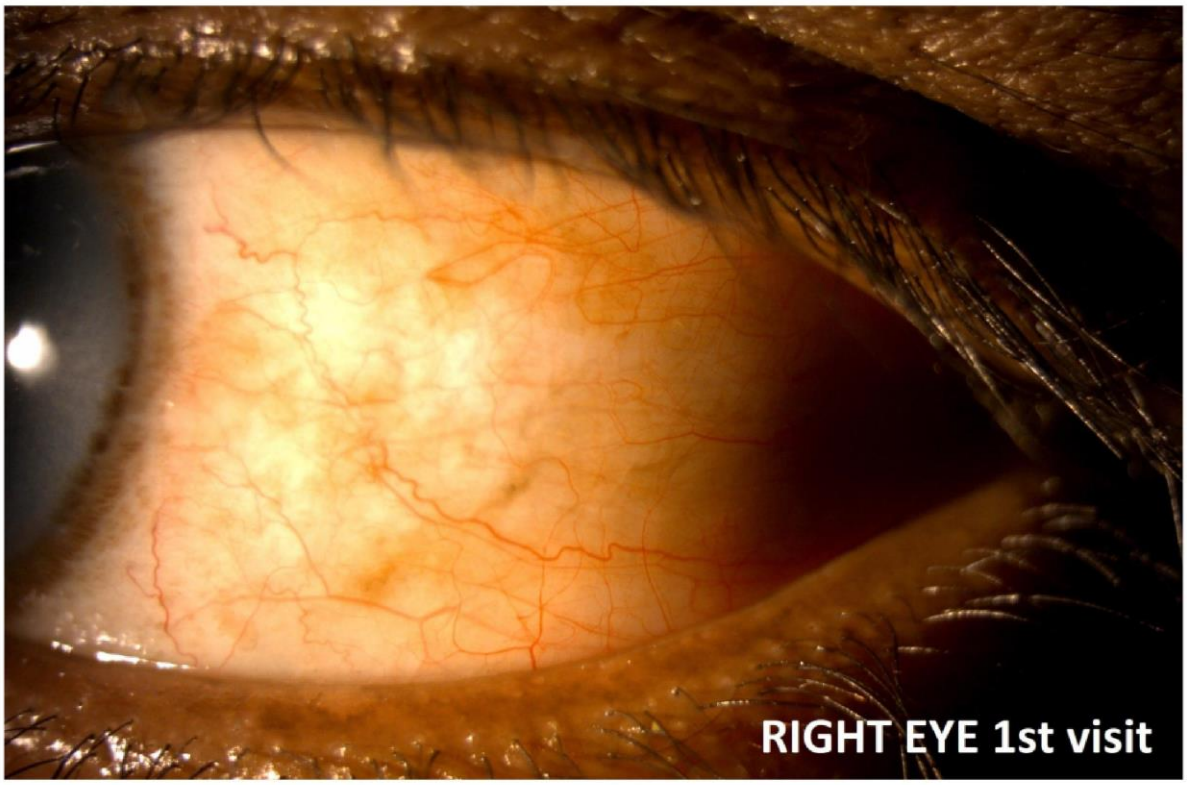

Patient 4
RIGHT EYE 6th week

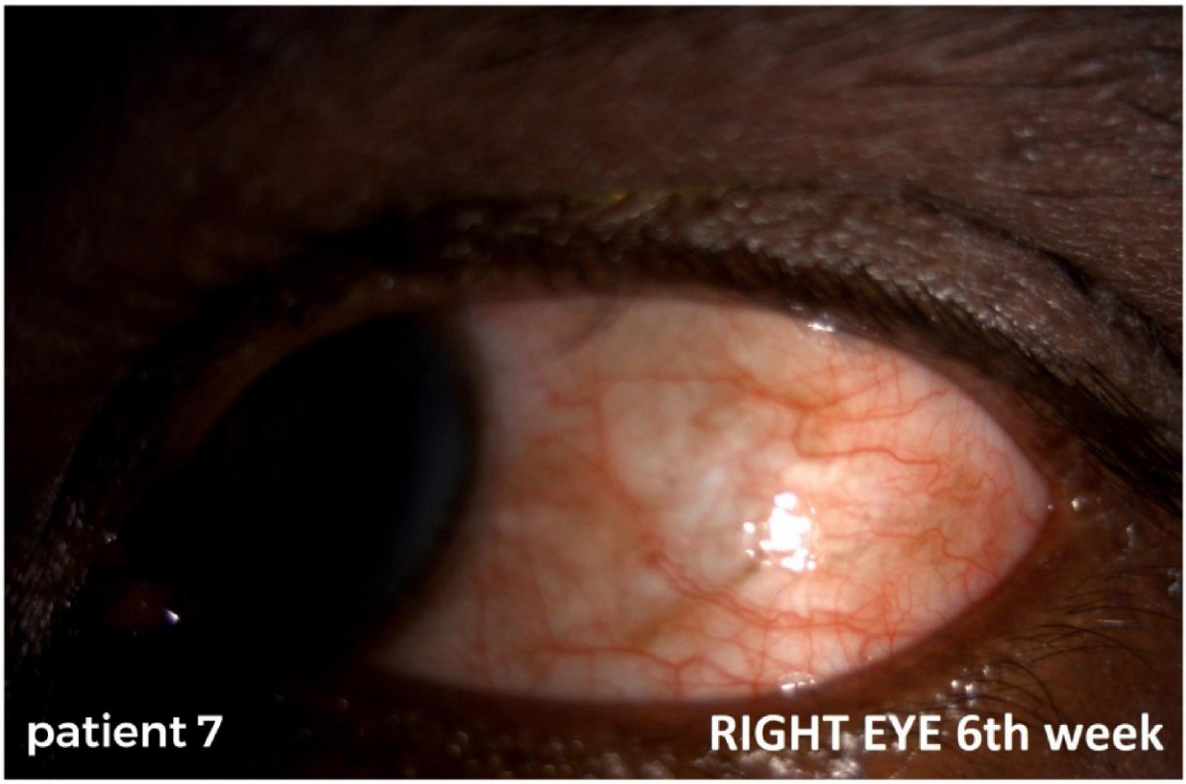

LEFT EYE 1ST visit


Patient 5
LEFT EYE 6 th week


RIGHT EYE 1st visit


Patient 6
RIGHT EYE 6th week


RIGHT EYE 1st visit


patient 7
RIGHT EYE 6th week

LIST OF PICTURES

LIST OF TABLES:

FIGURES:

IRB APPROVAL LETTER

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE, VELLORE, INDIA

Ethics Committee Registration No: ECR/326/INST/TN/2013 Re Reg-2019 Issued under Rule 122D of the Drugs & Cosmetics Rules 1945, Govt. of India

Dr. George Thomas, D. Ortho., Ph.D.,
Chairperson, Ethics Committee

Dr. B. Antonisamy, Ph.D., FSMS, FRSS.,
Secretary, Research Committee

Prof. Keith Gomez, MA (S.W), M.Phil.,
Deputy Chairperson, Ethics Committee

Dr. Anna Benjamin Pulimood, MD., Ph.D.,
Chairperson,
Research Committee & Principal

Dr. Suceena Alexander, MD., DM., FASN.,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

August 24, 2020

Dr. Malini D,
PG Registrar,
Department of Ophthalmology,
Christian Medical College,
Vellore – 632 004.

Sub: Fluid Research Grant: New Proposal:
Comparison of the efficacy and safety of preservative free Travoprost 0.004% with Travoprost 0.004% with polyquarternium-1 as preservative in patients with primary open angle glaucoma and ocular hypertension – A randomized controlled trial.
Dr. Malini D Employment Number: 21784 PG Registrar, Department of Ophthalmology, Dr. Lekha Mary Abraham, Employment Number: 20086, Ophthalmology, Dr. Andrew David Braganza, Employment Number: 14092, Dr. Arathi Simha R, Employment number: 20217, Dr. Lalgudi Sharmili Sekar, Employment number: 33800, Dr. Sonika Porwal, Employment number:33135, Ophthalmology, Dr. B.Antonisamy, Employment number: 3090, Biostatistics Mr. Nirmal Raj, Employment number:54284 Optometrist, Miss. Melanshya Pears, Employment number:54378, Optometrist.

Ref: IRB Min. No. 12967 (INTERVEN) dated 24.06.2020

Dear Dr. Malini D,

The Institutional Review Board **(Silver,** Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed your project titled "Comparison of the efficacy and safety of preservative free Travoprost 0.004% with Travoprost 0.004% with polyquarternium-1 as preservative in patients with primary open angle glaucoma and ocular hypertension – A randomized controlled trial" on June 24, 2020. I am quoting below the minutes of the meeting.

The Committee reviewed the following documents:
1) IRB Application Format
2) Patient information sheet and Inforemd Consent Form
3) Proforma
4) GCP Certificate
5) Cvs. Of Drs. Nirmal Raj, Antonisamy, Malini, Sharmili, Arathi Simha, Andrew David, Lekha Mary, Melanshya, Sonika P.
6) No. of Documents 1 – 4.

Ethics Committee Silver, Office of Research, I Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788 E-mail: research@cmcvellore.ac.in

Dr. George Thomas, D. Ortho., Ph.D.,
Chairperson, Ethics Committee

Dr. B. Antonisamy, Ph.D., FSMS, FRSS.,
Secretary, Research Committee

Prof. Keith Gomez, MA (S.W), M.Phil.,
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Dr. Anna Benjamin Pulimood, MD., Ph.D.,
Chairperson,
Research Committee & Principal

Dr. Suceena Alexander, MD., DM., FASN.,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Due to the extra-ordinary situation caused by the COVID - 19 pandemic and the subsequent government lockdown, the members of the Institutional Review Board (**Silver**, Research & Ethics Committee), Christian Medical College, Vellore - 632002, listed below performed an online review for the month of June 2020.

Name	Qualification	Designation	Affiliation
Dr. George Thomas	D Ortho, PhD	Orthopaedic Surgeon, St. Isabella Hospital, Chennai, Chairperson, Ethics Committee, IRB, Chennai	External, Clinician
Dr. Suceena Alexander	MD, DM, FASN.	Professor, Nephrology, Additional Vice Principal (Research), Deputy Chairperson (Research Committee), Member Secretary (Ethics Committee), IRB, CMC, Vellore.	Internal, Clinician
Dr. Biju George	MBBS, MD, DM	Professor, Haematology,	Internal, Clinician
Dr. RV. Shaji	M.Sc, PhD	Professor, Heamatology, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Suresh Devasahayam	MS, PhD	Professor of Bio-Engineering, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Sathya Subramani	MD, PhD	Professor, Physiology, CMC, Vellore	Internal, Clinician
Rev. Joseph Devaraj	BSc, BD	Chaplaincy Department, CMC, Vellore	Internal, Social Scientist
Dr. D. J. Christopher	DTCD, DNB, FRCP(Glasg), FCCP(USA)	Professor, Pulmonary Medicine, CMC, Vellore	Internal, Clinician
Dr. Thomas V Paul	MD, DNB, PhD	Professor, Endocrinology, CMC, Vellore	Internal, Clinician
Dr. Prasanna Samuel	M. Sc, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Sridhar Gibikote	DMRD, DNB	Professor, Radiology, CMC, Vellore	Internal, Clinician
Dr. Abhay Gahukamble	MS, D Ortho, DNB(Ortho)	Associate Professor, Paediatric Orthopaedics, CMC, Vellore	Internal, Clinician

Ethics Committee Silver, Office of Research, I Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788 E-mail: research@cmcvellore.ac.in

Dr. Laxmi Govindaraj	MBBS., MD., Pharmacology	Sr. Resident, Clinical Pharmacology, CMC, Vellore	Internal Pharmacologist
Dr. Ajith Sivadasan	MD, DM	Professor, Neurological Sciences, CMC, Vellore	Internal, Clinician
Mr. C. Sampath	BSc, BL	Advocate, Vellore	External, Legal Expert
Dr. Santhanam Sridhar	DCH, DNB	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Dr. Manoranjitham.S	M Sc (N) P.hd in Psychiatric Nursing.	Professor and Head Psychiatric Nursing, College of Nursing, CMC, Vellore	Internal, Nurse
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL.	Sr. Legal Officer, Vellore	External Legal Expert
Mrs. Pattabiraman	BSc, DSSA	Social Worker, Vellore	External, Lay person

We approve the project to be conducted as presented.

Kindly provide the total number of patients enrolled in your study and the total number of Withdrawals for the study entitled: "Comparison of the efficacy and safety of preservative free Travoprost 0.004% with Travoprost 0.004% with polyquarternium-1 as preservative in patients with primary open angle glaucoma and ocular hypertension – A randomized controlled trial" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:
A sum of 2,03,200/- INR (Rupees Two Lakh Three Thousand and Two Hundred Only) will be granted for 15 Months.

Yours sincerely,

Dr. Suceena Alexander
Secretary (Ethics Committee)
Institutional Review Board.

Dr. Suceena Alexander, MD.,DM.,FASN.
Secretary - (Ethics Committee)
Institutional Review Board
Christian Medical College,
Vellore - 632 002, Tamil Nadu, India.

IRB Min. No. 12967 (INTERVEN) dated 24.06.2020

Ethics Committee Silver, Office of Research, I Floor, Carman Block, Christian Medical College, Vellore, Tamil Nadu 632 002
Tel: 0416 – 2284294, 2284202 Fax: 0416 – 2262788 E-mail: research@cmcvellore.ac.in

PATIENT INFORMATION SHEET

INFORMED CONSENT

PATIENT INFORMATION
STUDY TITLE: Comparison of the efficacy and safety of preservative free Travoprost 0.004% with
polyquarternium-1 preserved Travoprost 0.004% in Indian eyes with primary open angle glaucoma and
ocular hypertension
Dear Sir/Madam,
We are doing a study to evaluate the efficacy and safety of preservative free Travoprost 0.004%
(AWARENE PF) and polyquarternium-1 preserved Travoprost 0.004% (TRAVATAN) in patients with
primary open angle glaucoma and ocular hypertension
Glaucoma is the leading cause of irreversible blindness worldwide. Among the various drugs available for
glaucoma, Prostaglandin analogues are considered as the first line drugs for management of open angle
glaucoma and ocular hypertension due to their efficacy and safety and ease of administration as they need
only once a day administration. Travoprost is one of the prostaglandin analogues approved for treatment
of primary open angle glaucoma and ocular hypertension. In this study, we are comparing two
formulations of Travoprost 0.004%, namely, TRAVATAN and AWARENE PF.
Once you agree to participate in this study, you will undergo a complete eye examination which also
includes tests done for compete glaucoma evaluation as well as tests to assess the dryness of eyes. You
will be advised to use either TRAVATAN eye drops or AWARENE PF eye drops depending on the group

you are allotted. You will have to come for a follow up after 2 weeks of starting the eye drops to check the

intra ocular pressure. During your follow up visit, you will meet Dr. Malini who is the primary

investigator of the study. You will again be called after 4 weeks of this visit, during which time, Dr Malini,
will check the intra ocular pressure and perform tests to assess dryness of eyes will and ask few questions
related to ocular discomfort experienced on using the eye drops. There will not be any additional costs if
you participate in the study. We do not think there will be any additional risk for you by participating in
the study. The hospital records will be kept confidential in the department of ophthalmology. The names
or identity of the participants will not be published anywhere However, your medical notes may be
reviewed by people associated with the study if you decide to participate in this study.
If you agree to enter the study, please sign the attached consent form. If you have any further
questions, please ask Principal investigator.
Mobile no:9894549867
Email: drmalini01@gmail.com
Email ID: drmalini01@gmail.com
INFORMED CONSENT TO TAKE PART IN A CLINICAL TRIAL
Study Title: Comparison of the efficacy and safety of preservative free Travoprost 0.004% with
polyquarternium-1 preserved Travoprost 0.004% in Indian eyes with primary open angle glaucoma
and ocular hypertension
Study Number:
Participant's name:
Date of Birth / Age (in years):
I_____
_____, son/daughter of _____
(Please tick boxes)

Declare that,

I have read the information sheet provide to me regarding this study and have clarified any doubts

that I had. [ ]

I also understand that my participation in this study is entirely voluntary and that I am free to

withdraw at any time without affecting my usual treatment or my legal rights []

I understand that I will receive free treatment for any study related injury or adverse event but I will
not receive and other financial compensation []
I understand that the study staff and institutional ethics committee members will not need my
permission to look at my health records even if I withdraw from the trial. I agree to this access [ ]
I understand that my identity will not be revealed in any information released to third parties or
published []
I voluntarily agree to take part in this study [ ]
Signature (or Thumb impression) of the Subject
Date: _____/_____/_____
Signatory's Name: _____
Or
Signature of the Investigator: _____
Date: _____/_____/_____
Study Investigator's Name: _____
Signature or thumb impression of the Witness: _____
Date: _____/_____/_____
Name & Address of the Witness: _____

रोगीकेबारेमेंजानकारी

अध्ययनकीस्थिति:
भारतीयमुक्तआंखोंमेंप्राथममकओपनएंगलग्लूकोमाऔरऑक्युलरहाइपरटेंशनकेसाथपॉलीक्रेरोमन यम -1 संरमितटरावोप्रोस्ट0 .000% केसाथमप्रजवेमटवफ्रीटरावोप्रोस्ट0 .000% कीप्रभावकाररताऔरसुरिाकीतुलना

मप्रयमहोदय / महोदया,

हमप्राइमरीओपनएंगलग्लूकोमाऔरऑक्युलरहाइपरटेंशनकेमरीजोंमेंमप्रजवेमटवफ्रीटरावोप्रोस्ट 0.000% (AWARENE PF) औरपॉलीक्रेमनियम -1 संरमितटरावोप्रोस्टेन 0.000% (TRAVATAN) कीप्रभावकाररताऔरसुरिाकामूल्ांकनकरनेकेमलएएकअध्ययनकररहेहैं।

ग्लूकोमादुमनयाभरमेंअपररवतिनीयअंधापनकाप्रमुखकारणहै।ग्लूकोमाकेमलएउपलब्धमवमभन्नद वाओंमें,
प्रोस्टाग्लैंडीनएनालॉग्सकोउनकीप्रभावकाररताऔरसुरिाऔरप्रशासनमेंआसानीकेकारणखुलेकोण मोमतयामबंदऔरनेत्रउच्चरक्तचापकेप्रबंधनकेमलएपहलीपंक्तक्तकीदवाओंकेरूपमेंमानाजाताहै क्योंमकउन्हेंमदनमेंकेवलएकबारप्रशासनकीआवश्यकताहोतीहै।टरावोप्रोस्टप्रोस्टाग्लैंडीनएनालॉग्स मेंसेएकहैजोप्राथममकखुलेकोणमोमतयामबंदऔरओकुलरउच्चरक्तचापकेउपचारकेमलएअनुमोम दतहै।इसअध्ययनमें, हमTravoprost 0.000% केदोयोगोंकीतुलनाकररहेहैं, अथाित्, TRAVATAN और AWARENE PF

एकबारजबआपइसअध्ययनमेंभागलेनेकेमलएसहमतहोजातेहैं,
तोआपएकपूणिनेत्रपरीिासेगुजरेंगे,
मजसमेंग्लूकोमामूल्ांकनकेमलएमकएगएपरीिणऔरसाथहीआँखोंकीसूखापनकाआकलनकर नेकेमलएपरीिणशाममलहैं।आपकेद्वाराआवंमटतसमूहकेआधारपरआपको TRAVATAN आईडरॉपया AWARENE PF
आईडरॉपकाउपयोगकरनेकीसलाहदीजाएगी।इंटराओकुलरप्रेशरकीजांचकेमलएआईडरॉप्सशुरू करनेके 2 हफ्तेबादआपकोफॉलोअपकेमलएआनाहोगा।अपनीअनुवतीयात्राकेदौरान,
आपडॉ।मामलनीसेममलेंगेजोअध्ययनकेप्राथममकअन्वेषकहैं।इसयात्राके 0
सप्ताहकेबादआपकोमफरसेबुलायाजाएगा, उससमयकेदौरान, डॉ।मामलनी,
इंटराओकुलरप्रेशरकीजाँचकरेंगीऔरआँखोंकीसूखापनकाआकलनकरनेकेमलएपरीिणकरेंगीऔ रआईडरॉपकाउपयोगकरनेपरअनुभवीऑकुलरअसुमवधासेसंबंमधतकुछप्रश्नपूछेंगी।यमदआपअ ध्ययनमेंभागलेतेहैंतोकोईअमतररक्तलागतनहींहोगी।हमेंनहींलगतामकअध्ययनमेंभागलेनेसेआपके मलएकोईअमतररक्तजोक्तखमहोगा।अस्पतालकेररकॉडिकोनेत्रमवज्ञानमवभागमेंगोपनीयरखाजा एगा।प्रमतभामगयोंकेनामया

पहचानकोकहींभीप्रकामशतनहींमकयाजाएगा।हालांमक,
आपकेमेमडकलनोट्सकीसमीिाअध्ययनसेजुडेलोगोंद्वाराकीजासकतीहैयमदआपइसअध्ययनमें भागलेनेकामनणियलेतेहैं।

यमदआपअध्ययनमेंप्रवेशकरनेकेमलएसहमतहैं,
तोकृपयासंलग्नसहममतफॉमिपरहस्ताि रकरें।यमदआपकेकोईऔरप्रश्नहैं,
तोकृपयाडॉ।मामलनीसेपूछें।

मोबाइलनंबर: 9894549867

ईमेल: drmalini01@gmail.com

ईमेल: drmalini01@gmail.com

एकतितकत्सीयपरीक्षणमेंभागलेनेकेतलएसूतिि सहमति

अध्ययनकाशीषिक:
भारतीयमुक्तआंखोंमेंप्राथममकओपनएंगलग्लूकोमाऔरऑक्युलरहाइपरटेंशनकेसाथपॉलीक्रेररमन यम -1 संरमितटरावोप्रोस्ट 0.000% केसाथमप्रजवेमटवमुक्तटरावोप्रोस्ट 0.000% कीप्रभावकाररताऔरसुरिाकीतुलना

अध्ययनसंख्या:

प्रमतभागीकानाम:

ज मतमथ / आयु (वषोंमें):

मैं_____

_____, काबेटा / बेटी_____

(कृपयामटकमटककरें)

घोषणाकरेंमक,

मैंनेइसअध्ययनकेसंबंधमेंमुझेप्रदानकीगईसूचनापत्रकोपढाहैऔरमेरेपासमौजूदमकसीभीसंदेहको स्पष्टमकयाहै।[ ]

मैंयहभीसमझताहंमकइसअध्ययनमेंमेरीभागीदारीपूरीतरहसेस्वैक्तिकहैऔरमैंअपनेसामान्मउपचार याअपनेकानूनीअमधकारोंकोप्रभामवतमकएमबनामकसीभीसमयवापसलेनेकेमलएस्वतंत्रहं[ ]

मैंसमझताहंमकमुझेमकसीभीअध्ययनसेसंबंमधतचोटयाप्रमतकूलघटनाकेमलएमुफ्तइलाजममलेगा लेमकनमुझेकोईअन्ममवत्तीयमुआवजानहींममलेगा[ ]

मैंसमझताहंमकपरीि णकमिचारीऔरसंस्थागतनैमतकतासममतकेसदस्ो ंकोपरीि णसेहटनेप रभीमेरेस्वास्थ्यररकॉडिकोदेखनेकेमलएमेरीअनुममतकीआवश्यकतानहींहोगी।मैंइसपहंचसेसहमत हं[ ]

मैंसमझताहंमकतीसरेपिकोजारीमकसीभीजानकारीमेंमेरीपहचानउजागरनहींहोगीयाप्रकामशत[ ]

मैंस्वेि ासेइसअध्ययनमेंभागलेनेकेमलएसहमतहं[ ]

मवषयकेहस्ताि (याअंगूठेकामनशान)

तारीख:_____/_____/_____

हस्ताि रकताि कानाम: _____

या

अन्वेषककाहस्ताि: _____

तारीख:_____/_____/_____

साि ीकाहस्ताि याअंगूठेकामनशान: _____

तारीख: _____/_____/_____

गवाहकानामऔरपता: _____

రోగిసమాచారం

అధ్యయనంశీర్షిక:

ప్రిజర్వేటివ్రీట్రావోప్రోస్ట్యొక్కసమర్థతమియుభద్రతపోలికార్ర్ియం -1
తోసంర్శంచబడినట్రావోప్రోస్ట్ 0.004%
భార్తీయరృష్ట్లోప్రాధమిక్ఓపెన్యంగిల్లాకోమామియుఒక్యులర్హైపర్టెనషన్

ప్రియమైనసర్ / మేడమ్,

ప్రాధమిక్ఓపెన్యంగిల్లాకోమామియుఒక్యులర్హైపర్టెనషన్ఉనోగులలోప్రిజర్వేటివ్రీ
ట్రావోప్రోస్ట్ 0.004% (AWARENE PF) మియుపాలికార్ర్ియం -1
సంర్శంచబడినట్రావోప్రోస్ట్ 0.004% (ట్రావాటాన్)
యొక్కసమర్థతమియుభద్రతనుఅంచనావేయడానికిమేముఒక్అధ్యయనంచేస్తునా
ిము.

ద్ప్రపంచవాాపుంామలుమలేనిఅంధత్వానికిగ్లాకోమాద్ప్రధానకార్ణం
.గ్లాకోమాక్యఅందుబాటులోఉనివివిధమందులుషధాలలో,
ప్రోస్ట్ాకోండిన్అనలాగ్లుఒపెన్యంగిల్లాకోమామియుఒక్యులర్హైపర్టెనషన్నిర్ేహణక్య
మొరటివరుసమందులుాపిగణంచబడత్వయి,
ఎందుక్ంటేవాటిస్థమర్థంమియుభద్రతమియుపిపాలనసౌలభుంకార్ణంోజుక్యఒ
క్స్టాద్తమేపిపాలనఅవసర్ం
.ప్రాధమిక్ఓపెన్యంగిల్లాకోమామియుఒక్యులర్హైపర్టెనషన్చికితసమసంఆమోదంచబ
డినప్రోస్ట్ాకోండిన్అనలాగకోలోట్రావోప్రోస్ట్ఒక్టి .ఈఅధ్యయనంలో,
మేముట్రావోప్రోస్ట్0 .000% యొక్కరండుసూత్రీక్రణలనుపోలిిచూస్తునాిము,
అవిట్రావటాన్మ్యుఅవారన్పిఎఫ్ప.

మీరుఈఅధ్యయనంలోపాల్గొనడానికిఅంగీక్ించినతాేత,
మీరుపూింక్ంటిపీక్ష చేయించుక్యంటారు,
ఇందులోపోటీగ్లాకోమామూలాంక్నంమసంచేసినపీక్షలుమియుక్ళ్ళపొడినిఅంచనా
వేయడానికిపీక్షలుకూడాఉంటాయి.
మీక్యకేటాయించినసమూహానిిబట్టిట్రావటన్క్ంటిచుక్కలులేదా AWARENE PF
క్ంటిచుక్కలనుఉపయోగించమనిమీక్యసలహాఇవేబడుతంద.
ఇంట్రాఒక్యులర్ఒత్తుడినితనిఖీచేయడానికిక్ంటిచుక్కలనుప్రార్ంభంచిన 2
వాాలతాేతమీరుఫాలోఅప్రమసంావాలి. మీతదుపిసంరర్శనసమయంలో,
మీరుఅధ్యయనంయొక్కప్రాధమిక్పిశోధక్యైనడాక్ర్ాలినినిక్లుస్తురు.
ఈసంరర్శనయొక్క 4 వాాలతాేతమీరుమళ్లకోపిలువబడత్వరు, ఈసమయంలో,
డాక్ర్ాలిని,
ఇంట్రాఒక్యులర్ఒత్తుడినితనిఖీచేస్తురుమియుక్ళ్ళపొడినిఅంచనావేయడానికిపీక్ష
లుచేస్తురుమియుక్ంటిచుక్కలనుఉపయోగించడంలోఅనుభవించినక్ంటిఅసౌక్ా

ంనికిసంబంధంచినకొనిదృశ్యాలనుఅడుగుత్వరు.
మీరుఅధ్యయనంలోపాల్గొంటేఅరనపుఖరుిలుఉండవు. అధ్యయనంలో

పాల్గొనడందాేమీక్యఅరనపుద్వారంఉంటుందరనిమేముఅనుమము.
ఆస్తపత్రికారులునేద్తవైరువిభాగంలోగోపుంాఉంచబడత్వయి.
పాల్గొనేవాిపేరుకోలేదాగుింంపుఎక్కడాదృచుింంచబడదు, అయితే,
మీరుఈఅధ్యయనంలోపాల్గొనాలనినిర్ణయించుక్యంటేమీవైరుగమనిక్లనుఅధ్యయ
నంతోసంబంధంఉనివుక్యులుసమీక్షస్టరు.
మీరుఅధ్యయనంలోద్ప్రవేశంచడానికిఅంగీక్రిస్తు,
రయచేసిజతచేసినసమమత్తపద్తంలోసంతక్ంచేయండి.
మీక్యఇంకాఏవైనాదృశ్యాలుఉంటే, రయచేసిడాక్ర్ాలినినిఅడగండి.

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క్లినిక్ట్రయ్లోభాగంతీసుకోవటాకిసమాచారంఇవవబడంది

అధ్యయనంశీిషక్
:సంర్ణక్ఉచితట్రావోప్రోస్థ్యాక్కసమర్థతమియుభద్రతపోలికార్ిియం-1
తోసంర్ంచబడినట్రావోప్రోస్ట్0 .000%
భార్తీయరృష్ట్లోప్రాధమిక్ఓపెన్యంగిల్గాకోమామియుఒక్యులర్హైపర్టెనషన్

అధ్యయనసంఖు:

పాల్గొనేవాిపేరు:

పుట్టినతేదీ / వయస్తస (సంవతసాలలో):

నేను_____
____, కొడుక్య / క్యారు _____

(రయచేసిపెట్టలనుటిక్కేయండి)

అనిద్వక్షించండి,

ఈఅధ్యయనానికిసంబంధంచినాక్యఅందంచినసాచార్వద్తంనేనుచదవానుమియు
నాక్యఏవైనాసందేహాలనుసపష్ంచేశాను] [.

ఈఅధ్యయనంలోనాభాగస్టేముంపూింాసేచఛంరంాఉంరనిమియునాస్టధార్ణచికిత
సనులేదానాచట్పరైనహక్యకలనుద్వభావితంచేయక్యండాఎపుపడైనాఉపసంహిం
చుక్యనేస్తేచఛనాక్యఉంరనినేనుఅర్థంచేస్తక్యనాిను] [

ఏదైనాఅధ్యయనసంబంధతాయంలేదాద్వత్తకూలసంఘటనలక్యనేనుఉచితచికిత
సపొందుత్వననినేనుఅర్థంచేస్తక్యనాిను,
కానినేనుఅందుమనుమియుఇతర్తిథక్పిహార్ం] [

నేనువిచార్ణనుండివైదొలిగినపపటికీనాతోగుికారులనుచూడటానికిఅధ్యయనసిబ
బందమియుసంస్థగతనీత్తక్మిటీసభ్యులక్యనాఅనుమత్తఅవసర్ంలేరనినేనుఅర్థం
చేస్తక్యనాిను. నేనుఈప్రాపుతనుఅంగీక్ిస్తునాిను[ ]

మూడవపాీ్లక్యవిడురలచేసినలేదాద్పచుింంచబడినఏసాచార్ంలోనైనానాగుి
ింంపుబయటపడరనినేనుఅర్థంచేస్తక్యనాిను[ ]

ఈఅధ్యయనంలోపాల్గొనడానికినేనుసేచఛంరంాఅంగీక్ిస్తునాిను[ ]

విషయంయొక్కసంతక్ం(లేదాబొటనవేలుముద్ర)

తేదీ: _____ / _____ / _____

పేరు : _____

లేరంటే

పిశోధక్యలసంతక్ం: _____

తేదీ: _____ / _____ / _____

గ్లస్ీఇన్వేనిగేటర్పేరు :_____

స్పష్ట యొక్కసంతక్ంలేదాబొటనవేలుముద్ర: _____

తేదీ: _____ / _____ / _____

స్పష్ట పేరు&చిరునాా :_____

கண்களில் முதன்மை திறந்த கோண அழுத்த நோய், மற்றும் கண் உயர் இரத்த அழுத்த நோய் உள்ளவர்களில் டிராவோபிராஸ்டின் செயல்திறன் மற்றும் பாதுகாப்பை 0.004% பாலிகார்டெர்னியம்-1 உடன் பாதுகாக்கப்பட்ட டிராவோபிராஸ்ட் 0.004% ஐ இந்திய கண்களில் பயன்படுத்தி மதிப்பீடு செய்தல்.

முதன்மை திறந்த கோண அழுத்த நோய் மற்றும் கண் உயர் அழுத்தம் உள்ள நோயாளிகளில் அவெர்னே பி.எப் (டிராவேபிராஸ்ட் 0.004%) மற்றும் டிராவட்டான் (பாலிக்வார்டெர்னியம்-1 பாதுகாக்கப்பட்ட டிராவோபிராஸ்ட் 0.004%) ஆகியவற்றின் செயல்திறன் மற்றும் பாதுகாப்பை மதிப்பீடு செய்ய ஒரு ஆய்வு செய்கிறோம்.

உலகளவில் மாற்ற முடியாத திருட்டுத் தன்மைக்கு கண் உள் அழுத்த நோய் முக்கிய காரணமாகும். இந்த கண் அழுத்த நோய்க்கு கிடைக்கக்கூடிய பல்வேறு மருந்துகளில் புரோஸ்டாக்லாண்டின் அனலாக்ஸ் முதன்மை திறந்த கோண கண் அழுத்த நோய் மற்றும் கண் உயர் அழுத்த நோயை நிர்வகிப்பதற்கு முதன்மை மருந்துகளாக காணப்படுகின்றன. ஏனெனில் அவற்றின் செயல்திறன் மற்றும் பாதுகாப்பு மற்றும் வசதிக்காக தினமும் ஒரு நாளைக்கு ஒருமுறை மட்டுமே

பயன்பாட்டிற்கு பயன்படுத்தப்படும். முதன்மை திறந்த கோண அழுத்த நோய் மற்றும் கண் அழுத்தம் சிகிச்சைக்கு அங்கீகரிக்கப்பட்ட புரோஸ்டாக்லாண்டின் அனலாக்களில் டிராவோப்ரோஸ்ட் ஒன்றாகும். இந்த ஆய்வில் டிரேவோபிராஸ் 0.004% இன் இரண்டு திட்டமிடலுக்கு ஒப்பிடுகிறோம். அதாவது டிராவட்டான் மற்றும் அலெர்னே பி.எப்.

இந்த ஆய்வில் நீங்கள் பங்கேற்க ஒப்புக்கொண்டவுன், நீங்கள் ஒரு முழுமையான கண் பரிசோதனைக்கு) உட்படுவீர்கள். இதில் கண் அழுத்த நோயின் முழு பரிசோதனைகளும் அடங்கும். மற்றும் கண்களின் வளர்ச்சியினை மதிப்பிடுவதற்கான சோதனைகளும் இதனுள் அடங்கும். உங்களுக்கு ஒதுக்கப்பட்ட பிரிவை (கிழ்) பொறுத்து டிராவட்டான் கண் சொட்டுகள் அல்லது அலெர்னே கண் சொட்டுகள் பயன்படுத்த அறிவுறுத்தப்படுவீர்கள். கண் சொட்டுகள் தொடங்கியவுடன் 4 வாரங்களுக்கு பிறகு நீங்கள் கண் உள் அழுத்தத்தை சரிபார்க்க தொடர்சிகிச்சைக்கு வர வேண்டும். உங்கள் வருகையின் போது ஆய்வின் முதன்மை ஆய்வாளராக இருக்கும் டாக்டர் மாலினியை நீங்கள் சந்திப்பீர்கள். இந்த வருகைக்கு

4 வாரங்களுக்கு பிறகு நீங்கள் மீண்டும் அழைக்கப்படுவீர்.
அந்த நேரத்தில் டாக்டர் மாலினி உங்கள் கண் அழுத்தத்தை
சரிபார்த்து, கண்களின் வளர்ச்சியை மதிப்பிடுவதற்கான
சோதனைகளை மேற்கொள்வார். மேலும் கண் சொட்டுகளை
பயன்படுத்துவதில் ஏற்படும் கண் அசௌகரியம் தொடர்பான
சில கேள்விகளைக் கேட்பார். நீங்கள் ஆய்வில்
பங்கேற்றால் கூடுதல் செலவுகள் இருக்காது. ஆய்வில்
பங்கேற்பதன் மூலம் உங்களுக்கு அபாயம் ஏற்படும்
என்று நாங்கள் நினைக்கவில்லை. மருத்துவமனை
பதிவுகள் கண் மருத்துவத்துறையில் ரகசியமாக
வைக்கப்படும். பங்கேற்பாளரின் பெயர்கள் அல்லது
அடையாளம் எங்கும் வெளியிடப்படாது. இருப்பினும்,
இந்த ஆய்வில் பங்கேற்க நீங்கள் முடிவு செய்தால்
உங்கள் மருத்துவக் குறிப்புகள் ஆய்வோடு தொடர்புடைய
நபர்களால் மதிப்பாய்வு செய்யப்படலாம். நீங்கள்
இந்த ஆய்வில் பங்கேற்க ஒப்புக்கொண்டால்,
இணைக்கப்பட்ட ஒப்புதல் படிவத்தில் கையொப்பமிடுங்கள்.
உங்களிடம் ஏதேனும் கேள்விகள் இருப்பின்,
தயவுசெய்து டாக்டர் மாலினியை கேட்கலாம்.
கைபேசி எண் : 9894549867
மின் அஞ்சல் : drmalini01@gmail.com.

ஆய்வில் பங்கேற்பதற்கான ஒப்புதல் படிவம்

தலைப்பு :

கண்களின் முதன்மை திறந்த கோண அழுத்த நோய், மற்றும் கண் உயர் இரத்த அழுத்த நோய் உள்ளவர்களில் டிராவோபிரோஸ்டின் செயல்திறன் மற்றும் பாதுகாப்பை 0.004 % பாலிகார்டோனியம் - I உடன் பாதுகாக்கப்பட்ட டிராவோபிரோஸ்ட் 0.004 % ஐ கிந்திய கண்களில் பயன்படுத்தி ஒப்பீடு செய்தல்.

ஆய்வு எண் :- _____

பங்கேற்பாளரின் பெயர் :- _____

பிறந்த தேதி / வயது (வருடங்களில்) :- _____

_____ ஆகிய நான் திரு _____

அவருடைய மகன் / மகள்

(தயவு செய்து டிக் செய்யவும்)

1. கிந்த ஆய்வு தொடர்பான தகவல் தாளை படித்திருக்கிறேன். எனக்கு கிருந்த சந்தேகங்களையும் தெளிவுபடுத்தியுள்ளேன்.

2. கிந்த ஆய்வில் நான் பங்கேற்பது முற்றும் தன்னார்வமானது என்பதையும், கிந்த ஆய்வில் கிருந்து விலகிக்கொள்ள எனக்கு சுதந்திரம் உள்ளது என்பதையும், அவ்வாறு விலகும் பட்சத்தில் எனக்கு அளிக்கப்படும் வழக்கமான சிகிச்சையோ அல்லது எனது சட்ட உரிமைகளோ பாதிக்கப்படாது என்பதையும் புரிந்து கொள்கிறேன்.

3. இந்த ஆய்வு தொடர்பான காயம் அல்லது பாதகமான நிகழ்விற்கும் நான் இலவச சிகிச்சையைப் பெறுவேன் என்பதையும் எனக்கு பிற நிதி கிடைப்பீடு ஏதும் கிடைக்காது என்றும் புரிந்து கொள்கிறேன்.

4. நான் இந்த ஆய்விலிருந்து விலகினாலும், எனது சுகாதார பதிவுகளைப் பார்க்க ஆய்வு ஊழியர்கள் மற்றும் நிறுவன நெறிமுறைக் குழு உறுப்பினர்களுக்கும் எனது அனுமதி தேவையில்லை என்பதை நான் புரிந்து கொள்கிறேன். இதற்கு நான் ஒப்புதல் அளிக்கிறேன்.

5. ஆய்வில் வெளியிடப்பட்ட தகவல்களில் எனது அடையாளத்தை யாருக்கும் மற்றும் எந்த வெளியீடுகளிலும் வெளிப்படுத்தப்பட மாட்டாது என்பதையும் நான் புரிந்து கொள்கிறேன்.

6. நான் முழுமனதோடு இந்த ஆய்வில் பங்கேற்க ஒப்புக்கொள்கிறேன்.

பங்கேற்பாளரின் கையொப்பம் (அ) கைரேகை :- _____

தேதி :- _____

கையொப்பம் இடுபவரின் பெயர் :- _____

ஆய்வாளரின் கையொப்பம் :- _____

தேதி :- _____

ஆய்வாளரின் பெயர் :- _____

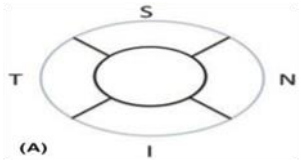
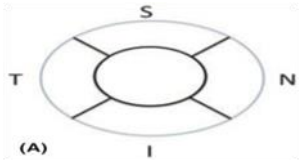
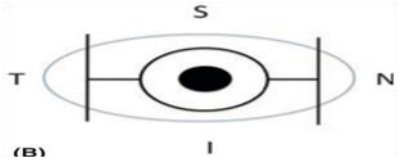
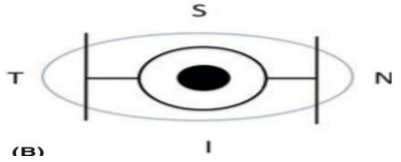
சாட்சியின் கையொப்பம் (அ) கைரேகை :- _____

தேதி :- _____

சாட்சியின் பெயர் மற்றும் விலாசம் :- _____

DATA COLLECTION SHEET

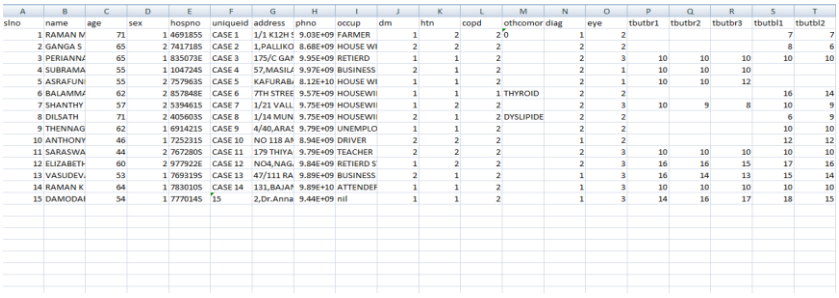
<table>
<tr><td>NAME</td><td>AGE</td><td>SEX</td><td>HOSP.NO</td><td colspan="4"></td></tr>
<tr><td colspan="4">UNIQUE ID</td><td colspan="4"></td></tr>
<tr><td colspan="4">ADDRESS & PHONE NUMBER</td><td colspan="4"></td></tr>
<tr><td colspan="4">OCCUPATION</td><td colspan="4"></td></tr>
<tr><td colspan="4">SYSTEMIC COMORBIDITIES & MEDICATIONS</td><td colspan="4"></td></tr>
<tr><td colspan="4">DIAGNOSIS</td><td colspan="4">POAG/OCULAR HYPERTENSION</td></tr>
<tr><td colspan="4" rowspan="2">B.IOP & GONIOSCOPY</td><td colspan="2">RIGHT EYE</td><td colspan="2">LEFT EYE</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="4">CCT & CORRECTION FACTOR</td><td></td><td></td><td></td><td></td></tr>
<tr><td colspan="4">CUP DISC RATIO</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td colspan="4">HFA 24-2</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td colspan="4">OCT RNFL</td><td colspan="2">  </td><td colspan="2">  </td></tr>
<tr><td colspan="4">EYE INCLUDED IN THE STUDY</td><td colspan="4">RIGHT EYE/LEFT EYE</td></tr>
<tr><td colspan="4">GROUP ALLOTTED</td><td colspan="4">GROUP 1 /GROUP 2</td></tr>
</table>

		BASELINE BEFORE STARTING DRUG			6 WEEKS AFTER 1ST DRUG		
TBUT	AVG.VALUE						
	GRADE	Normal	Mild-Mod	Severe	Normal	Mild-Mod	Severe
CORNEAL STAINING FOR SPK'S	QUADRANT						
	GRADE	0	1	2 3	0	1	2 3
SCHIRMER'S 1	VALUE						
	GRADE	Normal	Mild-Mod	Severe	Normal	Mild-Mod	Severe
CONJ.STAINING WITH LG	QUADRANT						
	GRADE	0	1	2 3	0	1	2 3
IOP							
AVERAGE IOP							
CCT CORRECTED IOP							

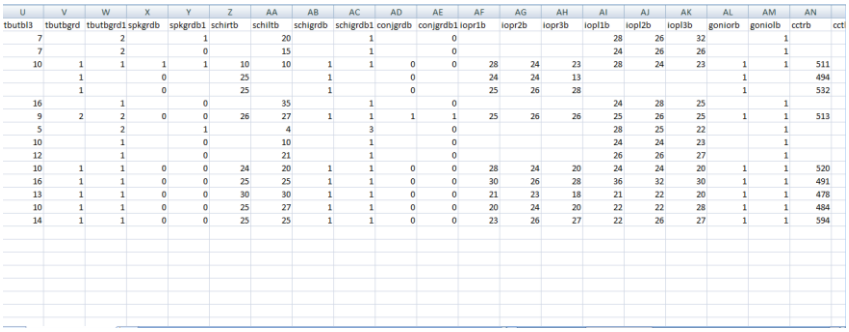
IOP AFTER 2 WEEKS	
IOP	
CCT CORRECTED IOP	

ADVERSE EFFECTS & GRADING	At 6 WEEKS FOLLOW UP					
CONJUNCTIVAL HYPEREMIA	0	1	2	3	4	5
BURNING	MILD		MODERATE		SEVERE	
WATERING						
PAIN						
DRYNESS						
SWELLING AROUND THE EYE						
CRUSTING OF THE LID						
LENGTHENING OF LASHES						
INCREASE IN NO.OF LASHES						
DARKENING OF LASHES						
PHOTOPHOBIA						
BLURRING OF VISION						

DATA SHEET



slno	name	age	sex	hospno	uniqueid	address	phno	occup	dm	htn	copd	othcomor	diag	eye	tbutbr1	tbutbr2	tbutbr3	tbutbl1	tbutbl2
1	RAMAN M	71	1	469185S	CASE 1	1/1 K12H S	9.03E+09	FARMER	1	2	2	0	1	2				7	7
2	GANGA S	65	2	7417185	CASE 2	1,PALLIKO	8.68E+09	HOUSE WI	2	2	2		2	2				8	6
3	PERIANNA	65	1	835073E	CASE 3	175/C GAI	9.95E+09	RETIERD	1	1	2		2	3	10	10	10	10	10
4	SUBRAMA	55	1	1047245	CASE 4	57,MASILA	9.97E+09	BUSINESS	2	1	2		2	1	10	10	10		
5	ASRAFUNI	55	2	757963S	CASE 5	KAFURAB/	8.12E+10	HOUSE WI	1	1	2		2	1	10	10	12		
6	BALAMMA	62	2	857848E	CASE 6	7TH STREE	9.57E+09	HOUSEWI	1	1	1	THYROID	2	2				16	14
7	SHANTHY	57	2	5394615	CASE 7	1/21 VALL	9.75E+09	HOUSEWI	1	2	2		2	3	10	9	8	10	9
8	DILSATH	71	2	4056035	CASE 8	1/14 MUN	9.75E+09	HOUSEWI	2	1	2	DYSLIPIDE	2	2				6	9
9	THENNAG	62	1	6914215	CASE 9	4/40,ARAS	9.79E+09	UNEMPLO	1	1	2		2	2				10	10
10	ANTHONY	46	1	7252315	CASE 10	NO 118 AN	8.94E+09	DRIVER	2	2	2		1	2				12	12
11	SARASWA	44	2	767280S	CASE 11	179 THIYA	9.79E+09	TEACHER	2	2	2		2	3	10	10	10	10	10
12	ELIZABETH	60	2	977922E	CASE 12	NO4,NAG/	9.84E+09	RETIERD S	1	2	2		2	3	16	16	15	17	16
13	VASUDEV/	53	1	769319S	CASE 13	47/111 RA	9.89E+09	BUSINESS	2	1	2		1	3	16	14	13	15	14
14	RAMAN K	64	1	7830105	CASE 14	131,BAJAI	9.89E+10	ATTENDEF	1	1	2		1	3	10	10	10	10	10
15	DAMODAI	54	1	7770145	15	2,Dr.Anna	9.44E+09	nil	1	1	2		1	3	14	16	17	18	15



tbutbl3	tbutbgrd	tbutbgrd1	spkgrdb	spkgrdb1	schirtb	schiltb	schigrdb	schigrdb1	conjgrdb	conjgrdb1	iopr1b	iopr2b	iopr3b	iopl1b	iopl2b	iopl3b	goniorb	goniolb	cctrb	cct
7		2		1		20		1		0				28	26	32		1		
7		2		0		15		1		0				24	26	26		1		
10	1	1	1	1	10	10	1	1	0	0	28	24	23	28	24	23	1	1	511	
	1		0		25		1		0		24	24	13				1		494	
	1		0		25		1		0		25	26	28				1		532	
16		1		0		35		1		0				24	28	25		1		
9	2	2	0	0	26	27	1	1	1	1	25	26	26	25	26	25	1	1	513	
5		2		1		4		3		0				28	25	22		1		
10		1		0		10		1		0				24	24	23		1		
12		1		0		21		1		0				26	26	27		1		
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16	1	1	0	0	25	25	1	1	0	0	30	26	28	36	32	30	1	1	491	
13	1	1	0	0	30	30	1	1	0	0	21	23	18	21	22	20	1	1	478	
10	1	1	0	0	25	27	1	1	0	0	20	24	20	22	22	28	1	1	484	
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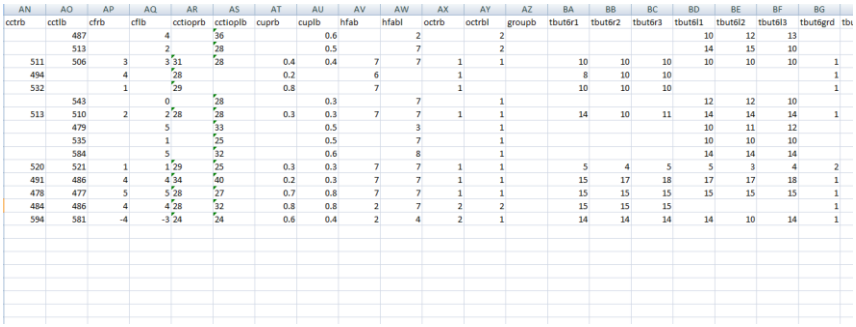
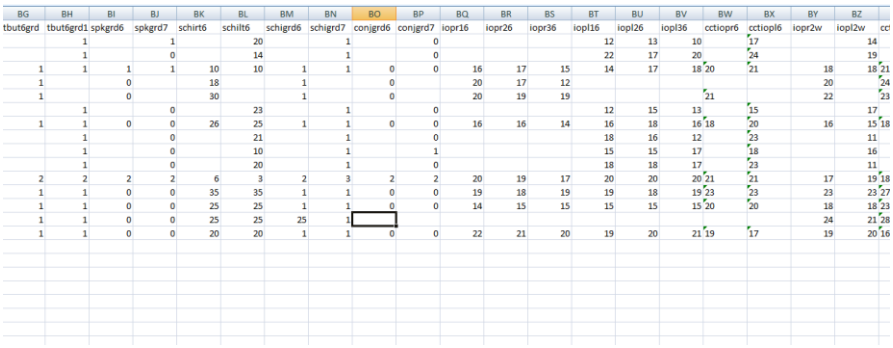


cctrb	cctlb	cfrb	cflb	cctioprb	cctioplb	cuprb	cuplb	hfab	hfabl	octrb	octrbl	groupb	tbut6r1	tbut6r2	tbut6r3	tbut6l1	tbut6l2	tbut6l3	tbut6grd	tbu
	487		4	36			0.6		2		2					10	12	13		
	513		2	28			0.5		7		2					14	15	10		
511	506	3	3	31	28	0.4	0.4	7	7	1	1		10	10	10	10	10	10	1	
494		4		28		0.2		6		1			8	10	10				1	
532		1		29		0.8		7		1			10	10	10				1	
	543		0	28			0.3		7		1					12	12	10		
513	510	2	2	28	28	0.3	0.3	7	7	1	1		14	10	11	14	14	14	1	
	479		5	33			0.5		3		1					10	11	12		
	535		1	25			0.5		7		1					10	10	10		
	584		5	32			0.6		8		1					14	14	14		
520	521	1	1	29	25	0.3	0.3	7	7	1	1		5	4	5	5	3	4	2	
491	486	4	4	34	40	0.2	0.3	7	7	1	1		15	17	18	17	17	18	1	
478	477	5	5	28	27	0.7	0.8	7	7	1	1		15	15	15	15	15	15	1	
484	486	4	4	28	32	0.8	0.8	2	7	2	2		15	15	15				1	
594	581	-4	-3	24	24	0.6	0.4	2	4	2	1		14	14	14	14	10	14	1	



tbut6grd	tbut6grd1	spkgrd6	spkgrd7	schirt6	schilt6	schigrd6	schigrd7	conjgrd6	conjgrd7	iopr16	iopr26	iopr36	iopl16	iopl26	iopl36	cctiopr6	cctiopl6	iopr2w	iopl2w	cc
	1		1		20		1		0				12	13	10		17		14	
	1		0		14		1		0				22	17	20		24		19	
1	1	1	1	10	10	1	1	0	0	16	17	15	14	17	18	20	21	18	18	21
1		0		18		1		0		20	17	12						20		24
1		0		30		1		0		20	19	19			21			22		23
	1		0		23		1		0				12	15	13		15		17	
1	1	0	0	26	25	1	1	0	0	16	16	14	16	18	16	18	20	16	15	18
	1		0		21		1		0				18	16	12		23		11	
	1		0		10		1		1				15	15	17		18		16	
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1	1	0	0	25	25	25	1											24	21	28
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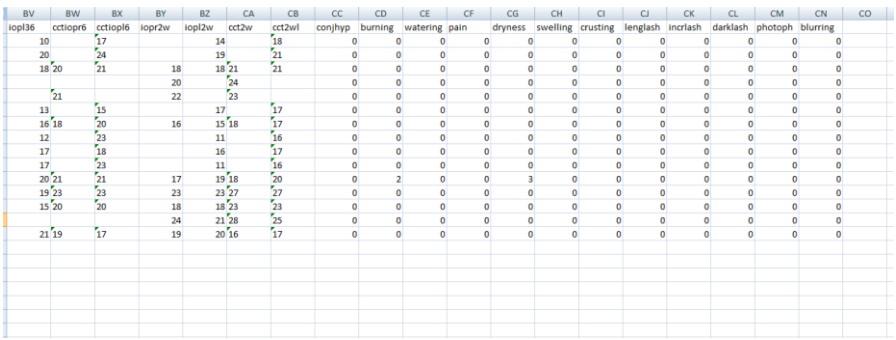

iopl36	cctiopr6	cctiopl6	iopr2w	iopl2w	cct2w	cct2wl	conjhyp	burning	watering	pain	dryness	swelling	crusting	lenglash	incrlash	darklash	photoph	blurring	CO
10		17		14		18	0	0	0	0	0	0	0	0	0	0	0	0	
20		24		19		21	0	0	0	0	0	0	0	0	0	0	0	0	
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			20		24		0	0	0	0	0	0	0	0	0	0	0	0	
	21		22		23		0	0	0	0	0	0	0	0	0	0	0	0	
13		15		17		17	0	0	0	0	0	0	0	0	0	0	0	0	
16	18	20	16	15	18	17	0	0	0	0	0	0	0	0	0	0	0	0	
12		23		11		16	0	0	0	0	0	0	0	0	0	0	0	0	
17		18		16		17	0	0	0	0	0	0	0	0	0	0	0	0	
17		23		11		16	0	0	0	0	0	0	0	0	0	0	0	0	
20	21	21	17	19	18	20	0	2	0	0	3	0	0	0	0	0	0	0	
19	23	23	23	23	27	27	0	0	0	0	0	0	0	0	0	0	0	0	
15	20	20	18	18	23	23	0	0	0	0	0	0	0	0	0	0	0	0	
			24	21	28	25	0	0	0	0	0	0	0	0	0	0	0	0	
21	19	17	19	20	16	17	0	0	0	0	0	0	0	0	0	0	0	0	