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Master of Science, Biomedical Sciences, December 2003

The Use of Prostaglandin Analogues (PGAs) in the Treatment of Patients with Open-Angle Glaucoma (OAG) or Ocular Hypertension (OHT)

Summary: Glaucoma is an ocular condition that causes damage to the optic nerve leading to a loss of visual function, and permanent blindness if left untreated. It is the leading cause of preventable blindness in the U.S. The main risk factor for glaucomatous optic neuropathy is elevated intraocular pressure (IOP), which can be controlled by pharmaceutical therapy, surgical therapy or both. Topical medication is usually recommended prior to surgical intervention. Objectives: This study had two main objectives. First, to determine the IOP lowering safety and efficacy of three concentrations of a new prostaglandin analogues (PGA), and secondly to determine the incidence of ocular hyperemia with once-daily dosing of study medication compared to it's vehicle and to latanoprost, a marketed PGA. Study Design: This was a Phase II, double-masked, dose-response study with five treatment arms (the three different concentrations of study drug), vehicle, and latanoprost. Study was conducted in fourteen days, with five study visits as follows: Screening and eligibility visit followed by three on-therapy visits scheduled on Day 1, Day 7, and Day 14. The primary efficacy variable was IOP measurements taken at four different time points on study visits. Results: Final data will not available in time to include in this paper.

CLINICAL INTERNSHIP WITH THE CLINICAL GLAUCOMA/VIABILITY GROUP AT ALCON RESEARCH, LTD.: THE USE OF PROSTAGLANDIN ANALOGUES IN THE TREATMENT OF PATIENTS WITH OPEN-ANGLE GLAUCOMA (OAG) OR OCULAR HYPERTENSION (OHT)

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CLINICAL INTERNSHIP WITH THE CLINICAL GLAUCOMA/VIABILITY GROUP AT ALCON RESEARCH, LTD.: LITERATURE REVIEW ON THE USE OF PROSTAGLANDIN ANALOGUES IN THE TREATMENT OF PATIENTS WITH OPEN-ANGLE GLAUCOMA (OAG) OR OCULAR HYPERTENSION (OHT)

THESIS

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MASTER OF SCIENCE

By

MAGALI G. HALL, B.S.

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CHAPTER 1

INTRODUCTION

Glaucoma is a common eye condition for which no specific cause has been determined. It is not a single clinical disease, but rather an ocular condition caused by damage to the optic nerve head (ONH) leading to an optic neuropathy, and a loss of visual function. Optic neuropathy refers to a disturbance of the nerves of the eye due to an interruption of blood circulation leading to degeneration or destruction of the optic nerve (Figure 1). This optic nerve damage is often caused by increased intraocular pressure (IOP)[1]. Most forms of glaucoma follow the classic triad, which include increased IOP, optic nerve damage, and a loss of visual function. It is extremely important to evaluate each of these three elements before forming a differential diagnosis of a certain type of glaucoma. The exact etiology of the disease remains unknown, it can be caused by many different disorders and it occurs in all races and at all ages. It is known that optic neuropathy is triggered, in most cases, by excessive pressure on the nerves due to

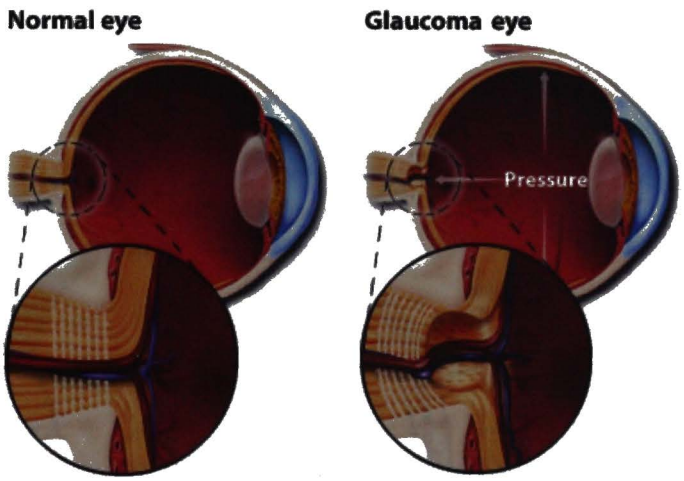


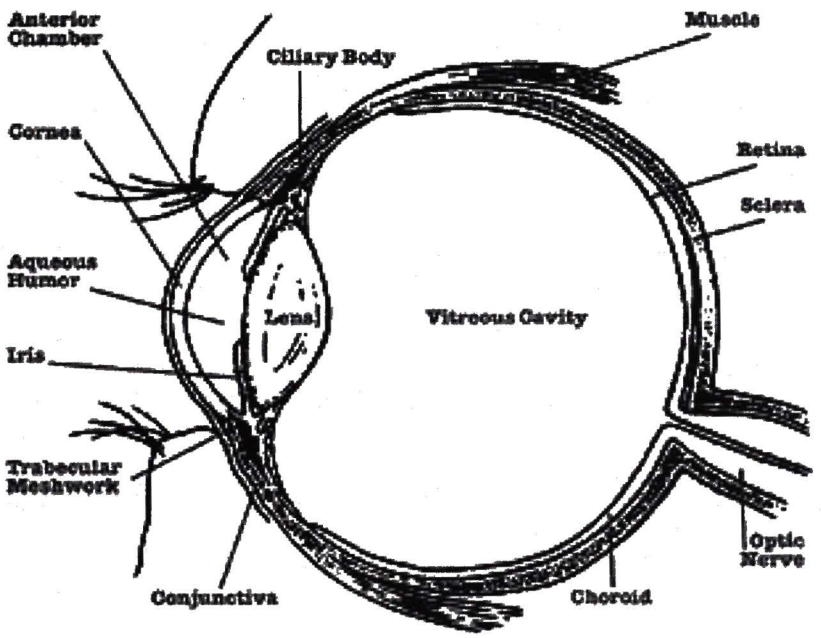
Figure 1: Topography of the Optic Nerve in a Normal Eye compared to a Glaucomatous Eye.[2]

elevated IOP. Over time, this pressure can cause irreversible vision loss and blindness if left untreated. However, early detection and intervention can preserve vision.

I. Physiology and Anatomy of the Human Eye

To understand the nature and impact of glaucoma in terms of its etiology, symptoms, disease process, diagnosis and treatment options available, it is essential to be familiar the basic anatomy of the human eye including it's structures, and the dynamics of aqueous humor (Figure 2).

Figure 2: Anatomy of the Human Eye[3]



The human eye is considered one of the most complex and essential organs of the body, and is an extension of the central nervous system. The eye is filled with a watery aqueous humor located in the anterior chamber, and a viscous fluid called vitreous humor located in the posterior chamber at the back of the eye.

Vision is the predominant sense, and to understand vision the analogy of a camera is useful to visualize how the eye functions. A camera needs a lens and film to produce an image, and in the same way, the eye needs a lens to refract incoming light, and film or the retina onto which to focus the light. The convex-shaped cornea at the front of the eye captures incoming light, the light travels through the lens where it's bent and refracted and focused onto the retina[4], a light-sensitive layer located at the back of the eye. Light is converted into electrical impulses by photoreceptors in the retina called rods and cones. The macula is the center of the retina, and in the middle of the macula is the fovea centralis, which has a high concentration of cones providing sharp, brilliant colored vision.

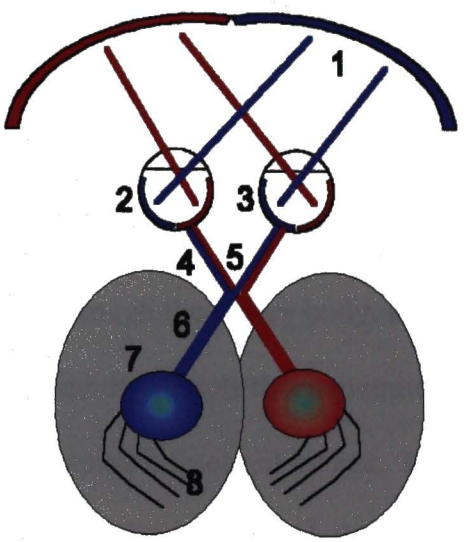
The output from the retina is millions of nerve fibers that converge and become the optic nerve, which exits the eye through the optic disc located at the back of the eye. From the optic disc, the optic nerve splits at the optic chiasm, and the information conducted by each side will come from the opposite visual field (Figure 3).
Once these fibers pass the optic chiasm, the axons are called the optic tract. The optical message will eventually travel to the primary visual cortex located in the occipital lobe of the brain. This is the area of the brain responsible for processing and interpreting electrical signals into visual images.[5]

One of the unique features of the eye includes a blood-aqueous barrier (anterior chamber), and a blood-retinal barrier (posterior chamber), allowing for site-specific drug delivery. In addition, the eye contains both vascular and avascular tissues, which is a feature that enables the transmission of light

to the retina, and makes the eye easy to access clinically.[6]

In order to have a basic understanding of the glaucoma disease process, it is necessary to be familiar with the dynamics of aqueous humor. Aqueous humor is located in the anterior chamber of the eye, and it serves two important functions. First, it nourishes the avascular structures in the area around the iris and behind the cornea. Secondly, it is responsible for the eye's IOP, which maintains the eye's structural integrity. Aqueous is continuously produced by a vascular structure called the ciliary body. Fluid flows from the posterior portion of the anterior chamber (between the iris and corı To offset this inflow of fluid and t through two main pathways.

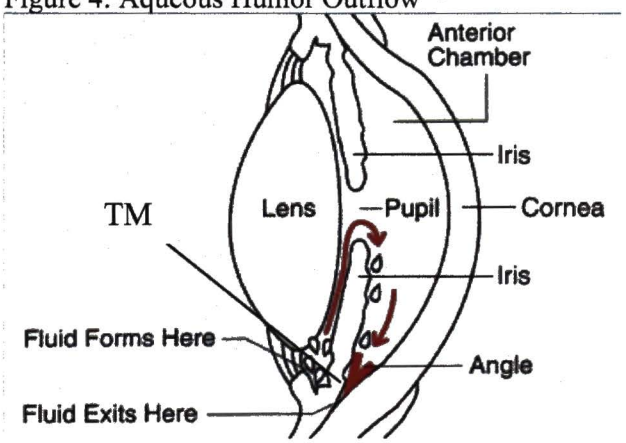
Figure 3: Visual Fields of the Eye and Visual Pathway to the Brain.[7]



1 visual field, **2,3** retina, **4** optic nerve, **5** optic chiasm, **6** optic tract, **7** lateral geniculate body, **8** optic radiations and occipital.[7]

The first pathway is called the conventional pathway. Fluid circulates from the anterior chamber through the trabecular meshwork (TM),[4] a spongy network of connective tissue which acts as the drain of the eye (Figure 4). From the TM, aqueous humor eventually journeys

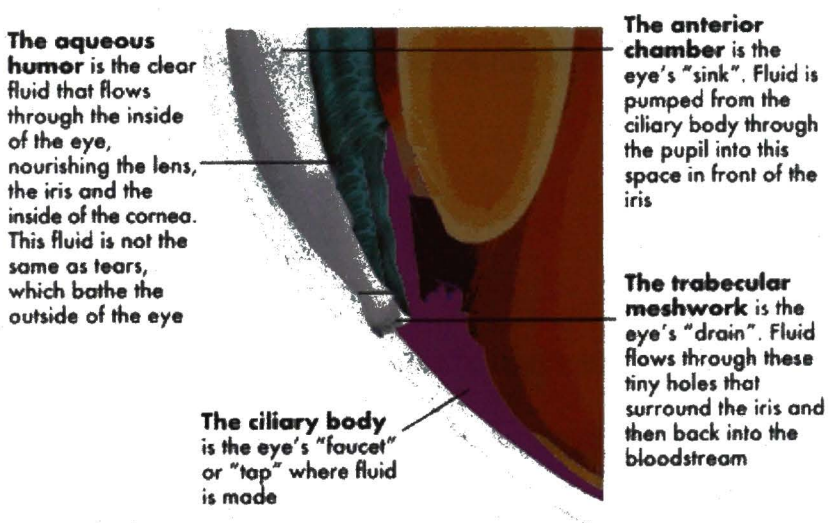
Figure 4: Aqueous Humor Outflow [3]



into the bloodstream via a special drainage system, called the Canal of Schlemn (CS) located within the chamber wall. This pathway is pressure-dependent, and is the primary site of aqueous outflow accounting for 83- 96% of outflow.[8] When IOP is low, the TM may collapse, or proteins and blood cells may reflux into the CS.[9]

The alternative pathway is the unconventional system [8], also commonly referred to as the uveoscleral outflow pathway because only 5-15% of aqueous humor moves through here. Fluid flows from the anterior chamber through the ciliary body, and exits the eye through the intact sclera, or along the nerves and the vessels that penetrate it. This pathway is pressure-independent, and is believed to be influenced by age. In fact, some experts suggest this pathway could possibly account for up to 50%[9]of aqueous outflow in normal eyes of young people (Figure 5).

Figure 5: Dynamics of Aqueous Humor through the TM [10]



Other important structures of the eye include the colored iris, which is a muscle that surrounds the pupil and regulates its size.[4,3] The pupil is a small opening in the

center of the iris through which light enters the eye. Covering the eye is a "white", fibrous, protective membrane called the sclera. The cornea is a transparent, avascular, anterior structure where incoming light is captured. It is also a powerful refracting surface, providing 2/3 of the eye's focusing power.[2]

II. Prevalence of Glaucoma

Glaucoma ranks as one of the leading causes of blindness in both developed and developing nations with 70 million people inflicted worldwide.[11] It is the second leading cause of preventable blindness in the United States (U.S.) after cataract,[10] three million American adults have the disease, and is the leading cause of blindness among African Americans.[3,12] Open angle glaucoma (OAG) is the most prevalent type of glaucoma affecting Caucasians and persons of African descent. This type of glaucoma affects at least 2 million people in the U.S.,[14,1] and an estimated thirty three million people worldwide have the disease.[13]

III. Glaucoma Disease Process

Chronic glaucoma is often called the "silent thief of sight" because the person has no symptoms, no hint their vision is deteriorating. Over years or decades, the elevated pressure compressing the nerves gradually destroys first the outer fibers, which reduces peripheral vision but not central vision. By the time the person notices loss of peripheral vision, permanent damage has already occurred. If the pressure remains high, the destruction can progress until tunnel vision develops. The last nerve fibers destroyed are

those responsible for central vision, and if this occurs, the glaucoma patient becomes totally blind.

There are conditions that block or obstruct the TM, or drainage channel. If this occurs aqueous humor can not leave the eye as fast as it is produced causing the fluid to build up beyond what the ocular tissue can handle, consequently increasing the pressure within the eye.[14] Once this IOP builds, the threat of damaging the optic nerve and developing glaucoma is imminent.

The mean IOP is 16 millimeter of mercury (mmHg) with a standard deviation of 3 mmHg, and the range of normal IOP is approximately between 10-22 mmHg with 2 mmHg standard deviations above and below the mean. However, measurements above 22 mmHg do not necessarily predict glaucoma, but could be indicative of ocular hypertension (OHT) if there is no visible optic nerve damage. Nevertheless, this elevated pressure does put these individuals at a higher risk for developing glaucoma.

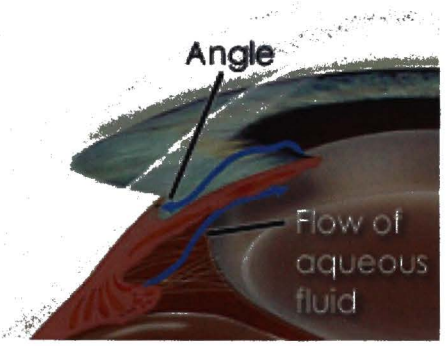
IV. Types of Glaucoma

There are several types of glaucoma. Primary glaucoma is diagnosed when there is no pre-existing medical condition warranting the onset of the disease, in other words, it is not related to other conditions and occurs on it's own. When other conditions or diseases cause glaucoma is it called secondary glaucoma. Secondary glaucoma may be caused by any of the following conditions: diseases that affect blood flow to the optic nerve such as diabetes, hypertension and migraines. Systemic conditions such as sickle-cell anemia, leukemia or hypothyroidism. Sleep apnea, which is a sleeping disorder that affects

breathing and reduces oxygen; physical injury to the eye can damage the TM; extreme myopia from weakened eye structures; previous eye surgery; and the use of corticosteroids. In fact, studying the effects of steroids on the eye is helping researchers understand the glaucoma disease process.[4,3,1]

The most common form of glaucoma is OAG. It is called "open-angle" because the drainage angle between the iris and cornea, remains open, but the channels in the TM become clogged slowing down the outflow of aqueous humor (Figure 6).

Figure 6: Angle Structures [2]



OAG is also referred to as "wide angle" glaucoma (chronic, simple), and the most common subtype of OAG is primary open angle glaucoma (POAG). Chronic POAG will not produce any symptoms until it has done irreversible damage. At this point, patients may notice a visual problem only when light is dim, some are sensitive to glare, and others may eventually lose the ability to differentiate between shades and brightness. This type of glaucoma tends to start in one eye and eventually involved both. Several clinical findings, other than elevated IOP, need to be present to support a diagnosis of OAG.[8,5]

Another type of glaucoma is closed angle glaucoma (CAG) or "angle-closure" glaucoma. This type is more common than OAG, and has a hereditary tendency. The drainage angle where aqueous outflow occurs is narrow and at risk of closing.[4] Drugs or conditions that suddenly dilate the pupils such as antihistamines, asthma medications or

even emotional stress may cause this shallow angle to close and precipitate an acute attack.[3]

Closed angle glaucoma is considered a medical emergency because the pressure inside of the eye increases very rapidly and symptoms are dramatic. If it is not treated within hours it may permanently damage vision. Symptoms include intense pain in the eyebrow area, blurred vision develops usually in one eye, and the usually reddens. CAG may rely on drug treatment to control the attack, although surgery may be required for long-term management (iridectomy, peripheral or complete).[15] In chronic CAG the process is gradual and painless.

Other types of glaucoma depend on a person's age. Congenital glaucoma, as the name implies, is due to abnormal development of the anterior chamber prior to birth, decreases aqueous outflow through the TM. This type of glaucoma appears between birth and ages 3-4, it is very rare only one in every ten thousand newborns have the disease, and it is almost always managed surgically.[2,16,5]

Juvenile glaucoma develops between ages 4-10 and is strongly hereditary. Adult onset glaucoma develops during adulthood. Normal tension glaucoma (NTG) is a form of OAG that is more common than previously thought. Patients with this form of OAG usually have IOPs within the normal range (10-22 mmHg) with values statistically considered average. Nevertheless, optic neuropathy develops and by definition, these patient's IOP never elevates above 22 mmHg. In Japan, twice as many people have NTG than OAG.[3] Clearly, what constitutes healthy IOP varies among individuals, and whether

NTG is a separate disease entity or if it is considered OAG with normal IOP is still debated.

V. Glaucoma Risk Factors

There are several risk factors associated with glaucoma. The prevalence of chronic glaucoma increases with age, and studies found it doubles every ten years after the age of sixty, one to four percent of individuals over age forty five have glaucoma, and it accounts for ninety percent of all cases in the U.S.[4,17] Across all age groups, the prevalence of glaucoma in African Americans is higher than in Caucasian Americans, and it also develops earlier at age forty five compared to age sixty in Caucasians.[4,1]

Glaucoma tends to run in families, one out of five sufferers has a close relative with the condition suggesting a genetic factor involved.[17] In fact, a number of genes are being identified as possible factors in glaucoma. One of these genes is called MYOC, and a defect in this gene appears to cause a blockage of the TM. Other strong risk factors include optic nerve cupping greater than 50% or asymmetry, central corneal thickness less than 555 microns (0.5 mm),[9] and high myopia (near sightedness related to the shape of the globe).

VI. Importance of Diurnal Fluctuations

The association between a person's IOP and blood pressure is not entirely clear but there seems to be a correlation with hypertension. Diabetes is also among the possible risk factors.[3,17,18] The reason diabetics are at a higher risk is because they tend to manifest

ocular complications, and are thus more likely to be seen by an ophthalmologist thereby leading to more diagnoses of glaucoma.

An elevated IOP is the main risk factor for glaucoma, but it is not the only risk factor involved in disease progression. Evidence suggests that frequent and large diurnal fluctuations in IOP, not simply high IOP, is associated with the greatest risk of vision loss. Aqueous flow rate in a healthy, non-glaucomatous person fluctuates over a twenty four hour period along with many other physiological values.[9,19] Several factors such as time of day, heartbeat, respiration, exercise, fluid intake, systemic medications, and topical drugs[9] all effect IOP fluctuations. IOP also varies diurnally as aqueous humor production changes.

In normal individuals, IOP fluctuates between 2-6 mmHg in a twenty-four hour period. In general, a diurnal fluctuation of greater than 10 mmHg from the normal IOP (10-22 mmHg), is suggestive of glaucoma.[9] This normal diurnal variation in IOP is attracting attention from the medical and scientific community as a potential risk factor for glaucoma patients. The correlation between IOP fluctuation, diurnal control and optic nerve damage has not been sufficiently studied, but is believed to be very important in the overall health of the optic nerve, and glaucoma disease progression.

Whether it is the IOP peak or the diurnal range that impacts glaucoma patients remains to be seen; however, it is postulated that a steady IOP throughout the day will help prevent optic nerve damage.[19] Maintaining a steady IOP throughout the day is important because it has been reported that some patients with IOP values within the normal range, between 10-22 mmHg, that are on medication for OAG still have

progressive deterioration of their visual fields.[4,19] These findings suggest that diurnal peaks of IOP not detected during the normal offices hours of 0900-1800 may be the cause of disease progression.

Zeimer *et al.*[5] suggested that it is the magnitude of the peak IOP, as opposed to the diurnal range or the daily mean, which is the significant value in regards to identifying at-risk patients. Furthermore, a prospective study performed by Asrani *et al.*,[19] aimed at determining the risk associated with diurnal IOP fluctuations (the range, the diurnal range, and the day-to-day variations), and differentiating between mean IOP and IOP fluctuations assessed whether variable diurnal IOP is a risk factor for further glaucomatous damage. They found that large diurnal IOP fluctuations are not only a significant risk factor, but have an effect on disease progression.

In this study, 64 patients with OAG performed home tonometry with a self-tonometer five times a day for 5 days. Even though home monitoring IOP was identical to the office IOP, the diurnal day-to-day variation was 10 mmHg on average, a somewhat surprising magnitude in this group who had office IOPs around 18 mmHg, and always below 25 mmHg.[33] The clinical implications of the correlation between IOP fluctuation, diurnal control and optic nerve damage remains important for diagnostic and therapeutic reasons, and should be addressed in managing glaucoma patients. It appears that the variation in IOP is the most important in preserving vision. Studies continue to address this issue in "normal" and in glaucomatous eyes in order to minimize vision loss.

CHAPTER 2

LITERATURE REVIEW

I. Historical Background of Glaucoma Medications

Historically, glaucoma therapy began in the second half of the nineteenth century with the introduction of cholinergic agonists (1876-1960).[12] The cholinergic agonists were followed by adrenergic agonists between 1898-1978. Prior to 1978 only three types of medications were available for the treatment of chronic glaucoma. These were the topical miotics, topical epinephrine, and oral carbonic anhydrase inhibitors (CAIs).

The topical miotics, although effective, produced poorly tolerated side effects such as diminished night vision, headaches, and vision changes. Topical epinephrine was helpful, but induced side effects including systemic tachycardia, nervousness, and rebound hyperemia.[17] The last class of drugs introduced during this time period (between 1954-1998),[12] the oral CAIs, proved to be effective but often carried significant systemic side effects from lethargy and depression to gastrointestinal upset.[17]

During 1969-1991, α-2 agonists were introduced, and reduction of elevated IOP with α-2 agonists proved to be an exciting new therapeutic approach for the treatment of glaucoma. However, it was not until 1977-1983, that the ubiquitous β-blocking agents were introduced as glaucoma medications. These agents revolutionized the medical therapy of glaucoma, and are still considered the first line of therapy.

In recent years (1992-1999),[12] a new class of IOP lowering topical medications were presented as agents to reduce IOP; these are the prostaglandin analogues (PGAs). In June 1996, the U.S. Food and Drug Administration (FDA) approved Xalatan® (latanoprost, Pharmacia & Upjohn Co.) for treatment of glaucoma. Rescula® (unoprostone isopropyl, CIBA Vision), Lumigan® (bimatoprost, Allergan), and TRAVATAN® (travoprost, Alcon Research, Ltd.).[20,12,21]

These novel agents are becoming first line therapy due to their IOP lowering efficacy combined with minimal systemic side effects to date. However, further studies and analysis of results is necessary to assess their long-term safety and efficacy given the fact they have not been on the market for sufficient time.

A. Clinical Presentation of Glaucoma

Glaucoma frequently goes undetected which is why it is often termed the "sneak thief of sight".[3,17] Since vision loss is gradual and symptoms are painless, patients do not realize their condition until visual field loss manifested as expansion of their blind spots, loss of peripheral vision, and eventual tunnel vision are present. By the time a person notices loss of peripheral vision, permanent nerve damage has already occurred. Therefore, early detection and treatment are key to successful management and prevention of glaucoma.

In defining glaucoma, one should also include IOP-independent causative factors, such as vascular and structural alterations to the optic nerve head. One of the IOP-independent risk factors gaining interest is the amount of blood flow reaching the eye.

According to one study, there has been a correlation between low blood flow and glaucomatous damage.[16]

Despite scientific advances, glaucoma remains a diagnosis of exclusion, a misnomer in that no specific abnormality causes the disease or separates it from other ocular diseases. Upon slit lamp examination (SLE), there might be no visible abnormality of the TM, and some experts believe that the cells in the TM are unable to carry out their normal function,[3] yet the exact cause of this malfunction is unknown. Others argue there may also be fewer cells present, as a natural result of aging.[17] Thus far, the exact pathophysiology underlying the cause of glaucoma has yet to be discovered.

B. Diagnosing and Treating Open-Angle Glaucoma

Diagnosing glaucoma is not as straightforward as it may appear. First, there is no set value constituting an eye pressure considered glaucomatous since what is considered normal IOP varies among individuals. Some individuals with normal or low IOPs develop glaucomatous damage, while others with above average IOPs show no signs of optic nerve damage. Secondly, elevated IOP is only a risk factor, and other clinical findings need to be present.

The commonly accepted range for normal IOP is between 10-22 mmHg,[9] however; an IOP consistently elevated above 22 mmHg over time can eventually result in irreversible, and presently incurable damage to the optic nerve leading to visual field loss and blindness if left untreated. Generally, an IOP consistently greater than 21 mmHg with no optic nerve damage is termed OHT,[13] which has the potential to cause

glaucomatous damage at any time. Therefore, clinical findings should include numerous tests including IOP measurements throughout the day to evaluate diurnal IOP fluctuations possibly with the use of a home tonometer. An evaluation of the optic nerve head in order to get an accurate cup to disc ratio, visual acuity assessments, and visual field tests to determine the amount of vision loss present.[19]

In addition, diagnosing glaucoma involves not only clinical findings but also requires an understanding and evaluation of the patient's medical history, family history, overall health, as well as social and psychological status.[16] Ophthalmologists must balance efficacy, cost, compliance and side effects when deciding on the best medical therapy to prescribe for glaucoma patients. It is also challenging to differentiate between patients manifesting OHT or OAG. The medical community's growing contention is that treatment for early stage glaucoma should be individualized based on age, IOP levels, and disease severity.[22] All of these factors are imperative to offer patients proper treatment and an improved quality of life.

Treating glaucoma largely depends upon the type of glaucoma present and the disease stage, and is ultimately aimed at lowering IOP to a point that stops progression. Treatment consists of eye drops, pills, surgery or a combination of these until the desired IOP is achieved for that patient. Frequently, multiple glaucoma medications are used in combination to adequately lower IOP,[17] and both eye drops and surgery work to help increase aqueous fluid drainage from the eye, and/or decrease the amount of fluid that is produced in the eye. each drug has a specific mechanism of action and IOP lowering efficacy (Table 1).

Table 1: Summary of the Mechanism of Action and IOP-lowering Efficacy of the Commonly Prescribed Glaucoma Medications.[12,16,23,24,6]

Drug Name	Mechanism of Action	IOP-lowering Efficacy
MIOTICS (CHOLINERGIC AGONISTS)	Increase conventional (TM) aqueous outflow: ciliary muscle contraction.[6]	20-30 percent[23]
CARBONIC ANHYDRASE INHIBITORS: (Topical and Oral)	Inhibit cholinesterase enzymes, thus enhancing acetylcholine action	19-23% [12]
BETA-BLOCKERS	Decrease aqueous production: inhibit carbonic anhydrase and HCO_3 production in ciliary process.[6]	15-20 percent [23]

COMBINATION DRUGS • CAI (dorzolamide) • β-blocker (Timolol)	Decrease aqueous humor formation: block adrenergic β-receptor from activation of adenylyl cyclase and cAMP formation in the ciliary process.[32,6]	22-30 percent[23]
ALPHA-ADRENERGIC AGONISTS	Both drugs decrease aqueous production	18-30 percent[23]
PROSTAGLANDINS	Decrease inflow of aqueous	15-24 percent[23]
	Increase uveoscleral outflow: stimulate PG FP receptors to increase MMP activation and ECM remodeling of ciliary body.[6]	25-35 percent[23]

Glaucoma therapy has changed over the years as the advent of new drugs has become available for clinical use. With the increasing choices of medications, the clinical use of drugs has evolved adapting to the introduction of each new drug. In spite of this progress, the therapeutic goal remains developing measures to control the flow and

drainage of aqueous humor in the inner-eye in order to restore IOP to a level that prevents disease progression.

C. Diagnostic Tools Used in Assessing Glaucomatous Damage

In order to identify whether a patient has glaucoma or is a 'glaucoma suspect', several tests must be performed. These tests are performed on a regular basis to determine if there has been disease progression. These include measuring the patient's IOP, evaluating the appearance of the drainage angle to determine whether the angle is open or closed, viewing the appearance and health of the optic nerve to determine the cup to disc ratio, testing for visual field defects, and visual acuity.

To be considered 'glaucoma', two or more of the following findings must be present: an optic nerve suggestive of glaucoma, IOP consistently greater than 22 mmHg, and suspicious visual field abnormality.[9] As a general rule, one-time examinations do not have the same value as serial screenings and follow-up visits.[18] Ophthalmologists have a variety of diagnostic tools available to determine whether a patient has glaucoma.

Tonometry tests the eye's IOP.[1] The Goldmann applanation tonometer involves numbing the eye(s) with a topical anaesthetic such as tetracaine (interferes with nerve conduction), and touching the cornea with a small probe. It calculates IOP directly in mmHg by measuring the force necessary to flatten an area of the cornea of 3.06 mm diameter.[9] Goldman applanation tonometer (Figure 7) is considered the "Gold Standard", and is the most reliable and accurate way to measure pressures because it makes contact with the eye.

Another method to test IOP is using a non-contact tonometer called the air puff test or the air puff tonometer. It is a quick, non-invasive device where a puff of air is sent onto the cornea to measure IOP. It is commonly used in routine eye examinations. This instrument is not as accurate as applanation tonometry because it does not come into contact with the cornea.

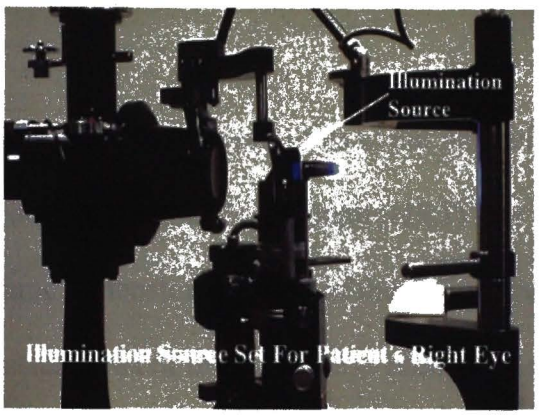


Figure 7: Goldman Applanation Tonometer [25]

Gonioscopy is essential to determine the type of glaucoma a patient has. It is performed by numbing the eyes with a topical anaesthetic. A lens is placed on the front surface of the eye, and with the use of mirrors it allows one to visualize the drainage angle. This test is very quick and determines if the angle is open or closed. It also allows one to see if there is any pigment or material clogging the drainage angle.

The dilated fundus exam is important in diagnosing and managing glaucoma. It magnifies the optic nerve and allows the optic nerve to be evaluated in order to get an accurate cup to disc ratio. The cup to disc ratio is the amount of the entire nerve head that has been cupped out or where glaucoma has caused damage. Readings range from 0 meaning no cupping, to 1.0 where the entire nerve has been cupped out. Cupping is the hallmark sign of glaucoma, and is directly related to the loss of peripheral vision.

Visual field testing is used to confirm that glaucoma has affected visual function, to evaluate severity and to monitor for progression. The automated perimeter is commonly used to determine where in the eye the optic nerve damage has occurred. Visual acuity tests the patient's vision using a logMAR visual acuity chart, the results should indicate best-corrected vision.

There also exist diagnostic imaging devices as additional tools to aid physicians in confirming glaucomatous damage. The Heidelberg Retinal Tomograph (HRT)[16] is a scanning laser imaging device that takes a three dimensional image of the optic nerve. It can detect changes in height, volume, depression, area of the cup to disc ratio, and is becoming an essential piece of equipment in diagnosing early glaucoma and monitoring for progression. These diagnostic tools and new devices such as the HRT should not replace traditional clinical evaluation methods used to diagnose glaucoma, but should rather be used in tandem as supportive tools to substantiate clinical evidence of glaucoma.[16]

Even though pharmaceutical therapy for glaucoma has introduced new medications over the years, lowering IOP continues to be the only proven method for reducing the risk of visual field loss, and remains the primary goal of therapy.[12]

II. Pharmaceutical Therapy

A number of pharmaceutical medications are available to treat glaucoma. These drugs reduce pressure in the eye, but carry mild to severe side effects depending on the medication used. The topical forms are usually recommended first before taking oral

medications. Currently, there are five classes of medications available to treat patients with glaucoma. The most frequently used are theβ-blockers, CAIs, α-agonists, miotics (cholinergic agonists), and the newest PGAs. These drugs may be used alone or in combinations to maximize IOP lowering effects.

A. Beta-Adrenergic Receptor Antagonists (β-blockers)

These agents have been an important part of glaucoma therapy and are traditionally considered first line of therapy due to excellent pressure-lowering efficacy, adequate duration of action, and a profile of generally well tolerated local and systemic adverse effects. β-blockers have a proven safety and efficacy record, and have been on the U.S. market for over twenty years. When applied topically they lower IOP by inhibiting aqueous humor production. However, since only a small amount is absorbed by the cornea, most of it enters the bloodstream and can cause long-term systemic side effects.

The cell has several β-receptors, β1- and β2-receptors will be discussed here. The selective β-blockers block β1-receptors more efficiently than β2-receptors, and β1-receptors are responsible for heart rate and the strength of heart muscle contraction. The nonselective β-blockers block both β1- and β2-receptors, and the β2- receptors are responsible for the function of smooth muscle (muscles that control body functions but that are not subject to conscious control).

Therefore, one of the drawbacks of using either β1- or β2-blockers is the long

term systemic side effects associated with these drugs. In the central nervous system, tremors, anxiety, insomnia, headaches, dizziness, confusion, hallucinations, cerebral hemorrhage, weakness, and drowsiness have been reported with β-1 blockers. Cardiovascular palpitations, tachycardia, hypertension, dysrhythmias, and increased T wave were also reported. Gastrointestial effects included anorexia, nausea, vomiting, and respiratory dyspnea.[12,17] The most common β2-mediated side effects include orthostatic hypotension, bradycardia, nausea, vomiting, and diarrhea. Serious side effects include bronchospasm, and congestive heart failure.[12,17,23]

There are selective and non-selective β blockers available to treat glaucoma. Betoptic S® (Alcon Research, Ltd.) is the only selective β-1 blocker, and appears to have fewer side effects on the heart. The non-selective β-blockers include timolol, levobunolol, metipranolol, carteolol, which act on both β1 and β2 receptors.[12, 17, 24] Timolol is the standard brand and is available in two forms, maleate (Timoptic) and hemihydrate (Betimol), and also as a gel (Timoptic XE and Falcon gel).[17,26,27] β1-blockers increase the safety profile in that fewer β2-mediated systemic side effects such as bronchospasm and bradycardia occur. However, these are not as effective in reducing IOP as their non-selective counterparts. Non-selective β-blockers lower IOP by 4-6mmHg, and Betoptic S®, a selective β1-blocker, lowers IOP by 3-4 mmHg.[12]

The IOP lowering efficacy of these drugs can be enhanced when used concomitantly with another agent or when used in combination. One such study indicated that the IOP lowering effect of timolol was enhanced by the twice daily (BID) dosing of 2% dorzolamide, a CAI, either concomitantly or in combination.[28]

B. Carbonic Anhydrase Inhibitors (CAI)

These agents are members of the sulfonamide family. CAIs are available as topical (dorzolamide and brinzolamide) and oral (acetazolamide, methazolamide) forms. They reduce aqueous humor formation with a reported IOP reduction of 16-23%, according to Soltau *et al.*,[12] and by as much as 40% according to others.[29] CAIs are now used when other drugs are not effective. Their mechanism of action is to improve blood flow in the retina and the optic nerve, theoretically slowing down the disease progression,[29] through a reduction in the accumulation of bicarbonate in the posterior chamber. This decreases sodium and associated fluid movement linked to the bicarbonate ion.[17]

The first oral CAI demonstrating IOP lowering efficacy was acetazolamide (Diamox®), introduced in 1954,[17] later followed by oral methazolamide (Neptazane®), and dichlorphenamide (Datanide®). Oral CAIs are the most potent of these ocular hypotensive drugs. They are more effective than the eye drops, but frequent systemic side effects have limited their long-term use. Unpleasant side effects include frequent urination, depression, anorexia, diarrhea, nausea and vomiting, sexual dysfunction, paresthesia and fatigue.[23,29]

Topical CAIs are associated with fewer systemic side effects than the oral forms, and are generally better tolerated by patients. Therefore, topical CAIs have dramatically reduced the use of oral CAIs, and the side effects associated with the oral agents.[16]

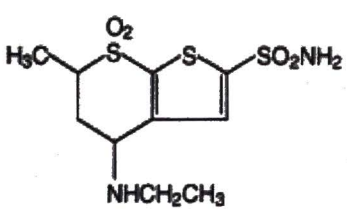
The evolution from oral forms to topical forms had a four-decade gap primarily due to the fact that "carbonic anhydrase (CA)-II, the isoenzyme which most likely plays

an important role in the production of aqueous humor in humans, must be essentially inhibited by 100% to elicit a pharmacological response."[28] A sufficiently high intraocular concentration of drug is, therefore, required to achieve the inhibition of CA, and attempts to do this in the past had historically failed.

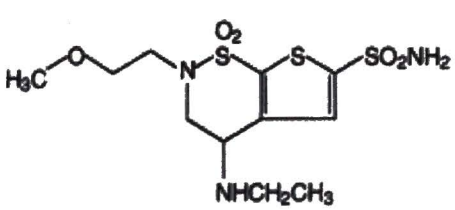
Trusopt® (dorzolamide) was introduced in 1995, and Azopt® (brinzolamide) in 1998. These are both topical forms currently available to treat OHT and/or glaucoma and as with oral forms work by decreasing the production of aqueous humor. Azopt® ophthalmic suspension 1% was designed by Alcon to be closer in pH to human tears, minimizing ocular stinging.[29] Trusopt® is a very potent inhibitor of CA-II, and its site of action is local within the eye. Azopt® and Trusopt® are generally prescribed BID, but are occasionally used three times daily (TID).

Dorzolamide is used in monotherapy as a 2% solution administered TID, and its ocular hypotensive effect is comparable to that of timolol, a β-blocker. Furthermore, topical dorzolamide is generally well tolerated and had a low drop-out rate in clinical studies. The most frequent ocular side effect is burning and stinging upon instillation, and a bitter taste. However, even though brinzolamide has a lower incidence of

Figure 8: Chemical Structures of Dorzolamide and Brinzolamide.[28]



Dorzolamide



Brinzolamide

burning/stinging, it elicits more blurred vision.[28] Studies have indicated that a 1%

suspension of brinzolamide is comparable to 2% dorzolamide in lowering IOP, both drugs being administered TID. The chemical structure of dorzolamide and brinzolamide are illustrated below (Figure 8).

C. Alpha-2 Adrenergic Receptor Agonists (α-2 agonists)

These agents stimulate α and β-adrenergic receptors and activate muscles in the eye that dilate the pupil and increase aqueous outflow. Newer variations called α-2 agonists reduce production of aqueous humor, and also increase aqueous outflow through the uveoscleral pathway.[29,5] Iopidine® (apraclonidine) and Alphagan® (brimonidine) are α-2 agonists. These are taken BID or TID, and are commonly used before glaucoma surgery such as a trabeculoplasty to further lower IOP since this surgical procedure only partially opens the drainage channels; however a number of studies indicate that these drugs may be useful as primary therapy when used in combination with β-blockers or other standard agents.[29,30]

Systemic side effects include hypertension, tachycardia, headache, dry mouth, fatigue, dizziness, somnolence, and decreased mental alertness. Ocular side effects include ocular allergic reactions, hyperemia, eye ache, and ocular discomfort on instillation.[5]

D. Miotics (Cholinergic Agonists)

Miotics, also called cholinergic agonists have been used as glaucoma therapy for over one hundred years. These agents narrow the iris muscle and constrict the pupil, this

pulls the iris away from the TM allowing aqueous outflow to increase. Their cellular mechanism of action is to prevent destruction of acetylcholine (Ach) known as cholinesterase inhibitors, resulting in an enhanced Ach effect facilitating transmission of impulses across the myoneural junction.[31,24] A study by Pang *et al.*[31] indicates that direct muscarinic effects on the TM may also play a role in the regulation of aqueous outflow and IOP because the TM itself contracts after muscarinic stimulation. Miotics are dosed four times daily (QID) for the long-term treatment of glaucoma,[16] and lower IOP by 20-30% through conventional pathways.

Miotics were the standard agents before topical β-blockers were discovered; however; their use is declining due to ocular and systemic side effects that include eye and brow pain, myopia, retinal problems and decreased vision.[29] Serious systemic side effects include respiratory depression, bronchospasm, laryngospasm, and respiratory arrest. Convulsions, paralysis, nausea, vomiting and diarrhea have also been reported.[17]

As a result, these agents have been replaced by newer drugs, but are still useful in carefully selected patients. Patients with aphakia (without a lens) or pseudophakia (with a synthetic lens), pigmentary glaucoma (accumulation of pigment from the iris in the TM), and patients with acute CAG are all candidates for this medication.[16] Their ocular side effects range from poor night vision/adaptation, induced myopia, and lens opacity to temporal or supraorbital headaches and orbital pain.[12,24]

Pilocarpine® is the standard miotic, but because these need to be taken several times a day patient compliance is an issue. The potential use of Pilocarpine® as adjunctive IOP lowering medication has been studied. Hartenbaum *et al.*[32] conducted a

12-week trial comparing the effectiveness and tolerability of dorzolamide hydrochloride ophthalmic solution 2% TID with pilocarpine hydrochloride 2% QID as adjunctive therapy to timolol maleate ophthalmic gel-forming solution (TG) 0.5% once daily as measured by changes in IOP and occurrence of adverse events. Results demonstrated that dorzolamide and pilocarpine were equally effective as adjunctive therapy in lowering IOP, but dorzolamide was better tolerated.

E. Prostaglandin Analogues (PGA)

These drugs are the newest agents recently been introduced to the array of ocular hypotensive medications used to treat glaucoma. Prostaglandins (PGs) are locally active hormones that are synthesized and released by various ocular tissues during inflammation;[33] however small amounts of topical exogenous PGs can reduce IOP without causing inflammation.[34]

Their mechanism of action is to increase aqueous humor outflow through the uveoscleral pathway. Recent animal and clinical studies reviewed by Weinreb et.al.[26] on the effects of exogenous PGs on the aqueous humor outflow pathways conclude that although the exact mechanism of action is not know, there appears to be activation of a molecular transduction cascade, and an increased biosynthesis of matrix metalloproteinases (MMPs), a family of proteinases that can cleave ECM components altering the collagen content in the ciliary muscle, iris root and sclera, reducing the hydraulic resistance in the uveoscleral pathway.[35, 36]

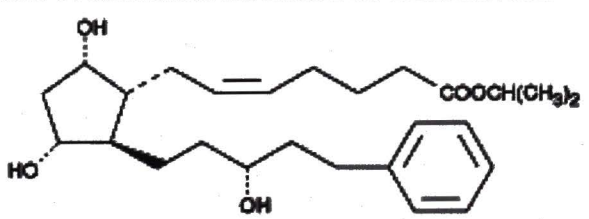
Studies indicate that aqueous outflow passes from the anterior chamber to the extracellular spaces among the ciliary muscle, to the back of the eye, and exits through the sclera and possibly the choroid vessels.[37,38] There is the possibility that reduction of ECM may contribute to the mechanism of increased uveoscleral outflow.

Other studies have also reported that $PGF_2\alpha$, and its analogs can increase total outflow facility in monkeys and humans.[23,39] PGs alter the structure of the uveoscleral pathway and can increase blood-aqueous barrier permeability,[40] which could alter uveoscleral outflow facility. However, only a limited number of studies have been published regarding the effects PGAs have on the microvasculature in the eye. Since these agents have only been on the market for six years, long-term use will provide additional information concerning the safety and efficacy of these agents.

TRAVATAN® (travoprost), Xalatan® (latanoprost), Lumigan® (bimatoprost), and Rescula® (isopropyl unoprostone) are commercially available.[36,41] Latanoprost was the first prostaglandin analogue introduced in 1996 [23] by Pfizer to reduce the IOP in patients with POAG or OHT by increasing uveoscleral outflow. Latanoprost is an ester analogue of F2alpha PG,[42,43] (Figure 9) and IOP lowering efficacy lasts for up to twenty four hours after a single topical dose.[43,44]

In 2000, the Food and Drug Administration (FDA) approved Unoprostone, a PGA designated as a docosanoid.

Figure 9: Chemical Structure of Latanoprost.[45]



Docosanoids are omega-3 polyunsaturated fatty acids that are endogenous to the central nervous

system including the retina. They are structurally similar to eicosanoids such as prostaglandins and leukotrienes; however, eicosanoids are derived from arachidonic acid, whereas docosanoids are derived from docosahexaenoic acid. Following topical dosing unoprostone isopropyl is rapidly absorbed through the cornea and conjunctival epithelium where it is hydrolyzed by esterases to a biologically active metabolite, unoprostone free acid.[21] Unoprostone lowers IOP by increasing uveoscleral outflow.

In 2001, two new medications were released, Lumigan® (bimatoprost), and TRAVATAN® (travoprost) whose chemical properties are generally similar to those of latanoprost,[41] and also lower IOP by increasing uveoscleral outflow.

An important difference in the molecular formula among these three drugs is that bimatoprost and travoprost both contain a double bond at the C13-C14 position. This bond remains saturated in latanoprost, and not in the other two PGs. The importance of this position tends to be associated with conjunctival hyperemia.[46,47]

Since little information is available that compares conjunctival hyperemia among the three different PGAs, Stewart *et al.*[20] evaluated hyperemia after short-term use of latanoprost 0.005%, bimatoprost 0.03% and travoprost 0.004% in healthy subjects. The results showed that latanoprost may cause significantly less short-term ocular hyperemia on average than bimatoprost or travoprost. The reason for this difference is not known, although speculation suggests the saturated double-bond at C_{13}-C_{14} with latanoprost is the cause for less hyperemia.

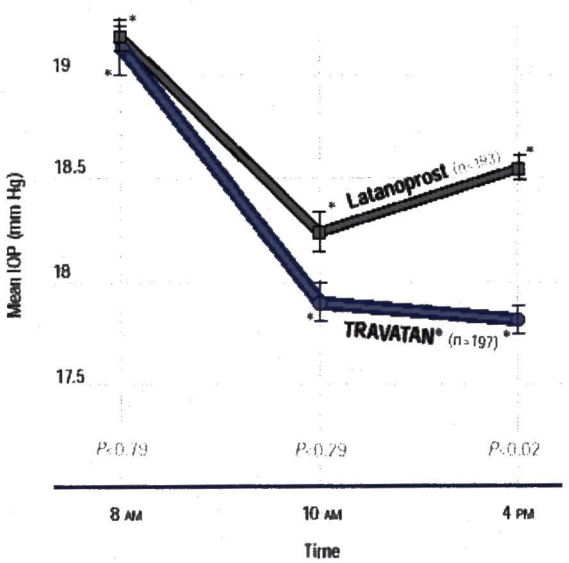
In another study, Parrish *et al.*[15] also evaluated hyperemia among the three PGAs, latanoprost, bimatoprost, and travoprost in a twelve week randomized study. The results

indicated that latanoprost was associated with the least hyperemia, followed by travoprost, and bimatoprost which showed the most hyperemia.

Furthermore, Stewart et.al.[41] randomly surveyed physicians from the American Academy of Ophthalmology to evaluate the clinical appearance and significance of conjunctival hyperemia associated with latanoprost, bimatoprost and travoprost. The survey indicates that bimatoprost appears to have the highest hyperemia, with latanoprost having the lowest, but in general, hyperemia was observed with all three prostaglandin-related medications with varying incidence and severity.

In addition, a 28-day prospective, randomized, double-masked study comparing travoprost to bimatoprost therapy found hyperemia to be significantly greater in

Figure 10: IOP lowering comparison between Latanoprost and TRAVATAN®[48]



* Error bars represent two standard errors of the mean.

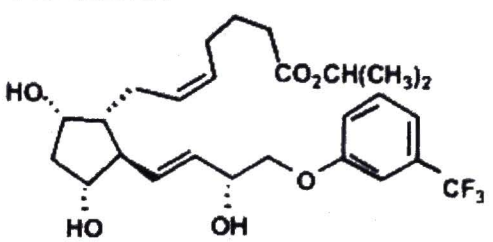
bimatoprost than travoprost patients. In addition, myalgia was reported to be significantly greater in bimatoprost than travoprost.[49]

To determine the IOP reducing effects of two concentrations of travoprost (0.0015% and 0.004%) with latanoprost 0.005% and timolol 0.5%, Netland et.al [48]

performed a twelve month study. Results indicate that after twelve months of treatment, both concentrations of travoprost (0.0015% and 0.004%) were equal or superior to latanoprost, and superior to timolol in lowering IOP in patients with OAG or OHT at all treatment visits. Mean IOP reductions ranged from 6.0 – 8.1 mmHg for travoprost (0.0015% and 0.004%), 6.2 – 8.1 mmHg for latanoprost, and from 4.7 – 7.1 mmHg for timolol (Figure 10).

The chemical structure of TRAVATAN® (Figure 11) is similar to latanoprost, and other PGAs. According to several studies,[7,50] TRAVATAN® is a full agonist at FP receptors and therefore, causes a maximum response in aqueous outflow and IOP reduction. TRAVATAN® has also been proven effective as adjunctive therapy, and has shown superiority over timolol and latanoprost for treating African Americans.[22]

Figure 11: Chemical structure of TRAVATAN®.[45]



In a recent 2003 study, patients with glaucoma or OHT who needed additional IOP lowering or who were intolerant of other glaucoma medications were placed on bimatoprost therapy over the course of two months. The results of this study indicated that not only does bimatoprost help patients achieve low target IOPs (mean decrease in IOP was 3.4 mmHg),[51] it is well-tolerated when used as a replacement for latanoprost.

Similarly, Gandolfi *et al.*[45] tested the efficacy of bimatoprost 0.03% for lowering IOP in patients with OAG or OHT who did not respond to treatment with latanoprost 0.005%. Fifteen patients were enrolled, and thirteen of fifteen patients showed a greater

than or equal to 20% IOP decrease with bimatoprost treatment. None of the fifteen patients showed a greater than or equal to 20% decrease of IOP after thirty days of latanoprost treatment. Therefore, most of the subjects exhibiting no significant IOP response to 0.005% latanoprost weree likely to be responders to 0.03% bimatoprost.

Ocular hyperemia is the main side effect reported with use of topical PGs, which can influence cosmetic appearance. Other side effects include permanent change in eye color from green or blue to brown. The pathogenesis of iris darkening is not clearly understood, and may be due to increased melanin synthesis, but findings are remain inconclusive.[36] Since PGs may increase blood flow to the eye, periorbital eyelid tissue thickens, and lashes also become longer and thicker in some patients.[24] Systemic side effects are rare, but include flu-like symptoms and myalgia.

F. Combination Therapy

It is believed that better compliance in the management of glaucoma is achieved if there is a decreased number and less frequent administration of drops. For these reasons, combination therapy was introduced as a means to reach lower target pressures and improve patient compliance, and combinations of drugs may prove to be more effective than using either drug alone.[52] The benefit of combination therapy is that it allows administration of two drugs simultaneously in one drop BID.

The only combination therapy currently on the U.S. market is Cosopt®, which combines timolol maleate 0.5%, a β-blocker , and dorzolamide 2%, a CAI. This

combination is very useful as a second-line therapy when prescribed BID. However, this medication is not as effective as simultaneous use of each of the two drugs separately.

Currently, a combination of timolol and latanoprost is being studied as combination therapy. A study conducted by Higginbotham et. al [52] demonstrated that the combination of timolol and latanoprost lowered IOP more effectively than either drop alone. However, results of this study were not clinically significant because only a difference of only 1 mmHg between latanoprost and the combination drug was demonstrated.

Konstas *et al.* evaluated the safety and efficacy (mean diurnal IOP) of latanoprost 0.005% given every evening versus timolol 0.5% and dorzolamide 2% fixed combination (TDFC) given twice daily to white Greeks. Diurnal curve IOPs were taken at six time point throughout the day. Thirty three patients with OAG or OHT completed the study. Mean diurnal IOP for latanoprost was 15.9 ± 2.3 mmHg and 15.3 ± 2.0 mmHg ($P = 0.05$) for TDFC. Due to the convenience of once daily dosing, eighteen patients overall preferred latanoprost versus two patients for the fixed combination.[53] The results of this study also indicate that the diurnal IOP is lowered more, by a small but statistically significant amount, with TDFC compared with latanoprost.

The pharmaceutical therapies mentioned are available commercially in the U.S. (Table 2). All of these drugs have entered the market adding to our ability to manage glaucoma. Recent studies have enhanced our understanding of the mechanism of action, efficacy, and safety of these therapeutic agents, and have provided us a better understanding of the differences among these medications. New treatment options and

the continuous release of new information regarding their use will continue to present clinicians with complex therapeutic decisions.

Table 2: Marketed Glaucoma Medications (Alcon Research, Ltd., 2003).

Generic Name	Trade Name
Miotics and Oral/Topical Carbonic Anhydrase Inhibitors	
Pilocarpine	Isopto Carpine®, Pilocar®, Pilostat®, Pilagan®
Carbachol	Isopto Carbachol®
Acetazolamide	Diamox®
Methazolamide	Neptazane®
Dorzolamide	Trusopt®
Brinzolamide	Azopt®
Alpha-agonists and beta-agonists	
Epinephrine	Epinal®, Eppy/N®, Epifrin®, Glaucon®
Dipivefrin	Propine®
Apraclonidine	Iopidine®
Brimonidine	Alphagan P®
Beta-antagonists, Prostaglandins, and Combination Drugs	
Betaxolol	Betoptic-S®, Betoptic®
Timolol	Timoptic®, Timoptic –XE®, Betimol®, Timoptic Gel-Forming Solution®

Carteolol	Ocupress®
Metipranolol	OptiPranolol®
Levobunolol	Betagan®
Travoprost	TRAVATAN®
Latanoprost	Xalatan®
Bimatoprost	Lumigan®
Unoprostone Isopropyl	Rescula®
Dorzolamide / Timolol	Cosopt®

III. Surgical Therapy

There are many surgical procedures available to treat glaucoma. Each one is advantageous in it's own right, but surgery is usually done when medications do not adequately lower IOP or when patients do not respond to medication.

A. Filtration Surgery

One of the most common surgical procedures is called filtration surgery or trabeculectomy. This procedure has been performed for over one hundred years, and is usually recommended when topical medication does not adequately lower IOP. Trabeculectomy opens the full thickness of the drainage angle and involves removing a tiny piece of the sclera leaving a tiny hole where the fluid can drain out and be absorbed

by the bloodstream.[54] A small bubble called a "bleb" usually forms over the incision site, which is a sign that aqueous is flowing out of the eye.

Trabeculectomy is painless, and a local anaesthetic along with a sedative is used. The majority of these are performed as outpatient visits, yet a stay in the hospital to have IOP and VA checked the next day is not uncommon. After this surgery, most patients are able to discontinue all anti-glaucoma medications. One of the drawbacks of trabeculectomy includes scarring over the incision site requiring addition surgery. This scenario is more commonly seen in younger patients since they have a stronger healing system than older patients. The procedure has a high success rate, but the IOP lowering effects often last less than a year requiring patient's to continue use of topical drops.

B. Laser Trabeculoplasty

Laser trabeculoplasty has become increasingly popular as an intermediate step between drugs and traditional surgery. This procedure uses a YAG laser to burn 80-100 tiny, evenly spaced holes into the TM , the heat from the beam may cause some areas of the drain to shrink. As a result, adjacent areas stretch open allowing fluid to drain more easily. Trabeculoplasty is painless, takes ten to twenty minutes, and can be performed in the office or at an outpatient facility. The IOP-lowering results vary per person, but it does not reduce pressure to the extent of trabeculectomy, and patients usually need to continue using eye drops. One of the benefits of this procedure is fewer complications and side effects.

Despite initial success in lowering IOP, studies show that two years after laser surgery, the pressure may increase again in more than half of all patients, thus, even though it is very good at getting the pressure down, its effects sometimes wear off over time.[54]

C. Filtration Shunts

Filtration shunts often called tube-shunt surgery involves inserting a plastic tube with an at tached silicone pouch into the eye's anterior chamber. Fluid collects onto a tiny plate that is sewn to the side of the eye, and is absorbed by the tissues in the eye. Patients most likely to benefit from this procedure are those in whom a more standard operation, such as trabeculectomy, was unsuccessful. This usually occurs because the opening made with trabeculectomy is more likely to become blocked by scar tissue than is the channel made with a filtration tube. This procedure is performed with local anesthesia. Little discomfort, except for minor irritation, is experienced. Nevertheless, they are effective treatment for those patients who can not tolerate drugs or whose IOPs are not sufficiently lowered with medication.[3]

D. The Future of Glaucoma Therapy

Although decreasing IOP is the only proven method of treating glaucoma, new medical treatments for glaucoma are being studied, including a new therapeutic class that increases uveosclral outflow, are locally active and receptor specific. Another area of study is neuroprotection to promote the survival of retinal ganglion cells either by

prevention apoptosis (programmed cell death) [16] or through blood flow regulation to increase outflow or decrease the disease progression. The most exciting area is genetics where gene therapy and stem cell transplants will be added to the array of glaucoma treatments.[5,12,16]

The future for treating and possibly curing glaucoma looks promising. However, prevention, rather than treatment, in my opinion, is the direction in which clinical research should go.

CHAPTER 3

CLINICAL STUDY – PROTOCOL C-03-25

I. Study Objective

There are a variety of glaucoma medications currently available on the U.S. market. All of these drugs efficaciously lower IOP in patients with OAG or OHT. However, the systemic and ocular side effects associated with these agents have led pharmaceutical companies to research new drugs in order to develop a better glaucoma medication with fewer systemic and ocular side effects in the hopes of delaying or preventing the progression of this disease.

Developing a better glaucoma therapy will not only improve patient compliance and lower ocular pressures, but will ultimately improve patients' quality of life. With these objectives in mind, the research plan is to study three concentrations of a new PGA to determine the drug concentration which shows optimum IOP lowering efficacy with minimal side effects. PGAs are a novel group of glaucoma medications aimed at demonstrating superior safety and efficacy.

This study has two main objectives:

1. To determine the IOP lowering efficacy and safety of three concentrations of a new PGA, and

2. To determine the incidence of ocular hyperemia with once daily dosing of the study medication compared to its vehicle and to latanoprost, a marketed PGA

II. Study Design

This is a Phase II, double-masked, dose-response study with five treatment arms, being the three different concentrations of the study medication, it's vehicle or placebo, and latanoprost 0.005%. This multi-center study will be conducted at five investigational sites in the U.S. with a total of one hundred patients equally divided where each site will enroll twenty patients. The treatment phase of the study will be conducted over the course of fourteen days.

There were five study visits total. All patients were seen for a screening visit followed by a washout period of five to twenty eight days where they discontinued use of IOP lowering medications. Those not on IOP lowering medications had a minimum washout of three days. Patients also signed informed consent according to the principles set forth by the Declaration of Helsinki.

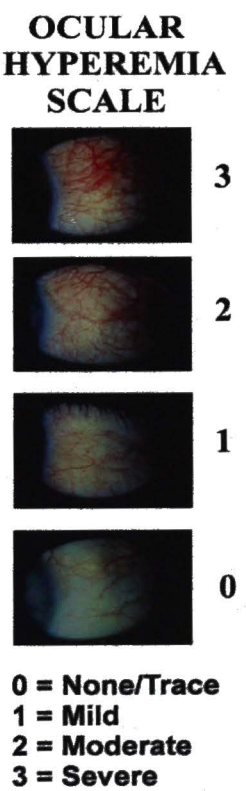
During eligibility patients had to satisfy all inclusion/exclusion criteria and IOP had to qualify in at least one eye at all four time points throughout the day. The last three visits were on-therapy visits were diurnal IOPs will be measured in the office on Day 1, Day 7, and Day 14. Those patient's whose IOP still qualified at the first time point on Day 1 were randomized to treatment by Alcon. Eligible patients were enrolled and instructed to dose daily at the first time point for fourteen days, except on visit days

where they were asked to bring masked medication with them. All medications will be administered topically, supplied to patients in identical bottled in order to maintain the integrity of masking.

III. Safety and Efficacy Variables

The following safety variables will be collected and evaluated to ensure patient safety throughout the study. Cardiovascular values included blood pressure and pulse measurements; ocular examinations included Slit Lamb Biomicroscopy Examination (SLE) to view the structures of the eye including the cornea, iris, lens, retina, and conjunctiva. Gonioscopy to determine the type of glaucoma present, whether OAG or CAG; logMAR VA to determine best-corrected vision; Automated Perimetry to analyze the amount of visual field loss present; dilated fundus exam to visualize the optic nerve and evaluate the cup to disc ratio to determine the amount of nerve damage; and ocular hyperemia assessments according to Alcon's hyperemia scale (Figure 12). The scale ranges from zero meaning none or trace hyperemia to three meaning severe ocular

Figure 12 Alcon Hyperemia Scale.



redness. All adverse events (AEs) and serious adverse events (SAEs) were captured and appropriately handled by the site and Alcon's monitor.

The primary efficacy variable was IOP measurements conducted at the four different time points throughout the day on Day 1, Day 7, and Day 14. IOP measurements will be performed using a Goldmann applanation tonometer.

IV. Materials and Methods

Once each patient is deemed eligible and appropriately randomized, one of three concentrations of masked investigational drug, latanoprost, or placebo will be dispensed. Each subject will be responsible for ensuring the masked drug is properly instilled. Protocol states one drop of masked drug will be instilled topically in the study eye(s), once daily. Patients will be required to dose for a period of fourteen days. On Day 14, study medication will be instilled in the office one last time.

Data collection will be kept for each patient in CRFs (CRFs), original source documents, and clinic charts, which will be maintained at the site. An Alcon clinical research scientist (CRS) and myself will conduct regular monitoring visits throughout the course of the study.

Patients enrolled in the study must satisfy the following inclusion criteria. At least eighteen years of age of any age or race with a diagnosis of OAG (with or without pigment dispersion or pseudoexfoliation component) or OHT. All patients must sign informed consent at the screening visit. All patients must meet the IOP qualifying

criteria, and be able to safely discontinue use of all IOP-lowering medication(s) for the required washout period.

Those patients excluded from the study had any one or all of the following: any form of glaucoma other than OAG or OHT (with or without pigment disperson or pseudoexfoliation component), women of childbearing potential must have been surgically sterilized at least three months prior to screening or be at least one year postmenopausal, patients who cannot be safely washed out of any chronic excluded therapy for the required length of time set forth in the protocol, patients with a history of specific ocular conditions as stated in the protocol, and patients with less than thirty days on a stable dosing regimen prior to eligibility visit of any non-glaucoma medication that may affect IOP.

Ocular hyperemia, IOP and cardiovascular measurements will be queried at every visit. At the end of the study on Day 14, patients will complete an exit exam. Once all procedures for the fourteen days are complete, the study will be closed, and all study medications both used and unused will be returned to Alcon.

V. Data Analysis

This study will be completed in November 2003, all data will be collected and at Alcon before the study is officially closed; however, the results will not be available in time to be included in this paper. Therefore, the table below (Table 3) represents hypothetical results with the five treatment arms, twenty patients per site, and other

Figure 13: Data Analysis

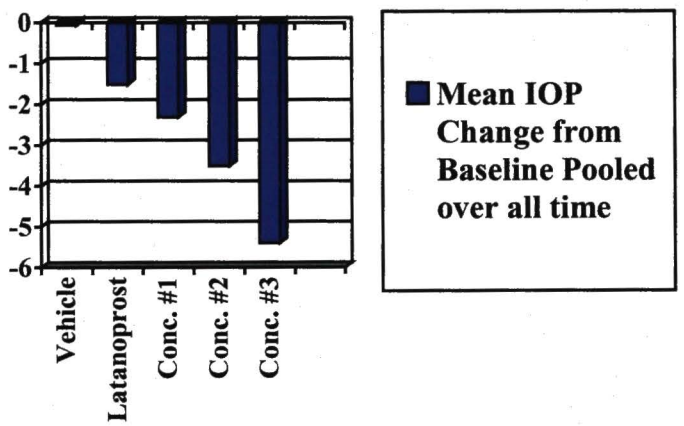


Table 3: Hypothetical Study Results

Treatment	N	Mean IOP Change	Std	Lower 95% CI	Upper 95% CI
Vehicle	20	-0.06	2.3	-4.4	0
Latanoprost	20	-1.5	2.3	-1.5	-2.4
Conc. #1	20	-2.3	2.8	-2.6	-1.8
Conc. #2	20	-3.5	2.5	-0.9	-2.1
Conc. #3	20	-5.4	2.3	-5.1	-4

statistical values. This data is represented in Figure 13.

All patients who receive study medication will be considered evaluable for the safety analysis. All patients who receive study medication and have at least one on-therapy study visit will be considered evaluable for the intent-to-treat analysis, and

patients who receive study medication, have at least one on-therapy study visit, and satisfy inclusion/exclusion criteria will be considered evaluable for the per protocol analysis.

The primary objectives of this study are to describe the safety and IOP-lowering efficacy of once-daily masked drug, and to select an optimum concentration. Latanoprost 0.005% and Vehicle, each dosed once daily, are included in the study as active and placebo controls. The primary efficacy parameter will be an assessment of the mean IOP change from baseline (time #1 and time #2 at eligibility visit) at the four different time points. The time point #1 IOP assessment on Day 1 will occur prior to initial instillation of drug, and only those patients meeting the IOP qualifying criteria will be entered into the treatment phase.

Descriptive statistics will be used in the primary analysis to evaluate the IOP-lowering efficacy of the three study drug concentrations. Secondary analytic objectives include the comparison of each masked drug concentration to the active and placebo controls. The optimum concentration will be selected based on statistical and clinical evaluation of the efficacy and safety outcomes.

A clinical study report (CSR) will be generated at the conclusion of the study to describe the mean IOP changes from baseline in a subset of patients enrolled in the clinical study. Tables will be presented for IOP change from baseline in the intent-to treat, per protocol data sets, and safety analysis.

VI. Results / Discussion

The final data collection is estimated to be complete by the end of 2003, therefore, this thesis does not include the actual results of this clinical study. The conduct of this study is important because previous attempts with other PGAs to lower IOP with a lower incidence and degree of producing hyperemia have justified the efforts required to develop a new drug. Ocular hyperemia may affect patient compliance due to cosmetic effects, and thus, the overall effectiveness of the topical PGAs.

We plan to demonstrate that a certain concentration of a NPA will efficaciously lower IOP with minimal ocular hyperemia in patients with OAG or OHT. Ocular hyperemia, though a cosmetic effect, dilates the vessels and may cause other ocular problems which is why developing a drug to minimize this side effect is important.

CHAPTER 4

INTERNSHIP DISCUSSION

The site of the internship was at Alcon Research, Ltd. in the Glaucoma/Viability division of Research and Development (R&D) under the supervision of Theresa Landry, Ph.D. I also worked closely with Sushanta Mallick, Ph.D., study manager for protocol C-03-25. The purpose of the internship was to provide hands-on experience in the pharmaceutical industry by offering a comprehensive look at the field of clinical research, and the drug development process.

Activities of the internship were focused on the series of events involved in a clinical trial. To accomplishing this, I was first immersed in a three-week training period referred to as "Clinical Boot Camp". Topics encompassed the entire spectrum of clinical research from Alcon standard operating procedures (SOPs) to global research standards. I felt a bit overwhelmed, but later found the information to be very helpful in the months to come.

Once training was complete I was given the opportunity to travel to clinical sites, interact with site personnel, conduct study initiation visits, interim monitoring visits, and close-out visits. While in-house I attended weekly meetings, worked on gathering study packets, patient evaluabilities to determine which patients are evaluable for the intent-to-treat and per protocol set, and helped with close the database, which is the final step in

completing a study. A database is locked when all of the data is considered accurate and other clerical corrections are complete.

As an intern, one of my objectives was to gain as much experience, and learn as much as possible about the role of a clinical research scientist (CRS) whose responsibilities are very important in the overall success of clinical trials.

The sponsor selects a CRS based on expertise, experience and training to monitor the progress of clinical studies. Responsibilities are many, and include the following: ensure the rights and welfare of subjects are protected, and reported data are accurate, complete and verifiable; responsible for verifying that the clinical sites are in compliance with good clinical practices (GCPs), corporate SOPs, and clinical protocols; verify informed consent is obtained and properly documented for each subject prior to screening; responsible for drug accountability, disposition and storage; ensure that the site investigator and staff receive study materials in a timely manner; verify source documents and regulatory binder is accurate and complete, and that case report form (CRF) data is recorded accurately. Essentially, the CRS acts as the main line of communication between the sponsor and the investigator.[7]

During the course of my internship I have observed the interactions between the various departments in R&D in order to understand the drug development process, and to pin-point the non-economic motivation behind the pharmaceutical industry. I have come to the conclusion that Alcon's driving force seems to be the ethical development of excellent products that not only improve the patient's welfare and quality of life, but also exceed market safety and efficacy standards.

I am impressed by Alcon's commitment to excellence in all of their endeavors. My experience at Alcon Research, Ltd. in the Glaucoma/Viability group has given me insight into the world of clinical research, drug development, and the pharmaceutical industry. My understanding of drug development, role of a CRS, federal regulations, GCPs, global industry standards, Alcon SOPs, and the legal and business ramifications of non-compliance have greatly expanded.

I. Drug Development Process

The development of safe and effective anti-glaucoma medications is a challenging task requiring a multi-disciplinary approach. One must consider various factors including anatomical, physiological, and metabolic considerations of the eye as well as physico-chemical properties of drugs as a basis for sound drug design. Drug bioavailability must be carefully evaluated in order to administer a concentration that provides optimally safe absorption.

Another important factor in the drug development process is the pharmacokinetics, pharmacodynamics, safety and efficacy profile of a product. Stereochemical factors may also affect drug metabolism, bioavailability and receptor interaction, hence, the differences in behavior between racemates and isomers should be an important consideration.

The drug development process is a long, complex and costly process that may or may not result in a profitable product in the end. All drugs to be marketed in the U.S. must undergo an extensive drug development process with contribution from the U.S.

Food and Drug Administration (FDA), institutional review boards (IRBs), sponsors and principal investigative teams. This dynamic process ultimately begins as an idea in the mind of a laboratory scientist, who develops or identifies a chemical compound, and this idea is eventually realized beginning with pre-clinical research.

During pre-clinical research, a sponsor is required by the FDA to evaluate a drug through *in vitro* and *in vivo* laboratory animal testing. This pre-clinical phase is used to measure a drug's pharmacologic profile (ADME - absorption, distribution, metabolism, and excretion), acute toxicity, and is predictive of it's effects in clinical trials in humans. This phase can last weeks to years depending on the duration and indication of the compound on intended subjects.

Prior to starting clinical research, the sponsor has the obligation to submit an investigational new drug (IND) application, which exempts the sponsor from statutes that prohibit interstate shipment of unapproved drugs. Following the IND review process by the FDA, clinical studies may begin after a 30 day waiting period. Clinical investigation from this point forward is divided into four phases (phases I – IV).

Phase I studies are closely monitored, usually conducted in healthy volunteers, and constitute the period of time during which metabolic effects and side effects of the drug are determined in humans. Valuable information regarding the pharmacokinetics of the drug is acquired and used to design a well-controlled, phase II clinical trial.

Phase II studies are the blinded, controlled, and monitored clinical trials used to obtain preliminary data on the effectiveness of the drug for a particular indication or disease. Short-term side affects are also captured during this phase.

Phase III studies provide additional information about the safety and efficacy of the drug once phase II studies are complete, and show efficacious results. Phase III studies analyze results across the general population, and include larger number of subjects (several hundred to thousands). You can think of phase III studies as "pivotal trials" that prove the point.[7] Once phase III is complete, the sponsor submits a new drug application (NDA) to the FDA for a license to market an investigational drug. At the end of this process, the drug can be marketed in the U.S., provided the FDA grants an approval.

Finally, phase IV trials are conducted for the purpose of capturing post-market safety evaluations and addition of supportive data, and continue after FDA approval of the drug. This entire process can take many years to complete making sound research design, and well-controlled clinical trials with appropriate post-market studies critical for success.

JOURNAL

*List of Acronyms in Appendix E

June 9, 2003

I spent the majority of the day attending training sessions, meeting Alcon employees, and driving to the Conner Bldg. Training sessions schedule and events as follows:

8:30 am – 10:30 am: Training Orientation, introductions, review of Legal Basics

2:00 pm – 4:30 pm: Archives format & Tour of archives, Test Article Label Basics, Diseases & Alcon Products. I thought the last class discussing ocular diseases and Alcon products was great! It gave an overview of the anatomy of the eye and various diseases (slide show was great), which was a nice review for me. Also, I especially thought the overview of Alcon's products and treatment of "Inflammation" provided a better understanding of Alcon's specific area of research. I also met Dr. Sushanta Mallick, the study manager, to discuss the study objective, drugs, time frame and goals. He asked me to call him Sushanta as he prefers to be called by his first name. I received drafts of CRFs, Protocol, and CIB to review.

June 10, 2003

Most of my morning and afternoon consisted of training sessions:

8:30 am – 10:30 am: IRB/IEC Basics, Clinical Protocol/Amendments Basics & OEM Basics

2:30 pm – 4:30 pm: R&D Systems and Organization & Program/Project Development

My computer arrived and I spend the rest of the afternoon setting up passwords, reading my inbox, and organizing files. I also read through the CRFs for the project I will be working on. I met Tomi, whom I may be helping with monitoring visits.

June 11, 2003

Attended training sessions as follows:

9:30 am – 10:30 am: Financial Disclosure Basics, I thought it was well presented and I found it very interesting.

1:30 pm – 4:30 pm: Intro to Alcon Clinical Research, Overview of Clinical Data Processing, and Initiating Studies

I met with Dr. Landry and discussed questions pertaining to the study protocol. Later, I continued organizing my files and supplies that arrived. I began searching references on-line.

June 12, 2003

Today I feel more comfortable finding my way around the office and familiarizing myself with names and faces. The morning and afternoon training sessions and events are scheduled as follows:

8:30 am – 9:30 am: Clinical Monitors Basics

1:30 pm – 2:00 pm: Study Management Planning

I spent the remainder of the afternoon working on my research proposal and searching on-line references.

June 13, 2003

This morning I came in early, 7:30 am. It seems I have miscellaneous paperwork and organizing to finish. I reviewed the book on Glaucoma, which I borrowed from Dr. Landry to better familiarize myself about the disease process. Specifically, I was unsure about the differences between conventional vs. uveoscleral outflow, which happen to be parameters tested in the study. [Conventional outflow is through the trabecular meshwork (90% of the time), and non-conventional or uveoscleral outflow occurs through the ciliary body face and iris root (10% of occurrence)]. I attended training sessions scheduled in the afternoon:

1:30 pm – 2:30 pm: AE Basics was helpful in clarifying the difference between baseline, AEs and SAEs and how each is reported.

2:30 pm – 4:30 pm: Final Clinical Data, discussed interim locks, re-locks and final locking of data. Overview of forms and database formats.

June 16, 2003

9:00 am – 10:00 am: I met with advisory committee to discuss and review my research proposal. Dr. Theresa Landry, Sushanta, and Dr. Annita Bens were present. Topics discussed included a general overview of the study I will be involved in, why it is being performed, its specific aim, current status and the time frame in which the proposal will be completed. Everyone read my proposed title and gave their input.

10:00 am – 11:30 am: Organized files, called UNT regarding registration, responded to emails, emailed Dr. Wordinger to update him on my progress

11:30 am – noon: EZWeb Training. Learned about CSRs, and other database information we may need in the future. I thought the class was worthwhile.

12:00 pm – 1:00 pm: Lunch

1:30 pm – 2:30 pm: CRF Basics. Reviewed CRFs, format, various templates available, contact person, and the CRF development process. This was an especially helpful session for me because I thought it was taught extremely well, organized, to the point, and provided pertinent information needed in the future…nice job!

2:30 pm – 3:30 pm: I met with Tomi, O.D., a CRS in Glaucoma. She gave me a basic overview of the entire development process from protocol development, monitoring and close-out visits. It was helpful in providing the chronology of steps involved. Tomi was great…very patient, helpful and answered all of my questions.

3:30 pm – 5:00 pm: Follow-up on email, called the library to set up an appointment for a search engine course, none available at this time. Literature search on MedLine, found a few articles of interest.

June 17, 2003

Training all day.

8:30am – 5:00 pm: Intro to Clinical Research Level 1 gave an overview of the clinical research development process.

June 18, 2003

Training all day.

8:30am – 5:00 pm: Intro to Clinical Research Level I was a continuation of yesterday's training. Included the monitoring process.

June 19, 2003

8:30 am – 9:30 pm: Test Article Shipment/Return Basics discussed the different forms filled out when shipping or returning an investigational product to or from a site.

1:30 pm – 4:30 pm: Study Files Basics described the study files (Official, Investigator, Working files); Report Completion Basics; Clinical Forms Basics.

10:00 am – 10:30 am: Clinical Intern Reception. This reception is in honor of all the new interns. Dr. Landry presented me to the group, we had cake.

10:30 am – 11:30 am: Replied emails, worked on research outlining proposal

11:30 am – 12:30 pm: Lunch

12:30 – 1:30 am: Searched the internet for articles, not much help

1:30 pm – 4:30 pm: Study files training, report completion basics and clinical forms basics training

4:30 pm – 5:30 pm: Drove to Conner Bldg. and met with Dr. Bergamini, Vice President, Pharmacology. We discussed my background, graduate studies and his role in clinical research.

June 20, 2003

8:00 am – 9:00 am: Organized for the day, answered email.

9:00 am – 9:30 am: Attended group meeting

9:30 am – 11:30 am: Training on Quality Management Systems

11:30 am – 1:00 pm: Lunch with Glaucoma group for Sushanta's birthday

1:00 pm – 1:30 pm: Meeting with Sushanta and Tomi to discuss project deadlines, status

1:30 pm – 2:30 pm: Drove to tower for marketing training

3:00 pm – 4:00 pm: International clinical development training, this session was excellent!

4:00 pm – 5:00pm: Worked on research proposal, copy to Sushanta for review this weekend as requested

June 23, 2003

8:00 am – 9:30 am: Organized for the day, updated journal, replied to emails, called-in time sheet

9:30 am – 10:30 am: Site Audit basic training

10:30 am – 11:45 am: On-line literature search

11:45 am – 12:45 pm: Lunch

12:45 pm – 1:30: Literature search

1:30 pm – 2:30 pm: Intro to CQAU training session

2:30 pm – 4:00 pm: Library literature search

June 24, 2003

8:00 am – 9:00 am: Organize for the day, reply to email

9:00 am – 11:20 am: Training on Health Economics and Introduction to Biostatistics

11:30 am – 12:30 pm: Lunch

12:30 pm – 2:30 pm: Internet research, read/review final protocol and inclusion/exclusion criteria for Tomi, print copy of source document for Thursday's meeting

2:30 pm – 3:30 pm: Intro to Global Regulatory Requirements

3:30 pm – 5:00 pm: Literature search, reply to email, coordinate Thursday schedule, call eye clinic for a tour

June 25, 2003

7:45 am – 9:30 am: Organize for the day, reply to e-mails

9:30 am – 11:30 am: Reviewed source document for Tomi and met with her to discuss phone initiation meeting tomorrow, reviewed initiation format and important questions to ask the site

11:30 am – 12:30 pm: Lunch

12:30 pm – 1:30 pm: Returned voicemail messages, fax to occupational health, spoke with Linda in Health Services for a blood draw, gave Dr. Landry copy of my proposal

1:30 pm – 2:30 pm: Monitoring training

2:30 pm – 4:30 pm: follow-up emails to Dr. Bens, Dr. Wordinger, Dr. Rudick; gave Dr. Bens copy of proposal for her review, reviewed site initiation report

4:30 pm – 5:00 pm: Update journal, organize training handouts, return emails, plan tomorrows schedule

June 26, 2003

8:00 am – 8:30 am: Went to Health Services to get my blood drawn, and gave them a copy of my immunization records

8:30 am – 10:30 am: Reply to emails, compared source document to CRF version 3

10:30 am – noon: CRF review meeting

12:00 am – 1:30 pm: Lunch, birthday cakes for the month

1:15 pm – 2:00 pm: Reply to email, organize for phone initiation

2:00 pm – 3:30 pm: Phone initiation with Sushanta and Tomi

3:30 pm – 4:00 pm: Read research article

4:00 pm – 5:00 pm: Meet with Dr. Goode, the Medical Monitor for the study

June 27, 2003

Today I spent the morning revising my research proposal.

After lunch I finished my proposal for Sushanta and Dr. Landry to review.

3:00 pm – 4:00 pm: Training session for clinical supplies, manufacture and distribution.

Took a tour of the manufacturing facility and watched a video.

4:00 pm – 5:00 pm: Completed research proposal for review.

June 30, 2003

Training is officially over. I thought it was an effective overview of, not only clinical research, but also Alcon in general and the different departments involved in the drug/device development process. It helped me understand how each division works in concert to successfully market a drug or device.

I now plan to concentrate on finalizing the proposal, having it reviewed/approved and begin writing my draft for the thesis.

This morning I spent time searching journals on the internet, and met briefly with Sushanta to discuss his comments on my proposal. After lunch, I spent the remainder of the afternoon working on my thesis introduction and works cited. I also made use of the library for a few hours.

July 1, 2003

This morning I organized literature articles and began work on the references list. I spent the remainder of the morning reading articles and forming the thesis. Also, I discussed the proposal with Sushanta and made a few corrections per his suggestions. This

afternoon Dr. Wordinger, Sushanta and I met for my committee review. We reviewed the proposal, discussed the outline, content, study aim, etc. A few changes were made to the formatting, but content was acceptable. I later met briefly with Sushanta for a final review before sending it to all committee members. The last 30 minutes I spent in the library.

July 2, 2003

I spent the morning reading printed research articles from last week, and searching for additional ones. I was able to print full text versions from the Alcon library, which was very helpful. I also spent time designing the chronology of the table of contents and citing references. In the afternoon I met briefly with Dr. Landry to update her and give her the last version of my research proposal.

July 3, 2003

I arrived especially early today to finish the table of contents, which I am still not pleased with. I will come back to it later. The remainder of the morning and afternoon I began to write the body of the thesis. I searched on-line and called UNTHSC library. This afternoon I continued to compose the thesis and added to my references. I also found several illustrations I will use.

July 7, 2003

This morning I organized my research files, and responded to emails. I was also able to order two journals from the library. I worked on the thesis, and gave Dr. Landry a very rough draft of the "Introduction". After lunch, Tomi and I discussed the time-frame for

our trip to San Antonio next week. The rest of the afternoon I read journals, articles and textbook of glaucoma.

July 8, 2003

This morning I received final comments from committee members in regards to my research proposal. Once I incorporated the changes, I gave Sushanta a copy for his review. Mid-morning I continued to work on the table of contents from last week. So far the "study results/discussion" will be strictly research results, as permitted by Alcon. Late afternoon I went to UNTHSC and filed my research proposal. I emailed the final proposal to all committee members.

July 9, 2003

I worked on citing my references and searching "glaucoma" web sites most of the morning. After lunch I continued to write the introduction for my thesis. I am not pleased with it, definitely needs more work! I think I need to defer my attention to a different section for a while, maybe references, then come back to the introduction with a fresh view. This afternoon I helped Sushanta verify CRF working copy binders. I went through seven or eight binders (page by page) checking for consistency and missing pages.

July 10, 2003

First thing this morning I read my introduction. My opinion is that it is vague and needs more content, background information, statistics, etc. I searched articles most of the morning. I also started reading "Glaucoma Medical Therapy", very helpful. This afternoon I decided to insert "generic" molecular structures of the different glaucoma

medications in my thesis, but could not find what I want on-line. I continued reading this afternoon, and searched more websites. There is so much information available, I need to focus or I will never finish literature review. I spent time organizing the thesis and working on my references.

July 11, 2003

This morning after replying to email, and checking phone messages I worked on building a "glaucoma drug medications" table. It lists the drug name, mechanism of action and side effects. For me, it is easier to visualize all the drugs side by side, and compare each one before starting to write. The library called and the journals I ordered have arrived. A group of us took Charles to lunch for his belated birthday. After lunch I caught up on journal writing. I also searched for chemical structures, but I can not find the specific drugs I need. I also read a study comparing three prostaglandin analogues Xalatan®, Lumigan®, and TRAVATAN®. Sushanta mentioned this study to me as one that is cited frequently. Performed literature searches and read most of the afternoon.

July 14, 2003

Worked on literature review in the morning. After lunch I spent 3 hours in the library reading references, removing unnecessary articles that I will not incorporate into my thesis, and printing additional articles. The remainder of the afternoon I spent writing in my journal, organizing for tomorrow, answering UNTHSC email, reading journal articles, and calling UNTHSC regarding graduation deadlines, etc.

July 15, 2003

The majority of the morning I worked on the thesis introduction. It is finally coming together slowly but surely. Mid-morning I met with Sushanta and Tomi to review the status of three studies and briefly discuss the business trip tomorrow. Tomi and I will be going to San Antonio, TX to close a site, and I will be initiating the study my thesis is based on. After lunch, I continued editing the introduction and reading several sources. Tomi and I met late afternoon to discuss our trip tomorrow. She explained the initiation process, what to expect at the site, and she also exposed me to the monitoring log, reviewed the monitoring report and reviewed important points to discuss with the site.

July 16 through July 18, 2003

I traveled with Tomi to San Antonio for a site initiation, and close out visit. We arrived at the site the morning of July 16th, and worked until that evening. I had the opportunity to meet Dr. Evans and his staff. Tomi invested time training me. For each patient, the informed consent, source document and CRFs were reviewed for completeness, inconsistencies and clerical errors in documentation. Each discrepancy was at that time corrected by the coordinator at the site. On July 17th we returned to the site early in the morning to complete additional corrections with the coordinator. We also flagged charts pending Dr. Evans's signature or approval since he was out of the office that day. After completing each chart, Tomi coached me on drug accountability. I confirmed every bottle sent to the site from Alcon was accounted for and completed the required form/log. While Tomi finished discussing specific questions with Naomi (site coordinator) I reviewed the study binder and confirmed documentation. On July 18th, we arrived at the

site early in the morning. We met with Dr. Evans, Robert, and Naomi. Dr. Evans reviewed and signed pending charts. Afterwards, I initiated the next study with the group. I discussed the protocol, inclusion/exclusion criteria and all pertinent information regarding the study. Tomi and I answered questions with the staff. We left the site mid-morning to return to Fort Worth.

July 21, 2003

This morning I answered emails, and completed journal entries for last week. Dr. Landry and I met briefly to discuss the trip. In the afternoon, I went with Tomi to the copy center to request copies of protocol and related materials for the sites. I read my introduction again and although it is coming along I need a second opinion. I asked Sushanta if he would review it for me. I will also give Dr. Landry a copy for her review.

July 22, 2003

I wrote in my journal and spent the rest of the morning reading "Glaucoma Medical Therapy". I also began writing the Summary/Purpose portion of my thesis. Mid-morning I assisted Tomi in completing and verifying the site initiation checklist. After lunch Tomi and I prepared the study packages to be sent to the sites. Each package contained source documents, drug accountability log, ocular hyperemia scale, study binder, laminated inclusion/exclusion worksheet with flowchart, and patient instruction baggies.

July 23, 2003

This morning I completed the site initiation form for the study I initiated last Friday in San Antonio. Read glaucoma article from Wills Eye Hospital. I worked on thesis and jotted-down ideas for the thesis power-point presentation.

July 24, 2003

Worked on thesis, specifically the table. Sushanta offered to let me borrow a nursing drug reference book, very helpful. I spent some time on the Summary/Purpose, and contemplated an Appendix for the illustrations vs. inserting them in the text. My preference is to insert them into the text if it is allowed in the guidelines.

July 25, 2003

I attended an "All Clinical Meeting" where CDM, clinical experiences, and Trip Reports were presented and discussed. After lunch, I called one of the sites to confirm several documents have been sent to us. Worked on thesis the remainder of the afternoon.

July 28, 2002

This morning I attended a mandatory SOP meeting that discussed recent changes to Alcon SOPs. I worked on compiling the documents that will be sent to QAU. These include the PIs CV, subinvestigator CVs, statement of Investigator/FDA 1572, IRB approval letter, approved informed consent, signed protocol page, site initiation visit form, and correspondence between Alcon and the sites. Sushanta will review, sign and return to me.

July 29, 2003

Today I completed the necessary study documents for the QAU, and also made copies for our working files. This morning Sushanta suggested I give a brief presentation on August 15th to prepare me for my final thesis defense. I think it is a great idea, and I am confident I will appreciate this opportunity in the near future. The topic will include my thesis synopsis, and an overview of the protocol. I will also discuss my site initiation and close-out visits to-date, and present a general discussion of my internship experience.

July 30, 2003

I worked on power point presentation, outline of the slides, and length of presentation. Reviewed glaucoma statistics to include in presentation. I spent the remainder of the time organizing my thesis outline again.

July 31, 2003

Planned and organized for the day. I updated the enrollment log this morning for Tomi, who is off-campus at a site. This afternoon I received email regarding my Concur account which reimburses expenses. My account is not set-up properly so I spent most of the afternoon making phone calls to the helpdesk. This included faxing information to security.

August 1, 2003

Went through the morning ritual of answering emails and organizing for the day. I read two articles from last week on glaucoma statistics, aging and glaucoma, diabetes and glaucoma, race and glaucoma, myopia and glaucoma, hypertension and glaucoma. I found useful information that I will use in my thesis and presentation. I met briefly with

Tomi who will be out of town on business again next week. She asked me to complete the QAU package and send drugs to the new site next week.

August 4, 2003

I recorded the past two days work in journal. Replied to emails, phone messages. I am completing the drug package for one of the sites. Since Tomi is out of town this week I will be responsible for drug shipment and study material shipment to the sites. This afternoon I went to UNTHSC's library to return several books and conduct additional literature searches. No new information was found.

August 5, 2003

I worked on the check-list for QAU. I am gathering all of the information needed to ship study materials and drug to the site. I can not ship until we receive both the IRB approval letter, and the IRB approved informed consent. I reviewed the latest CRF draft and source documents, it looked fine to me. Contacted helpdesk to set-up my Concur account.

August 6, 2003

I worked on power-point presentation this morning. I spoke with Theresa at IKON to coordinate drug shipment next week. I gave the source documents and CRFs to Sushanta for final review. This afternoon I attended a reception for Vigamox® in the water gardens atrium.

August 7, 2003

This morning I answered email and phone messages, wrote in my journal. I sent Tomi a message regarding drug shipment. In the afternoon I read two articles, "Glaucoma

Primer For Pharmacists", and a study comparing combination drugs vs. timolol and latanoprost. I also worked on the drug table.

August 8, 2003

I completed the study materials package this afternoon after confirming receipt of the IRB approval letter and informed consent form. Worked on thesis.

August 11, 2003

This morning I responded to emails and messages, organized for the day. I spent the morning working on my presentation. I mailed study materials to the site. After lunch, I worked on thesis, read a glaucoma article, reviewed the study protocol. I also talked to Dr. Wordinger regarding the student assessment evaluation form.

August 12, 2003

After organizing for the day I worked on my presentation. Sushanta was kind enough to review my power point slides. After lunch, I helped Tomi prepare and mail CRFs to all of the sites. I continued working on presentation in the afternoon.

August 13, 2003

I spent time this morning on the phone with UNTHSC, registering for classes, faxed immunizations to the nurse, and updated my account. I answered email and phone messages. I worked on summary/purpose of thesis the remainder of the day.

August 14, 2003

This morning I went to UNTHSC to meet with Dr. Wordinger, and complete the faculty assessment of graduate student's form. I had my IOP checked –glaucoma runs in my

family, and after speaking with the medical monitor I knew I needed to have it measured. It was normal. This afternoon I finished my presentation and went to UNTHSC library.

August 15, 2003

This morning was the glaucoma/viability group meeting where I gave my presentation. I was a little nervous, but it was a good experience and a great opportunity to practice for my defense. I worked on the summary/purpose of my thesis, which I plan to finish by next week. Mid-afternoon one of the interns asked to interview me regarding my contact lens use. It is a survey he will be using for a portion of his thesis.

August 18, 2003

This morning I updated my journal, answered emails, and filed study documents. After organizing for the day I worked on summary/purpose portion of the thesis the remainder of the afternoon.

August 19, 2003

Most of the morning was spent at an R&D employee meeting presented by the senior Vice President of R&D. Several speakers presented and gave updates with regards to R&Ds current product status, objectives, and future goals. After lunch, I finished the summary/purpose portion of the thesis.

August 20, 2003

This morning I wrote in my journal, and read through the completed sections of my thesis. I will send Dr. Bens a copy for her review and comments later this week. After lunch, I organized my references and continued to work on thesis.

August 21, 2003

The majority of the morning I worked on thesis, I also answered emails, organized files, and wrote in journal. I spent all afternoon doing evaluabilities for C-02-33.

August 22, 2003

This morning I attended the glaucoma group meeting. I thought it was a great meeting, we accomplished a lot, and also enjoyed doing it. Glaucoma is a great group. After lunch, I worked on evaluabilities.

August 25, 2003

I worked on evaluabilities in the morning. After lunch, I focused again on my thesis. I need to finalize the references I will be using, I still have a lot of references to verify. I attended an Ethics training meeting.

August 26, 2003

I worked on thesis most of the day, specifically, the illustrations and tables. Next week I plan on finalizing several sections of the thesis for Dr. Landry and Sushanta to review.

August 27, 2003

I helped with evaluabilities this morning. This afternoon I continued working on the thesis.

August 28, 2003

This morning I filed research articles, and verified sources. After lunch, Sushanta reviewed in-house monitoring with me, and provided helpful guidelines to follow. I updated my journal this afternoon.

August 29, 2003

I met with Dr. Bens this morning. We reviewed my thesis so far, and she had helpful suggestions for me. In the afternoon, I incorporated the changes Dr. Bens and I had discussed. Continued to work on thesis remainder of the afternoon.

September 2, 2003

I spent all day working on the thesis, particularly the table of contents, and the introduction. I also updated the literature review.

September 3, 2003

I gathered and mailed study documents to a new site. The package includes a CIB, CRF, source document, hyperemia scale, and inclusion/exclusion criteria. Once they receive these materials, Sushanta will initiate the site. The remainder of the day I worked on thesis.

September 4, 2003

First item on my list this morning was to update the enrollment log for C-03-25, and print the faxed updates from each site. I confirmed the update with Tomi. Lunch with Dr. Bens and Dr. Rudick. We discussed the internship, our projects and overall experience at Alcon. I worked on thesis the remainder of the day.

September 5, 2003

Attended Concur training course all morning. Worked on thesis in the afternoon, and gave Dr. Landry and Sushanta portions of the thesis to review.

September 8, 2003

Read several articles, and searched on-line for updated articles/references. Worked on evaluabilies.

September 9, 2003

Attended the GSA meeting at UNTHSC, the speaker was Dr. Bens. I updated the enrollment log, and worked on thesis.

September 15, 2003

Organized and planned for the day. Met with Tomi this morning to discuss evaluabilities, travel plans and enrollment log. The rest of the day was spent looking for illustrations, and updating the literature review.

September 16, 2003

This morning I packaged and mailed study materials to a site, and continued with evaluabilities. I also helped compile the packet for QAU.

September 17, 2003

I attended employee training this morning. The rest of the day was spent setting up folders for the study, and doing evaluabilities.

September 18, 2003

Worked on thesis, read protocol again. Worked on thesis, literature review.

September 19, 2003

In the morning, Tomi and I organized study folders and files for next week's trip. After lunch, I continued gathering data necessary to finish literature review.

September 22, 2003

Worked on evaluabilities and study folders. Met with Tomi and discussed the trip objective, goals and time frame.

September 23-September 24, 2003

Traveled to San Antonio with Tomi for interim monitoring visit.

September 25, 2003

This morning I organized the files from the trip, will work on monitoring report, replied to emails/messages. I went to the library this afternoon, found an article on "normal IOP diurnal fluctuations".

September 26, 2003

I went to UNTHSC this morning for an article, worked on thesis. This afternoon was the glaucoma meeting, and the remainder of the day I wrote in journal, and gathered my references to work on thesis over the weekend.

September 29, 2003

Worked on thesis- literature review and read articles.

September 30, 2003

Worked on thesis all morning. After lunch I attended SOP training class from 2:00-3:30pm. The remainder of the day I wrote in journal and helped with evaluabilities.

October 1-3, 2003

Worked on thesis – editing the introduction, and methodology sections.

October 6, 2003

Worked on evaluabilities all day. Thesis is on-hold for the week. I gladly agreed to help Tomi and the group prepare for a database lock later this month.

October 7, 2003

October is officially "Clinical Boot Camp" month. My first session began this morning. I attended training on Alcon travel and procedures. The afternoon was spent on evaluabilities and filing CRFs.

October 8, 2003

Arrived early to work this morning, checked email and continued with evaluabilities. The database lock is scheduled for the end of this month so we need to meet this deadline. I also filed the CRFs for C-03-25.

This afternoon I attended an ATLAS class presented by Abe Clark, Ph.D. I thought it was very interesting and informative. Topics discussed were the leading causes of blindness, the pathogenic mechanisms for the leading ocular diseases, and how these diseases are treated.

October 9, 2003

I arrived early this morning and finished reviewing charts. Met with Tomi to discuss upcoming travel, workload, and deadlines. We are traveling to San Antonio next week. I will be helping her close C-03-25, the study my thesis is based on. I wrote in journal. Attended the Eye Clinic training session this afternoon.

October 10, 2003

I attended a morning test article shipment training session. Discussion was a very good review of the forms, documentation of supplies, and personnel responsibilities now that I have worked with product shipment forms. After lunch, I attended CIB basics training session, again for review and to clarify questions. I gathered two more articles for literature review.

October 13-October 14, 2003

Traveled to San Antonio with Tomi for an interim and close-out visit for study C-03-25. We arrived at the site Monday morning, and monitored charts. We flagged charts and discussed each with the site coordinator. The next day we arrived early to finish monitoring and addressing issues with the coordinator. I completed the sites study binder, checked the drug log and confirmed drug accountability for each patient, and reviewed each chart again to make certain signed informed consent forms were present. On our way back to the airport we took the site to lunch.

October 15, 2003

Since there is a database lock next week I have been doing evaluabilities and helping the glaucoma group. Today I started evaluabilities for the site we closed, C-03-25. I also continued to work on C-02-33 evaluabilities and I-review.

October 16, 2003

This morning I arrived early to finish reviewing each C-02-33 chart before 8AM. Once complete, I began I-review and Q-monitoring. I spent a few hours reading my thesis and

making minor corrections, but the bulk of the day was spent performing I-reviews and retrievals.

October 17, 2003

Attended glaucoma meeting this morning. I worked on organizing the literature review, confirming each one is properly cited, and reading two more articles I found last week. I have officially stopped looking at articles or I will never finish the literature review.

October 20-October 31, 2003

These are the last two weeks of the internship practicum. I spent this time writing and editing the thesis. Jerianne reserved a room for my defense, and I was able to confirm the defense date with all committee members.

October 31, 2003

All glaucoma meeting this morning, and also officially my last day as an intern.

APPENDIX A

Alcon Research, Ltd.

MONITORING REPORT

Protocol No.: C-_____
Inv. No.: _____
Visit Date(s): _____

Interim Visit ☐
Close-out Visit ☐

Investigator Name: _____ Address: _____

SECTION A – STUDY BINDER	YES	YES*	NO*	N/A	Not Reviewed
FDA 1572 / Statement of Investigator					
1. Signed / dated copy	☐	☐	☐	☐	☐
2. Information Current	☐	☐	☐	☐	☐
3. List of Sub-investigators complete	☐	☐	☐	☐	☐
Financial Disclosure					
4. Principal Investigator	☐	☐	☐	☐	☐
5. Sub-investigators	☐	☐	☐	☐	☐
Curriculum Vitae					
6. Principal Investigator	☐	☐	☐	☐	☐
7. Sub-investigators	☐	☐	☐	☐	☐
Study Agreements					
8. Confidentiality	☐	☐	☐	☐	☐
9. Clinical Study Agreement	☐	☐	☐	☐	☐
Clinical Investigators Brochure					
10. Revision #(s) _____	☐	☐	☐	☐	☐
Protocol					
11. Approved Protocol	☐	☐	☐	☐	☐
12. Signature page signed / dated by P.I.	☐	☐	☐	☐	☐
13. Amendment(s) signed / dated by P.I.	☐	☐	☐	☐	☐
Amendment(s) #(s) _____	☐	☐	☐	☐	☐
14. Final Case Report Form	☐	☐	☐	☐	☐
IRB/IEC Records					
15. Copy of Site / Protocol approval / CIB review	☐	☐	☐	☐	☐
16. Description of IRB/IEC make-up / assurance letter	☐	☐	☐	☐	☐
17. Protocol amendments reviewed / approved	☐	☐	☐	☐	☐
18. Required periodic IRB/IEC reports submitted	☐	☐	☐	☐	☐
19. Serious Adverse Events reported to IRB/IEC	☐	☐	☐	☐	☐
20. IRB/IEC correspondence fully documented	☐	☐	☐	☐	☐
21. Advertisement approval	☐	☐	☐	☐	☐
Informed Consent Form					
22. IRB/IEC approved informed consent form	☐	☐	☐	☐	☐
23. Informed consent amendments approved	☐	☐	☐	☐	☐

* See Comments N/A - Not applicable

Alcon Research, Ltd.

MONITORING REPORT - CONTINUED

Protocol No.: C-
Inv. No.:
Visit Date(s):

SECTION A – STUDY BINDER (CONTINUED)	YES	YES*	NO*	N/A	Not Reviewed
Monitoring Records					
24. Monitoring log complete	☐	☐	☐	☐	☐
25. Study Site Personnel log complete	☐	☐	☐	☐	☐
26. Site Initiation Report	☐	☐	☐	☐	☐
27. Subject log	☐	☐	☐	☐	☐
28. Monitoring Report(s)	☐	☐	☐	☐	☐
29. Site Summary CS020-B (if Required)	☐	☐	☐	☐	☐
Clinical Supplies					
30. Receipt of clinical supplies documented	☐	☐	☐	☐	☐
31. Record of Test Article dispensed	☐	☐	☐	☐	☐
32. Record of returned supplies to Alcon	☐	☐	☐	☐	☐
Correspondence (includes telephone, letters, e-mail & faxes)					
33. Correspondence from Alcon	☐	☐	☐	☐	☐
34. Correspondence from site	☐	☐	☐	☐	☐
Overall Summary					
35. Records easy to access	☐	☐	☐	☐	☐
36. Records found in orderly fashion	☐	☐	☐	☐	☐
Other Items					
37. _____	☐	☐	☐	☐	☐
38. _____	☐	☐	☐	☐	☐

SECTION B – SOURCE DOCUMENTATION / CRFs	YES	YES*	NO*	N/A	Not Reviewed
CRF Review					
1. CRFs accurate / complete	☐	☐	☐	☐	☐
2. CRFs signed / dated by P.I. / Sub-investigator	☐	☐	☐	☐	☐
3. Telephone corrections verified	☐	☐	☐	☐	☐
4. Corrections initialed & dated	☐	☐	☐	☐	☐
5. Corrections supported in source documents	☐	☐	☐	☐	☐
Protocol Compliance					
6. Adherence to Inclusion / Exclusion criteria	☐	☐	☐	☐	☐
7. Exams / tests performed per Protocol	☐	☐	☐	☐	☐
8. Test article dispensed per Protocol	☐	☐	☐	☐	☐
Source Documents					
9. Reflect that subjects are study participants	☐	☐	☐	☐	☐
10. Visit dates documented	☐	☐	☐	☐	☐
11. CRF data well documented / verified	☐	☐	☐	☐	☐

* See Comments N/A - Not applicable

Alcon Research, Ltd.

MONITORING REPORT - CONTINUED

Protocol No.: C-_____
Inv. No.: _____
Visit Date(s): _____

SECTION B – SOURCE DOCUMENTATION / CRFS (CONTINUED)	YES	YES*	NO*	N/A	Not Reviewed
Adverse Events					
12. All Serious Adverse Events reported to Alcon	☐	☐	☐	☐	☐
13. Adverse Event causality, follow-up, resolution documented	☐	☐	☐	☐	☐
Other Items					
14. _____	☐	☐	☐	☐	☐
15. _____	☐	☐	☐	☐	☐

SECTION C – INFORMED CONSENT	YES	YES*	NO*	N/A	Not Reviewed
1. Original consent on file for each subject	☐	☐	☐	☐	☐
2. Consent signed and dated prior to subject involvement	☐	☐	☐	☐	☐
3. Each subject's consent matches the IRB approved consent	☐	☐	☐	☐	☐
Other Items					
4. _____	☐	☐	☐	☐	☐
5. _____	☐	☐	☐	☐	☐

* See Comments N/A - Not applicable

Alcon Research, Ltd.

MONITORING REPORT - CONTINUED

Protocol No.: C-
Inv. No.:
Visit Date(s):

CHECKLIST BY SUBJECT

Subject Reviewed:										
1. Subject Status										
2. CRF Page No. (s) Reviewed										
3. CRF Review										
4. Protocol Compliance										
5. Source Documents										
6. Adverse Events										
7. Informed Consent										
8. Test Article Documentation										
9.										
10.										
Subject Reviewed:										
1. Subject Status										
2. CRF Page No. (s) Reviewed										
3. CRF Review										
4. Protocol Compliance										
5. Source Documents										
6. Adverse Events										
7. Informed Consent										
8. Test Article Documentation										
9.										
10.										
Subject Reviewed:										
1. Subject Status										
2. CRF Page No. (s) Reviewed										
3. CRF Review										
4. Protocol Compliance										
5. Source Documents										
6. Adverse Events										
7. Informed Consent										
8. Test Article Documentation										
9.										
10.										

Legend: X = Acceptable; * = Comments; A = Active; C = Completed Pt./Subject; D/C = Discontinued Pt./Subject; N/A = Not Applicable; N/R = Not Reviewed; S/F = Screen Failure

Alcon Research, Ltd.

MONITORING REPORT - CONTINUED

Protocol No.: C-
Inv. No.:
Visit Date(s):

COMMENTS (list by item number)

Prepared by:

Monitor (signature) Date

Reviewed by:

Study Manager (signature) Date

APPENDIX B

PARTICIPANT INFORMED CONSENT FORM AND AUTHORIZATION TO USE AND DISCLOSE MEDICAL INFORMATION

STUDY TITLE: A Multicenter, Double-Masked, Placebo-Controlled, Dose-Response Study of the Safety and Efficacy of Once-Daily Masked Ophthalmic Solution in Patients with Open Angle Glaucoma or Ocular Hypertension

PROTOCOL NO.: C-03-25

STUDY DOCTOR: ,

STUDY SITE:

TELEPHONE:

SPONSOR: Alcon Research, Ltd.
6201 South Freeway
Fort Worth, Texas 76134-2099

INTRODUCTION

ABOUT THE STUDY DRUGS

NATURE OF STUDY

PROCEDURES

Screening Visit:

Eligibility Visit:

Day 1:

Day 7:

Day 14:

RISKS AND PRECAUTIONS:

SAFEGUARDS

COMPENSATION FOR STUDY RELATED INJURY

COSTS TO YOU

PAYMENT FOR PARTICIPATION

BENEFITS

ALTERNATIVE TREATMENTS

WITHDRAWAL FROM THE STUDY

Participation in this research study is completely voluntary.

NEW FINDINGS

CONFIDENTIALITY

CONFIDENTIALITY AND AUTHORIZATION TO COLLECT, USE AND DISCLOSE YOUR MEDICAL INFORMATION:

The Information that will be collected about you as a part of this research includes:

- Name
- Address
- Telephone number
- Birth date
- Race
- Sex

- Social security number
- Family medical history
- Allergies
- Medications you take (current and past)
- Information from the physical examination done by the study doctor
- Results of tests and procedures you have as necessary for this study
- Other information from other doctor' offices, clinics, hospitals that is needed for the research

Information collected about you for the research study will be kept in a research file that is separate from your medical chart. You will not be able to see your research file until after the end of the study.

The study team will know your identity. However, they may label your records with your initials or a code assigned to you. The research staff are the only people who will have this code and its key. The study sponsor and the people who work with them on the study may review and use your information. They will review the study information to make sure it is correct. They will also review how the doctor(s) and study team completed the study to make sure they conducted the study correctly.

These people include:
- The U.S. Food and Drug Administration
- The Institutional Review Board
- The Department of Health and Human Services
- Other government agencies in other countries

We need to release your information to the groups listed above. If your health information is reviewed by these people, they may need to see your entire medical record. Because of this, we cannot promise your privacy will always be protected. It is possible that your information will be shared (re-disclosed) in a way that it would no longer be protected.

Your information may also be presented at meetings or in articles written about the study (publications). You will not be identified by name in any presentation or publication that uses your research or health information.

This permission (authorization) will expire at the end of the study, following expiration of any required record retention period.

You have a right to see your records. However, you will not be able to see your study records until after the study is ended.

You may also take away (withdraw) your permission for us to use your health information at any time. If you choose to take away your permission, you must write your study doctor a letter.

I authorize the use and disclosure of my information as described in this section.

QUESTIONS

For questions about the study or a research-related injury or reaction to the study medication, contact Dr. ____ or the study doctor' staff at _____ .

Do not sign this consent unless you have had a chance to ask questions and have received satisfactory answers to all of your questions. You will receive a signed and dated copy of this consent.

PARTICIPANT STATEMENT AND AUTHORIZATION:

I have read and understand the Participant Informed Consent and I agree to participate voluntarily in this study.

I give my permission to the study doctor to use and disclose my personal health information as described in this consent form.

I will receive a signed copy of this form.

I have received answer to all of my questions.

I have not waived any of my legal rights by signing this document.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

_____ _____
Signature of Legally Authorized Representative (if applicable) Date

_____ _____
Signature of Witness (if applicable) Date

_____ _____
Signature of Person Explaining Consent Date

APPENDIX C

Adverse Event Form

ALCON RESEARCH, LTD.

PROTOCOL NO. _____ _____
INVESTIGATOR NO. _____
SUBJECT NO. _____
SUBJECT INITIALS _____
EXAM DATE ___/___/___ (MM DD YYYY)

ADVERSE EVENT FORM

Visit Day: _____

A. **Description of Adverse Event** (One event per form) _____

_____

B. **Was event life threatening?** ☐ 1-No ☐ 2-Yes

C. **Date of Event's Onset** ___/___/___ (MM DD YYYY)

D. **How often did event occur?**
- ☐ 1-Event occurred one time
- ☐ 2-Event occurred intermittently
- ☐ 3-Event occurred with each instillation for _____ (Number) days.

E. **How soon after last study drug administration did event occur?**
- ☐ 1-Upon instillation
- ☐ 2-Within 1 hour of instillation
- ☐ 3-Within 24 hours of instillation
- ☐ 4-Beyond 24 hours of instillation

F. **Duration of Event** (Fill in number and check unit if event has resolved)
Duration _____ (Number) ☐ 1-Seconds ☐ 3-Hours ☐ 2-Minutes ☐ 4-Days

G. **Severity of Event**
- ☐ 1-Mild (Aware or unaware of event, but easily tolerated)
- ☐ 2-Moderate (Discomfort enough to cause interference with usual activity)
- ☐ 3-Severe (Incapacitating; unable to work or do usual activity)

H. **Action Taken With Study Drug** (Explain in Comment Section)
- ☐ 1-None
- ☐ 2-Reduced frequency of administration
- ☐ 3-Discontinued drug temporarily ___/___/___ (MM DD YYYY) to ___/___/___ (MM DD YYYY)
- ☐ 4-Discontinued drug permanently ___/___/___ (MM DD YYYY)
- ☐ 9-Other _____

I. **Other Action Taken** (Check all that apply)
- ☐ 1-Dropped subject from study
- ☐ 2-Hospitalized subject from ___/___/___ (MM DD YYYY) to ___/___/___ (MM DD YYYY)
- ☐ 3-Prolonged a current hospitalization
- ☐ 4-Surgery required
- ☐ 9-None of the above

J. **Outcome of Event**
- ☐ 1-Resolved without treatment ___/___/___ (MM DD YYYY)
- ☐ 2-Resolved with treatment (Explain in Comment Section) ___/___/___ (MM DD YYYY)
- ☐ 3-Continuing without treatment
- ☐ 4-Continuing with treatment (Explain in Comment Section)
- ☐ 5-Subject lost to follow-up, no further data available
- ☐ 6-Subject Died ___/___/___ (MM DD YYYY) (List cause of death in Comment section)

K. **Rechallenge** (If allowed by protocol)
- ☐ 1-Not attempted
- ☐ 2-Usual dose
- ☐ 3-Reduced dose

L. **Recurrence of Event Upon Rechallenge?**
☐ 1-No ☐ 2-Yes ☐ 3-NA

M. **Relationship of Event to Study Drug** (See Definitions)
- ☐ 1-Definitely unrelated
- ☐ 2-Unlikely
- ☐ 3-Possible
- ☐ 4-Probable
- ☐ 5-Definitely related

N. **Possible Explanation(s) for Event** (Check all that apply - Explain in Comment Section)
- ☐ 1-Illness being treated
- ☐ 2-Intercurrent illness
- ☐ 3-Study drug
- ☐ 4-Nonstudy drug (Identify nonstudy drug in Comment section)
- ☐ 5-Drug interaction (Identify drug in Comment section)
- ☐ 6-Idiosyncratic effect
- ☐ 9-Other _____

COMMENT SECTION _____

_____

Investigator Signature

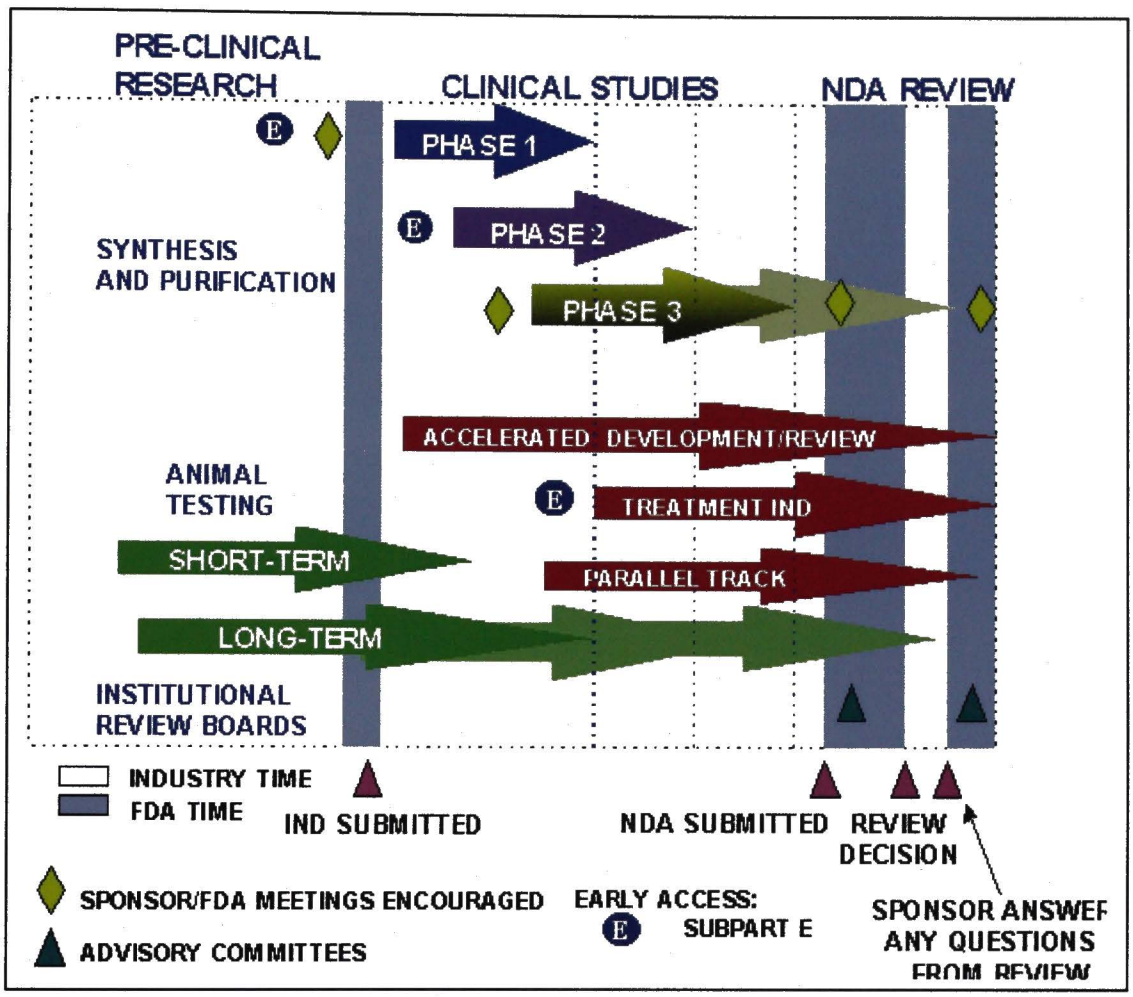
Date

PLEASE USE BLACK INK
AEF3 Aug 2001

Adverse Event 01227

APPENDIX D

Outline of the Drug Development Process



http://www.fda.gov/cder/handbook/develop.htm[54]

APPENDIX E

List of Acronyms

CDM: Clinical Data Management

CIB: Clinical Investigator Brochure

CSR: Clinical Study Report

CQAU: Clinical Quality Assurance Unit

CV: Curriculum Vitae

FDA: Food & Drug Administration

IEC: Independent Ethics Committee

IRB: Institutional Review Board

PI: Principal Investigator

QAU: Quality Assurance Unit

R&D: Research & Development

SOP:Standard Operating Procedure

REFERENCES

1. Podolsky, MM. Primary Care Physicians Are Instrumental In Early Detection. Exposing Glaucoma. 103(5), May 1998. Postgraduate Medicine Web site. http://www.postgradmed.com/issues/1998/05_98/podolsky.htmz

2. Illustration by Mark Erickson. St. Lukes Cataract and Laser Institute. http://www.stlukeseye.com.

3. The Glaucoma Foundation. About Glaucoma. www.glaucomafoundation.org/education_content.php?i=7, 2003.

4. The Thomson Corporation. Glaucoma. www.ehendrick.com/healthy/000596.htm, 2002.

5. Optic Chiasm diagram from website http://www.eyetec.net/group3/M11S2.htm

6. Clark A., Yorio, T. Ophthalmic Drug Discovery. www.nature.com/reviews/drugdisc, Volume 2, pages 449-459, June 2003.

7. MedTrials, Inc. Aligning the Art and Science of Clinical Research.® Provided by the University of North Texas Health Science Center at Fort Worth. Introduction to Clinical Research and Studies. 5; 7-10.

8. Hardman JG, Limbird LE, Molinoff PB, et al. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 9th ed. New York, NY: McGraw-Hill; 1996

9. Cantor, L., Fechtner, R.D., Michael, A.J., Simmons, S.T., Wilson, M.R., Brown, S.V.L. The Foundation of the American Academy of Ophthalmology. *Glaucoma.* Section 10:30-31, 2001-2002.

10. http://www.allerganindia.com/glaucomahome.htm

11. Ritch, R. What's New In Glaucoma- Medical Update. Eye to Eye. pp 1-5, 2003

12. Soltau, J.B., Zimmerman, T.J. Changing Paradigms in the Medical Treatment of Glaucoma. *Survey of Ophthalmology.* 47(1), August 2002.

13. Reardon, G., Schwartz, GF, Mozaffari, E. Patient Persistency with ocular prostaglandin therapy: A population-based, retrospective study. Clinical Therapy. 25(4):1172-85, April 2003

14. Brooks, D.W. Healthy Seniors: Understanding Glaucoma. WebMD http://content.health.msn.com/content/article/48/1738_52042, December 2001.

15. Parrish, R.K., Palmberg, P., Sheu, W.P. A Comparison of Latanoprost, Bimatoprost, and Travoprost in Patients With Elevated Intraocular Pressure: A 12-week, Randomized, Masked-evaluator Multicenter Study. *American Journal of Ophthalmology.* 135:688-703, 2003.

16. Stamper, R.L. Primary Drug Treatment for Glaucoma: Beta-Blockers Versus Other Medications. *Surv Ophthalmology.* 47:63-73, 2002.

17. Netland, O.A., Allen, R.C. Glaucoma Medical Therapy: Principles and Management. The Foundation of the American Academy of Ophthalmology. 13:26-30, 51-61, 77-78, 99-109, 1999.

18. Common Oral Antihypertensive Drugs by Class. Website: http//www.apollomanagedcare.com/PharmTherMgmt-HyperTxExpp.htm

19. Asrani, S., Zeimer, R., Wilensky, J., Gieser, D., Vitale, S., Lindenmuth, K. *Large Diurnal Fluctuations in Intraocular Pressure Are an Independent Risk Factor in Patients With Glaucoma.* J. of Glaucoma, 9 (2):134-142, 2000.

20. Stewart, W.C., Kolker, A.E., Steward, J.A., Leech, J., Jackson, A.L. Conjunctival Hyperemia in Healthy Subjects After Short-term Dosing With Latanoprost, Bimatoprost, and Travoprost, *American Journal of Ophthalmology.* 135 (3):314-320, March 2001.

21. New Drugs of 2000. Journal of American Pharmaceutical Association. 41(2):229-272, 2001.

22. Barclay, L. Early Intervention Reduces Progression of Glaucoma. *Archives of Ophthalmology.* 120:1268-1279, 1371-1372, 2002.

23. Brown, J.H. and Taylor, P. Muscarinic Receptor Agonists and Antagonists. The Pharmacologial Basis of Therapeutics, (Hardman, J.G, Limbird, L.E, Molinoff, P.B., Ruddon, R.W, and Gilman, A.G.,eds) TheMcGraw-Hill Companies, Inc.,1996, pp.149-150. Pharmacology: Cholinergic Drugs

24. Shelton, B., Castle, S., Cordes, M. Glaucoma Primer For Pharmacists. America's Pharmacist, March 2003, Web site http://www.ncpanet.org

25. Photography of the Goldmann Applanation Tonometer by Dr. H.D. Riley.

26. Weinreb, RN, Toris, CB, Gabelt, BT, Lindsey, JD, Kaufman, PL: effects of prostaglandins on the aqueous humor outflow pathways. Surv Ophthalmol 47 (suppl 1): S53-S64, 2002.

27. Shedden, A., Laurence, J., Tipping, R., and Timoptic-XE 0.5% Study Group: Efficacy and tolerability of timolol maleate ophthalmic gel-forming solution versus timolol ophthalmic solution in adults with open-angle glaucoma or ocular hypertension: a six-month, double-masked, multicenter study, Clinical Therapeutics, Volume 23, Issue 3, March 2001, Pages 440-450

28. Sugrue, MF: Pharmacological and ocular hypotensive properties of topical carbonic anhydrase inhibitors, *Progress in Retinal and Eye Research, Volume 19, Issue 1, January 2000, Pages 87-112*

29. University of Maryland Medicine. Web site http://www.umm.edu/patiented/doc25drugs.html

30. Higginbotham, EJ, Schuman, JS, Goldberg, I, et al. One-Year, Randomized Study Comparing Bimatoprost and Timolol in Glaucoma and Ocular Hypertension. *Archives of Ophthalmology*. 120(10):1286-1293, 2002.

31. I.H. Pang, D.L. Shade and A.F. Clark. Effect of Muscarinic Compounds on Intracellular Calcium Concentrations in Human Trabecular Meshwork Cells, Life Sciences, 56 (11-12): 1034, February, 1995 (Abstract).

32. Hartenbaum, D., Maloney, S., Vaccarelli, L., Liss, C., Wilson, H., and Gormley, GJ: comparison of dorzolamide and pilocarpine as Adjunctive therapy in patients with open-angle glaucoma and ocular hypertension, Clinical Therapeutics, Volume 21, Issue 9, September 1999, pp1533-1538.

33. Kulkarni, PS: The role of endogenous eicosanoids in rabbit intraocular inflammation J Ocular Pharmacol. 7:227-41, 1991.

34. Camras, C. Safety and side-effects of latanoprost, in Weinreb, R., Kitazawa, Y., Krieglstein, G (eds): Glaucoma in the 21st Century. London: Mosby International Ltd., 2000, pp 201-211.

35. Schachtschabel, U., Lindsey, JD, Weinreb, RN: The mechanism of action of prostaglandins on uveoscleral outflow. Curr Opin Ophthalmol 11:112-5, 2000

36. Susanna R., Medeiros, FA: the pros and cons of different prostanoids in the medical management of glaucoma. Current Opinion in Ophthalmology, 12:149-56, 2001.

37. Inomata, H., Bill, A., Smelser, GK: Unconventional routes of aqueous humor outflow in Cynomolgus monkey (Macaca irus). Am J Ophthalmology 73:893-907, 1972.

38. Pederson, JE, Gaasterland, DE, MacLellan, HM: Uveoscleral aqueous outflow in the rhesus monkey: importance of uceal reabsorption. Invest Ophthalmol Vis Sci 16: 1008-17, 1977-1992

39. Camras, CB, Siebold, EC, Lustgarten, JS, et al: Maintained reduction of intraocular pressure by prostaglandin F2 alpha-1-isopropyl ester applied in multiples doses in ocular hypertensive and glaucoma patients. Ophthalmology 96:1329-36, 1989.

40. Crawford, K., Kaufman, PL: Effects of topical PGF2 alpha on aqueous humor dynamics in cynomolgus monkeys. Curr Eye Res 6:1035-44, 1987.

41. Stewart, W.C., Rhodes, J.S., Leech, J.N. (2002). Survey Assess Red Eye And Prostaglandin Use. Review of Ophthalmology, 9:04, April 15, 2002.

42. Ritch, R., Liberman, J. Glaucoma Associates of New York.

www.glaucoma.net/gany/faq/figure5/html

43. Perry, C., McGavin, J., Culy, C., Ibbotson, T. Latanoprost : An Update of its Use in Glaucoma and Ocular Hypertension. Drugs Aging. 20(8):597-630, 2003

44. Sharif, N.A., Williams, G., Kelly, C.R. Bimatoprost (Lumigan) and its Free Acid Are FP Prostaglandin Receptor Agonists, *European Journal of Pharmacology*, 432:211-213, 2001.

45. Chemical structure of TRAVATAN. Web site. http://www.caymanchem.com/neptune/servlet/neptune/template/Product.vm/catalog/16812/a/z

46. Stjernschantz, JW. From PGF2_-Isopropyl Easter to Latanoprost: A review of the development of Xalatan. The proctor lecture. Invest Ophthalmol Vis Scie. 42:1134-1145, 2001

47. Stjernschantz, JW. Phenyl substituted prostaglandin analogues for glaucoma treatment. Drugs of the Future, 17(8):691-704, 1992.

48. Netland, P.A., Landry, T, Sullivan, K.D., Andrew, R., Silver, L., Weiner, A., Mallick, S., Dickerson, J., Bergamini, M.V.W., Robertson, S.M., Davis, A.A., and the Travoprost Study Group. Travoprost Compared With Latanoprost and Timolol in Patients With Open-angle Glaucoma or Ocular Hypertension. American Journal of Ophthalmology, 132:472-484, 2001.

49. Robin, A.L., Protzko, E., Visco, D., Schwartz, A.L., LaBorwit, S., Smearman, S.M., Seidenberg, J., Reed, D., Stottlemyer, J., Weiss, H.S., Khanna, S., Brummett, M., Baltimore, MD; Havre de Grace, MD; York, PA; Chevy Chase, MD. Hyperemia and Myalgia: A 28-Day Prospective Double-Masked Comparison Of Travoprost and

Bimatoprost Therapy in Primary Angle Glaucoma and Ocular Hypertension. American Glaucoma Society, Annual Meeting in 03/6-9/03, San Francisco, CA.

50. Hellberg MR, Sallee VL, McLaughlin MA, et al. Preclinical efficacy of travoprost, a potent and selective FP prostaglandin receptor agonist. *J Ocul Pharmacol Ther.* 2001;17:421-432.

51. Bournias, TE, Lee, D., Gross, R., Mattox, C. Ocular hypotensive efficacy of bimatoprost when used as a replacement for latanoprost in the treatment of glaucoma and ocular hypertension. *J Ocul Pharmacol Ther.* 19(3):193-203, June 2003.

52. Higginbotham, E.J., Stiles, M., Feldman, R., Dubiner, H. Latanoprost and Timolol Combination Therapy vs. Monotherapy: One-Year Randomized Trial. *Archives of Ophthalmology.* 120(17):915-922, 2002.

53. Orengo-Nania, S., Landry, T., Von Tress, M., et al. Evaluation of travoprost as adjunctive therapy in patients with uncontrolled intraocular pressure while using timolol 0.5%. *Am J Ophthalmol.* 132:860-868, 2001.

54. Outline of the Drug Development Process. http://www.fda.gov/cder/handbook/develop.htm

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