UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SLAYBACK PHARMA LLC,

Petitioner,

v.

EYE THERAPIES, LLC,

Patent Owner.

Case IPR2022-00142
U.S. Patent No. 8,293,742

DECLARATION OF ROBERT J. NOECKER, MD, MBA

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I. Introduction

1. I, Robert J. Noecker, submit this declaration to state my opinion on the matters described below.

2. I have been retained by Eye Therapies, LLC, as an independent expert in this proceeding before the United States Patent and Trademark Office.

3. I understand that this proceeding involves U.S. Patent No. 8,293,742 ("the '742 patent"), and that I have been asked to provide my opinions of whether the subject matter of the claims of the '742 patent is patentable.

4. This declaration sets forth my opinions from the perspective of a person ordinarily skilled person in the art, which I have formed in this proceeding based on my education, training, clinical research, knowledge, personal and professional experience, my understanding as an expert in the field, and my study of the evidence.

5. I am being compensated for my time at the rate of $750 per hour. This compensation is not contingent upon the nature of my findings, the presentation of my findings in testimony, or the outcome of this proceeding.

II. Qualifications and Professional Experience

6. My curriculum vitae is submitted with this declaration as Appendix A. I have summarized my educational and professional background below.

7. I received a Bachelor of Science in Biology from the Massachusetts Institute of Technology in 1985. I also received a Bachelor of Science in Materials

Science and Engineering, as well as a Bachelor of Science in Humanities and Engineering (Literature) from the Massachusetts Institute of Technology in 1986.

8. After completing my undergraduate studies, I went on to obtain an M.D. degree from the University of North Carolina School of Medicine in 1990. After completing medical school, I undertook an internship in internal medicine at the Moses H. Cone Memorial Hospital in Greensboro, North Carolina from July of 1990 until June of 1991. In July of 1991, I began my residency in ophthalmology at the University of Arizona. I completed that residency in June of 1994. I then went on to complete a clinical fellowship in ophthalmology at the New England Eye Center at Tufts University School of Medicine in Boston, Massachusetts from July of 1994 to June of 1995.

9. Since completing my residency and fellowship, I have held a number of academic positions at universities across the country. Starting in June of 1994, I held the position of Assistant Professor of Ophthalmology at Tufts University School of Medicine. In June of 1996, I returned to the Department of Ophthalmology at the University of Arizona, first as an Assistant Professor of Ophthalmology (1996-2002), and then as an Associate Professor of Ophthalmology (2002-2003). During my time at the University of Arizona, I also served as Residency Director from July of 1998 until June of 2003, as a Faculty Member in the Biomedical Engineering Interdisciplinary Program in the Graduate College of the University of Arizona from

July of 1998 until December of 2003, and as the Associate Chair for Clinical Activities for the Department of Ophthalmology from July of 2002 until December of 2003.

10. In January of 2004, I became a member of the faculty of the Department of Ophthalmology at the University of Pittsburgh School of Medicine, first as a Visiting Associate Professor of Ophthalmology (2004-2007), then as an Associate Professor of Ophthalmology (2007-2009), and finally as a Professor of Ophthalmology (2009-2011). I also served as the Vice Chair of the UPMC Eye Center at the University of Pittsburgh School of Medicine from January 2004 through June 2011.

11. Since 2011, I have worked as an ophthalmologist and director of glaucoma at the Ophthalmic Consultants of Connecticut. I am on the staff of St. Vincent's Hospital, Hartford Hospital, and the West Haven Veteran's Hospital. I am a Clinical Professor at the Frank Netter School of Medicine at Quinnipiac University, and I am an Assistant Clinical Professor at Yale School of Medicine in the Department of Ophthalmology. I lecture, teach, and train ophthalmology residents, optometry residents, students, and medical students.

12. I have received a number of honors and awards throughout my career. Those awards include, among other things, being selected to the Best Doctors in America every year since 2004, as well as a Top Doctor by a number of other

services. Additionally, I have been selected as the Clinical Instructor of the Year by the ophthalmology residents three times during my tenure at the University of Pittsburgh and have received teaching awards at each institution where I have been a faculty member. I am currently the Acting President of Connecticut Glaucoma Society.

13. I have conducted research in the field of ophthalmology for nearly 30 years and have been an investigator on numerous clinical trials for ophthalmic products, a full list of which can be found in my curriculum vitae. *See* Appendix A at 33-35

14. Over the course of my career, I have authored or co-authored over 100 peer-reviewed publications and have had several hundred abstracts published. I also serve as a contributing editor for seven different publications and as a peer-reviewer for twelve additional publications. I frequently lecture on the subjects of diagnosis and treatment of ophthalmic disorders. My other qualifications are set forth in my curriculum vitae.

15. I have participated in multiple clinical trials for brimonidine and related ophthalmic medications and have published peer review papers on its use. I prescribe brimonidine on a daily basis (and have done so for over twenty years) for the treatment of multiple ocular conditions. I also treat patients on a daily basis with eye redness and the associated underlying conditions.

16. I have consulted for numerous pharmaceutical companies over the years. I also have served as an expert witness in the field of ophthalmology, and my testimony has been credited in court.

17. I have been a member of several professional associations for many years. I have been a member of the Association for Research in Vision and Ophthalmology since 1989, and a fellow of American Academy of Ophthalmology since 1991. I have also been a member of American Society for Cataract and Refractive Surgery since 1992, and an associate member of Association of University Professors in Ophthalmology since 1998. I have been and still am an active member of American Glaucoma Society since 2000. I have been a member of Connecticut Glaucoma Society and Connecticut Society for Eye Physicians since 2011. In 2020, I have been elected as a co-chair of Connecticut Glaucoma Society. And since 2021, I have been elected as the acting president of Connecticut Glaucoma Society.

18. On the basis of my education and experience, I believe I am qualified to express the opinions provided below.

III. Information Considered

19. In forming my opinions, I had available the documents cited herein and in Appendix B, as well as the publications listed in my *curriculum vitae* at Appendix A. I additionally have based my opinions on my professional and academic

experience in the area of pharmaceutical formulation. I reserve the right to testify about these materials and experience. For the reasons discussed below, I disagree with Dr. Sher's and Dr. Laskar's conclusions that the claims of the patents are invalid based on anticipation and obviousness.

IV. Summary of Opinions

20. I have been asked to provide my opinion as to whether the methods of reducing redness recited in claims 1-6 of the '742 patent are patentable over certain prior art references. It is my opinion that the methods of claims 1-6 are patentable.

21. Dr. Sher has failed to establish that the '553 patent or Walters 1991 destroys the novelty of the methods of claims 1 and 2, expressly or inherently. Neither the '553 patent nor Walters 1991 discloses or even suggests using low concentration brimonidine to reduce eye redness. And there is no data indicating that any of the patients administered with low concentration brimonidine necessarily and inevitably experienced redness reduction in the eye.

22. Dr. Sher has failed to establish that any of the cited prior art references render any of claims 1-6 obvious.

23. First, brimonidine was known to cause high incidences of ocular allergic reactions, clinically reaching rates of 13%. While this may have been a tolerable property for treating the serious disease of glaucoma, it would have been yet another property that would have discouraged skilled artisans from considering

it in an OTC redness reliever, where the potential for misuse exists and a heightened need for safety arises.

24. Second, there is no evidence that a POSA would have been motivated to use low-concentration brimonidine—a highly selective α_2 agonist with very little α_1 effect—to reduce eye redness when the art at the time clearly indicated that eye whitening is an α_1-mediated effect and brimonidine's whitening effect was concentration dependent, sharply decreasing as its concentration decreased.

25. Third, even if a POSA would have pursued an α_2 agonist as a redness reliever—which Dr. Sher failed to prove—the POSA would have looked toward α_2 receptor agonists other than brimonidine that still had a relatively high selectivity for α_1 adrenergic receptors, such as apraclonidine and oxymetazoline.

26. Further illustrating the patentability of the '742 patent claims, there is substantial evidence supporting the '742 patent's objective indicia of non-obviousness, including unexpectedly superior redness reducing efficacy, coupled with rapid onset, long duration of action, and little or no rebound hyperemia and tachyphylaxis. This superior efficacy and safety profile have garnered significant industry praise that is reflected in the '742 patented invention's commercial success and the current copying by competitors.

V. Level of Ordinary Skill in the Art

27. I understand that the Petitioner contends that "[a] POSA was a composite person (or team) that included a medical doctor and a pharmaceutical formulator." Pet. at 15. I understand that the Petitioner further contends that "[t]he medical doctor was an ophthalmologist with at least three to four years of experience in LASIK surgery, clinical trials and U.S. FDA regulation of eye products, and had experience in the use of topical brimonidine and apraclonidine and topical vasoconstrictors such as naphazoline and tetrahydrozoline" and that "[t]he pharmaceutical formulator had a doctorate in pharmaceutics or a related degree and at least three to five years of experience developing eye drop formulations for clinical trial and regulatory approval." *Id*.

28. In my opinion, the qualifications that the Petitioner attributes to a POSA go far beyond those of a person of ordinary skill. In any event, my opinions expressed herein would not change regardless of which definition is applied.

29. The field to which the '742 patent pertains is interdisciplinary. I agree that a person of ordinary skill in the relevant art may be represented by a team of individuals with experience and various skills relating to eye care, including, *inter alia*, the medical and pharmaceutical formulation arts. Furthermore, a person of ordinary skill in the relevant art may also have been part of or have access to a team of individuals with experience in chemistry, in designing and evaluating ophthalmic

formulations, and/or in administering ophthalmic formulations to treat ocular conditions obtained by some combination of education and work experience.

30. The medical doctor is a specialist in treating diseases of the eye, such as an optometrist or ophthalmologist, with three to four years of experience, who also has experience designing and running clinical trials on ophthalmic formulations. In my opinion, the pharmaceutical formulator had a Bachelor's degree in pharmaceutics or a related discipline with about three to five years of work experience in this area, or a comparable level of education and training, such as a Ph.D. with one to two years of experience in this area.

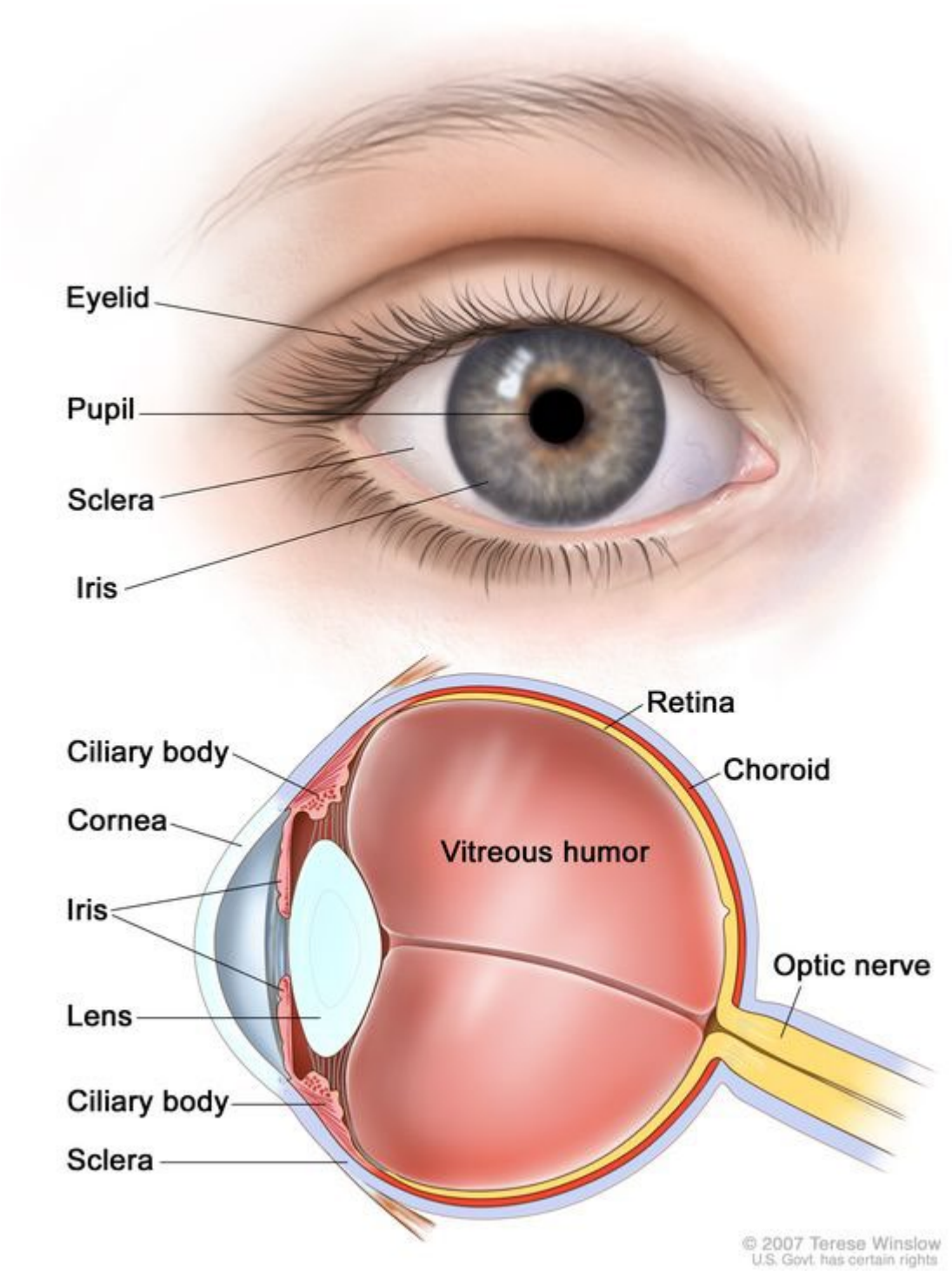
31. In light of the above, I believe the POSA should be defined as follows: The POSA is a composite person engaged in developing pharmaceutical formulations and treatment methods for the eye, and includes a medical doctor and pharmaceutical formulator with the qualifications outlined above. This person may also work in collaboration with other scientists and/or clinicians who have experience with chemistry; developing, designing, and/or evaluating ophthalmic formulations; administering ophthalmic formulations; running clinical trials related to such formulations; and/or treating patients using such formulations.

VI. Technical Background

A. Anatomy of the Eye

32. The eye is a complex, multi-layered organ. Even today, the exact mechanisms of action involved in certain ocular physiological processes are not completely understood. Thus, there are still significant uncertainties surrounding many eye treatments. *See* EX-2030 (Agarwal) at 13.

33. I provide the following images of the eye and its anatomy to guide the discussion in the succeeding paragraphs:



Anatomy of the Eye.

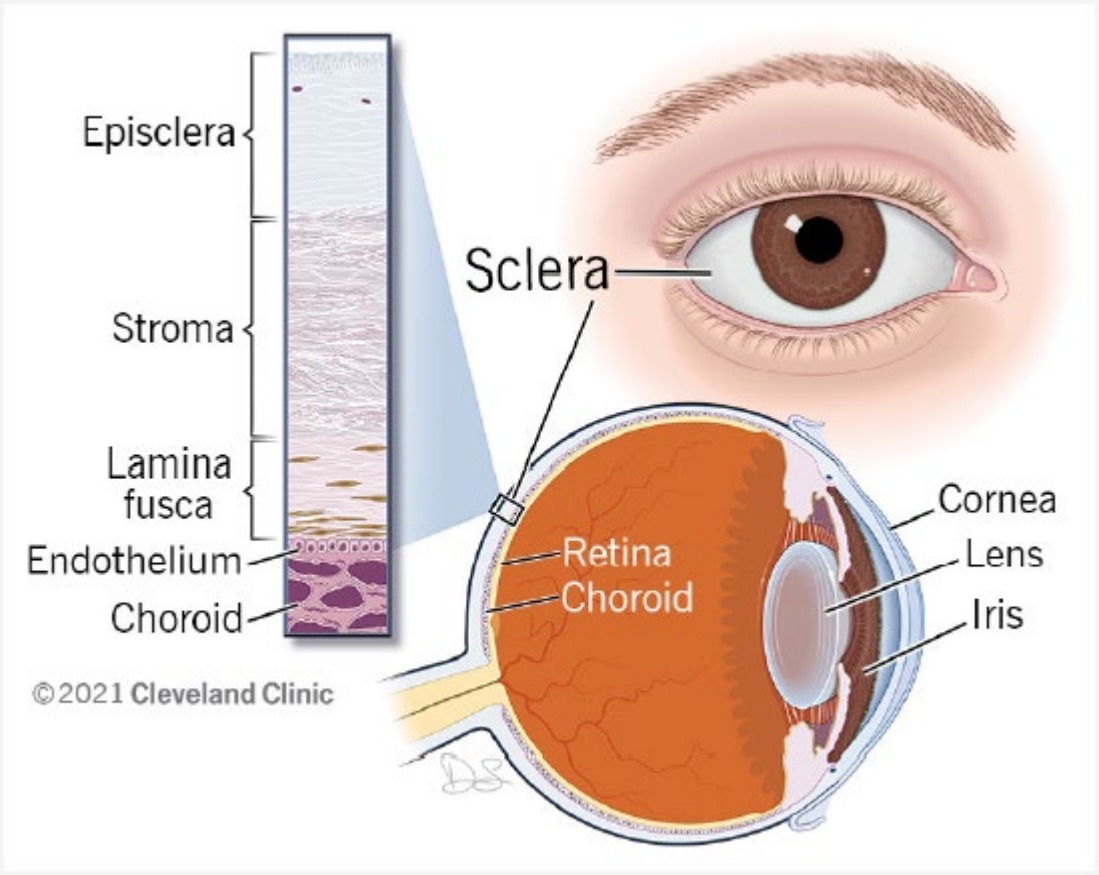
34. This image shows a cross-section of the eye. Ophthalmic products aimed at reducing redness—sometimes referred to as ophthalmic decongestants or redness relievers—target the "white" of the eye, which consists of the conjunctiva, the episclera, and the sclera. EX-1001 ('742 patent) at 14:7-14; EX-1002, ¶71 ("scleral whitening makes the eye look less red.").

35. The cornea is a transparent surface of the eyeball in front of the lens and acts as the major refractive element in the optical pathway. The cornea lacks blood vessels (i.e., avascular) so that light may pass through it easily and be focused onto the retina. EX-2177 at 1. Any abnormal growth of blood vessels onto the cornea can significantly impair vision. *See id*.

36. The conjunctiva is a clear, thin tissue that covers the sclera and lines the inside of the eyelids. EX-2172 at 4. Some of its roles are to lubricate the ocular surface, transport substances to and from the surface, and provide a line of defense against external insults. The sclera, also commonly referred to as the white of the eye, is a semi-rigid structure of connective tissue that provides a protective covering of the eyeball. EX-2178 at 2. It acts as the supporting wall for the eyeball, maintaining the eyeball's shape and protecting delicate interior parts from injury. *Id*. at 3.

37. As shown in the image below, the sclera consists of four layers. The outermost layer is the episclera, which is a clear, thin tissue resting on top of the

eyeball. *Id*. at 3. The second layer (stroma) and the third layer (lamina fusca) are fibrous connective tissue layers. *See id*. The bottom layer is endothelium, which is a thin inner cellular lining of the choroid. *See id*.



Layers of the sclera.

38. Each of the conjunctiva, episclera, and sclera has blood vessels. The conjunctiva and the episclera have blood vessels known as superficial and deep conjunctival capillary and episcleral plexuses. EX-2179 at 1. Dilation of these blood vessels makes them more visible, triggering eye redness. The surface of the sclera, deep into the episclera, also contains blood vessels. When dilated, these blood

vessels at the sclera interface with the episclera, which can make the eye appear red. *Id*.

39. The ciliary body is located inside of the eye and performs multiple functions. EX-2171 at 1. The ciliary body changes the shape of the lens when the eye focuses. *Id*. It also produces clear fluid (aqueous humor) that fills the space located between the cornea and the lens, providing nutrients to these parts of the eye. *Id*. As further explained below, an increased amount of the aqueous humor increases the intraocular pressure, which can cause glaucoma. Glaucoma is a serious disease that, if not properly treated, can lead to blindness.

40. The eyes have a natural defense mechanism to protect them from the external environment. When a foreign substance is introduced, the eye produces tears or secretes mucus to eliminate that substance.

B. Adrenergic Receptors

41. Adrenergic receptors are receptors on the surface of the cells in the sympathetic nervous system ("SNS"), which is a network of nerve cells found in organs, including the eyes. EX-2169 (Derick 1995) at 1. There are two types of adrenergic receptors: alpha and beta. *Id*. at 2. The alpha-adrenergic receptors are further categorized into two subtypes, known as alpha 1 (α_1 receptors) and alpha 2 (α_2 receptors), both of which are found in the eye. *Id*. The α_1 receptors are located in

the post-synaptic effector cells, frequently in smooth muscle. *Id*. The α_2 receptors are located presynaptically and postsynaptically. *Id*.

42. The adrenergic receptors interact with a specific type of neurotransmitters known as catecholamines (e.g., epinephrine and norepinephrine) to send messages across the SNS and elicit bodily responses. *Id*. at 1. Importantly, the two types of α-adrenergic receptors work in different ways to mediate different systemic responses, excitatory versus relaxation responses. *See id*. at 4.

43. When activated, α_1 receptors release norepinephrine and produce an excitatory response (i.e., a fight-or-flight response), vasoconstricting blood vessels or causing smooth-muscle contraction. *Id.* at 2, 4; EX-2162 (Sher Dep. Tr.) at 74:9-24, 75:11-17. This is known as an α_1 mediated effect. EX-1016 (Griffith 2003) at 12-13; EX-1035 at 2 (Burke). As discussed further below, the α_1 effect was widely accepted as responsible for the ocular vasoconstriction that reduced eye redness. *See* EX-1016 (Griffith 2003) at 12-13; EX-1035 (Burke) at 2; *see also* EX-1023 (Scruggs 2000) at 5; EX-1019 (Lachkar 1998) at 3 ("[v]asoconstriction is mediated mainly via α-1 adrenergic receptors").

44. The α_2 receptors, however, can work in opposition to the α_1 effect mediated by the α_1 receptors. They can mediate an inhibitory effect that decreases

the release of the neurotransmitters, like norepinephrine.[1] EX-2169 (Derick 1995) at 2-3. Importantly, these effects can cause blood vessels to dilate, triggering relaxation that can clinically manifest as sedation, depression, hypotension, and eye redness. *Id*. at 4; Ex. 1001 at 1:38-55; *see also* EX-2169 (Derick 1995) at 5 (describing the sedative effect clonidine, an α_2 agonist). EX-1019 (Lachkar 1998) at 3 ("[B]rimonidine tartrate may also produce vasodilatation via the α_2-adrenergic receptors on endothelial cells, which release endothelial-derived relaxing factor."); EX-2012 (Alphagan® Label 2001) at 3, 8, 9, 12; EX-2014 (Alphagan P® Label 2005) at 2, 4 (noting that fatigue and drowsiness are common side effects of the Alphagan® products, which contain 0.2% brimonidine, a highly selective α_2 receptor agonist); EX-1035 (Burke) at 2 (because of brimonidine's high affinity for the α_2 receptor, "brimonidine would be the least likely to produce α_1-adrenoceptor mediated side effects, such as mydriasis and ocular vasoconstriction").

[1] At the cellular level, when α_2 receptors are triggered pre-synaptically by an α_2 agonist, a cascade of cellular activity results that decreases norepinephrine release. EX-2169 (Derick 1995) at 2. Post-synaptically, α_2 receptor agonists can also exert an inhibitory effect on the SNS by inhibiting release of adenyl cyclase. *Id.* at 3.

45. Needless to say, the mechanism of action of the adrenergic receptors involves "complicated chemical reactions" and has been the subject of "hundreds, if not thousands, of papers on receptors." EX-2162 (Sher Dep. Tr.) at 76:12-77:3. In my opinion, any efforts to develop a treatment involving the adrenergic receptors is an unpredictable endeavor that requires a careful balancing of clinical efficacy and unintended side effects. This is particularly true, as explained below, for over-the-counter (OTC) redness relievers, which are subject to potential misuse that leads to serious ocular side effects.

C. Ocular Conditions

46. There are many ocular conditions. The signs and symptoms of ocular conditions differ, as do the methods of treating them. Below, I discuss the ocular conditions of eye redness and glaucoma, which are relevant to the subject matter of the '742 patent.

1. Eye redness

47. Red eye, also known as ocular hyperemia, refers to a common ophthalmic condition caused by vasodilation—an increase in the diameter of blood vessels on the eye and the influx of blood that "congests" the vessel. EX-2162 (Sher Dep. Tr.) at 112:18-113:5 (testifying that hyperemia involves "dilated but unbroken blood vessels"). It can occur in any of the visible layers of the eye that have vasculature, such as the conjunctiva, the episclera, or the sclera. *See id*. at 82:17-

83:7 (testifying that eye whitening occurs through the vasoconstriction of "blood vessels in the ocular surface").

48. There is a social stigma linked to red eyes, as they are often associated with drinking, drug abuse, and lack of sleep. EX-2011 at 1-2; EX-2211. Additionally, it is a common side effect of glaucoma medication use is eye redness, which can lead to decreased adherence with glaucoma therapy. *See id*. at 1. This is particularly dangerous because glaucoma patients who do not use their medication as prescribed could be on a slippery slope towards blindness. *See id*.

49. Because of the social stigma associated with red eyes, affected individuals are often eager to efficiently manage the redness. *See id.* at 1-2. But to determine how to treat the red eye, the physician must first determine the underlying cause and the location of redness. Common causes of red eye include conjunctivitis (infectious and noninfectious), foreign body, environmental eye irritation, and dry eye. The manner in which red eye should be managed will differ depending on the underlying cause.

50. Conjunctivitis occurs when blood vessels in the conjunctiva dilate due to allergens (noninfectious), or virus or bacteria (infectious). Conjunctivitis typically only affects the blood vessels in the conjunctiva.

51. Foreign body redness can arise when materials or irritants are caught on the surface of the eye and cause inflammation. The inflammation triggers an

immune response involving conjunctival leukocytes, causing eye lid edema (puffy eye) and possibly hyperemia. Contact lenses can also trigger eye redness, primarily near the limbus, which is the border between the cornea and the sclera.

52. Dry eye can arise due to a variety of reasons, including exposure to a dry environment, dehydration, nutrition, medication, etc. Regardless of the root cause, dry eye redness presents as a consistent pattern of ocular hyperemia—fine horizontal vessel dilation mainly in the intrapalpebral fissure of the conjunctiva.

53. Rebound hyperemia is a type of eye redness that occurs when a patient stops using a redness reliever (ophthalmic decongestant). The initial vasoconstriction resulting from the use of the ophthalmic decongestant causes oxygen deficiency (i.e., ischemia) in the blood vessels. EX-1001 ('742 patent) at 4:40-46 (explaining that the art at the time "considered the complication of rebound hyperemia to be intrinsic to vasoconstriction, wherein blood flow is reduced, causing attendant ischemia with some inflammatory cascade, precipitating rebound hyperemia in many cases and often leading to medicamentosa"). When the drug wears off, compensatory vasodilation occurs to flood/engorge the vessels with blood and bring in the needed oxygen. *Id*. The user thus experiences more eye redness than before. *Id*.

54. Distinct from rebound hyperemia—and even tolerance, which occurs with chronic use of a drug—tachyphylaxis is a rapidly decreasing response to an

ocular decongestant following its initial administration. EX-2185 (Abelson 2006) at 1. It occurs due to a reduction in the availability of α_1 receptors (downregulation) in an attempt to maintain homeostasis within the affected cells. *Id*. Because tachyphylaxis leads to a rapid reduction in the efficacy of ocular decongestants, it could prompt the patient to instill more drops more frequently to obtain the same level of whitening, leading to misuse and overuse of the drug. *See id*. This could cause toxic conjunctivitis and medicamentosa of the eye—which could manifest as a chronic red eye that persists even after discontinuation of the offending eye drop. EX-2183 (Spector) at 1.

2. Glaucoma

55. Glaucoma is an eye disease that gradually damages the optic nerve, which can ultimately lead to blindness. EX-2011 at 1. While the pathology of all types of glaucoma are not completely understood, a fluid buildup in the anterior chamber—the area between the cornea and the lens—is thought to be a major risk factor. EX-2173.

56. In a healthy eye, the fluid produced by the ciliary body drains out through a tissue called trabecular meshwork into the episcleral veins. *Id*. at 2. When the eye does not properly drain it out, the excess fluid in the anterior chamber increases the intraocular pressure (IOP), gradually damaging the optic nerve. *Id*.; EX-2011 at 1.

57. Alpha-2 receptor agonists, such as brimonidine and apraclonidine, have long been used as glaucoma treatments. *See* EX-1016 (Griffith 2003) at 13-14. Studies indicate that the α_2 agonists primarily reduce the production of aqueous humor that flows into the anterior chamber and increase the aqueous humor drainage from the eye, both of which work together to decrease IOP in the eye. EX-1017 (Wikberg 2001) at 1.

D. State-of-the-art redness relievers: "an α_1 mediated effect"

58. By August 2008, which I have been informed is the earliest effective filing date of the '742 patent, those skilled in the art understood that reduction in eye redness or whitening (also known as blanching) occurred through vasoconstriction, which was recognized as an α_1 mediated effect. EX-1016 (Griffith 2003) at 12-13; EX-2169 (Derick 1995) at 1, Table 2. The art taught that "[a]ll selective α_1-agonists are vasoconstrictors, which is the basis of their therapeutic activity." EX-1016 (Griffith 2003) at 12. Indeed, selective α_1 agonists were widely used as vasoconstrictors in topical nonprescription drugs for "treating nasal congestion or bloodshot eyes." *Id.* at 13.

59. Early on, the Federal Register 1988 defined vasoconstriction as "[a] pharmacologic agent which, when applied topically to the mucous membranes of the eye, causes transient constriction of conjunctival blood vessels." EX-1009 (Federal Register 1988) at 15. Coupled with that definition was the understanding that

vasoconstriction was mediated mainly by α_1 receptors. EX-1019 (Lachkar 1998) at 3; EX-2169 (Derick 1995) at Table 2; EX-1035 (Burke 1996) at 2; EX-1016 (Griffith 2003) at 12. Not coincidently, the approved drugs before August 2008 for reducing eye redness were either α_1 selective receptor agonists or mixed α_1/α_2 agonists having a predominant α_1 effect. EX-1009 (Federal Register 1988) at 16 (listing approved ophthalmic vasoconstrictors, including ephedrine hydrochloride, naphazoline hydrochloride, phenylephrine hydrochloride, and tetrahydrozoline hydrochloride). *See also* EX-1016 (Griffith 2003) at 13 (identifying naphazoline, oxymetazoline, tetrahydrozoline, and xylometazoline as primarily α_1-agonists, "widely employed as vasoconstrictors in topical nonprescription drugs for treating nasal congestion or bloodshot eyes").

60. Many of the leading products approved for reducing eye redness as of August 2008 were nonprescription OTC products containing these α_1 or mixed α_1/α_2 adrenergic receptor agonists as the active ingredient. The following table provides a list of some of those products:

Commercial Name	α-Agonist API	α-Agonist Type
Naphcon®	naphazoline 0.012%	Mixed α_1/α_2 agonist
Naphcon-A®	naphazoline 0.025%	Mixed α_1/α_2 agonist
All Clear®	naphazoline 0.012%	Mixed α_1/α_2 agonist
Ocu-Clear®	oxymetazoline 0.025%	Mixed α_1/α_2 agonist
Visine Original®	tetrahydrozoline 0.05%	Selective α_1 agonist
Visine Advanced Redness Relief®	tetrahydrozoline 0.05%	Selective α_1 agonist

61. While these vasoconstrictors reduced redness, they have also triggered various side effects, including rebound hyperemia, tachyphylaxis, and medicamentosa. EX-1001 ('742 patent) at 2:11-13, 2:21-28; EX-1009 (Federal Register 1988) at 10; EX-2185 (Abelson 2006) at 2. Because OTC products treat self-diagnosable conditions without a health care provider's instructions, they are susceptible to misuse through overuse. Therefore, they must not only be efficacious, but they must also be particularly safe. *See, e.g.*, EX-2170 (FDA Website); EX-2162 (Sher Dep. Tr.) at 98:24-100:5; EX-1003, ¶40. Yet many of these OTC redness relievers—including tetrahydrozoline (Visine), naphazoline (Clear Eyes), and phenylephrine (Prefrin Liquifilm)—caused conjunctive hyperemia in a statistically significant number of cases. EX-1009 (Federal Register 1988) at 10; EX-2182 (Soparkar) at 4-5; EX-2183 (Spector) at 2-3; EX-2184 (Stafford-Smith) at 2. It was postulated that the conjunctival hyperemia was likely induced by tachyphylaxis or rebound hyperemia from discontinuation of the vasoconstrictor. EX-2182 (Soparkar) at 4-5.

62. It was known that tetrahydrozoline and naphazoline caused rebound hyperemia, and in some cases eye drops containing these vasoconstrictors required shorter intervals between administrations to obtain redness relief. EX-2183 (Spector) at 3. This suggests the onset of tachyphylaxis that can unwittingly lead to misuse because the user may not realize the rapidly decreasing effect of the drug. *See id*.

That overuse often causes chronic rebound hyperemia even after discontinuing the eye drops (*id.*), leading to the development of the toxic conjunctivitis or medicamentosa.

E. Not all α-adrenergic agonists characterized as "vasoconstrictors" work similarly

1. Vasoconstriction (α_1 effect) versus vasodilation (α_2 effect)

63. As discussed, it was known that ocular vasoconstriction for the purposes of reducing redness was an α_1 mediated effect. EX-2169 (Derick 1995) at 4, Tables 2 and 3. Alpha-2 receptors, however, can work in opposition to an α_1 effect, mediating vasodilation of endothelial cells by releasing endothelial-derived relaxing factor when activated by α_2 agonists. *Id.* at 2-3 (referring to brimonidine's potent ocular hypotensive effects, consistent with relaxation occurring due to vasodilation); *see also* EX-1019 (Lachkar 1998) at 3; EX-2169 (Derick 1995) at 5 (noting the sedation effect of the α_2 agonist clonidine). It was known, moreover, that most of the conjunctiva vessels are made up of endothelial cells. EX-2176 (Raviola) at 1 ("Most of the vessels in the conjunctival plexus have the diameter of capillaries, while the vast majority of vessels in the episcleral plexus are venules. Both types of vessels have a simple wall, which consists of an endothelium and a discontinuous layer of pericytes."). Therefore, using an α_2 agonist (particularly those with a high affinity

for α_2 receptors) on conjunctival vessels would have been expected mainly to cause dilation rather than ocular vasoconstriction.

64. Indeed, the systemic response to α_2 receptor activation by an α_2 agonist is sedation, depression, and hypotension. *See* EX-2169 (Derick 1995) at 4, 5, Table 2. These responses are consistent with relaxation brought about by vasodilation, as opposed to ocular vasoconstriction that leads to redness reduction and blanching.

2. Adrenergic receptor location and effect of agonist selectivity on reduction of eye redness

65. It was also known that the effect of an adrenergic receptor agonist will depend on a number of factors, including the location of the adrenergic receptors. EX-2169 (Derick 1995) at 3-4. Prior art taught that α_1 receptors are located on vascular smooth muscle located in, for example, the conjunctiva. *Id*. at 4, Table 3. Stimulation of these receptors leads to vasoconstriction (*id*.) and ultimately to conjunctival blanching. By contrast, the art taught that α_2 receptors were located on ciliary body and that stimulation of these receptors caused a decrease in aqueous humor production. *Id*. While that may have been through a poorly understood process affecting the ciliary epithelial cells, it is not external ocular vasoconstriction in the anterior segment of the eye that a skilled person would have associated with conjunctival blanching. *Id*.

66. Besides receptor location, receptor selectivity (or affinity for a particular receptor) can impact the effect of adrenergic medications. *Id*. In addition

to selective α_1 receptor agonists and mixed α_1/α_2 receptor agonists, there are selective α_2 agonists. Those skilled in the art understood that selectivity refers to the propensity of a drug to interact with a specific receptor subtype for which it is selective at concentrations too low to interact with another subtype for which it is not selective. *Id.* at 1. For a selective α_2 agonist, the lower its concentration, the less likely it will activate an α_1 effect. As recognized by Dr. Sher's cited reference, if drug concentrations "are insufficient to produce α_2 effects, then α_1 effects are highly improbable." EX-1018 (Robin 1998) at 2. At higher drug concentrations, however, the other receptor subtype (e.g., α_1 receptor) could be affected. *Id*. Apraclonidine, for example, is a relatively selective α_2 agonist, and at higher, therapeutic concentrations, it "produces conjunctival blanching, which is an α_1 effect." EX-2169 (Derick 1995) at 1.

67. Brimonidine is a highly selective α_2 agonist, having a potency ratio of α_2 to α_1 of at least 1000:1 and has been reported as high as 1812:1. EX-1023 (Scruggs 2000) at 5; EX-1035 (Burke 1996) at 2, Fig. 1. In other words, it is at least 1000 times more selective for α_2 receptors over α_1 receptors, which, as the prior art taught, would have made it the least likely among other selective α_2 agonists, including apraclonidine and clonidine, to produce an α_1 mediated effect, such as ocular vasoconstriction. EX-1035 (Burke 1996) at 2.

F. Brimonidine—a highly selective α_2 agonist

68. Brimonidine was discovered in the early 1970s. *See generally* EX-2190 ('319 patent). It was first approved by the FDA in 1996 for treating open-angle glaucoma or ocular hypertension as the prescription drug product known as Alphagan®. EX-2012 (Alphagan® Label 2001) at 7. The first approved strength of Alphagan® was a 0.2% brimonidine tartrate formulation. *See generally* EX-1031 (Alphagan NDA). Allergan later obtained FDA approval for a higher concentration product Alphagan® (0.5%). EX-2012 (Alphagan® Label 2001) at 1. Alphagan®, and particularly its active ingredient brimonidine, worked by suppressing aqueous humor production in the ciliary body and increasing uveoscleral outflow. EX-1035 (Burke 1996) at 7.

1. Brimonidine's known adverse side effects

69. Brimonidine-containing Alphagan® exhibited a fairly large spectrum of adverse events. *See, e.g.*, EX-1031 (Alphagan NDA) at 52-55. Of particular relevance here was its high incidence of ocular hyperemia, consistent with its vasodilation properties, and its incidence of ocular allergic reactions. In fact, ocular hyperemia and ocular allergic reactions were identified in the Alphagan® NDA as among the most common adverse events occurring with brimonidine treatment, with ocular hyperemia being listed as either the most common or the second most common adverse event. *Id.* at 57 ("The most frequently reported ocular adverse

events included ***ocular hyperemia***, burning and stinging, blurring, foreign body sensation, ocular pruritus, conjunctival follicles, photophobia, lid edema, ***ocular allergic reactions***, and ocular pruritus." (emphases added)), 90, 136. Additionally, as reported in the Alphagan® NDA for the clinical studies conducted using brimonidine, "[t]he most frequent causes of terminations due to adverse events in the brimonidine group were ocular allergic reaction, asthenia, headache, and oral dryness." *Id*. at 136; *see also id*. at 286. Indeed, Alphagan® is contraindicated in patients with hypersensitivity to brimonidine tartrate, who can develop eye redness resembling viral follicular conjunctivitis. EX-1008 at 3 (Alphagan® Label 1998).

70. With respect to ocular hyperemia, the Alphagan® NDA reports on two phase III studies using 0.2% brimonidine to treat patients with glaucoma and/or ocular hypertension. *Id.* at 21 (A342-103-7831 and A342-104-7831; Studies "103" and "104"). The percentage of patients in Study 103 experiencing ocular hyperemia was 39%, and for Study 104 it was 23%. *Id*. at 52, 86. A meta-analysis was done combining the data from the two studies and reported the incidence of hyperemia at 28.7%. *Id*. at 109.

71. With respect to the adverse event of ocular allergic reactions, the Alphagan® NDA reported that almost 10% of the patients in Study 104 experienced ocular allergic reactions. *Id.* at 86. The meta-analysis results from combing the data

from Studies 103 and 104 showed that almost 13% of the patients experienced ocular allergic reactions. *Id*. at 109.

72. The next generation Alphagan® products were serially approved in 2001 (Alphagan P®, 0.15% brimonidine tartrate) (*see* EX-2017 at 2) and 2005 (Alphagan P®, 0.1% brimonidine tartrate) (*see* EX-2019 at 1, 3). At the time, the only ophthalmic product on the market containing brimonidine at a concentration of 0.1% was the Alphagan® 0.1% product. In the combined label for Alphagan® P, 0.1% and 0.15%, hyperemia was reported as one of the most common side effects for these products. And even at these lower concentrations, brimonidine caused hyperemia at a comparably high level, occurring in approximately 10-20% of subjects.[2] EX-2014 (Alphagan P® Label 2005) at 4.

73. All in all, the allergic reactions appeared in nearly 32.3% of patients administered with brimonidine. EX-1032 (Rahman 2010) at 4. Brimonidine's long-term use was considered "limited by its propensity to cause ocular allergic reactions," which one study found included conjunctival hyperemia (occurring in 26.3-30.3% of patients), blepharitis, belpharoconjunctivitis, and follicular

[2] The label for Alphagan® P 0.1% and 0.15% grouped allergic conjunctivitis, conjunctival hyperemia, and eye pruritis. Allergic conjunctivitis or eye pruritis either give rise to ocular hyperemia or are a manifestation of that condition.

conjunctivitis. *Id*. It is thus contraindicated in patients with hypersensitivity to brimonidine tartrate and patients receiving monoamine oxidase (MAO) therapy. EX-1008 (Alphagan® Label 1998) at 3. Based on my experience, brimonidine can cause significant ocular allergic reactions by remaining on the surface of the eye and oxidizing.[3] The relatively high incidence of ocular allergic reactions observed in patients treated with brimonidine caused discontinuation of the drug in 7.2% of patients. EX-1022 (Schuman 1997) at 4.

74. Hyperemia associated with use of glaucoma drugs was and still remains today a significant problem. It is one of the most common reasons for noncompliance and discontinuation of glaucoma medication. *See* EX-2011 at 1-2. When dealing with a serious disease like glaucoma, many of the adverse side-effects from brimonidine could be tolerated for the greater cause of preventing blindness. But with nonprescription, OTC redness-reducing products, these side-effects would have disincentivized one skilled in the art from considering brimonidine when looking to develop a better redness reducer. EX-2162 (Sher Dep. Tr.) at 98:24-100:5 (testifying

[3] Knowing this oxidative potential of brimonidine, a skilled person would have been motivated to reduce brimonidine's residence time on the surface of the eye by facilitating its penetration into the deeper layers and decrease the potential for ocular allergic reactions.

that OTC redness relievers could be misused). Because OTC products treat a self-diagnosable condition without a health care provider's instructions, increasing the potential for misuse and abuse, they must be particularly safe and efficacious. *Id*.

75. Beset by high incidences of hyperemia, consistent with brimonidine's vasodilation properties and the antithesis of what one looks for in a redness reducer, as well as its propensity for ocular allergic reactions deterring any kind of long-term use, the skilled person would have looked elsewhere in seeking to improve upon the existing line of OTC redness reducers. A POSA would not have pursued low-concentration brimonidine redness reliever absent hindsight knowledge of the '742 patent because the prior art taught that lowering the concentration of brimonidine would effectively eliminate its blanching effects.

2. The prior art established that brimonidine's blanching effects were concentration dependent, rapidly diminishing as the concentration decreased

76. As discussed, selectivity in an alpha-adrenergic receptor agonist refers to its propensity to interact with a specific receptor subtype at concentrations too low to interact with another subtype for which it is not selective. EX-2169 (Derick 1995) at 1. But selectivity is not absolute. At higher concentrations, even a highly selective α_2 agonist like brimonidine could exhibit some α_1 vasoconstrictive effect and cause ocular blanching. *Id*. And as its concentration decreases, so too does brimonidine's α_1 effect and its corresponding ability to blanch. *See id*.; *see also* EX-1018 (Robin

1998) at 2 ("The degree of selectivity is only important if tissue concentrations are within the range required for α_1 activity. If tissue or circulating levels of drug are insufficient to produce α_2 effects, then α_1 effects are highly improbable.").

77. In a clinical study of about 250 patients to evaluate the effectiveness of 0.5% brimonidine to reduce IOP, it was observed that brimonidine caused conjunctival blanching at a rate of about 41% (in 183 patients). EX-1029 (David 1993) at 3. This is consistent with the clinical trials for Alphagan®. In a clinical trial of 0.5% brimonidine versus placebo, 0.5% brimonidine exhibited "[s]ignificantly greater incidences of conjunctival blanching," which its label confirms at 50%. EX-1031 (Alphagan NDA) at 13, Study S342-108-8042; EX-2012 (Alphagan® Label 2001) at 4. In Study 103, in which the concentration was lowered to 0.2% brimonidine, the rate of conjunctival blanching sharply dropped to 6.8%. EX-1031 (Alphagan NDA) at 52. And in Study 104, also at 0.2% brimonidine, no patients were reported as experiencing conjunctival blanching, though it clearly would have been reported if it occurred. *Id*. at 86-87. The meta-analysis of the data for the combined studies (103 and 104) was only 3.5%—a significant drop off in blanching when the concentration was only lowered slightly more than half. *Id*. at 109. This concentration relation for blanching in fact continued for Alphagan® P, where the concentration was lowered further (0.15% and 0.1%) and no conjunctival blanching was observed, although there was still significant hyperemia. *See* EX-2014

(Alphagan P® Label 2005) at 1, 4 (conjunctival blanching not listed as an adverse event).

78. In sum, prior to August 2008, those skilled in the art would have appreciated that not all compounds labelled as "vasoconstrictors" functioned similarly. The α_1 receptor agonists and nonselective mixed α_1/ α_2 receptor agonists used in all prior art redness relievers triggered a predominant α_1 vasoconstriction effect on blood vessels to "decongest" and reduce redness. By contrast, selective α_2 agonists, like the highly selective α_2 agonist brimonidine having very little α_1 effect, primarily caused blood vessels to vasodilate and flood with blood, manifesting as hyperemia or eye redness—exactly the property a POSA would not want for a compound when seeking to develop a redness reducer.

79. Brimonidine was also beset by high incidences of ocular allergic reactions. *See supra* Section VI.F.1, *infra* Section IX.B.1; EX-2011 at 1-2. While this may have been a tolerable property for brimonidine in treating the serious disease of glaucoma, it would have been yet another property of brimonidine that would have discouraged skilled artisans from considering using it in an OTC redness reliever. And although at high concentrations, brimonidine exhibited conjunctival blanching due to its minimal α_1 effect, the prior art established that that effect was concentration dependent. As the concentration of brimonidine decreased, so too did its propensity to blanch, essentially disappearing at concentration of 0.15% and

0.1%. Against this backdrop of prior art information for brimonidine, those skilled in the art would not have had any reason to use brimonidine with any expectation that at even lower concentrations (e.g., 0.025%), it would have effectively reduced redness.

3. A POSA would not have chosen brimonidine as an α_2 agonist redness reliever absent hindsight knowledge

80. Several α_2 receptor agonists other than brimonidine were known at the time of the invention of the '742 patent, including apraclonidine and clonidine. EX-1018 (Robin 1998) at 2; *see also* EX-1035 (Burke 1996) at 8. Apraclonidine was reported in the art as having an α_2 to α_1 potency ratio of 72:1. EX-1035 (Burke 1996) at 2, Fig. 1.[4] For perspective, the art reported an α_2 to α_1 potency ratio for brimonidine as high as 1812:1. *Id*. Apraclonidine was thus known to produce conjunctival blanching due to its higher affinity for α_1 receptors that would induce ocular vasoconstriction and reduce redness. EX-2169 (Derick 1995) at 6.[5] Indeed, the art

[4] The legend of Figure 1 of Burke et al. (EX-1035) states "α_1/α_2 - Adrenoceptor Selectivity." As is clear from the description beneath the figure, and as was known in the art, Figure 1 is referring to the α_2 to α_1 potency ratio of the drugs reported.

[5] Clonidine has an α_2 to α_1 potency ratio of 183:1 and also had a much higher potential than brimonidine to activate an α_1-effect and induce ocular vasoconstriction. EX-1035 at 2, Fig. 1.

taught that "compared to clonidine and apraclonidine, brimonidine would be the least likely to produce α_1-adrenoceptor-mediated side effects, such as mydriasis and ocular vasoconstriction." EX-1035 (Burke 1996) at 2. Moreover, apraclonidine was known to produce fewer systemic side effects than brimonidine, such as dry mouth and sedation. *See* EX-1018 (Robin 1998) at 2, 3. Thus, a POSA looking to develop an over-the-counter ophthalmic formulation for reducing redness using an α_2 receptor agonist, which has not been established, would not have considered brimonidine absent knowledge of its effectiveness as reported in the '742 patent. Instead, if anything, the skilled person would have looked to clonidine, apraclonidine, or even oxymetazoline—a mixed α_1/α_2 agonist with an even better α_2 to α_1 potency ratio than apraclonidine—and either modified it chemically or improved it through formulation innovations. Moreover, I understand Patent Owner's expert Dr. Davies will explain that if a POSA wanted to retain certain chemical features highlighted by Dr. Laskar, the POSA would have had many options for modifying other, known redness relievers like tetrahydrozoline and naphazoline, and that the POSA would not have landed on brimonidine.

81. Dr. Sher and Dr. Laskar argue that the use of vasoconstrictor eye drops to reduce eye redness was a well-established field. *See* EX-1002, ¶29; EX-1003, ¶31. As I explained above, the vasoconstrictor eye drops available at the time were all α_1

or mixed α_1/α_2 agonists, and there was no vasoconstrictor eye drop containing an α_2 agonist, let alone brimonidine. *See supra* Sections VI.D, VI.E.

82. Dr. Sher and Dr. Laskar argue that brimonidine was known to be a potent vasoconstrictor with favorable properties for an eye redness reducer. *See* EX-1002, ¶¶30-33; EX-1003, ¶¶37-39. I disagree. As explained in Sections VI.E and VI.F, *supra*, brimonidine was known as a highly selective α_2 agonist with ***vasodilation*** effects and plagued with undesirable side effects, including ocular redness and ocular allergic reactions, which exacerbate redness in patients.

83. Dr. Sher and Dr. Laskar argue that brimonidine was approved in 1996 for use in eye drops. *See* EX-1002, ¶¶34-37; EX-1003, ¶¶40-43. They fail to mention, however, that it was approved for treating glaucoma and lowering intraocular pressure. It was approved to treat serious medical conditions that can lead to blindness, rather than for reducing external eye redness. *See supra* Sections VI.C, VI.F. As explained in Section VI.F, *supra*, the target sites and the mechanisms of action of glaucoma treatments are different from those for reducing eye redness.

84. Dr. Sher argues that the prior art reported the use of brimonidine drops to reduce eye redness associated with LASIK surgery. *See* EX-1002, ¶38. But the study used 0.2% brimonidine formulation, not low concentrations of brimonidine in the ’742 patent. *See infra* Section IX.B.5.

85. Dr. Sher and Dr. Laskar argue that the prior art discloses "low concentrations" of brimonidine, relying on the '553 patent and Walters 1991. *See* EX-1002, ¶¶39-43; EX-1003, ¶¶44-50. As explained in Section IX.B.3-4, *infra*, however, neither reference discloses the use of "low concentrations" of brimonidine for reducing eye redness. In fact, as explained in Section VI.F.1, *supra*, brimonidine was known to ***cause***, not reduce, ocular hyperemia, which would have deterred a POSA from choosing it as a redness reliever.

86. Dr. Sher argues that the prior art disclosed brimonidine eye drops with a pH of 6.3 to 6.5. *See* EX-1002, ¶44; EX-1003, ¶51. As Dr. Williams will opine, Dr. Sher failed to recognize that a POSA would have been motivated to increase, not decrease, the pH of the formulation from the pH of the Alphagan® product.

VII. The '742 Patent

87. I provide the following summary of the '742 patent in response to Dr. Laskar's oversimplified overview of the '742 patent. EX-1003, ¶¶51.b-55.

88. The '742 patent relates to the use of low-concentration, highly selective α_2 adrenergic receptor agonists to unexpectedly and significantly reduce redness while beneficially not causing rebound hyperemia. *See* EX-1001 ('742 patent) at 4:47-58, 5:35-45. I understand that the effective filing date for the claims of the '742 patent is August 1, 2008, which I have used for my analysis.

89. The ’742 patent has six claims, two of which are independent (claims 1 and 3) and four are dependent (claims 2 and 4-6). *Id.* at 22:16-39.

Claim 1 is directed to a method of reducing eye redness resulting from an ocular condition by administering brimonidine at a concentration of about 0.001% and about 0.05% weights by volume. *Id*. at 22:17-21.

Claim 2 further defines the concentration of brimonidine in claim 1 to about 0.001% and about 0.025% weights by volume. *Id*. at 22:22-24.

Claim 3 is another independent claim drawn to a method for reducing eye redness resulting from an ocular condition consisting essentially of topically administering a composition consisting essentially of brimonidine at a concentration between about 0.001% and about 0.025%, and the pH of the composition is between about 5.5 and about 6.5. *Id*. at 22:25-32.

Claim 4 further defines the method of claim 3 by indicating that the composition of claim 3 is topically administered within about 24 hours after a LASIK surgery. *Id*. at 22:33-35.

Claim 5 depends from claim 1 and indicates that the ocular condition is chronic red eye. *Id*. at 22:36-37.

Claim 6 depends from claim 3 and indicates that the ocular condition is chronic red eye. *Id*. at 38-39.

90. The ’742 patent explains that alpha-adrenergic agonists were known to have some vasoconstrictive properties. *Id.* at 1:61-63. In clinical use, however, the alpha-adrenergic agonists were known to cause significant side effects, including rebound hyperemia (compensatory rebound vasodilation leading to engorgement of the blood vessels that make the eyes redder) and medicamentosa, even after a few doses. *Id*. at 1:63-2:2, 2:8-13. These side effects were observed in all commercially available non-selective alpha agonists for topical decongestants, including tetrahydrozoline, naphazoline, oxymetazoline, xylometazoline, methoxamine, and phenylephrine. *Id*. at 2:8-13.

91. Brimonidine was no exception. The only brimonidine product available on the market at the time of the invention—Alphagan® for treating glaucoma and lowering intraocular pressure—was also associated with significant rebound hyperemia, including primary and delayed onset rebound hyperemia. *Id*. at 2:2-7. It was thus believed that rebound hyperemia is intrinsic to vasoconstriction by reducing blood flow and causing ischemia, triggering the body’s inflammatory responses manifesting in rebound hyperemia and ultimately medicamentosa. *Id*. at 2:21-28, 4:40-46.

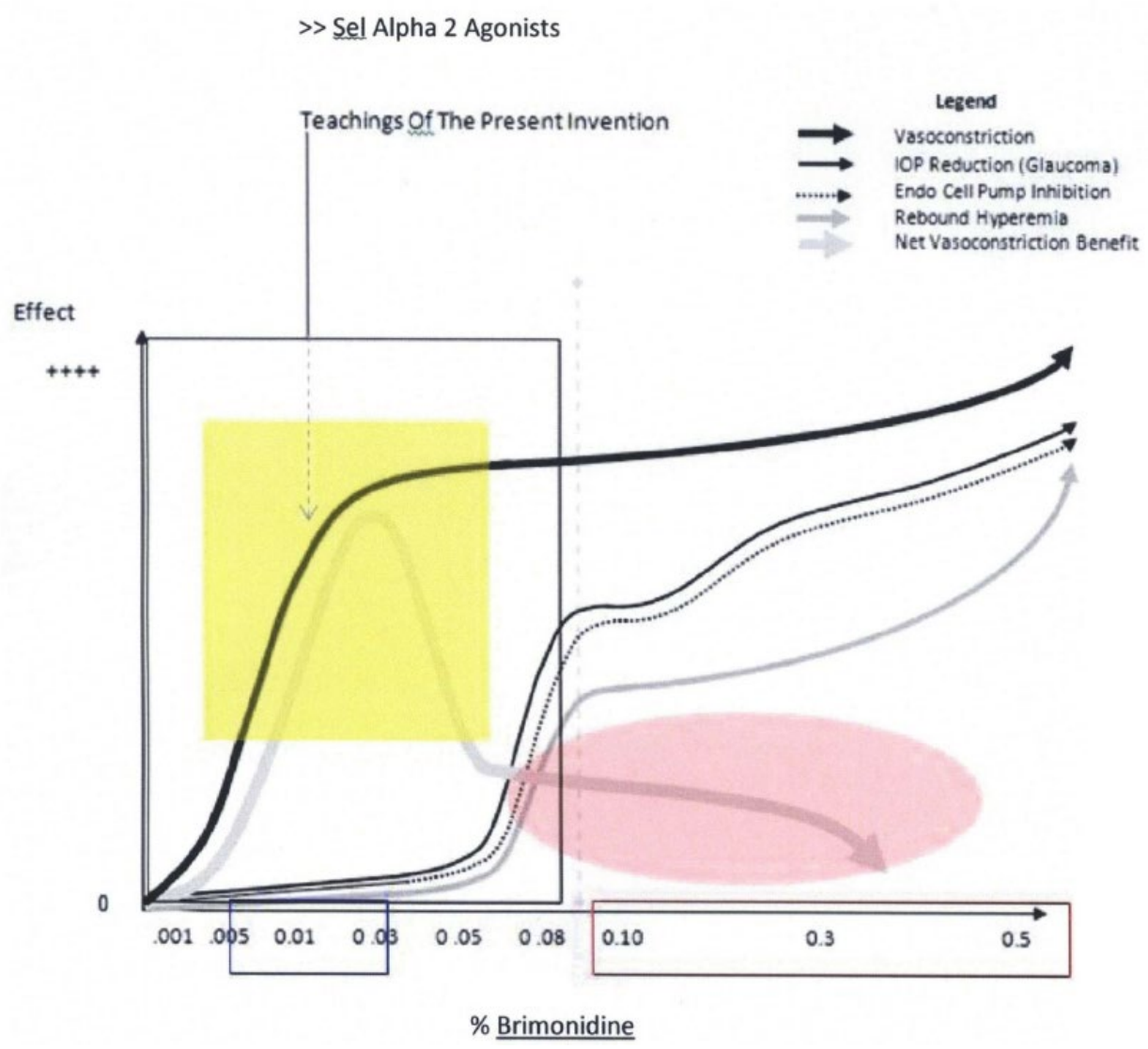
92. Contrary to these teachings, the inventor of the ’742 patent unexpectedly and surprisingly discovered that low concentrations of brimonidine—well below those previously commercialized—reduced redness caused by an ocular

condition with significantly reduced incidence of rebound hyperemia. *Id*. at 2:37-41, 4:47-58. The skilled person would appreciate this from viewing Figures 2 and 6 of the ’742 patent together, as Figure 6 is effectively an expanded version of Figure 2.

93. Figure 2, reproduced below in color from the U.S. Patent and Trademark Office (USPTO),[6] is a graph illustrating several concepts regarding the use of low-concentration brimonidine according to the ’742 patent, including vasoconstrictive effects, rebound hyperemia, and net vasoconstriction benefit (*see* “Legend” of Fig. 2), at different concentrations. Figure 2 and its Legend is a predicate for understanding how a POSA would understand Figure 6.

[6] I understand that the USPTO maintains two versions of the ’742 patent: one with colored figures and one with black and white figures. I use colored figures from the ’742 patent to illustrate how the skilled person would understand the various principles taught by the patent regarding the use of low-concentration brimonidine. EX-2161.

FIG. 2



’742 Patent (EX-2161 (colored)), Fig. 2.

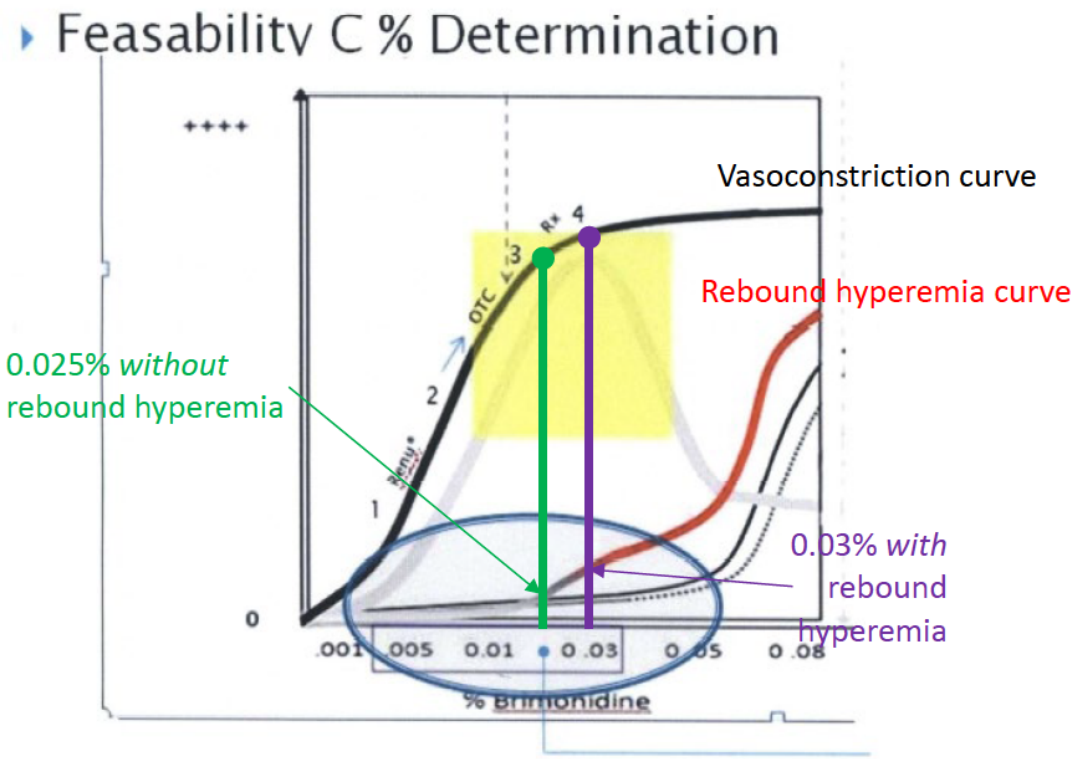
94. As shown from the thick black arrow in Figure 2 above, brimonidine’s vasoconstriction benefit begins at relatively low concentrations until it effectively maximizes and plateaus at about 0.03%. Also, Figure 2 shows that at a concentration of 0.03%—see the thin gray arrow (Legend: “Rebound Hyperemia”) that starts to

lift off the x-axis—brimonidine begins to exhibit rebound hyperemia. This will be illustrated more clearly in Figure 6 (below). Relatedly, Figure 2 teaches that brimonidine's maximum vasoconstriction effect after netting out its tendency to cause rebound hyperemia is at 0.03%, as seen from the apex of the thick gray arrow (Legend: "Net Vasoconstriction Benefit"). *See also* EX-1001 ('742 patent) at 18:52-55. Thus, Figure 2 conveys to a skilled ophthalmologist a critical distinction between brimonidine at a concentration of 0.03% (maximum vasoconstriction with rebound hyperemia) and concentrations less than 0.03% (slightly lower vasoconstriction without, importantly, rebound hyperemia).

95. In effectively an expanded version of Figure 2, the '742 patent illustrates this distinction even more clearly in Figure 6, which, notably, is entitled "Feasibility C[oncentration] % Determination.[7] I have annotated Figure 6 to explain these points and their importance to a skilled person reading the figure in context of the patent to determine an amount of brimonidine that will give effective redness reduction without inducing rebound hyperemia.

[7] A POSA reading the title of Figure 6 would have understood the "C %" to mean "Concentration %."

FIG. 6



’742 patent (EX-2161 (colored)), Fig. 6 (annotated).

As the annotated version of Figure 6 shows, brimonidine at 0.03% (purple line) produces maximum vasoconstriction effects, but it starts causing rebound hyperemia, as indicated by the rebound hyperemia curve transitioning from dark gray to red. This is consistent with the teachings in the ’742 patent, stating that “FIG. 6 depicts a graphical representation of a finding of the present invention that an increased ***rebound hyperemia begins at around 0.03%*** for brimonidine.” EX-1001 (’742 patent) at 19:52-54 (emphasis added). On the other hand, brimonidine at

0.025% (green line) produces a slightly reduced level of vasoconstriction effects (although still high), while keeping rebound hyperemia at a minimum, as indicated by the light gray color in the rebound hyperemia curve.[8] To a POSA trained and experienced in ophthalmology, this combination of near-maximal vasoconstriction effects and minimal rebound hyperemia allowed the patented invention to produce a more effective scleral whitening in the eye without the side effects associated with prior art redness relievers. *See id.* at 14:7-14.

96. The superior efficacy of the patented invention was further demonstrated in several human experiments. The experiments compared the efficacy of low-concentration brimonidine against prior art redness relievers on the market, including tetrahydrozoline (Visine®), naphazoline (Naphcon-A®), and oxymetazoline (Visine L.R.®). I discuss these experiments, *see infra* Section IX.D.2.

[8] Although Figure 6 may not be drawn with exacting precision, it is clearly conveying with the blue dot on the x-axis that is placed slightly to the right of the visual middle point between 0.01% and 0.03% a concentration of about 0.025%. This is consistent with several other parts of the specification identifying about 0.025% as part top end of a preferred concentration range. EX-1001 ('742 patent) at 5:49-51, 5:59-61, 7:4-8, 7:9-19, 7:20-26, 8:4-11, 8:12-16, 9:20-24, 9:28-34, 9:35-42, 9:53-55, 9:63-67, 10:3-8, 10:9-17, 11:26-31, 12:60-67.

VIII. Claim Construction

A. Relevant Legal Principles

97. I have been informed and understand that patent claims, and their terms and phrases, are interpreted by a court according to their ordinary and customary meaning to a person of ordinary skill in the art as of the earliest filing date of claimed invention. I understand that interpreting a term or phrase contained in a patent claim involves reading the language of the claim and considering other materials relevant to the claim, including the patent specification and the prosecution history, which I have been informed constitutes the "intrinsic record" of the patent. I understand that evidence extrinsic to the patent and its prosecution history may also be consulted, but that such materials should only be considered so long as they are not inconsistent with the claim language, the patent specification and the prosecution history.

98. I have been informed that when a claim uses the term "about" in a numerical limitation avoids a strict numerical boundary, and the term is construed in its technologic and stylistic context as informed by the language of the claims and the specification.

B. "ocular condition"

99. In my opinion, the phrase "ocular condition" means a condition of the eye causing ocular hyperemia that can be reduced.

100. I have been informed that a typical patent claim has three parts: a preamble, a transition term, and a body. I understand that in the context of a method

of use claim, such as in the ’742 patent, the preamble sets out the purpose or objective of the invention. As I have been informed, the transition term provides a bridge between the invention’s purpose recited in the preamble and the claim’s body, informing the POSA whether elements defined in the body of the claims are inclusive or exclusive to additional steps or components. I understand that the body of the claim provides the elements that describe the invention within the confines of the preamble’s stated purpose that also distinguishes the invention from the prior art.

101. The preamble of the claims recites that the claimed method is directed to “reducing eye redness.” A POSA would clearly understand from the claims and specification of the ’742 patent that that redness sought to be reduced by the claimed methods is ocular hyperemia, which arises from dilated, intact blood vessels in the eye. EX-1001 (’742 patent) at, *e.g.*, 2:37-41, 4:26-39, 4:47-58, 5:27-34.

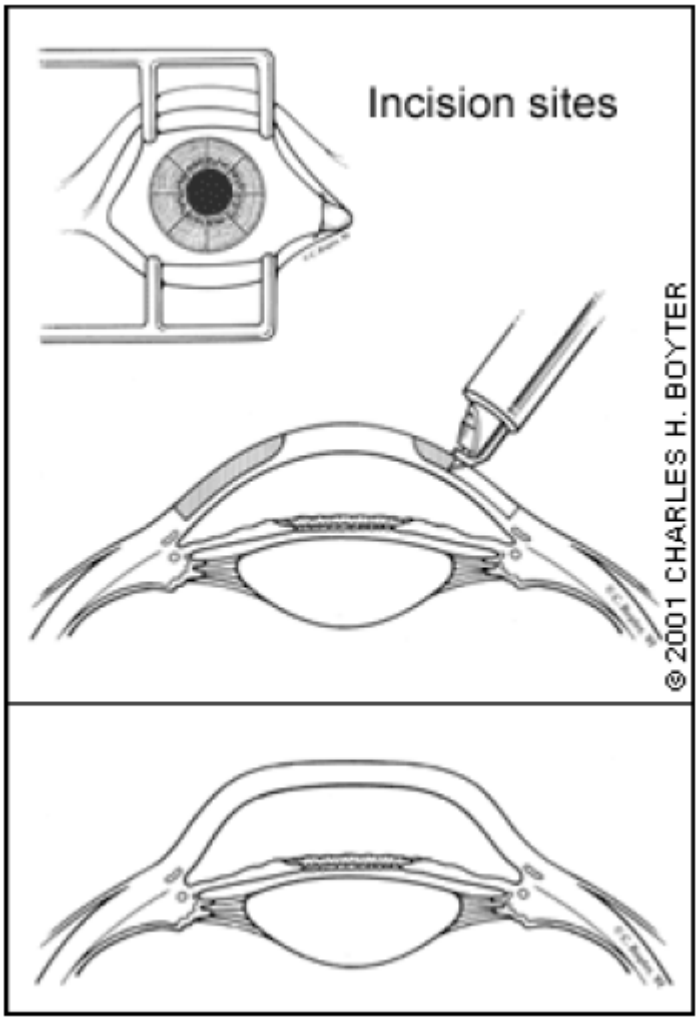
102. That is distinguished, for example, from the eye redness resulting from a hemorrhage, such as subconjunctival hemorrhage that can result from trauma to the eye. The trauma breaks ocular blood vessels and blood leaks out, settling beneath the conjunctiva and manifesting as a collection of blood or hematoma. EX-2162 (Sher Dep. Tr.) at 111:14-112:23. This is different from the eye redness resulting from vasodilated, intact ocular blood vessels. *Id*. at 112:24-113:5.

103. The “***eye*** redness” in the preamble then ties to the phrase “patient having an ***ocular*** condition” in the body of the claims. Reading the preamble and the

body of the claim in light of the specification of the ’742 patent, a POSA would have logically understood that the ocular hyperemia sought to be reduced arose from the patient’s ocular condition.[9]

104. As opposed to LASIK, for example, radial keratotomy may not constitute an ocular condition within the scope of the ’742 patent claims if performed properly. While radial keratotomy is a type of refractive surgery, it is a completely different type of refractive surgery from LASIK. In radial keratotomy, a surgeon makes microscopic incisions in the cornea—which is avascular—in a radial or spoke-like pattern using a blade. *See* EX-2197 (Overview of Refractive Surgery) at 5-6, Fig. 2; EX-2162 (Sher Dep. Tr.) at 113:6-114:4 (testifying that the goal of radial keratotomy is to make the incisions in a healthy, avascular cornea). As shown in the diagram below, these incisions cause the cornea to flatten, correcting vision acuity:

[9] With respect to the transition phrase “consisting essentially of,” I understand that the parties do not dispute that it at least means that brimonidine is the only active ingredient administered as recited in the claims for reducing a patient’s eye redness caused by an ocular condition. Accordingly, I do not opine on that phrase.



105. When the radial keratotomy surgeon properly makes precise incisions to only the avascular cornea, it may not cause any redness in the conjunctiva, the episclera, or the sclera. EX-2162 (Sher Dep. Tr.) at 113:6-114:4. In this regard, it is noted that radial keratotomy is not listed as an ocular condition in column 12 of the ’742 patent. With LASIK, on the other hand, the surgeon places a suction ring over the eye to lift the cornea for ablation by a laser, and resultingly causes hyperemia and even significant subconjunctival hemorrhage on the eye. *Id*. at 110:1-111:10.

Thus, a POSA would not equate radial keratotomy with LASIK as an ocular condition giving rise to ocular hyperemia.

C. "about 0.025%"

106. In my opinion, "about 0.025%" means "0.025% plus or minus 10%," equating to an upper limit of 0.0275%. I understand that Dr. Williams will opine on how a POSA would arrive at the upper and lower limits of about 0.025.

107. I understand that Petitioner and Petitioner's expert, Dr. Laskar, contends that the term "about 0.025%" in claims 2 and 3 of the '742 patent includes "0.03%." *See* EX-1003, ¶57. I disagree.

1. "about 0.025%" does not include 0.03%

108. In my opinion, a POSA would not equate "about 0.025%" with 0.03% because (1) the specification quantitatively distinguishes 0.025% from 0.03%, (2) the specification conveys a critical difference for 0.025% by clinically distinguishing it from 0.03%, and (3) clinical and formulation criteria (including release tolerances for pharmaceutical products requiring FDA approval) would have been known to those skilled in the art so that they would not have understood "about" to impart a 20% variation from 0.025% to encompass 0.03%, as argued by Dr. Laskar.

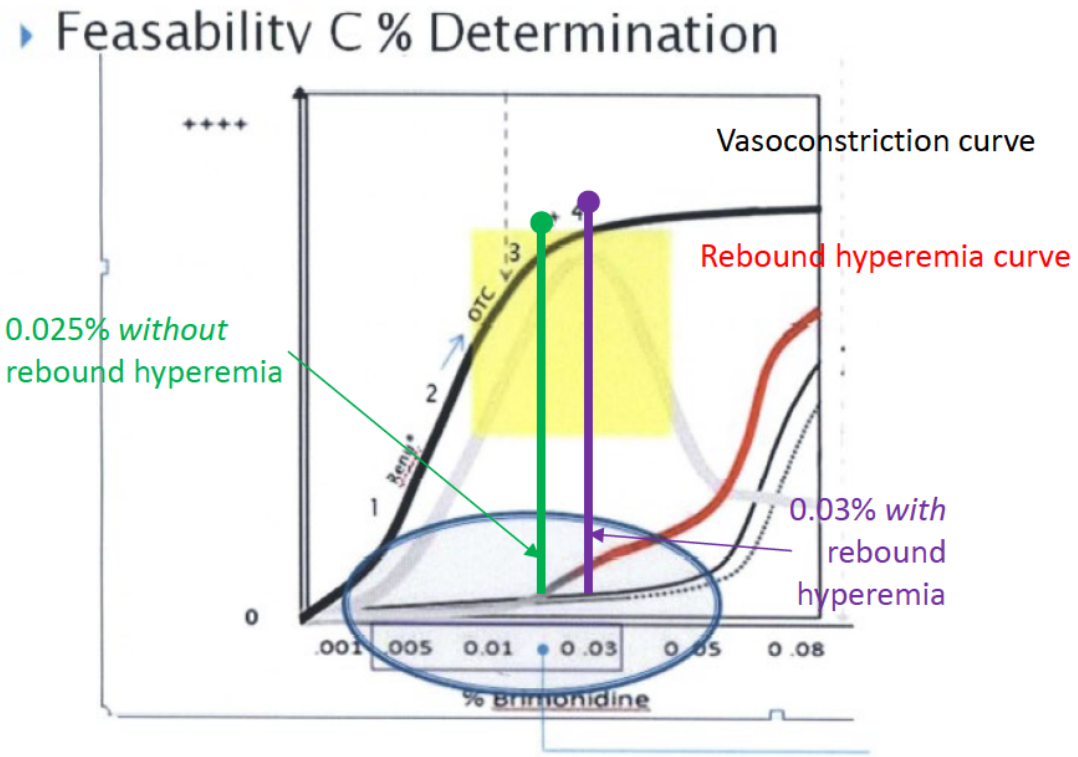
109. The specification clearly conveys that "about 0.025%" constitutes a different concentration from 0.03%. The '742 patent separately discloses

concentrations of "about 0.025%" and "about 0.03%" within the broader concentration range of less than 0.05% brimonidine. For example, in two successive paragraphs, the '742 patent teaches using "about 0.001% to about 0.025%" brimonidine (EX-1001 ('742 patent) at 8:46-55) and separately "about 0.001% to about 0.03%" brimonidine (*id.* at 8:56-63). *See also id.* at 21:6-16 (Example 3) (describing the use of a composition containing 0.03% brimonidine). That both concentrations are separately described conveys to a POSA that "about 0.025%" is not the same as "about 0.03%." And because the specification conveys that these two concentrations modified by "about" are not the same, it logically follows that "about 0.025%" is not the same as 0.03%, unmodified by "about."

110. Moreover, the '742 patent conveys to a skilled ophthalmologist that 0.03% is clinically different from 0.025%. As discussed above, the skilled ophthalmologist considering Figures 2 and 6 together would have understood that they convey a clinical distinction between brimonidine at a concentration of 0.03% (maximum vasoconstriction with rebound hyperemia) and concentrations less than 0.03% (slightly lower vasoconstriction without, importantly, rebound hyperemia). Figure 6, entitled "Feasibility C[oncentration] % Determination," and effectively an expanded version of Figure 2 and its accompanying Legend, guides the clinician in determining an appropriate concentration for brimonidine that would minimize or eliminate rebound hyperemia. *Id.* at 4:26-30.

111. I have reproduced my annotated version of Figure 6 below. Annotated Figure 6 illustrates that brimonidine at 0.03% (purple line) produces maximum vasoconstriction effects. But at that concentration, it starts causing rebound hyperemia, as clearly indicated by the rebound hyperemia curve transitioning from gray to red.

FIG. 6



'742 patent (EX-2161 (colored)), Fig. 6 (annotated).

This graphically describes what the specification tells the skilled clinician: "FIG. 6 depicts a graphical representation of a finding of the present invention that an

increased ***rebound hyperemia begins at around 0.03%*** for brimonidine." EX-1001 ('742 patent) at 19:52-54 (emphasis added).

112. Importantly, to the skilled clinician seeking to determine a concentration of brimonidine that would be highly effective in reducing redness but without the possibility of inducing rebound hyperemia, Figure 6 shows that brimonidine at 0.025% does that. The added green line that connects with the blue dot on the x-axis—also called out by the blue dotted line beneath the x-axis—lies slightly to the right of the visual middle point between 0.01% and 0.03% and would have been understood as a concentration of about 0.025%. The skilled clinician would have thus understood that about 0.025% brimonidine is differentiated from 0.03% in producing a slightly reduced (but still high) level of vasoconstriction, as indicated by the light gray color in the rebound hyperemia curve, while avoiding the rebound hyperemia associated with 0.03% and the red line.

113. In sum, the '742 patent clearly teaches that "about 0.025%" brimonidine was quantitatively and clinically different from 0.03% brimonidine. The skilled ophthalmologist would not have equated a concentration that the specification indicates can cause rebound hyperemia (0.03%) with a concentration that the specification conveys does not (0.025%). This would have been especially important for OTC products containing alpha adrenergic agonists, known to cause rebound hyperemia and tachyphylaxis, in order to minimize or prevent misuse

through overuse. EX-2162 (Sher Dep. Tr.) at 98:24-100:5; *see* EX-2182 (Soparkar) at 4-5.

2. Responses to Dr. Laskar's Opinions

114. I understand that Dr. Laskar, a non-clinician, has opined that the '742 patent discloses that 0.03% brimonidine accomplishes the purpose of "about 0.025%" brimonidine in the patented invention. EX-1003, ¶64. Dr. Laskar states that the '742 patent defines "low concentrations" of brimonidine to include up to 0.05%, which would include 0.03% (as well as 0.025%), that low concentrations of brimonidine perform the purpose of the claimed invention, and, presumably, therefore "about 0.025%" includes 0.03%. *Id.*, ¶65. I disagree. By Dr. Laskar's logic, "about 0.025%" would also literally embrace 0.05%, which makes no sense.

115. Next, Dr. Laskar states that the '742 patent specification identifies preferred embodiments that include concentration ranges up to about 0.05%, citing passages at columns 12 and 13 (*id.*, ¶66 (citing Ex-1001 at 12:60-63, 13:14-16)), and one other passage for a preferred concentration amount of up to about 0.035% at column 9 (*id.*, ¶67 (citing EX-1001 at 9:11-16)). From this, he concludes that because these preferred embodiments include 0.03%, they evidence that "about 0.025%" includes 0.03%. *Id.* Just because 0.025% and 0.03% fall within "about 0.05%" does not support equating "about 0.025%" with 0.03%, particularly when

the specification ***more than 20 times*** identifies "about 0.025%" as a preferred concentration at the top-end of numerous ranges that do not include 0.03%.[10]

116. Dr. Laskar argues that keeping the brimonidine concentration below 0.03% is not critical because Figure 2 shows that 0.03% is included in the range where "Net Vasoconstriction Benefits" are the highest. *Id.*, ¶71. For all the reasons I provided above regarding how a clinician would interpret Figures 2 and 3, I disagree. A skilled clinician would clearly see an important and clinically meaningful difference between a concentration of 0.03% (maximum vasoconstriction with rebound hyperemia) and concentrations less than 0.03% (slightly less vasoconstriction without, importantly, rebound hyperemia). A POSA would have understood Figures 2 and 6 to teach about 0.025% brimonidine as sacrificing a small amount of efficacy while minimizing the side effects—an optimum balance of efficacy and minimal side effects. This is consistent with the specification identifying "about 0.025%" more than 20 times as a preferred top-end concentration in various ranges.

[10] *See, e.g.*, EX-1001 ('742 patent) at 5:49-51, 5:59-61, 7:4-8, 7:9-19, 7:20-26, 8:4-11, 8:12-16, 9:20-24, 9:28-34, 9:35-42, 9:53-55, 9:63-67, 10:3-8, 10:9-17, 11:26-31, 12:60-67.

117. Dr. Laskar also refers to Figure 4E and notes that administering 0.033% brimonidine did not result in rebound hyperemia. *Id.*, ¶69. He argues that this touting of 0.033% brimonidine "further informs the POSA that 'about 0.025%' is not meant to exclude '0.03%.'" *Id*. I disagree.

118. A POSA would have readily recognized that "0.033%" brimonidine in Figure 4E does not make sense in the flow of the experiment conducted serially from Figures 4C through 4E and would have concluded that it represents a typographical error coming from the "0.033% naphazoline." Figures 4C through 4E represent three sequential applications of brimonidine to the same subject every four hours. It would make logical and experimental sense that the same concentration of brimonidine should be applied to the same eye in all three applications.

119. In Figure 4C, the subject was given 0.02% brimonidine to the left eye in a test against 0.025% oxymetazoline. EX-1001 ('742 patent) at 3:20-24. Four hours after, in Figure 4D, the subject was treated again with 0.02% brimonidine to the same eye, but this time compared with ***0.033% naphazoline***. *Id*. at 3:25-29. For Figure 4E, even though the '742 patent states that the patient was given the third application of 0.033% brimonidine four hours later to the same eye, a POSA would have expected, for experimental consistency purposes, that a 0.02% brimonidine drop would have been instilled to complete the sequence and evaluate whether the 0.02% concentration caused hyperemia. It would not have made sense to suddenly

apply a higher concentration of brimonidine in the third application, and an ordinarily skilled ophthalmologist would have noticed and concluded that the 0.033% was inadvertently transposed from the 0.033% naphazoline.

120. Even if this was not an inadvertent error, it would not alter may opinion as provided above. Indeed, it would constitute a single test in a single eye and would not have detracted from the clear and consistent messaging in Figures 2 and 6, as well as column 19 of the specification, that about 0.025% is a different and distinct concentration that does include 0.03%.

121. Dr. Laskar also argues that a POSA would round 0.025% up two decimal points to 0.03%. I understand that Dr. Williams will address this argument.

122. For these reasons, it is my opinion that the specification clearly conveys to a POSA that "about 0.025%" constitutes a different concentration from 0.03%.

IX. The '742 patented methods would not have been obvious

123. Dr. Sher asserts that the claims of the '742 patent are unpatentable on the following grounds:

- **Ground No. 1** – Claims 1 and 2 of the '742 patent are allegedly anticipated by U.S. Patent No. 6,294,553 (EX-1004 ("the '553 patent"))
- **Ground No. 2** – Claims 1 and 2 of the '742 patent are allegedly anticipated by Walters 1991 (EX-1005)

- **Ground No. 3** - Claims 1-6 of the ’742 patent are allegedly rendered obvious by the ’553 patent (EX-1004) in combination with Norden 2002 (EX-1006), U.S. Patent No. 6,242,442 (EX-1007 (“the ’442 patent”)), Alphagan® Label 1998 (EX-1008), and Federal Register 1988 (EX-1009).

124. As discussed in further detail below, it is my opinion that Dr. Sher has failed to establish that the challenged claims are unpatentable on any of these grounds.

A. Relevant Legal Principles

125. I understand that anticipation is shown only if each and every element as set forth in the claim is found, either expressly or inherently, in a single prior art reference. I understand that inherency is shown only if the limitation at issue is the natural result flowing from the explicit disclosure of the prior art, and that inherency may not be established by mere probabilities or possibilities.

126. I understand that an obviousness analysis involves a review of the scope and content of the prior art, the differences between the prior art and the claimed subject matter, the level of ordinary skill in the art, and objective indicia of nonobviousness, such as unexpected results, industry acclaim and commercial success. I understand that for an invention to be regarded as obvious, a person of ordinary skill in the art must have had a reason to modify the prior art or to combine

one or more prior art references in a manner that would result in the claimed subject matter with a reasonable expectation of success.

B. Discussion of References Relied on by Dr. Sher

127. In my opinion, Dr. Sher's cited references fail to provide any motivation for a POSA to have used low-concentration brimonidine to reduce eye redness, much less with any reasonable expectation that it would have worked.

128. As an initial matter, those skilled in the art recognize that not all prior art is valued equally, even for scientific literature. There is a "hierarchy of evidence" relating to the weight a POSA assigns to various pieces of prior art, be it patent or scientific literature. Where a particular reference falls on the hierarchy of evidence depends, at least in part, on how much data are provided, how robust the data are, and how reproducible. References having little, if any, meaningful data would tend to fall on the low end of the hierarchy of evidence. Similarly, a POSA would not rely too heavily, if at all, on subjective opinions and anecdotal reports lacking substantiating evidence.

1. Alphagan® Label 1998 and Alphagan® NDA

129. Dr. Sher and Dr. Laskar identify the Alphagan® Label 1998 (EX-1008) as a reference disclosing ocular drops with 0.2% brimonidine tartrate with a pH of 6.3-6.5 and purport to summarize the disclosure of the Alphagan® Label 1998. EX-1002, ¶¶96-97; EX-1003, ¶92.

130. As explained earlier, Alphagan® was the only FDA-approved brimonidine product available on the market before the filing date of the ’742 patent. Allergan introduced variations of Alphagan® with different brimonidine concentrations, starting with the higher concentrations at 0.2% and 0.5% (Alphagan®) and then lowering it to 0.15% and 0.1% (Alphagan P®).

131. But the Alphagan® products, regardless of their brimonidine concentrations, were known to cause various side effects, including ocular hyperemia and ocular allergic reactions. The higher concentration Alphagan® products (0.2% and 0.5%) reported a high rate of hyperemia in patients. In particular, ocular hyperemia was repeatedly identified as one of the most common side effects of the drug in glaucoma patients. *See* EX-1008 (Alphagan® Label 1998) at 3; EX-2012 (Alphagan® Label 2001) at 9, 14.

132. In two clinical studies for Alphagan® 0.2%, the percentage of patients experiencing ocular hyperemia was 38.9%, and 23.3%. EX-1031 (Alphagan NDA) at 52, 86. And a meta-analysis combining the data from the two studies reported the incidence of hyperemia at 28.7%. *Id*. at 109. Indeed, ocular hyperemia was one of the top reasons for the brimonidine-treated patients terminating the study. *See id.* at 51 (reporting that 3.1% of brimonidine-treated group terminated the clinical study due to ocular hyperemia), 129 (“The most frequent causes of terminations due to adverse events in the brimonidine group were ocular allergic reaction and ocular

hyperemia."). Even the lower concentration Alphagan P® products (0.15% and 0.1%) reported a comparably high incidence of conjunctival hyperemia occurring in approximately 10-20% of the subjects. *See* EX-2014 (Alphagan P® Label 2005) at 1, 4.

133. The scientific literature also recognized that Alphagan® and Alphagan P® products both caused a high rate of ocular allergic reactions in patients, appearing in nearly 32.3% of patients administered with brimonidine. EX-1032 (Rahman 2010) at 4. One study found that brimonidine's long-term use is limited due to its propensity to cause ocular allergic reactions, including conjunctival hyperemia occurring in 26.3-30.3% of the subjects, as well as blepharitis, belpharoconjunctivitis, and follicular conjunctivitis. *Id*.

134. While these side effects may have been tolerable for prescription products for treating a serious disease like glaucoma that could lead to blindness, they would have been a deterrent for OTC products, for which patients self-diagnose their eye conditions often without any instructions from health care providers regarding the proper dose and frequency of administration. EX-2162 (Sher Dep. Tr.) at 98:24-100:5. Thus, brimonidine's side effect profile would have disincentivized a POSA from using it in an OTC product for redness relief, which would have enhanced concerns for potential misuse.

135. Moreover, based on the data from the Alphagan® clinical studies, a POSA would have been motivated to increase, not decrease, the concentration of brimonidine to produce eye whitening effects. The Alphagan® label and the clinical studies in the Alphagan® NDA establish that brimonidine's blanching effects are concentration dependent, showing blanching effects at high brimonidine concentration that decrease as the concentration decreases. The Alphagan® label reports that conjunctival blanching occurred in approximately 50% of the patients administered with Alphagan® 0.5%, but sharply declined to only 3.5% with Alphagan® 0.2%. EX-2012 (Alphagan® Label 2001) at 4; EX-1031 (Alphagan NDA) at 109. And no blanching was reported in the lower concentration Alphagan P® products (0.15% and 0.1%) (*see* EX-2014 (Alphagan P® Label 2005) at 1, 4 (blanching is not listed in the adverse reactions)), though hyperemia was still high (*id.*).

136. Brimonidine's concentration-dependency for blanching is logical and consistent with what the prior art taught. While brimonidine is a highly selective α_2 agonist, it can produce more α_1 vasoconstrictive effects at higher concentrations.

137. Still, brimonidine's α_2 mediated effects remain prevalent, causing vasodilation of blood vessels leading to high incidences of hyperemia, as well as hypotensive effects, such as fatigue and/or drowsiness, in some patients. *See* EX-2012 (Alphagan® Label 2001) at 9-10; EX-2014 (Alphagan P® Label 2005) at

4. Indeed, one study report on the blanching effects of brimonidine indicates that blanching and hyperemia can co-exist at 0.2% brimonidine. *See* EX-1023 (Scruggs 2000) at 5 (reporting that a patient instilling 0.2% brimonidine eye drops showed hyperemia surrounding the blanching on the cheek where runoff of the excess drop occurred).

138. I understand that Dr. Williams will explain that a POSA would not have been motivated to formulate at the claimed pH of about 5.5 to about 6.5. I understand that Dr. Williams will explain that, as a general matter, it is preferable to formulate a topical eye drop at or around the physiological pH (~7.4) unless there is some other consideration that necessitates doing so. I understand that Dr. Williams will explain that no such consideration exists here. Specifically, I understand that Dr. Williams will explain that the art taught a relationship between pH and concentration—at a pH closer to the pKa of brimonidine, it is able to more readily cross the cellular membranes and exhibit comparable efficacy despite having a lower concentration. Some degree of penetration is required to reach the vessels of the episclera and sclera. I understand Dr. Williams will explain that this would have motivated a POSA to target a pH above 7 to ensure that brimonidine is able to penetrate and reach these vessels. In my experience, administration of a topical eye drop with an acidic pH leads to burning and stinging, tear production, or redness. I understand that Dr. Williams will explain that this would further motivate a POSA to target a

pH above 7 to minimize the likelihood that the drug is washed away. Finally, I understand that Dr. Williams will explain that neither solubility nor stability would motivate a POSA to target a pH below 7.

2. Federal Register 1988

139. Dr. Sher and Dr. Laskar identify Federal Register 1988 as a reference purportedly disclosing that 2-imidazoline derivatives were used in prior art OTC redness relievers and purport to summarize the disclosure of Federal Register 1988. EX-1002, ¶98; EX-1003, ¶¶95-96.

140. Federal Register 1988 is an excerpt from Federal Register Vol. 53, No. 43 and was published on March 4, 1988. EX-1009 (Federal Register 1988) at 1. Federal Register 1988 is the final rule issued by the FDA entitled "Ophthalmic Drug Products for Over-the-Counter Human Use; Final Monograph." *Id.*

141. Federal Register 1988 discloses that OTC ophthalmic vasoconstrictor ingredients can be used to whiten the conjunctiva. *Id.* at 7. But it only lists ephedrine, naphazoline, phenylephrine, and tetrahydrozoline as vasoconstrictors known at the time, which are either α_1 or mixed α_1/α_2 agonists. *Id*. at 14. Federal Register 1988 does not list any selective α_2 agonists as vasoconstrictors, let alone brimonidine, corroborating the view in the prior art that vasoconstriction and blanching are primarily α_1 mediated effects. *See id*.

142. The Federal Register 1988 also discloses that both tetrahydrozoline and naphazoline were known to cause rebound hyperemia, which could lead to overuse of the products and exacerbate ocular hyperemia. *Id*. at 10.

143. I understand that Dr. Williams will explain in his declaration that Federal Register 1988 lists ingredients that it considered to be a monograph condition for OTC ophthalmic drug class, including ephedrine hydrocholoride (0.123%), naphazoline hydrochloride (0.01 to 0.03%), phenylephrine hydrocholoride (0.08 to 0.2%) and tetrahydrozoline hydrocholoride (0.01 to 0.05%). *Id.* at 14. A POSA would have pursued these ingredients first because they had been generally recognized as safe and effective for their intended use, as opposed to brimonidine, which does not even appear on the list.

3. U.S. Patent No. 6,294,553

144. Dr. Sher and Dr. Laskar identify the ’553 patent as a reference purportedly disclosing the use of low dose brimonidine for reducing eye redness and purport to summarize the ’553 patent. EX-1002, ¶¶87-93; EX-1003, ¶¶76-82. I disagree.

145. The ’553 patent is directed to a “method for treating ocular pain” associated with corneal injuries using brimonidine. EX-1004 (’553 patent) at 2:52-54. It discloses that pain is an indicator or response to “neurogenic inflammation,” which can also manifest as vasodilation, edema, and increased vascular

permeability. *Id*. at 1:16-18, 40-43. But a POSA would have understood that a single ocular inflammatory event does not necessarily manifest with all the neurogenic responses.

146. It has long been known that inflammation, including ocular inflammation, produces five cardinal symptoms, including swelling, pain, redness, heat, and loss of function. EX-2162 (Sher Dep. Tr.) at 104:23-106:14. A patient suffering from ocular inflammation can exhibit some but not all of these symptoms. For example, a patient who has ocular pain may not necessarily have eye redness or pupillary constriction. EX-2174 (Morgan 1987) at 4 (explaining that "[i]n more severe burns the conjunctiva and episclera are blanched"). And a patient suffering from corneal injuries may not exhibit any redness in the conjunctiva, episclera, or the sclera. EX-2162 (Sher Dep. Tr.) at 107:2-11 (testifying that it is possible to have pain without redness), 109:3-11 (testifying that it is possible to relieve pain without affecting redness).

147. The '553 patent includes five examples. I understand that Dr. Sher relies on Example 1 for anticipation and Examples 1 and 4 for obviousness.

a. Example 1 of the '553 patent fails to teach or suggest a method of reducing redness

148. Example 1 is a description of a prospective clinical study that could be performed and seeks to only assess whether topically administered brimonidine reduced pain following radial keratotomy surgery. EX-1004 ('553 patent) at 4:46-

48. It makes no mention of redness or even suggests an assessment of redness, let alone measuring redness reduction. Indeed, the study is written in the present tense, which I understand means it was not conducted, and thus contains no actual study results of any type—not even of pain relief. *See id.* at 4:53-61 (describing that "[e]ach subject ***receives*** one drop of the assigned study medication," "[e]ach subject then ***undergoes*** unilateral radial keratotomy," and "[f]ollowing surgery, each subject ***receives*** one drop of the study medication in the operated eye . . . ." (emphases added)); EX-2162 (Sher Dep. Tr.) at 116:15-117:13 (acknowledging that Example 1 is a prophetic example that had not been carried out at the time it was written).

149. As I discussed, an inflammatory event resulting in pain does not necessarily also present as redness. Here, the radial keratotomy patients could have pain, but they would not necessarily have accompanying ocular redness. If the radial keratotomy was properly performed by making precise microscopic incisions in an avascular cornea, ocular redness may not necessarily and inevitably result. And radial keratotomy can be performed on patients with no eye redness at all. [redacted], making it possible that some patients in Example 1 may have no baseline redness and 0.03% brimonidine would have no redness-reducing effect. *See* EX-2166 (NDA clinical study No. 10-100-0008) at 16 ([redacted]). There are no

inclusion/exclusion criteria for this hypothetical study ***that was not actually performed***, making Dr. Sher's position regarding Example 1 more theoretical than real. Indeed, it is also possible for the radial keratotomy patients to have taken a commercial vasoconstrictor and have no redness at any time pre- or post-operatively.

150. Naturally, the hypothetical study in Example 1 does not contain any study results regarding pain relief and merely states that "[t]his appears to suggest that brimonidine, administered preoperatively, blocks the perception of pain." EX-1004 ('553 patent) at 5:1-2. That is all. It makes no mention or suggestion of any redness reduction and, in fact, could not because no baseline and subsequent measurement of redness are even remotely contemplated by the hypothetical study. And because brimonidine at 0.03% could have caused, not abated, redness at 0.03% (*see* EX-1001 ('742 patent) at Fig. 6, 19:52-54), this study cannot necessarily establish that 0.03% brimonidine reduced redness.

151. Moreover, blocking the perception of pain, such as by blocking neuronal transmission of pain signals, may relieve the sensation of pain, but it will have no effect on any inflammation and its (possible) presentation as redness. *See* EX-1004 ('553 patent) at 1:54-55 ("Anesthetics block neuronal transmission and affect sensation as well as pain."); EX-2162 (Sher Dep. Tr.) at 109:12-15 (acknowledging that anesthetics block the perception of pain); EX-1006 (Norden 2002) at 7 (stating that brimonidine is an anesthetic).

152. Example 1 notes that "[s]ymptoms of ocular inflammation (burning/stinging, tearing, etc.) are also recorded," but redness does not necessarily also present with these other symptoms of inflammation. EX-1004 ('553 patent) at 4:63-65. A hypothetical example that merely says that burning, stinging, and tearing can be observed says nothing to the skilled person that redness—a different symptom of inflammation—should or even could be observed in a radial keratotomy procedure that may not cause any redness and for which no indication about observing redness was even mentioned or contemplated.

153. Thus, a POSA would not have concluded that the hypothetical, prospective clinical study of Example 1 to treat ocular pain explicitly or implicitly disclosed a method of reducing redness using brimonidine. Simply put, the example makes no mention of reducing redness, the radial keratotomy patients may have no redness after surgery, they could have zero hyperemia pre- and post-operatively, no measurements of redness were contemplated, and 0.03% could have caused hyperemia (EX-1001 ('742 patent) at Fig. 6, 19:52-54). All that Example 1 concludes is that it "appears to suggest that brimonidine, administered preoperatively, blocks the perception of pain." EX-1004 ('553 patent) at 5:1-2. But consistent with brimonidine's known anesthetic effect (EX-1006 (Norden 2002) at 7) for blocking nerve transmissions and the perception of pain, which would not have ameliorated any redness associated with inflammation, the POSA would not

have understood Example 1 to teach or even remotely suggest a method of reducing redness using brimonidine.

b. Example 4 of the '553 patent fails to teach or suggest a method of reducing redness

154. Example 4 relates to another prospective rabbit study for determining "the effects of brimonidine on ocular surface sensation" using the "Corneal Nerve Conduction Model," which measures the "nerve traffic generated as the cornea is exposed to various stimuli." EX-1004 ('553 patent) at 5:20-24, 5:34-35. It is essentially a model to assess whether brimonidine can block nerve transmissions and the perception of pain, like Example 1. Also, like Example 1, Example 4 is written in the present tense, indicating that it describes a hypothetical study and thus presents no actual study results. *See id.* at 5:20-45 (describing that "[t]he effect of brimonidine on ocular pain ***is*** also studied using the Corneal Nerve Conduction Model" (emphasis added)).

155. Example 4 makes a broad, general statement that neurogenic inflammation, including redness and pupillary constriction, can be observed in rabbits from external stimuli. *Id.* at 5:39-41. Even assuming that such statement is referring to the model in Example 4, which is not clear, stimulating the cornea may not manifest as redness. There is no evidence, moreover, that the corneal conduction model in Example 4 can be validly used to assess redness. I have never measured, or heard of anyone who has measured, eye redness using the corneal nerve

conduction model. *See* EX-2162 (Sher Dep. Tr.) at 122:6-122:22 (admitting that Example 4 fails to disclose any data validating the corneal nerve conduction model for measuring eye redness).

156. Nor does Example 4 mention measuring baseline redness or any subsequent measurements of redness from which any conclusion of redness reduction could be made or assessed. In fact, as a hypothetical animal study that was not performed, Example 4 contains no study data of any kind regarding the purported reduction in neurogenic responses. At most, therefore, a POSA would have interpreted the statement that "[b]rimonidine is effective in reducing such neurogenic responses" (EX-1004 ('553 patent) at 5:44-45) to refer to brimonidine's hypothesized ability to block nerve signals and relieve the perception of ocular pain, which is the purpose of the study. But like Example 1, the POSA ophthalmologist would have understood that relieving pain by blocking nerve signals would have no effect on inflammation or any possible redness associated with it. As such, Example 4 would not have been understood as a method of reducing redness with brimonidine.

157. Furthermore, Example 4 is performed in rabbits whose eyes are surgically altered. The rabbits studied are "under deep anesthesia," and their "retro-orbital space is surgically exposed and a hook electrode is placed around the ciliary nerve that sits adjacent to the optic nerve." *Id*. at 5:24-28. Then, "[t]he ocular surface

is fitted with a chamber through the use of a conjunctival pharyngeal ring into which test formulations can be added." *Id*. at 5:28-30. But Example 4 fails to explain how redness can be measured in these rabbits despite numerous devices installed in their eyes. For example, the conjunctival pharyngeal ring placed on the rabbit eye would make it impossible to accurately assess redness.

158. There is also no basis to assume that the results of this rabbit study are applicable to human patients. In fact, rabbit study results are not directly transferable to human eyes due to significant anatomical and physiological differences, including location of alpha-adrenergic receptors as well as α_2 receptor responses to α_2 agonists. *See* EX-1035 at 3 (explaining that "tolerance does not develop to the chronic administration of brimonidine in rabbits"). And there is no evidence that the dose administered to a rabbit would elicit the same response when administered to a human.

159. Example 4 purports to assess a broad range of concentrations from "0.01% to 0.5%," and the highest concentration (0.5%) is up to ten times as high as the highest concentration (0.05%) in claim 1 and up to 20 times as high as the highest concentration of claim 3 (0.025%). EX-1004 ('553 patent) at 5:31-34. Without any information about whether the rabbit model for assessing ocular pain through transmitted nerve signals could actually measure redness, without any data of redness measurement at a minimum of two timepoints, and without any data of any

type (not even pain relief data), a POSA ophthalmologist would have only understood this dose ranging study to prospectively seek to determine if brimonidine could block the perception of pain. But that would not have suggested anything about brimonidine's ability to reduce redness.

160. Given the dearth of data and lack of any sufficiently precise or meaningful description of what was studied in the '553 patent, a POSA would have placed the '553 patent and its examples on the low end of the hierarchy of evidence. In my opinion, neither Example 1 nor Example 4 would have even remotely suggested using brimonidine to reduce eye redness.

4. Walters 1991

161. Dr. Sher and Dr. Laskar identify Walters 1991 as disclosing the use of low concentration brimonidine to reduce IOP in patients with glaucoma or ocular hypertension and purport to summarize Walters 1991. EX-1002, ¶¶68-70; EX-1003, ¶¶83-89. To the extent that Drs Sher and Laskar attempt to interpret Walters 1991 to disclose, explicitly or inherently, a method of reducing redness, I disagree such an interpretation.

162. Walters 1991 is a one-paragraph abstract for a pilot study assessing the efficacy and safety of AGN 190342-LF (i.e., brimonidine) 0.02% and 0.08% in patients with elevated intraocular pressure. EX-1005 (Walters 1991) at 4. The study

is merely a preliminary abbreviated study that, as far as I know, was never published as a complete article.

163. Walters 1991 states that "13 patients with open-angle glaucoma or ocular hypertension" were administered with brimonidine at 0.08% or 0.02%, or vehicle. *Id*. It states that overall mean reductions in IOP were 23.9%, 13.8%, and 7.2%, respectively. *Id*. The abstract also notes that brimonidine reduces IOP by reducing aqueous humor production through stimulation of "alpha$_2$-adrenoceptors located, in part, on ocular sympathetic nerve endings." *Id*.

164. Walters 1991 was focused solely on brimonidine's ability to reduce IOP. It does not indicate that the patient population had any baseline redness. It is also possible that the patient population in Walters 1991 could have been taking redness relievers to eliminate eye redness. Walters 1991 is simply devoid of any individual patient data to establish that all patients had baseline redness that could be reduced using brimonidine. Furthermore, Walters 1991 indicates that it studied both 0.08% and 0.02% brimonidine, but it lacks any information on who received the 0.02% dose and whether those patients had baseline redness.

165. Moreover, Walters 1991 does not describe any methodology for assessing redness or redness reduction in the patient population. There is no indication that Walters 1991 measured redness at least twice (i.e., before and after the treatment) in these patients. And it fails to provide any information about redness

reduction. Given the limited information provided in Walters 1991, the Petitioner and Dr. Sher make a multitude of inferences without providing any basis. Thus, a POSA would not conclude that Walters 1991 necessarily is a method for reducing redness at a concentration less than 0.05%.

5. Norden 2002

166. Dr. Sher identifies Norden 2002 as a reference purportedly disclosing the prophylactic use of 0.2% brimonidine to prevent subconjunctival hemorrhage and ocular hyperemia after LASIK surgery and purports to summarize Norden 2002. EX-1002, ¶¶82-86. For the reasons that follow, I disagree with Dr. Sher's summary of Norden 2002.

167. Norden 2002 is a paper discussing a study on the effect of prophylactic administration of 0.2% brimonidine (Alphagan®) on bleeding complications (subconjunctival hemorrhage, hyperemia, and micropannus bleeding) and flap adherence after LASIK surgery. EX-1006 (Norden 2002) at 4.

168. During a LASIK surgery, a suction cup (also known as a suction ring) is used to hold the eyeball in place during the surgery. The suction pressure frequently damages the surface blood vessels and causes subconjunctival hemorrhaging and micropannus bleeding, presenting as collection of blood or hematoma beneath the conjunctiva. EX-2162 (Sher Dep. Tr.) at 111:21-113:17. In contrast, hyperemia is a type of redness arising in intact blood vessels due to the

vasodilation of ocular blood vessels. Subconjunctival hemorrhage cannot be treated once it develops. It must be prophylactically addressed, as Norden 2002 did, before the blood vessels break. When subconjunctival hemorrhage, micropannus bleeding, and hyperemia occur simultaneously in patients, as in LASIK patients, the extensive bleeding in the eye makes it very difficult, if not impossible, to assess an accurate level of hyperemia.

169. Upon reading Norden 2002, a POSA would immediately recognize flaws in the study's design to show that 0.2% brimonidine prophylactically reduces hyperemia—a conclusion that in fact was contemporaneously questioned by other ophthalmologists.

170. First, Norden 2002 measured redness only once, five minutes after the LASIK surgery. *See* EX-1006 (Norden 2002) at 5. At least two measurements, however, must be made to conclude that brimonidine reduced redness in patients. The first measurement should occur immediately after the LASIK surgery when the patient presents with redness, and a second measurement should have been made a reasonable time thereafter. Those patients also presenting with a hematoma (and it appears that 22 of 61 eyes had subconjunctival hemorrhaging) should have been eliminated from the study, for their hematoma could spread over a 24-hour period shrouding the eye and preventing accurate readings of hyperemia. EX-2180 (Sher

article, Red Eye) at 10-11 (noting hematoma may worsen over 24-48 hours as it spreads).

171. Norden 2002 concludes that the amount of hyperemia "was notably lower in eyes treated prophylactically with brimonidine," pointing to a number of patients having grade 1 hyperemia. EX-1006 (Norden 2002) at 6 and "Figure". But it is possible that these patients had no redness immediately after the LASIK surgery and that the 0.2% brimonidine treatment triggered hyperemia due to allergic reactions. Indeed, a letter to the editor submitted in response to Norden 2002 challenged Norden's conclusion on this point. EX-2186 (Uretmen). In a study of similar design to Norden's, the surgeons' use of prophylactic brimonidine caused allergic reactions which led to hyperemia severe enough to postpone surgery in 30% of the patients. In the absence of any baseline comparison, a POSA simply cannot draw any conclusion about whether 0.2% brimonidine in Norden 2002 reduced redness in patients.

172. Second, Norden 2002 failed to establish proper exclusion criteria. A POSA would understand that [redacted]. *See* EX-2166 (NDA clinical study No. 10-100-0008) at 10. There is no indication that patients

taking such medications have been properly screened from the study. *See* EX-1006 (Norden 2002) at 4.

173. In fact, Norden 2002 describes that the patients were pre- and post-operatively treated with a myriad of other eye medications, such as antibiotics (ofloxacin), anti-inflammatory drugs (diclofenac and prednisolone acetate), a topical antiseptic (betadine), and a dry eye reliever (Refresh Plus® lubricant), any of which could have skewed the hyperemia measurements and ultimately the results. *See id.* at 4-5. For example, if a patient had an inflamed episclera with redness from the suction ring used in the LASIK surgery, diclofenac or prednisolone acetate could have reduced hyperemia. Similarly, if a patient had hyperemia caused by bacteria or other micro-organisms, ofloxacin or betadine could have reduced redness. Also, if a patient had hyperemia due to dry eyes, Refresh Plus® lubricant could have reduced redness rather than brimonidine. But Norden 2002 does not indicate that the study was sufficiently controlled to determine that brimonidine, rather than any of the other drugs, was responsible for any purported redness reduction.

174. Third, the study protocol in Norden 2002 had too many variables to make any meaningful assessment. In assessing hyperemia, Norden 2002 used "a subjective scale that indicated severity, with 0 being none and 3 being the most severe." *Id*. at 5. As an initial matter, Norden provides little information on the subjective scale used to assess its ability to accurately assess redness. Norden 2002

also fails to describe what standards the operating surgeon used to distinguish different redness scores. This is especially problematic where, as here, patients often exhibit both hemorrhage and hyperemia, making it difficult to accurately discern the degree of hyperemia. Indeed, 19 out of 22 bloody eyes that did not receive brimonidine could have been misclassified as exhibiting a high level of hyperemia because their redness was measured merely five minutes after the surgery, when the level of hemorrhage was present and could be spreading, which would have masked the actual level of hyperemia in the eyes. *See id.* at 6.

175. Thus, a POSA would have seriously questioned Norden 2002's findings considering the design flaws in the study, as did contemporaneous reports of other surgeons in the industry. *See* EX-2175 (Munoz); EX-2186 (Uretmen).

6. U.S. Patent No. 6,242,442

176. Dr. Sher identifies the '442 patent as purportedly disclosing the use of brimonidine in combination with brinzolamide to treat certain ocular diseases and purports to summarize the '442 patent. EX-1002, ¶¶94-95.

177. I understand that Petitioner bears a heightened burden to show invalidity of a patent when the USPTO examiner has already thoroughly considered the prior art reference and issued the patent over it. I have been informed that the patent examiner at the Patent Office already considered the '442 patent during the prosecution of the '742 patent and allowed the '742 patent over it. *See* EX-1001

('742 patent) at 1; EX-1024 (File History of the '742 patent) at 58, 95-98, 104, 114-132, 142-145.

178. The '442 patent is entitled "Brinzolamide and Brimonidine for Treating Ocular Conditions" and is assigned to Alcon Laboratories, Inc. EX-1007 ('442 patent) at 1. It "is directed to the use of brinzolamide in combination with brimonidine to treat ocular diseases," namely, lowering intraocular pressure. *Id.* at 2:21-24.

179. The '442 patent states that brimonidine "has been shown to cause the side effects of sedation and ocular hyperemia in an allergic like reaction in some patients." *Id*. at 2:38-43. To reduce these side effects, the '442 patent proposes using a relatively low concentration of brimonidine, but only in combination with brinzolamide to maintain the overall efficacy of the formulation in reducing intraocular pressure. *Id*. at 2:47-54. For example, the formulations in Examples 7 and 9 contain 0.05% and 0.02% brimonidine, respectively, in combination with 1% brinzolamide. *Id*. at 6:11-24, 6:42-55. When brimonidine is administered alone (prior to administration of a separate brinzolamide composition), the '442 patent teaches that the preferred concentration is 0.1%-0.2%. *Id.* at 5:20-40.

180. The '442 patent does not teach or suggest that brimonidine can be used to reduce redness. In fact, it teaches the opposite—that brimonidine "has been shown to cause the side effects of sedation and ocular hyperemia in an allergic like reaction

in some patients" (*id.* at 2:38-41), consistent with its vasodilation properties known at the time. The '442 patent acknowledges that "[t]he mechanism by which brimonidine causes hyperemia is not well understood" and speculates that hyperemia could be caused by "frequent instillation of relatively high drug concentrations." *Id.* at 2:45-47. The '442 patent hypothesizes that lowering the dose of brimonidine could reduce the incidence of hyperemia, but it does not teach or suggest that low dose brimonidine can reduce redness. *See id.* at 2:45-50. Moreover, there are no working examples or any data in the '442 patent for a POSA to conclude that low dose brimonidine can reduce redness.

181. I understand that the only commercial product developed based on the '442 patent is Simbrinza®, which comprises 1% brinzolamide and 0.2% brimonidine. EX-2181 (Simbrinza™ label) at 1, 2. Notably, Alcon never developed a brimonidine product with a concentration below 0.2%, evidencing that lowering the brimonidine concentration did not produce the clinical effects that Alcon sought.

182. In my opinion, a POSA reading the '442 patent would have concluded that lowering the concentration of brimonidine would not have reduced eye redness in a patient having an ocular condition that caused the redness. As explained earlier, it was understood in the art that brimonidine exhibited blanching at high concentrations and that this was concentration dependent, given its low affinity for α_1 receptors. *See* EX-1018 (Robin 1998) at 2 ("The degree of selectivity is only

important if tissue concentrations are within the range required for α_1 activity. If tissue or circulating levels of drug are insufficient to produce α_2 effects, then α_1 effects are highly improbable."). A POSA would have thus believed that lowering the concentration of brimonidine in the '442 patent would have decreased brimonidine's α_1-mediated vasoconstrictive effects, thereby decreasing the blanching effects. *Compare* EX-2012 (Alphagan® Label 2001) at 4 and EX-1031 (Alphagan NDA) at 109 (reporting blanching in 50% of patients who received Alphagan® 0.5% and in 3.5% of patients who received Alphagan® 0.2%, respectively), *with* EX-2014 (Alphagan P® Label 2005) at 1, 4 (no blanching reported for Alphagan P® 0.1% and 0.15%).

7. Scruggs 2000

183. Dr. Laskar identifies Scruggs 2000 as purportedly disclosing that brimonidine drops dripping from the eye caused blanching of the skin on the cheeks and purports to summarize Scruggs 2000. EX-1002, ¶93.

184. Scruggs 2000 is a letter to the editor reporting "a rare dermatological reaction to brimonidine." EX-1023 (Scruggs 2000) at 5. In Scruggs 2000, a patient who was treated with brimonidine 0.2% ophthalmic solution exhibited "cheeks blanched in a streak pattern where runoff of the excess eyedrop occurred (Fig. 1)." *Id.* The patient's "cheeks became red and his conjunctiva became hyperaemic." *Id.* "The blanching intensified over a period of 30 minutes, and erythema developed in

the surrounding skin." *Id*. The patient's cheek presented with a trail of whiteness surrounding by hyperemia. *Id*. These side effects "recurred with subsequent brimonidine administration and later resolved upon discontinuation of the drug." *Id*.

8. U.S. Patent No. 6,562,873

185. Dr. Sher relies on the '873 patent to opine that a POSA would have been motivated to formulate a brimonidine ophthalmic product between pH 5.5 and 6.14 because solubility of brimonidine is lower at a higher pH based on Table II of the '873 patent. *See* EX-1003, ¶100.

186. I understand that Dr. Williams provides a summary of the '873 patent in his declaration.

C. Response to the Petitioner's Grounds of Purported Invalidity

1. Ground No. 1 – The '553 patent does not expressly or inherently anticipate claims 1 and 2

a. Relevant legal principles of inherency

187. I understand that anticipation is shown only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. I understand that inherency is shown only if the limitation at issue is the natural result flowing from the explicit disclosure of the prior art, and that inherency may not be established by probabilities or possibilities. I understand that inherency requires that a limitation which is not expressly disclosed in the prior art reference to be necessarily and inevitably present in the disclosure, as an innate

property or functional characteristic. I understand that in order to show inherency, faithful repetition of the prior art must necessarily and inevitably produce all elements of the claimed invention, and the claim invention must always result from exactly reproducing the prior art. I understand that mere probabilities and possibilities of producing claimed invention based on the prior art is insufficient to establish inherency.

b. The ’553 patent does not expressly or inherently anticipate Claims 1 and 2

188. Dr. Sher opines that Example 1 of the ’553 patent anticipates each element of claims 1 and 2. EX-1002, ¶¶52-67. I disagree.

189. Example 1 of the ’553 patent is a prospective hypothetical study (never performed) to assess whether topically administered brimonidine reduced pain following radial keratotomy surgery. EX-1004 (’553 patent) at 4:46-48. The radial keratotomy patients could have pain, but they would not necessarily have accompanying ocular redness. EX-2162 (Sher Dep. Tr.) at 107:2-11 (acknowledging it is possible for ocular pain to not manifest as redness). Indeed, if the radial keratotomy was properly performed, by making precise microscopic incisions in an avascular cornea, ocular redness may not necessarily and inevitably result. *Id*. at 113:12-19, 113:24-114:4 (the goal of radial keratotomy is to make incisions in a healthy avascular cornea).

190. Radial keratotomy can be performed on patients with no eye redness at all. [redacted], making it possible that some patients in Example 1 may have no baseline redness, and 0.03% brimonidine would thus have no redness-reducing effect. *See* EX-2166 (NDA clinical study No. 10-100-0008) at 16 ([redacted]). Additionally, without any inclusion/exclusion criteria for this hypothetical study that was not actually performed, it is possible for the radial keratotomy patients to have taken a commercial vasoconstrictor and have no redness at any time pre- or post-operatively.

191. Example 1 makes no mention of redness or even suggests an assessment of redness, let alone measuring redness reduction. And because brimonidine at 0.03% could have caused, not abated, redness at 0.03% (*see* EX-1001 ('742 patent) at Fig. 6, 19:52-54), this study cannot necessarily establish that 0.03% brimonidine reduced redness.

192. As a hypothetical study, moreover, in Example 1 does not contain any study results regarding pain relief, merely stating that "[t]his appears to suggest that brimonidine, administered preoperatively, blocks the perception of pain." EX-1004 ('553 patent) at 5:1-2. Blocking the perception of pain, such as by blocking neuronal transmission of pain signals, may relieve the sensation of pain, but it will have no

effect on any inflammation and its (possible) presentation as redness. *See id.* at 1:54-55 ("Anesthetics block neuronal transmission and affect sensation as well as pain."); EX-2162 (Sher Dep. Tr.) at 109:12-15 (acknowledging that anesthetics block the perception of pain); EX-1006 (Norden 2002) at 7 (stating that brimonidine is an anesthetic).

193. Thus, a POSA would not have concluded that the hypothetical, prospective clinical study of Example 1 to treat ocular pain expressly or inherently disclosed a method of reducing redness using brimonidine claimed in the '742 patent. Simply put, the example makes no mention of reducing redness, the radial keratotomy patients may have no redness after surgery, they could have zero hyperemia pre- and post-operatively, no measurements of redness were contemplated, and 0.03% could have caused hyperemia (EX-1001 ('742 patent) at Fig. 6, 19:52-54). All that Example 1 concludes is that it "appears to suggest that brimonidine, administered preoperatively, blocks the perception of pain." EX-1004 ('553 patent) at 5:1-2. But consistent with brimonidine's known anesthetic effect (EX-1006 (Norden 2002) at 7) to block nerve transmissions and the perception of pain, which would not have ameliorated any redness associated with inflammation, the POSA would not have understood Example 1 to teach a method of reducing redness using brimonidine.

194. Given the dearth of information in this hypothetical example, the only way to determine whether it inherently destroys the novelty of claims 1 and 2 of the ’742 patent would be to conduct the proposed trial. For reasons that should be readily apparent, that cannot be done, making Dr. Sher’s position on Example 1 more theoretical than real, which I understand cannot establish inherency.

2. Ground No. 2 – Walters 1991 does not expressly or inherently anticipate claims 1 and 2

195. Dr. Sher opines that Walters 1991 anticipates claims 1 and 2 of the ’742 patent. I disagree. EX-1002, ¶¶71-81.

196. Walters 1991 is a one-paragraph abstract for a pilot study assessing the efficacy and safety of AGN 190342-LF (i.e., brimonidine) 0.02% and 0.08% in patients with elevated intraocular pressure. EX-1005 (Walters 1991) at 4. The study is merely a preliminary abbreviated study that, as far as I know, was never published as a fulsome article.

197. But as with Example 1 of the ’553 patent, Walters 1991 does not even use the word “redness,” let alone mention anything about reduction in eye redness. It provides no information to indicate whether any patient had a reduction in eye redness when administered with brimonidine, nor does it describe any patient having redness prior to administration.

198. Walters 1991 does not disclose whether any of the patients had redness that could be reduced using 0.02% brimonidine. For instance, since Walters 1991

contained no patient data relating to redness, it is possible that at least one or more patients in the study had no baseline redness at all (i.e., [redacted]). *See* EX-2166 (NDA clinical study No. 10-100-0008) at 16, Table 5. Even if some patients may have had eye redness—which Dr. Sher has not shown—it is not known whether those patients only received the 0.08% brimonidine solution or the placebo instead of the 0.02% brimonidine solution. The information provided in this abstract is too scant to draw any meaningful conclusion about the effects of 0.02% brimonidine on reducing eye redness.

199. The abstract also fails to mention any inclusion/exclusion criteria to determine, for example, whether the patients in the study took any commercially available eye whiteners, anti-inflammatory drugs, or any other eye drops that could have reduced eye redness. In those patients, 0.02% brimonidine would not have had any redness-reducing effects.

200. Put simply, there are far too many unknowns surrounding Walters 1991. With no data to prove redness reduction, no information on the individual patient's ocular condition, no information on which dose each patient received, and no inclusion/exclusion criteria, a multitude of inferences are required to be drawn. With this untenable foundation, lack of real evidence and only speculation, a POSA would not have accorded any weight to this abstract as necessarily and inevitably being a method for treating redness.

3. Ground No. 3 – Claims 1-6 are not obvious

a. Relevant legal principles

201. I understand that an obviousness analysis involves a review of the scope and content of the prior art, the differences between the prior art and the claimed subject matter, the level of ordinary skill in the art, and objective indicia of nonobviousness, such as unexpected results, acclaim, copying, and commercial success. I understand that for an invention to be regarded as obvious, a person of ordinary skill in the art must have had a reason to modify the prior art or to combine one or more prior art references in a manner that would result in the claimed subject matter with a reasonable expectation of success.

202. I understand that a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Rather, I have been informed that a party challenging the validity of a patent must establish a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. A challenger must also show that the POSA would have had a reasonable expectation of success in achieving the claimed invention.

203. To show a reasonable expectation of success, I understand that there must be actual support as to why a POSA would have been motivated to make an alleged modification or combination. I understand that it is important not to fall for

hindsight bias or using the patent disclosures as a roadmap to find its prior art components. I understand that the proper question for obviousness is not what a POSA would have been able to do, but rather what a POSA would have been motivated to do at the time of invention.

204. I understand that unpredictability in the art to which the claimed invention pertains impacts the determination of reasonable expectation of success. I understand that chemical and pharmaceutical arts are generally recognized as unpredictable art fields. In these fields, potential solutions are less likely to be genuinely predictable, and thus nonobvious.

b. There would have been no motivation to use low-concentration brimonidine to reduce eye redness, nor a reasonable expectation it would work

205. The subject matter of the invention—methods of reducing redness in the eye—is a highly complex subject matter dealing with an organ that is highly sensitive, vascularly complicated, and not completely understood even to this day. Treating eye conditions is thus inherently complex because it is difficult to predict how different medications may interact in the eye and affect clinical efficacy or cause unwanted side effects. *See* EX-2162 (Sher. Dep. Tr.) at 108:5-23.

206. The drug delivery requirements and the characteristics of the drug product that will be necessary to achieve therapeutic effects will vary depending on the type of treatment and which part of the eye needs to be treated. As a result, the

characteristics of a formulation intended to treat one ophthalmic condition may not be suitable (and may in fact be disadvantageous) for a product intended to treat another condition. *See supra* Section VI.C- VI.E; EX-2030 (Agarwal) at 13.

207. Also, the outcome of a study on animals, such as rabbits and monkeys, may not fairly represent how the medication may perform in the human eye due to numerous anatomical and physiological differences. Clinical studies or experiments involving human patients are a much-preferred platform for developing and evaluating ophthalmic products. *Id.* at 51:1-52:7.

c. A POSA would not have chosen and more likely would have been led away from even considering brimonidine as a redness reliever

208. In considering a direction of exploration for a new drug product, particularly for an FDA-approved product, a POSA takes into account the clinical efficacy and side effect profiles of the existing drugs for the particular disease sought to be treated. Here, a POSA would not have considered brimonidine, at any concentrations, to be an obvious choice for a redness reliever.

209. I understand that Dr. Williams explains in his declaration how a POSA would not have chosen brimonidine because it is ***not*** identified in the OTC monograph at all, much less in the vasoconstrictor class. When seeking to develop a new eye redness reliever, if anything, a POSA would have started by exploring active ingredients that have already been monographed (including containing a

monographed ingredient at the appropriate concentration for its intended use), such as ephedrine, phenylephrine, tetrahydrozoline, and naphazoline because they had been generally recognized as safe and effective for their intended use and can be marketed without first obtaining FDA clearance.

i. Not all agonists labelled broadly as "vasoconstrictors" would have been expected to perform similarly

210. Dr. Laskar and Dr. Sher argue that brimonidine would have been an obvious choice because it is a 2-imidazoline derivative, similar to known vasoconstrictors naphazoline and tetrahydrozoline, and would have been expected to reduce redness in the eye. EX-1002, ¶30; EX-1003, ¶¶32-36. I disagree with this overly simplistic argument.

211. The 2-imidazoline group of compounds encompasses a broad range of compounds that have different chemical structures with different properties. EX-2198 (Laskar Dep. Tr.) at 36:5-12 (admitting that "[t]he different chemical compounds have different physical and chemical properties"). Indeed, the chemical structures reproduced in Dr. Laskar's declaration underscore that the naphazoline, tetrahydrozoline, and brimonidine have significant structural dissimilarities, which would have indicated to a POSA that they have significant differences in physical and chemical properties. *See* EX-1003, ¶33. I understand that Dr. Davies, a renowned chemist, will opine on this topic.

212. Dr. Sher and Dr. Laskar opine that brimonidine would have similiar vasoconstriction properties as naphazoline and tetrahydrozoline. EX-1002, ¶30; EX-1003, ¶36. As explained above in *supra* Sections VI.D-E, naphazoline and tetrahydrozoline were known to cause side effects, such as rebound hyperemia and tachyphylaxis. Thus, a POSA would have expected brimonidine to cause the same undesirable side effects.

213. As discussed, the Federal Register 1988, on which Dr. Sher relies, does not even identify brimonidine as a vasoconstrictor compound. *See* EX-1009 (Federal Register 1988) at 14. In fact, the "vasoconstrictor" list in the Federal Register 1988 conspicuously lacks α_2 agonists and lists α_1 agonists, such as naphazoline, phenylephrine, and tetrahydrozoline. *See id.* A POSA would not have expected brimonidine—a highly selective α_2 agonist—to produce the same vasoconstrictive properties as the known α_1 agonists, such as naphazoline and tetrahydrozoline.

214. In this regard, those skilled in the art understood that α_1 agonists bind to α_1 receptors in the eye and constrict blood vessels, producing the known α_1 effect of whitening or blanching effects. EX-2169 (Derick 1995) at 4 ("In the eye, α_1-adrenoceptors are located on vascular smooth muscle located in the conjunctiva, ciliary processes, retina, and choroid. Stimulation of these adrenoceptors leads to vasoconstriction."), Tables 2-3 (indicating that α_1 receptor activation triggers

constriction); EX-1019 (Lachkar 1998) at 3 (vasoconstriction is mediated mainly via α_1-adrenergic receptors).

215. By contrast, α_2 agonists bind to alpha-2 receptors, which mediate vasodilation effects to produce a sense of relaxation, manifesting as sedation, depression, and hypotension. EX-1019 (Lachkar 1998) at 3 ("[B]rimonidine tartrate may also produce vasodilation via the α_2-adrenergic receptors on endothelial cells, which release endothelial-derived relaxing factor."); EX-2169 (Derick 1995) at 4 ("For example, absorption of an α_2-agonist in the central nervous system (CNS) will cause depression and hypotension."); *see also* EX-1001 ('742 patent) at 1:25-29. Alpha-2 mediated vasodilation of ocular blood vessels floods the blood vessels with blood, engorging them to produce ocular hyperemia.

216. Brimonidine is highly selective for the α_2 receptors, having a potency ratio of α_2 to α_1 ranging in the art from almost 2000:1 (EX-1035 at 2, Fig. 1) to 1000:1 (EX-1023 (Scruggs 2000) at 5). At low concentrations, minimizing further its already low α_1 effect, brimonidine would not have been expected to reduce eye redness. EX-1018 (Robin 1998) at 2 ("If tissue or circulating levels of drug are insufficient to produce α_2 effects, then α_1 effects are highly improbable."). To the extent the concentration would have been expected to be in the range of brimonidine's α_2 activity, the POSA would have expected brimonidine to cause vasodilation, exacerbating redness rather than reducing redness in the eye. Indeed,

the FDA clinical studies for Alphagan® 0.2% list ocular hyperemia as the second most common adverse event occurring at a rate of about 30% and the second most frequent cause of termination from the studies. *See* EX-1031 (Alphagan NDA) at 109, 129. Even at lower concentrations, 0.15% and 0.1%, brimonidine reported high incidences of ocular hyperemia in 10-20% of the subjects. EX-2014 (Alphagan P® Label 2005) at 1, 4.

217. Brimonidine was also beset by a high incidence of ocular allergic reactions. The 0.2% Alphagan® product caused ocular allergic reactions in 10-30% of the patients and were the most frequent cause of termination from the study. EX-2012 (Alphagan® Label 2001) at 9; EX-1031 (Alphagan NDA) at 129.

218. Although it was known in the art that even a highly selective α_2 agonist like brimonidine can produce blanching effects, it was only at high concentrations sufficient to activate its minimum α_1-mediated vasoconstriction effects. The art established that brimonidine's blanching effects is concentration dependent—as the concentration of brimonidine decreased, so too did its α_1-mediated blanching effects—while its vasodilation effects remained high. *See* EX-2012 (Alphagan® Label 2001) at 12, 14 (noting that conjunctival hyperemia occurred in 10-20% of the subjects receiving 0.1-0.2% brimonidine).

219. Indeed, the Alphagan® label, the Alphagan P® label, and the Alphagan® NDA clinically established the concentration dependency of brimonidine's

blanching effects. For example, Alphagan® 0.5% reported the incidence of conjunctival blanching in 50% of the subjects, which sharply declined to 3.5% when brimonidine's concentration decreased by slightly more than half in Alphagan® 0.2%. *Compare id.* at 4 (reporting that Alphagan® 0.5% caused conjunctival blanching in 50% of the subjects), *with* EX-1031 (Alphagan NDA) at 109 (reporting that Alphagan® 0.2% caused conjunctival blanching in 3.5% of the patients). When the concentration of brimonidine further decreased to 0.15% and 0.1% in Alphagan P®, no blanching was reported at all. To the extent one would have contemplated using brimonidine to whiten eyes, which has not been established, this would have informed the skilled person that the concentration of brimonidine should be increased to maintain α_1-mediated whitening effects.

220. In sum, against this backdrop of prior art information for brimonidine, a POSA would not have reasonably expected to reduce eye redness with low concentration brimonidine formulations. A highly selective α_2 agonist having very little α_1 vasoconstricting effect, brimonidine primarily caused ocular blood vessels to vasodilate and flood with blood, causing ocular hyperemia (i.e., eye redness)—the very property a POSA would have ***avoided*** when seeking to develop a redness reliever.

221. Brimonidine was also plagued by high incidences of ocular allergic reactions, which further contributed to ocular hyperemia. *See supra* Section VI.F.1,

infra Section IX.B.1; EX-2011 at 1-2. While this may have been a tolerable side effect for brimonidine when treating more serious diseases like glaucoma, it would have been yet another property of brimonidine that would have discouraged a POSA from considering it as a suitable candidate for an OTC redness reliever.

222. Although brimonidine exhibited conjunctival blanching at high concentrations due to its minimal α_1 effects, the prior art clinically established that the α_1 whitening effects are concentration dependent, such that higher concentrations of α_1 agonists caused whitening. *See* Section VI.F.2-3. In other words, when the concentration of brimonidine decreased, so too did its propensity to whiten the eye, and those blanching effects essentially disappeared at concentrations 0.15% and below. Thus, the skilled person would not have had any motivation to choose brimonidine as a redness reliever with any expectation that even at lower concentrations (e.g., 0.025% in the claimed invention), it would have effectively reduced eye redness.

ii. Contrary to Dr. Sher's position, the POSA ophthalmologist would not have looked to the '553 patent examples to "optimize" brimonidine's concentration

223. Even if a POSA were to consider brimonidine as a redness reliever—which they would not have—the POSA would have ***increased*** brimonidine's concentration in the direction that brimonidine's blanching effects were achievable, for example, 0.2% and above.

224. Dr. Sher opines, based on the ’553 patent, that a POSA would have been motivated to explore the range of 0.01% to 0.08%. EX-1002, ¶126. Dr. Sher relies on Examples 1 and 4 of the ’553 patent, which hypothesize the use of 0.03% brimonidine (Example 1) and a dose range of 0.01%-0.5% to block the perception of pain (Example 4). EX-1004 (’553 patent) at 4:45-5:2, 5:18-45. I disagree.

225. As discussed previously, a POSA would not have concluded that the hypothetical clinical study of Example 1, designed to assess relief of ocular pain, disclosed or suggested a method of reducing redness using brimonidine. The example makes no mention of reducing redness, the radial keratotomy patients may have no redness after surgery, no measurements of redness were contemplated, and 0.03% could have actually caused hyperemia (EX-1001 (’742 patent) at Fig. 6, 19:52-54). And because Example 1 concludes only that brimonidine may block the perception of pain (EX-1004 (’553 patent) at 5:1-2), likely through blocking nerve transmissions that would not have ameliorated any redness associated with inflammation, the POSA would not have understood Example 1 to teach or even remotely suggest a method of reducing redness using brimonidine.

226. Nor would Example 4 of the ’553 patent have been understood by the POSA as disclosing a method of reducing eye redness. Like Example 1, Example 4 is a hypothetical study (in rabbits), which was not performed and contains no actual study data. Its “Corneal Nerve Conduction Model” seeks to assess whether

brimonidine can block nerve transmissions and the perception of pain. *Id.* at 5:18-45. The ’553 patent provides no data to validate the model for assessing redness, nor were any measurements contemplated for doing so. *See* EX-2162 (Sher Dep. Tr.) at 122:6-22 (admitting that Example 4 does not provide any data validating that the corneal nerve conduction model measures redness). Thus, a POSA would have only understood Example 4 to prospectively seek to determine if brimonidine could block the perception of pain by blocking nerve transmissions, but that would not have suggested anything about brimonidine’s ability to reduce redness.

227. Thus, a POSA would have considered the ’553 patent’s examples to be at the very low end of the hierarchy of evidence and would not have referred to them as a starting point for optimizing brimonidine’s concentration with the goal of reducing redness. If anything, a POSA would have given more weight to clinical study data, such as Alphagan®’s FDA labels, that actually measured brimonidine’s propensity for blanching.

228. Specifically, knowing brimonidine’s low potency for the α_1 effects responsible for blanching, coupled with the ample clinical study information that blanching effects are concentration dependent—sharply decreasing at concentrations below 0.2%, but increasing with the increasing concentration—a POSA would have started, if at all, at 0.2% and increased the concentration.

d. Though not established, if a POSA were to pursue an α_2 agonist as a redness reliever, it would have been one other than brimonidine

229. As explained earlier, it is my opinion that a POSA would not have been motivated to choose an α_2 agonist as a redness reliever at all. But even if a POSA were to consider it as a candidate for a redness reliever, the POSA would have looked not to brimonidine but, if anything, to the relatively selective α_2 agonists, such as clonidine and apraclonidine. Apraclonidine was reported in the art as having an α_2 to α_1 potency ratio of 72:1. EX-1035 at 2, Fig. 1. Clonidine was reported to have an α_2 to α_1 potency ratio of 183:1. *Id*. For perspective, the art reported an α_2 to α_1 potency ratio for brimonidine at 1812:1. *Id*.

230. A POSA would have recognized that, as compared to brimonidine, apraclonidine and clonidine have a higher affinity for α_1 receptors to produce blanching effects, and thus more appropriate redness reliever candidates among the α_2 agonists. Indeed, the art taught that "compared to clonidine and apraclonidine, brimonidine would be the least likely to produce α_1-adrenoceptor-mediated side effects, such as mydriasis and ocular vasoconstriction." *Id.* at 2.

e. None of Dr. Sher's obviousness prior art references (the '553 patent, Norden 2002, the '442 patent, the Federal Register 1988, and the '873 patent), alone or in combination, renders obvious the redness reducing method of claim 3

231. Claim 3 is an independent claim that reads as follows:

> A method for reducing eye redness consisting essentially of topically administering to a patient having an ocular condition a composition consisting essentially of brimonidine into ocular tissue, wherein pH of said composition is between about 5.5 and about 6.5, wherein said brimonidine concentration is between about 0.001% and about 0.025% weight by volume and wherein said composition is formulated as an ocular drop.

EX-1001 ('742 patent) at 22:25-32.

232. In my opinion, the method of reducing eye redness as recited in claim 3 of the '742 patent would not have been obvious to a POSA.

i. The '553 patent fails to render the elements of claim 3 obvious

233. In his obviousness analysis, Dr. Sher argues that Example 1 of the '553 patent combined with Norden 2002 discloses "[a] method for reducing eye redness consisting essentially of" and "topically administering to a patient having an ocular condition a composition." EX-1002, ¶¶141-144. I disagree.

234. The '553 patent is directed to a method of using brimonidine to reduce pain, not redness, arising from corneal injuries and ocular inflammation resulting from such injuries. EX-1004 ('553 patent) at 2:52-54. But a POSA would have understood that a single ocular inflammatory event does not necessarily manifest with all the neurogenic responses. EX-2162 (Sher Dep. Tr.) at 104:23-109:11 (admitting that an inflammatory event does not exhibit all symptoms of ocular inflammation). For example, a patient who has ocular pain may not necessarily have eye redness. EX-2174 (Morgan 1987) at 4.

235. The POSA would not have concluded that the hypothetical clinical study of Example 1, designed to assess relief of ocular pain, disclosed or suggested a method of reducing redness using brimonidine. The example makes no mention of reducing redness, the radial keratotomy patients may have no redness after surgery, and no measurements of redness were contemplated. Example 1 concludes only that brimonidine may block the perception of pain (EX-1004 ('553 patent) at 5:1-2), likely through blocking nerve transmissions that would not have ameliorated any redness associated with inflammation. *See id.* at 1:54-55 ("Anesthetics block neuronal transmission and affect sensation as well as pain."); EX-2162 (Sher Dep. Tr.) at 109:7-15 (acknowledging that anesthetics block the perception of pain); EX-1006 (Norden 2002) at 7 (stating that brimonidine is an anesthetic). Thus, the POSA would not have understood Example 1 to teach or even remotely suggest a method of reducing redness using brimonidine.

236. Nor would Example 4 of the '553 patent have been understood by the ophthalmologist POSA as disclosing a method of reducing eye redness from a rabbit model study designed to assess pain relief. Though Example 4 broadly states that neurogenic inflammation, including redness and pupillary constriction, can be observed in rabbits from external stimuli (*see* EX-1004 ('553 patent) at 5:38-40), it contains no data to validate the model's ability to measure redness. It also does not contemplate measuring baseline redness or any subsequent measurements of redness

from which any conclusion of redness reduction could be assessed. In fact, as a hypothetical animal study that was not performed, Example 4 contains no study data of any kind regarding the purported reduction in neurogenic responses.

237. At most, therefore, a POSA would have interpreted the statement that "[b]rimonidine is effective in reducing such neurogenic responses" (*id.* at 5:44-45) to refer to brimonidine's hypothesized ability to block nerve signals and relieve the perception of ocular pain, which is the purpose of the study. But like Example 1, the POSA ophthalmologist would have understood that relieving pain by blocking nerve signals would have no effect on inflammation or any possible redness associated with it. As such, Example 4 would not have been understood as a method of reducing redness with brimonidine.

238. In short, a POSA would have placed the '553 patent's examples to be at the very low end of the hierarchy of evidence and would not have considered them in developing a new redness reliever. In fact, Dr. Sher, a clinical ophthalmologist of over 40 years and well versed in the prior art relating to redness relievers, was not aware of the '553 patent until he began working on this matter. EX-2162 (Sher Dep. Tr.) at 114:8-16, 116:4-8.

ii. Norden 2002 fails to render the elements of claim 3 obvious

239. Norden 2002 also fails to disclose the claimed method of reducing eye redness. Nor would it have been combined with the '553 patent, which would have

been understood by a POSA neither to teach nor suggest a method of using brimonidine to reduce eye redness.

240. As an initial matter, the subconjunctival hemorrhage that occurs in LASIK surgery results from breaking blood vessels in the eye, spilling blood under the conjunctiva, and producing a bright red patch (hematoma) in the eye. EX-2180 (Sher article, Red Eye) at 10. It is not the eye redness that is targeted for reduction by the '742 patent's methods, which is hyperemia and presents when the intact blood vessels in the eye dilate. EX-2162 (Sher Dep. Tr.) at 111:14-113:5.

241. Norden 2002 also states that 0.2% brimonidine reduced the amount of hyperemia. EX-1006 (Norden 2002) at 4. But a POSA would immediately recognize that the study in Norden 2002 is not properly designed to assess brimonidine's effects on hyperemia and would have seriously questioned its conclusion.

242. First, Norden 2002 measured redness only once, five minutes after the LASIK surgery. *See id.* at 5. At least two measurements, however, must be made to conclude that brimonidine reduced redness in patients. Those patients, moreover, presenting with a hematoma (and it appears that 22 of 61 eyes had subconjunctival hemorrhaging) (*id*. at 6) should have been eliminated from the study, for their hematoma could spread over a 24-hour period, obscuring the sclera and preventing the surgeon from making accurate hyperemia readings. EX-2180 (Sher article, Red Eye) at 10-11 (noting hematoma may worsen over 24-48 hours as it spreads).

243. Second, though concluding that the amount of hyperemia "was notably lower in eyes treated prophylactically with brimonidine," pointing to a number of patients having grade 1 hyperemia (*see* EX-1006 (Norden 2002) at 6 and "Figure"), because only a single measurement was made, it is possible that these patients had no redness immediately after the LASIK surgery and that the 0.2% brimonidine treatment triggered hyperemia due to allergic reactions. In a contemporaneously submitted letter to the editor about the Norden 2002 study, other surgeons using a similar study design to Norden's reported prophylactic brimonidine caused hyperemia severe enough to postpone surgery in 30% of the patients. *See* EX-2186 (Uretmen). In the absence of any baseline comparison, a POSA simply cannot draw any conclusion about whether 0.2% brimonidine in Norden 2002 reduced redness in patients.

244. Third, the subjects in Norden 2002 were given a host of anti-inflammatory drugs and antibiotics in addition to brimonidine before and after the LASIK surgery, any of which could have reduced eye redness in the patients instead of brimonidine. The list includes an antibiotic (ofloxacin), anti-inflammatory drugs (diclofenac and prednisolone acetate), a topical antiseptic (betadine), and a dry eye reliever (Refresh Plus® lubricant), any of which could have skewed the hyperemia measurements and impacted the reliability of the results. *See* EX-1006 (Norden 2002) at 4-5.

245. Fourth, there are too many variables in Norden 2002's study for a POSA to make any meaningful assessment. For example, Norden 2002 used the operating surgeon's "subjective scale" of 0 to 3 to grade hyperemia in the patients (*id.* at 5) without any information to evaluate its ability to accurately assess redness. Furthermore, Norden 2002 failed to set proper exclusion criteria to eliminate certain patient populations who could have skewed the study results. For example, [redacted]. *See* EX-2166 (NDA clinical study No. 10-100-0008) at 10-11 ([redacted]). But Norden 2002 only excluded patients who had inadequate corneal thickness, frank keratoconus, or active ocular disease, and patients who were immunocompromised or immunosuppressed, and it does not indicate that any other patient populations were excluded. EX-1006 (Norden 2002) at 4.

246. For these reasons, a POSA would not have accepted Norden 2002's conclusion as a suggestion that brimonidine could reduce hyperemia. And even if the conclusion in Norden 2002 were accepted for what it may suggest, a POSA would have increased, not decreased, the concentration of brimonidine to increase

the α_1-mediated blanching effects. As a known highly selective α_2 agonist, brimonidine had very low α_1 effects, and the clinical studies expectedly showed that increasing brimonidine's concentrations above 0.2% increased its blanching effects.

iii. The '442 patent would not have led a POSA to use a low-concentration brimonidine to reduce eye redness

247. Dr. Sher opines that a POSA would have been motivated to decrease the concentration of brimonidine because the '442 patent discloses that 0.2% brimonidine was associated with rebound hyperemia in some patients. EX-1002, ¶158. I disagree that the '442 patent supports Dr. Sher's opinion.

248. The '442 patent discloses that another active pharmaceutical ingredient (API), such as brinzolamide, must be combined with lower concentration brimonidine to maintain a clinically effective level of IOP reduction. *See* EX-1007 ('442 patent) at 2:51-54. Indeed, the only working example in the '442 patent with brimonidine as the sole API is formulated at 0.2%, suggesting that a high concentration of brimonidine is required for the intended clinical efficacy. *See id*. at 6:57-7:8 (Example 10). Moreover, the '442 patent states that brimonidine's side effects include sedation, consistent with its vasodilation properties associated with relaxation and ocular hyperemia, further leading a POSA away from selecting brimonidine as a redness reliever. *See id*. at 2:38-45. The '442 patent even

acknowledges that "[t]he mechanism by which brimonidine causes hyperemia is not well understood." *Id*. at 2:45-47.

249. Thus, for all the reasons given above, none of the cited references in Ground 3 would have rendered the use of low-concentration brimonidine, particularly 0.025%, obvious for reducing eye redness.

iv. Using a pH of 5.5 to 6.5 with about 0.025% brimonidine would not have been obvious to a POSA

250. I understand that Dr. Williams explains in his declaration that the pH range in claim 3 would not have been obvious to a POSA.

251. Based on my experience, when the pH of a formulation is further away from the physiological pH (7.4), the likelihood of eye irritation increases.

252. A formulation with a pH below 7 is considered acidic. Based on my experience, administration of a topical eye drop with an acidic pH may lead to irritation, burning, or stinging. The Alphagan® 0.2% product has an acidic pH (6.3-6.5), which likely would have been at least a contributing factor to the "burning and stinging" observed in approximately 10-30% of patients. EX-1008 (Alphagan® Label 1998) at 3. A POSA would have avoided formulating at an acidic pH due to its propensity to trigger tear or mucus production, which would increase the rate at which the drug is eliminated from the eye, reducing its efficacy.

253. As of 2013, the only 0.1% brimonidine product on the market was the Alphagan® P 0.1% product, which had a pH between 7.4 and 8.0. EX-2014 (Alphagan P® Label 2005) at 1. Because the Alphagan® P 0.1% product does not have an acidic pH and, in fact, has a pH at or near the physiological pH, it would be less likely to cause burning and stinging upon administration.

v. The prior art undercuts Dr. Sher's opinion as to why it would have been obvious to use low-concentration brimonidine to reduce ocular redness

254. In his declaration, Dr. Sher provides six reasons why a POSA would have used low-concentration brimonidine to reduce ocular redness. EX-1002, ¶¶37, 150. I disagree that these reasons would have led a POSA to the claimed invention.

255. First, Dr. Sher argues that "2-imidazoline derivatives had been in commercial use for decades as vasoconstrictor compounds in redness reducing topical eye drops." EX-1002, ¶¶37, 150. The commercial vasoconstrictors, however, were either α_1 or mixed α_1/α_2 agonists because the art at the time believed that vasoconstriction redness relief is an α_1 effect. EX-1016 (Griffith 2003) at 12, 13; EX-2169 (Derick 1995) at 1, Table 2. Accordingly, selective α_2 agonists, let alone highly selective α_2 agonists with little to no α_1 effect, would not have been viewed as a viable option for developing a redness reliever. Even if an α_2 agonist was considered, a POSA would have increased its concentration to obtain α_1 blanching effects. Also, I understand that Patent Owner's expert Dr. Davies will explain that

brimonidine is actually an amino-imidazoline and that Dr. Laskar's underlying chemical assumptions are incorrect.

256. Second, Dr. Sher states that "brimonidine was a 2-imidazoline derivative and was known to be a potent vasoconstrictor." EX-1002, ¶¶37, 150. I disagree. While it is true that some prior art references characterize brimonidine as a strong vasoconstrictor, that provides an incomplete picture. As explained earlier, the art also recognized that brimonidine's α_1-mediated vasoconstriction effects are concentration dependent and only observed at high concentrations of 0.2% or above. EX-1031 (Alphagan NDA) at 13, 52. When the concentration of brimonidine is decreased below 0.2%, for example, to 0.15% and 0.1%, the blanching effects disappear. *See* EX-2014 (Alphagan P® Label 2005). Also, the art at the time recognized that the activation of α_2 receptors produces hypotensive effects, including vasodilation, inducing eye redness. *See* EX-2169 (Derick 1995) at 4, Table 2. Lowering the concentration of brimonidine below the concentration needed to exert α_1-mediated blanching would have only been expected to produce ocular hyperemia through its activation of the α_2 receptors. Thus, a POSA would not have been motivated to formulate brimonidine at low concentrations as a redness reliever. Also, I understand that Patent Owner's expert Dr. Davies will explain that brimonidine is actually an amino-imidazoline and that Dr. Laskar's underlying chemical assumptions are incorrect.

257. Third, Dr. Sher states that "brimonidine was known to exert its vasoconstrictor activity on the front but not the back portion of the eye." EX-1002, ¶¶37, 150. But, as explained earlier, brimonidine's vasoconstrictive effects on the ocular surface—the conjunctiva, episclera, and sclera—are only seen at high concentrations, at or above 0.2%. EX-1031 (Alphagan NDA) at 109; EX-2012 (Alphagan® Label 2001) at 4.

258. Fourth, Dr. Sher states that "brimonidine was approved by the U.S. FDA for use in a topical eye drop for over ten years." EX-1002, ¶¶37, 150. Dr. Sher fails to point out that the only FDA-approved ophthalmic product containing brimonidine at the time was glaucoma medication for decreasing IOP. Unlike eye redness, glaucoma is a serious disease that arises due to high IOP, which damages the optic nerve and can ultimately lead to blindness. As explained earlier, the target tissues to treat glaucoma are completely different from those of eye redness, such that a POSA would not have been motivated to use low-concentration brimonidine as a redness reliever without the benefit of hindsight.

259. Fifth, Dr. Sher states that "brimonidine was considered to be safe, well tolerated and with a low rate of allergic response." EX-1002, ¶¶37, 150. While brimonidine may have been considered safe and well tolerated with a relatively low rate of allergic response for a treatment for glaucoma—a disease that can lead to blindness if the treatment regimen is not followed—the same side-effect profile

would have deterred a POSA from using brimonidine as an OTC product for redness relief. As explained earlier, the FDA-approved Alphagan® products (0.1%, 0.15%, and 0.2%) caused significant hyperemia (up to 30% in the patient population) and a relatively high rate of ocular allergic reaction (up to 13% of the patient population). EX-2012 (Alphagan® Label 2001) at 9; EX-1032 (Rahman 2010) at 4; EX-1031 (Alphagan NDA) at 109. A POSA would have considered these rates of adverse events unacceptable for OTC redness relievers. Moreover, a POSA would have been further deterred from formulating brimonidine at low concentrations because the art taught that it was concentration dependent. EX-2012 (Alphagan® Label 2001) at 4; EX-1031 (Alphagan NDA) at 109. Lowering brimonidine's concentration to the claimed concentration would have been expected to effectively eliminate brimonidine's α_1 blanching effects, and thus its ability to reduce eye redness.

260. Sixth, citing Scruggs (EX-1023), Dr. Sher states that brimonidine drops dripping from the eye caused blanching of the skin on the cheeks, suggesting that a POSA could use brimonidine to produce the same blanching effects in the eye. EX-1002, ¶¶37, 150. The patient in Scruggs was administered with 0.2%, which at the time was known to cause blanching effects (EX-1023 (Scruggs 2000) at 5), although only in about 3.5% of the patients—down sharply from a high of 50% for a concentration of 0.5%. EX-1031 (Alphagan NDA) at 109; EX-2012 (Alphagan® Label 2001) at 4. When, however, brimonidine's concentration was reduced even

further to 0.15% and 0.1%, the patients no longer exhibited the blanching effects, though they still exhibited a relatively high rate of ocular hyperemia at 10-20%. EX-2014 (Alphagan P® Label 2005) at 1, 4. Accordingly, a POSA would not have had any reason to use brimonidine with any expectation that it would reduce redness at significantly lower concentrations, for example, at 0.025%.

f. Dr. Sher's prior art references fail to render obvious claims 1, 2, and 4-6

261. Claim 1 is directed to "[a] method for reducing eye redness consisting essentially of administering brimonidine to a patient having an ocular condition, wherein brimonidine is present at a concentration between about 0.001% weight by volume and about 0.05% weight by volume." EX-1001 ('742 patent) at 22:17-21. For the same reasons explained above for claim 3, claim 1 is patentable because there would have been no motivation or reasonable expectation of success that low-concentration brimonidine between about 0.001% to about 0.05% would have effectively reduced redness.

262. Claim 2 depends from claim 1 and further defines that "wherein brimonidine is present at a concentration between about 0.001% to about 0.025% weight by volume." *Id.* at 22:22-24. For the same reasons explained above for claim 3, claim 2 is patentable because there would have been no motivation or reasonable expectation of success that low-concentration brimonidine between about 0.001% to about 0.025% would have effectively reduced redness.

263. Claim 4 depends from claim 3 and further defines that "wherein said composition is topically administered within about 24 hours after a Lasik surgery on said patient." *Id.* at 22:33-35. For the same reasons explained above for claim 3, claim 4 is patentable because there would have been no motivation or reasonable expectation of success that low-concentration brimonidine would have effectively reduced redness.

264. Dr. Sher also argues that Norden 2002 and the '553 patent render claim 4 obvious. As Dr. Sher acknowledges, however, Norden 2002 discloses prophylactic administration of 0.2% brimonidine "to reduce subconjunctival hemorrhage and improve the post-operative appearance." EX-1002, ¶170. Claim 4, however, requires topical administration of brimonidine "within about 24 hours ***after*** a Lasik surgery on said patient." EX-1001 ('742 patent) at 22:33-35 (emphasis added). Dr. Sher failed to provide any evidence that Norden 2002 or any other prior art administered low-concentration brimonidine as a treatment of red eye after LASIK surgery. Dr. Sher's opinion is particularly unjustified here given that Norden 2002's findings were challenged by contemporaneous clinicians noting that brimonidine was known to cause significant ocular allergic reactions causing severe ocular hyperemia. EX-2186 (Uretmen) (describing that in a prospective study with a similar design, authors observed that "the use of prophylactic brimonidine caused an allergic reaction," and "[t]he resulting hyperemia was so severe that [they] had to postpone surgery").

265. Claim 5 depends from claim 1 and further recites "wherein said ocular condition is chronic red eye." EX-1001 ('742 patent) at 22:36-37. Chronic red eye is a persistent and constant ocular disorder. For the same reasons explained above for claim 3, there would have been no motivation or reasonable expectation of success that low-concentration brimonidine would have effectively reduced the redness caused by chronic red eye. *See supra* Sections IX.C.3, IX.D. Moreover, because of the chronic nature of this disorder, the skilled person would have been deterred from the long-term regular use of brimonidine due to its well-known adverse event profile of high hyperemia and ocular allergic reactions. To the extent that a POSA would have looked to tetrahydrozoline and naphazoline to predict brimonidine's ability to reduce eye redness—which the POSA would not have—the POSA would have concluded that brimonidine is not suitable for treating a chronic, long-term condition given its propensity to cause rebound hyperemia and tachyphylaxis. *See supra* Section VI.F.

266. Claim 6 depends from claim 3 and further recites "wherein said ocular condition is chronic red eye." *Id.* at 22:38-39. For the same reasons explained above for claim 3, claim 6 is patentable because there would have been no motivation or reasonable expectation of success that low-concentration brimonidine would have effectively reduced redness.

D. Objective, real-world evidence of nonobviousness

267. I have been informed that the law recognizes that there can be objective evidence of nonobviousness, which is not just a confirmatory part of the obviousness assessment but can constitute independent evidence of the inventiveness or nonobviousness of an invention. I understand that such evidence can include unexpected results attributable to the invention, industry acclaim for the invention, copying of the invention by others, licensing of the patented invention, and commercial success for the invention in the marketplace. I am told that courts have recognized this type of evidence as often the most probative and cogent evidence of nonobviousness.

268. With respect to unexpected results, for example, I understand that they can be shown by either establishing that the claimed invention possesses unexpectedly superior properties compared to the closest prior art or that the claimed invention unexpectedly has benefits and properties that the closest prior art does not have. Here, it is my opinion that low-concentration brimonidine, as represented by Lumify®—an embodiment of the ’742 patent—is unexpectedly superior to the closest prior art in reducing redness, including Visine® and other similar products that have been market leaders for decades.

269. This superior redness reduction, attributable to the formulation claimed in the ’742 patent, advantageously and unexpectedly led to a cascade of real-world

benefits provided by Lumify®. It beneficially works within one minute and lasts for eight hours, 30% longer than the Visine L.R. (oxymetazoline). It has been clinically proven to cause little or no rebound hyperemia or tachyphylaxis, which is particularly important for OTC products that are subject to misuse or overuse, and can lead to additional and serious ocular problems, such as medicamentosa. Indeed, Lumify®'s superior redness-relieving efficacy, its rapidity of onset and duration of action, and its very favorable adverse-event profile has drawn praise in the industry from ophthalmologists, who have frequently recommended Lumify® over the prior art commercial eye redness relievers.

1. Lumify® Product

270. The Lumify® product is an embodiment of the brimonidine tartrate redness reliever eye drop in certain claims of the '742 patent, as discussed below. The Lumify® product is described in NDA 208144. *See, e.g.*, EX-2195 (NDA 208144, 2.2 Introduction (excerpt)).

271. The Lumify® product is an ophthalmic solution for relieving eye redness. *See, e.g.*, EX-2191 (Lumify® label) at 2 (describing that Lumify® is "brimonidine tartrate ophthalmic solution 0.025% redness reliever eye drops"), '742 patent at claims 1-3.

272. The Lumify® product consists essentially of administering brimonidine to a patient having an ocular condition. *See, e.g.*, EX-2191 (Lumify® label) at 2

(describing that Lumify® is used to relieve "redness of the eye due to minor irritations"); '742 patent at claims 1-3.

273. The Lumify® product consists essentially of 0.025% brimonidine tartrate because its sole API is brimonidine tartrate. *See, e.g.*, EX-2191 (Lumify® label) at 2; '742 patent at claims 1-3; '742 patent at claims 1-3.

274. The Lumify® product is administered into ocular tissue. *See* EX-2191 (Lumify® label) at 2 ("instill 1 drop in the affected eye(s) every 6-8 hours"); '742 patent at claim 3.

275. The Lumify® product has a pH of [redacted]. *See, e.g.*, EX-2196 (NDA 208144, Section 2.3.P.1.1 Finished Product Composition (excerpt)); '742 patent at claim 3.

276. The Lumify® product is formulated as an ocular drop. *See* EX-2191 (Lumify® label) at 2 (describing that Lumify® is "brimonidine tartrate ophthalmic solution 0.025% redness reliever eye drops.").

277. I understand that Mr. Ferris will explain that the industry recognition and commercial success of the Lumify® product is driven by the unique formulation containing low dose brimonidine tartrate and beneficial effects flowing from that formulation.

2. Unexpected superiority of the ’742 patent’s invention over prior art ophthalmic redness reducers

a. The closest prior art

278. The claims of the ’742 patent are all directed to methods of reducing eye redness. Regarding the closest prior art for comparison against the claimed invention, Dr. Laskar has stated that that would be 0.03% brimonidine from Example 1 of the ’553 patent and 0.02% brimonidine in Walters 1991. EX-1003, ¶105. He specifically states that 0.1% or 0.2% brimonidine would not constitute the closest prior art. *Id*. I agree with Dr. Laskar that neither 0.1% nor 0.2% brimonidine would constitute the closest prior art. But I disagree with him that 0.03% brimonidine from Example 1 of the ’553 patent and 0.02% brimonidine in Walters 1991 would be the closest prior art. Neither Example 1 of the ’553 patent nor Walters 1991 is directed to a method of reducing eye redness.

279. As explained previously, Example 1 of the ’553 patent is a hypothetical clinical study designed to assess relief of ocular pain using brimonidine. It does not describe or even remotely suggest a method of reducing redness. It concludes only that brimonidine may block the perception of pain (EX-1004 (’553 patent) at 5:1-2), likely through blocking nerve transmissions, but that would not have ameliorated any redness associated with inflammation. *See id.* at 1:54-55 (“Anesthetics block neuronal transmission and affect sensation as well as pain.”); EX-2162 (Sher Dep.

Tr.) at 109:12-15 (acknowledging that anesthetics block the perception of pain); EX-1006 (Norden 2002) at 7 (stating that brimonidine is an anesthetic).

280. Walters 1991 focused solely on brimonidine's ability to reduce IOP. Walters 1991 never mentions redness nor describes any methodology for assessing redness or redness reduction in its patient population. A POSA would not have understood Walters 1991 as describing or suggesting a method of reducing redness.

281. In my view, the closest prior art for comparison against the claimed invention would have been the prior art commercial redness relievers, that is, tetrahydrozoline, naphazoline, and oxymetazoline. They have been around for decades and, in various brands (e.g., Visine® product lines, Clear Eyes®, Opti-Clear®, Ocu-Clear®), they were market leaders. Because they were either α_1 or mixed α_1/α_2 agonists, they had a high α_1 effect and would have been expected to impart the greatest ocular vasoconstriction to reduce eye redness. EX-1016 (Griffith 2003) at 12-13. They were the standard of redness reduction that all new redness relievers would have to be compared against. Showing superior redness reduction to these market leaders would be an objective indication of a new redness reducer's inventiveness, as well as its material and significant contribution to the art of ophthalmic decongestants as a whole.

b. The expectation of brimonidine compared to the closest prior art

282. The prior art taught that brimonidine was a highly selective α_2 agonist with minimal α_1 effect. EX-1035 (Burke 1996) at 2, Fig. 1 (potency ratio of α_2 to α_1 of 1812:1); EX-1023 (Scruggs 2000) at 5 (stating that "brimonidine is almost 1000-fold more selective for the α_2 than the α_1"). As such, brimonidine would not have been expected to produce effective reduction of ocular redness, particularly at low concentrations where its slight α_1 effect would be even further minimized. EX-1018 (Robin 1998) at 2 ("The degree of selectivity is only important if tissue concentrations are within the range required for α_1 activity. If tissue or circulating levels of drug are insufficient to produce α_2 effects, then α_1 effects are highly improbable."). This expectation was consistent with the concentration dependency established in prior art clinical studies for brimonidine, showing that as its concentration decreased, so too did its blanching effect, essentially disappearing at concentrations of 0.15% and 0.1%. EX-2012 (Alphagan® Label 2001) at 4; EX-1031 (Alphagan NDA) at 109; EX-2014 (Alphagan P® Label 2005) at 4. If anything, given brimonidine's high α_2 selectivity, a skilled person would have expected it to vasodilate and cause eye redness, not reduce it. EX-1031 (Alphagan NDA) at 52, 86, 109.

c. Low-concentration brimonidine, as claimed, was unexpectedly better than tetrahydrozoline in reducing eye redness

283. Example 1 of the ’742 patent is a clinical study that compared the efficacy of low-concentration brimonidine against tetrahydrozoline 0.05% HCL (VISINE Original®), the well-known prior art redness reliever commercially marketed for decades. *See* EX-1001 (’742 patent) at 19:65-20:8. Figure 4A below illustrates the baseline redness in a patient before any treatment in this study. *Id.* at 20:5.

Fig 4a: pretreatment baseline – contact lens irritation and allergic reaction

FIG. 4A

Id. at Fig. 4A. The patient was then given 0.05% tetrahydrozoline in the right eye (shown as “OD” on the left side of the figure) and 0.01% brimonidine in the left eye (shown as “OS” on the right side of the figure). *Id*. at 20:6-8. Brimonidine, which has a significantly lower affinity for α_1 receptors than tetrahydrozoline, recognized in the art as a selective α_1 agonist,[11] would have been expected to have a weaker α_1-

[11] EX-1016 (Griffith 2003) at 13 (“The imidazolines naphazoline . . . , oxymetazoline . . . , [and] tetrahyd[r]ozoline . . . are all selective α_1 agonists . . . .”). With an α_2:α_1 affinity ratio of at least ~1000:1, brimonidine’s affinity for α_1 over α_2

mediated vasoconstrictive effect and produce less whitening or blanching of the ocular surface than tetrahydrozoline.

Fig 4b: Tetrahydrozoline 0.05% OD Brimonidine 0.01% OS

+/- ++□2

Id. at Fig. 4B.

284. As illustrated in Figure 4B, 0.01% brimonidine quite unexpectedly reduced eye redness visually much better than 0.05% tetrahydrozoline, even after 180 minutes after the drops had been administered. *Id.*

285. In another clinical study described in Example 4 of the ’742 patent, a comparison was made between the efficacy of VISINE Original® (tetrahydrozoline) and 0.018% brimonidine in fifteen patients, who were administered VISINE Original® in one eye and brimonidine in the other eye. *Id*. at 21:18-23. After a single application, 0.018% brimonidine showed 68.71% reduction in redness score compared to VISINE Original®, which only showed 31.06% reduction in redness

would be at most 1/1000 =0.001 (i.e., the inverse of its α_2:α_1 ratio); EX-1035 (Burke 1996) at Fig. 1. Thus, tetrahydrozoline’s affinity for α_1 is clearly many times greater than brimonidine.

score. *See id.* at 21:20-33. Thus, brimonidine unexpectedly produced more than twice the amount of reduction of redness than tetrahydrozoline.

d. Low-concentration brimonidine, as claimed, was unexpectedly better than naphazoline in reducing eye redness

286. The unexpected superior efficacy of low-concentration brimonidine against naphazoline—another well-known prior art redness reliever that has long been on the commercial market—was also demonstrated in the '742 patent. In Example 2 of the '742 patent Naphcon-A® (containing naphazoline HCL 0.25%) and 0.02% brimonidine were administered to two groups of patients receiving LASIK surgery and graded post-operative ("post-op") hyperemia using a scale of 1+ hyperemia, 2+ hyperemia, 2.5+ hyperemia, and 3+ hyperemia. *Id*. at 20:39-46, 20:54-60. Brimonidine's affinity for α_1-receptors is ~500 times lower than naphazoline, leading a POSA to have expected it to be much less potent in reducing redness than naphazoline.[12] Surprisingly, however, brimonidine performed far better

[12] Naphazoline has an $\alpha_1$receptor affinity of about 0.5. *See* EX-2187 (Ruffolo 1984) at Fig. 2. In Fig. 2's graph "a" on the left side, increasing levels of α_1-receptor's relative selectivity over α_2 are illustrated by ascending values on the y-axis (from 0.01 at the bottom of the axis to 100 at the top of the axis). Based on

than naphazoline. While 65% of the naphazoline-treated patients showed 2+ or higher post-operative ("post-op") hyperemia (i.e., including 2+ hyperemia, 2.5+ hyperemia, and 3+ hyperemia), 75% of the brimonidine-treated patients showed 1+ or less and only 25% showed 2+ or higher hyperemia post-op. *See id.* at 20:39-46, 20:54-60.

e. Low-concentration brimonidine, as claimed, is unexpectedly better than oxymetazoline in reducing eye redness

287. [redacted] EX-2166 (NDA clinical study No. 10-100-0008) at 1. Oxymetazoline HCL 0.025% (Visine® L.R.) has been an FDA-approved redness reliever for over three decades. Oxymetazoline is a mixed α_1/α_2 agonist. *See* EX-2187 (Ruffolo 1984) at Fig. 2. Its affinity for α_1 receptors is 200 times greater than brimonidine.[13]

Fig. 2a, naphazoline has an ~0.5 α_1:α_2 affinity. Thus, naphazoline's α_1 affinity is at least 500 times (i.e., 0.5/0.001=500) greater than brimonidine.

[13] Oxymetazoline has an $\alpha_1$receptor affinity of about 0.2. *See* EX-2187 (Ruffolo 1984) at Fig. 2a. Thus, oxymetazoline's α_1 affinity is at least 200 times (i.e., 0.2/0.001=200) greater than brimonidine.

i. Description of the clinical study

288. [redacted] EX-2166 (NDA clinical study No. 10-100-0008) at 5, 20. [redacted]

289. [redacted]

290. Given that oxymetazoline has an affinity for α_1 receptors that is 200 times greater than brimonidine, oxymetazoline would have been expected to produce a much greater amount of redness reduction than brimonidine. Surprisingly, however, the study showed that

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302. From the perspective of a POSA, the compilation of these representative results from the above clinical studies of low-concentration brimonidine compared to tetrahydrozoline, naphazoline, and oxymetazoline constitute strong objective evidence of nonobviousness commensurate with the claimed invention as whole. The unexpectedly superior redness relief exhibited by brimonidine over these commercial vasoconstrictors also debunks Dr. Laskar's oversimplified view of the art that just because compounds are labelled as vasoconstrictors and are 2-imidazolines, they would be expected to exhibit comparable redness reduction. EX-1003, ¶¶32-36.

ii. The cascade of real-world benefits attributable to use of low-concentration brimonidine claimed in the '742 patent

303. The unexpected superiority of low-concentration brimonidine in reduction of ocular redness also led to a cascade of real-world benefits for users of Lumify®, whose use in reducing eye redness is an embodiment of the '742 patent's invention. In several clinical studies, brimonidine demonstrated multiple advantageous properties, which prior art ocular commercial vasoconstrictors do not possess, including rapidity of action, duration of action, and lack of rebound hyperemia with no significant tachyphylaxis.

iii. Lumify®'s rapid onset of action and significantly longer duration of action

304. Prior art ocular vasoconstrictors, such as tetrahydrozoline, naphazoline, and oxymetazoline, touted redness relief lasting up to 6 hours. *See, e.g.*, EX-2194 (VISINE Original® Label); EX-2192 (Naphcon-A® label); EX-2193 (Visine® L.R. Label) at 3. Given brimonidine's significantly weaker α_1 selectivity, a POSA would have expected it to be less efficacious and have a shorter duration of action than these prior art ocular decongestants. [redacted] EX-2168 (NDA clinical study No. 13-100-0005) at 6-7, Table 11-6. Thus, it was not only surprising that brimonidine steadily outlasted prior art redness relievers, but to do so by over 30% (6 versus 8 hours) is a significant and unexpected benefit for users.

305. In addition to the superior duration of action, low-concentration brimonidine also exhibited a rapid onset of redness reduction. [redacted]. EX-2168 (NDA clinical study No. 13-100-0005) at 2, Table 11-4, and at 4-5, Table 11-5.

306. In fact, the FDA, after independently reviewing the data from this clinical study, recognized the "pivotal" nature of the study in contributing to the

basis of approval for 0.025% brimonidine and provided positive affirmation of 0.025% brimonidine's rapidity and duration of action, stating that "the sponsor's efficacy studies supported a statement regarding the onset of action ('works in 1 minute') and duration of action ('lasts up to 8 hrs')." EX-2066 (Lumify NDA Summary Overview) at 22-23. As a result, Lumify®'s label now states that it works within one minute and last up to eight hours. *See* EX-2191 (Lumify® Label) at 2.

iv. Lumify® lacks rebound hyperemia and tachyphylaxis

307. As explained above, naphazoline, tetrahydrozoline, and possibly oxymetazoline, have been known to cause rebound hyperemia and tachyphylaxis, which can unwittingly result in overuse and lead ocular toxicity and eventually medicamentosa. *See supra* Section VI.D-E.

308. Surprisingly, however, Lumify® has been proven in clinical studies not to cause rebound hyperemia in patients. The phenomenon of rebound hyperemia is characterized by a worsening amount of ocular redness beyond the baseline level after initiating the ophthalmic drop, which is commonly associated with usage of prior art ocular decongestants. *See* EX-2182 (Soparkar) at 4-5; EX-2183 (Spector) at 2-3. Surprisingly, however, a clinical study demonstrated that brimonidine does not produce rebound hyperemia. EX-2167 (NDA clinical study No. 11-100-0015) at 2, Table 25. In the study, even though the instillation of brimonidine 0.025% was discontinued for 7 days in between two clinical visits, the amount of ocular redness

did not exceed the baseline redness measured prior to these visits, thereby demonstrating that Lumify® had no rebound hyperemia. *Id*.

309. Clinical studies also proved that brimonidine unexpectedly did not cause significant tachyphylaxis. [redacted] EX-2168 (NDA clinical study No. 13-100-0005) at 4-5, Table 11-5. [redacted] *Id*. at 3. [redacted] *Id*. at 4-5, Table 11-5.

310. The prior art commercial vasoconstrictors, e.g., naphazoline, tetrahydrozoline, and possibly oxymetazoline, have been known to cause rebound hyperemia and tachyphylaxis. EX-1009 (Federal Register 1988) at 10; EX-2182 (Soparkar) at 4-5; EX-2183 (Spector) at 2-3; EX-2184 (Stafford-Smith) at 2; EX-2162 (Sher Dep. Tr.) at 104:2-21. For users of OTC redness relievers, this is a serious problem. As discussed, with rebound hyperemia, the eye becomes redder than before. This can lead consumers to use either more drops per instillation or more frequent instillations. When this happens, the body downregulates the number of available α_1 receptors. Unbeknownst to the users, this causes a rapid increase in

tolerance to the drug. They consequently continue their overuse, leading to ocular toxicity and potentially to medicamentosa. Advantageously, these clinical trial results established that Lumify® lacks rebound hyperemia and no significant tachyphylaxis, benefiting users and leading many clinicians like me to recommend its use over the other leading redness relievers.

311. The FDA agrees. The team leader at the FDA responsible for recommending approval of Lumify®, having considered the clinical studies, agreed that Lumify® did not show rebound hyperemia or tachyphylaxis and recognized the lack of those side effects as an advantage to OTC consumers:

> Brimonidine tartrate ophthalmic solution 0.025% ***did not show tachyphylaxis or rebound congestion*** in clinical trials. The absence of tachyphylaxis or rebound congestion with an OTC ophthalmic vasoconstrictor to relieve redness of the eye is a ***potential advantage for the OTC consumer***.

EX-2066 (Lumify NDA Summary Overview) at 3 (emphases added).

v. The '742 patented method's unexpected superiority to 0.2% brimonidine

312. As stated above, it is my opinion, with which Dr. Laskar agrees, that 0.2% brimonidine is not the closest prior art. [14] In any event, lowering brimonidine's

[14] Nor is 0.1% brimonidine the closest art, with which Dr. Laskar also agrees. The prior art neither taught nor suggested using 0.1% brimonidine to reduce eye redness arising from an ocular condition.

condition would not have been expected to produce effective reduction of ocular redness, especially at low concentrations as embodied by Lumify®, where its slight α_1 effect would be even further minimized. EX-1018 (Robin 1998) at 2. [redacted] EX-2166 (NDA clinical study 10-100-0008) at 25-29. Additionally, Lumify® exhibited no significant rebound hyperemia or tachyphylaxis. *See* EX-2167 (NDA clinical study No. 11-100-0015) at 2, Table 25. By contrast, 0.2% brimonidine was beset by a high occurrence of ocular hyperemia (around 30%) and ocular allergic reactions (about 13%). *See* EX-1031 (Alphagan NDA) at 109.

3. Lumify®—the commercial embodiment of the patented invention—enjoyed significant industry praise

Lumify® is the first and only OTC eye drop developed with low-concentration brimonidine tartrate for the treatment of ocular redness due to minor eye irritation. EX-2165 (Bausch Press Release) at 1. Its unique and patented formulation, which contains low-concentration brimonidine (0.025%), has yielded an efficacy and safety profile for Lumify® that far exceeds that of other redness relievers on the market (e.g., Clear Eyes®, Visine®, and Rohto®). Lumify® not only reduces redness unexpectedly better than these other commercial products, but it has a rapid onset of action (one minute) that lasts up to eight hours, exceeding the other redness relievers (six hours) by over 30%. That is not all. Lumify®'s use of low-concentration

brimonidine surprisingly and advantageously lacks rebound hyperemia and has no significant tachyphylaxis. This is especially important for OTC products subject to potential misuse through overuse, for it could avoid ocular toxicity that could lead to medicamentosa.

313. But I am not alone in my views of Lumify®— the #1 eye-doctor recommended redness reliever on the market. Other medical practitioners have praised Lumify®'s performance, similarly recognizing its efficacy in reducing eye redness without side effects that were commonly seen in prior art redness relievers. Dr. Paul Karpecki noted that "[p]atients with eye redness and irritation can experience negative social connotations, which may impact daily life," and "[h]aving a drop that reduces redness without the side effects of rebound hyperemia or tachyphylaxis . . . is a very exciting option that I look forward to recommending to my patients." EX-2163 (The Science of Lumify) at 9; EX-2165 (Bausch Press Release) at 1. As another example, Dr. Melissa Toyos explained that "[f]or all of my patients who have occasional eye redness, I always recommend LUMIFY. They're amazed at how well it works . . . . My patients are happy, so I'm happy." EX-2163 (The Science of Lumify) at 2. Dr. Toyos further stated that "Lumify redness reliever drops specifically reduce redness due to minor eye irritations while reducing concerns of rebound hyperemia, dependency or tachyphylaxis--conditions that can lead to serious or permanent damages to the eye. I am excited to recommend Lumify

to my patients to effectively relieve redness . . . ." *Id.* at 5. Even after Lumify® obtained FDA approval, people remained skeptical that it could deliver the promised results, but after using Lumify®, they were shocked to find that it delivered the promised results. *See, e.g.*, EX-2164 (Lumify Lovers) at 1.

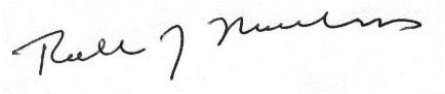
314. In my opinion, these praises coming directly from eye care professionals is unusual for a redness reliever. I understand that Mr. Ferris will explain how eye care professionals were hesitant to recommend any eye redness relievers because they were known to cause undesirable side effects, such as rebound hyperemia and tachyphylaxis. Lumify® changed that. As the testimonials from the eye doctors confirm, eye care professionals recommend Lumify® to patients without worrying about the undesirable side effects of the prior art redness relievers. *See* EX-2199 (Enhancing the Management of Red Eye). Indeed, I have recommended Lumify® to my patients before I began consulting for this case.

315. Even the FDA, the gatekeeper of safe and efficacious drugs for U.S. consumers, and whom Dr. Laskar noted is "especially careful about the chemicals it would approve for use in topical eye drops" (EX-1003, ¶40), recognized that Lumify®'s brimonidine tartrate ophthalmic solution 0.025% "did not show tachyphylaxis or rebound congestion," and the "absence of tachyphylaxis or rebound congestion with an OTC ophthalmic vasoconstrictor to relieve redness of the eye is

a potential advantage for the OTC consumer." EX-2066 (Lumify NDA Summary Overview) at 3.

316. In addition, Lumify®'s ability to efficaciously reduce eye redness with little or no rebound hyperemia has further unforeseen advantages for glaucoma patients. Various glaucoma medications can cause eye redness. For glaucoma patients, that could become a potential serious problem if it causes them to not regularly take their medication. Noncompliance puts them on a slippery slope toward blindness. By so effectively reducing redness without rebound hyperemia, Lumify® can advantageously foster compliance and reduce the risk of patients experiencing permanent vision loss.

317. I declare under the penalty of perjury that the foregoing is true and correct.



Dated: August 24, 2022 By: _____

Robert J. Noecker, MD, MBA

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Appendix A

CURRICULUM VITAE
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EDUCATION

9/82-6/85	**B.S.**	Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts
9/82-6/86	**B.S.**	Materials Science and Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts
9/82-6/86	**B.S.**	Humanities and Engineering (Literature), Massachusetts Institute of Technology, Cambridge, Massachusetts
8/86-5/90	**M.D.**	University of North Carolina School of Medicine, Chapel Hill, North Carolina
8/98-8/2000	**M.B.A.**	University of Arizona, Eller School of Management, Tucson, Arizona

POSTDOCTORAL

Internship and Residency

7/90-6/91	**Intern in Medicine**, Moses H. Cone Memorial Hospital, Greensboro, North Carolina
7/91-6/94	**Resident in Ophthalmology**, University of Arizona, Tucson, Arizona

Fellowship

7/94-6/95	**Clinical Fellow in Ophthalmology** *(Glaucoma),* New England Eye Center, Tufts University School of Medicine, Boston, Massachusetts

LICENSURE & BOARD CERTIFICARON

1992 - 2015	Arizona No. 21029
1993 - 2007	Massachusetts No. 78727
1996 - present	American Board of Ophthalmology
2003 - 2014	Pennsylvania No. MD422990
2011 - present	Connecticut No. 049731
2011 – present	New York No. 261542-1

ACADEMIC APPOINTMENTS

7/94-6/96	**Assistant Professor of Ophthalmology**, Tufts University School of Medicine, Boston, MA
7/96-6/02	**Assistant Professor of Ophthalmology,** University of Arizona School of Medicine, Tucson, Arizona
7/98-6/03	**Residency Director,** University of Arizona School of Medicine, Tucson, Arizona
7/98-12/03	**Faculty Member,** Biomedical Engineering Interdisciplinary Program, University of Arizona Graduate College, Tucson, Arizona
7/02-12/03	**Associate Professor of Ophthalmology,** University of Arizona School of Medicine, Tucson, Arizona
7/02-12/03	**Associate Chair for Clinical Activities,** Department of Ophthalmology, University of Arizona School of Medicine, Tucson, Arizona
7/02-12/03	**Associate Residency Director,** University of Arizona School of Medicine, Tucson, Arizona
7/02-12/03	**Associate Clinical Professor of Ophthalmology,** University of Arizona School of Medicine, Tucson, Arizona
1/04-7/07	**Visiting Associate Professor of Ophthalmology,** University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
1/04-06/11	**Vice Chair**, UPMC Eye Center, Department of Ophthalmology, University of Pittsburgh School of Medicine
8/07-06/11	**Associate Professor of Ophthalmology,** University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
2/08-06/11	**Vice Chair of Information Technology**, UPMC Eye Center, Department of Ophthalmology, University of Pittsburgh School of Medicine
2/08-06/11	**Vice Chair of International Affairs**, UPMC Eye Center, Department of Ophthalmology, University of Pittsburgh School of Medicine
8/09-06/11	**Professor of Ophthalmology,** University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania
1/12- present	**Assistant Clinical Professor,** Yale University School of Medicine, New Haven, Connecticut
8/13- present	**Clinical Professor**, Quinnipiac School of Medicine, New Haven, Connecticut

HOSPITAL APPOINTMENTS

7/94-6/96	**Ophthalmologist,** New England Eye Center, New England Medical Center, Boston, MA
7/94-6/96	**Director,** New England Eye Center at St. Elizabeth's Medical Center, Boston, MA
7/94-6/96	**Staff Physician**, Department of Ophthalmology, Veterans Administration Medical Center, Boston, MA
7/94-6/96	**Staff Physician**, St. Elizabeth's Medical Center, Boston, MA
7/96-12/03	**Ophthalmologist**, University Medical Center, Tucson, Arizona
7/96-12/03	**Staff Physician**, Kino Community Hospital, Tucson, Arizona
7/96-12/03	**Staff Physician**, Veterans Administration Medical Center, Tucson, Arizona
7/96-12/03	**Director,** Clinical Studies Unit, Department of Ophthalmology, University of Arizona
7/99-12/03	**Director,** Glaucoma Service, Department of Ophthalmology, University of Arizona
1/04- 06/11	**Director,** Glaucoma Service, UPMC Eye Center, Department of Ophthalmology, University of Pittsburgh School of Medicine
4/05-6/11	**Staff Physician**, Department of Surgery, Division of Ophthalmology, VA Pittsburgh Healthcare System
7/07-06/11	**Assistant Medical Director**, eRecord Physician Advisory Council, University of Pittsburgh Medical Center
7/11-present	**Staff Physician**, St. Vincent's Medical Center, Bridgeport, Connecticut
3/12-present	**Staff Physician**, Veterans Administration Medical Center, West Haven, Connecticut
4/14-present	**Staff Physician**, Hartford Hospital, Hartford, Connecticut

HOSPITAL/DEPARTMENT COMMITTEES

1997-2004	University Medical Center; OR Committee
1997-2004	University Medical Center; Laser Safety Committee
1999-2004	University Medical Center; Hours of Operation Team of the Perioperative Process Improvement Project
1999-2004	Ophthalmology Department; Facilities Steering Committee
1999-2004	University Physicians Ambulatory Surgery Center Management Committee
2004-2011	UPMC Ophthalmology Surgical Purchasing Committee
2004-2011	UPMC Technology Committee
2004-2011	UPMC Operating Room Committee
2004-2011	UPMC Eye Center Residency Committee
2004-2011	UPMC Ophthalmology Surgical Purchasing Committee
2004-2011	UPMC Eye Center Operations Committee
2005-2011	UPMC Eye Center eRecord Committee
2006-2011	UPMC eRecord Physician Advisory Council
2007-2011	UPMC Ophthalmology Commodity Management and VAT Chair
2012-2017	Quality Committee, St Vincent's PHO

ACADEMIC ACTIVITIES

1997-2004 Preceptor, College of Medicine, Longitudinal Clinical Curriculum
1997-2004 Preceptor, College of Medicine, Preparation for Clinical Medicine
1997-2004 Evaluator, College of Medicine, Preparation for Clinical Medicine
1997-2004 Interviewer, College of Medicine, Admissions
1997-2004 Clinical Advisor, College of Medicine, Third-Year Medical Students
1998-2004 Sponsor, Honors College, Undergraduate Research Grant Program
1999-2004 Grader, University Composition Board, Upper-Division Writing Proficiency Exam
2004-2011 Research Preceptor, University of Pittsburgh School of Medicine
2012-present Research Preceptor, Yale University School of Medicine
2012-present Clinical Preceptor, Yale University School of Medicine
2011-present Clinical Preceptor, St. Vincent's Hospital
2014-present Clinical Preceptor, Frank Netter School of Medicine, Quinnipiac University

AWARDS & RECOGNITION

1994 Resident of the Year, Department of Ophthalmology, University of Arizona
1997 American Medical Association; Physician's Recognition Award in Continuing Medical Education
2000 Best Surgical Instructor, Department of Ophthalmology, University of Arizona
2001 The Joint Commission on Allied Health Personnel in Ophthalmology, Faculty Award for Five Years of Distinguished Service
2002 The American Academy of Ophthalmology, Achievement Award for Distinguished Service
2004 Selection to Best Doctors of Tucson
2004 Best Doctors in America
2005 Who's Who in America 2005
2005 Best Doctors in America
2006 America's Top Ophthalmologists, Consumers' Research Council of America
2006 James R. Carl, MD Clinical Instructor of the Year Award
2006 Best Doctors in America
2006 Nursing and Allied Health Program of the Hawaiian Eye 2006 Meeting Award of Excellence
2007 Best Doctors in America
2007 UPMC's Award for Commitment and Excellence in Service (ACES)
2007 James R. Carl, MD Clinical Instructor of the Year Award
2008 Best Doctors in America
2008 James R. Carl, MD Clinical Instructor of the Year
2009 America's Top Ophthalmologists
2009 Best Doctors in America
2010 Best Doctors in America
2011 Best Doctors in America
2011 Best Doctors in Pittsburgh
2011 Best Glaucoma Lecture, Royal Hawaiin Eye Meeting
2012 Best Doctors in America
2012 INFORMS 2012 Case Competition Second Place Winner

2013 Best Doctors in America
2013 American Academy of Ophthalmology Senior Achievement Award
2014 Best Doctors in America
2014 Clinical Instructor of the Year, Yale University Department of Ophthalmoogy
2015 Best Doctors in America
2015 Connecticut Best Doctors
2016 Top 100 Professionals
2016 Best Doctors in America
2017 Leading Physicians of the World
2017 Best Doctors in America
2017 Castle and Connelly Top Doctors
2018 Best Doctors in America
2018 Red Book of Ophthalmologists
2018 Castle and Connelly Top Doctors
2018 3rd place SLAG poster presentation
2019 Best Doctors in America
2019 Castle and Connelly Top Doctors
2020 Best Doctors in America
2020 Castle and Connelly Top Doctors in New York
2021 Best Doctors in America
2021 Castle and Connelly Top Doctors
2022 Best Doctors in America
2022 Castle and Connelly Top Doctors in Connecticut
2022 America's Most Honored Doctors

MEMBERSHIPS IN PROFESSIONAL SOLICITES

1986 Member, American Medical Association
1989 Member, Association for Research in Vision and Ophthalmology
1991 Fellow, American Academy of Ophthalmology
1991 Member, Arizona Ophthalmological Society
1991 Member, Tucson Ophthalmological Society
1992 Member, American Society for Cataract and Refractive Surgery
1993 Member, SPIE- International Society for Optical Engineering
1994 Member, Massachusetts Medical Society
1996 Member, Pima County Medical Society
1996 Member, Chandler Grant Glaucoma Society
1998 Member, Research to Prevent Blindness
1998 Associate Member, Association of University Professors in Ophthalmology
2000 Active Member, American Glaucoma Society
2005 Member, Pittsburgh Ophthalmology Society
2005 Member, PAO Pennsylvania Academy of Ophthalmology
2006 Member, Allegheny County Medical Society
2011 Member, New York Glaucoma Society

2011 Member, Connecticut Glaucoma Society
2011 Member, Connecticut Society for Eye Physicians
2020 Co-Chair, Connecticut Glaucoma Society
2021 Acting President, Connecticut Glaucoma Society

PROFESSIONAL ORGANIZATION COMMITTEES

2005-2006	American Glaucoma Society Finance Committee
2012-2016	American Glaucoma Society Practice Management Subcommittee
2013-2017	American Glaucoma Society Finance Committee
2014-2019	New England Ophthalmology Society Program Committee
2014-present	New England Ophthalmology Society Foundation Committee
2017- present	ASCRS Glaucoma Program Committee
2021-present	American Academy of Ophthalmology, Glaucoma Program Committee

JOURNALS - CONTRIBUTING EDITOR

1998- present Review of Ophthalmology
2000- present Ophthalmology Management
2003- present Glaucoma Todas
*2009- present eyetube Ophthalmic Video Resource (*http://eyetube.net/channels/glaucoma/*)*
2009- present Case Reports in Medicine
2009-present Refractive Eyecare
2009- present Advanced Ocular Cari
2006-2012 Young Ophthalmologist
2017-present Eye World Editorial Board
2017-present Glaucoma Physician

JOURNALS - PEER-REVIEWER

American Journal of Ophthalmology
Archives of Ophthalmology
Ophthalmic Surgery and Losers
Ophthalmology
Investigative Ophthalmology and Visual Science
British Journal of Ophthalmology
Journal of Glaucoma
Journal of Cataract and Refractive Surgery
Journal of Anestesia
Journal of Ocular Pharmacology & Therapeutics
European Journal of Ophthalmology
Clinical Ophthalmology
Graefe's Ophthalmology

COMMUNITY SERVICE

1996-2004 Volunteer, Arizona Mobile Eye Unit

1996-2004 Volunteer, Lions Surgery Mission, Nogales, Arizona
2005-2011 Volunteer, Friends of the Congressional Glaucoma Caucus Foundation Screenings
2008-2011 EyeCare America (ECA) Glaucoma EyeCare Program

TELEVISION/NEWSPAPER/RADIO

Ocular Sports Injuries, KOLD-TV, Tucson, AZ, November 11, 1996.
Glaucoma, KOLD-TV, Tucson, AZ, January 20, 1997.
Glaucoma Therapy, Discovery Health, May, 2003
SLT, Feature Segment on Healthcast, WTAE-TV, Pittsburgh, PA, December 10, 2004
Doctors get updated training in diagnosing vision-robbing glaucoma: To catch a thief, Pittsburgh Post Gazette, Pittsburgh, PA June 15, 2005
Glaucoma and update on eye health, March 15, 2008 KDKA, Pittsburgh, PA
25 Things your eye doctor won't tell you. Readers Digest, July 2011
New Glaucoma Clinical Trials, CBS, Channel 8, New Haven, CT January 16, 2012
New Glaucoma Therapies, Selective Laser Trabeculoplasty. TC and Kristen Show, January 20, 2012
Glaucoma Awareness and New Therapies, WTIC CBS Radio, January 25, 2012
New Glaucoma Surgical Therapy, WTNH, September 28, 2012
Intense Pulsed Light Therapy for Ocular Surface Disease, August 5, 2012
Glaucoma Awareness and New Therapies, WTIC CBS Radio, October 25, 2012
Intense pulsed light for treatment of ocular surface disease, Connecticut 12 on Health, Norwalk, CT, January 31, 2013.

ELECTRONIC MEDIA

Noecker RJ, Patterson E. Primary open angle glaucoma. In: *E-medicine online textbook*, 1999.
Noecker RJ, Patterson E. Angle closure glaucoma. In: *E-medicine online textbook*, 1999.
Noecker RJ Medtronic *AAO ECP Course Video Email, 2004*.
Noecker RJ Glaucoma Medication, Effect of Glaucoma Therapy on the Ocular Surcase In: *Audio-Digest Ophthalmology* Vol 44 Issue 01 iSSN 0271-1281 January 2006
Noecker RJ Glaucoma Topics, When Is It Time to Refer Your Patient? In: *Audio-Digest Ophthalmology* Vol 45 Issue 23 ISSN 0271-1281 October 2007
Update on Glaucoma: Roundtable Discussion Series. Updateonglaucoma.com 2007
Do computer glasses really work? http://lifehacker.com/5980509/do-computer-glasses-really-work?popular=true January 31, 2013.

TEACHING EXPERIENCE

COURSES AND LECTORES

1997 **Course Director**, "*Glaucoma I: Review of Glaucoma and Tonometry for Ophthalmic Technicians,"* Accredited by the Joint Commission on Allied Health Personnel in

Ophthalmology (JCAHPO). Tucson, AZ, January 18, 1997.
Instructor, Glaucoma course for primary care physicians, Davis Monthan Air Force Base, Tucson, AZ, February 18, 1997.
Instructor, *"Glaucoma Medications,"* University of Arizona College of Pharmacy, Tucson, AZ, March 3 & 5, 1997.
Course Director, *"Introduction to First Assisting in Cataract Surgery,"* Accredited by the Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO). Tucson, AZ, March 21-23, 1997.
Course Faculty, Glaucoma Course, Southern California College of Optometry Continuing Education Course, Flagstaff, AZ, April 16, 1997.
Course Director, *"Retina I: Review of Macular Degeneration, Diabetic Retinopathy and Fundus Photography for Ophthalmic Technicians,"* Accredited by the Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO), Tucson, AZ, April 19, 1997.
Course Director, *"Refractometry and Retinoscopy I for Ophthalmic Technicians,"* Accredited by the Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO), Tucson, AZ,
July 19, 1997.
Course Faculty, *"Selective Laser Trabeculoplasty,"* Nantucket Glaucoma '97, Nantucket, MA, August 15, 1997.
Instructor, *"General Examination/Tonometry,"* University of Arizona College of Medicine, Ophthalmology Practicum, August 20 & 27, 1997.
Instructor, *"Surgical Pharmacology,"* Annual Meeting of the Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO), San Francisco, CA, October 28, 1997.
Course Faculty, *"Ocular Infectious Disease,"* Arizona Optometric Association, Flagstaff, AZ, November 9, 1997.
Course Director, *"Ocular Infectious Disease for Ophthalmic Technicians and Opticians,"* Accredited by the Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO) and the American Board of Optometry, Tucson, AZ, November 22, 1997.

1998 **Guest Speaker**, *"Recent Trends in Glaucoma Therapy,"* Reno Ophthalmological Society, Reno, NV, February 19, 1998.
Course Faculty, *"Recent Advances in the Treatment of Glaucoma,"* 31st Annual Southwestern Clinical Pharmacy Seminar, Tucson, AZ, February 21, 1998.
Instructor, *"Treatment of Glaucoma,"* University of Arizona College of Pharmacy, Tucson, AZ, March 12, 1998.
Instructor, *"Glaucoma Case Review,"* University Medical Center Ambulatory Care Conference, Tucson, AZ, March 16, 1998.
Invited Speaker, "Ocular Effects of Drugs," Tucson Police Department Drug Recognition Program, Tucson, AZ, March 24, 1998.
Course Director, *"Cataract Surgery, Keratometry and Biometry for Ophthalmic Technicians,"* Accredited by the Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO), Tucson, AZ, March 28, 1998.
Course Faculty, *"Use of Anti-Glaucoma Agents in the Perioperative Period.*

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Pharmacology of Cataract and Refractive Surgery," American Society of Cataract and Refractive Surgery 1998 Symposium on Cataract, IOL and Refractive Surgery, San Diego, CA, April 18, 1998.

Co-Instructor, *"Teaching Residents Phacoemulsification Course,"* American Society of Cataract and Refractive Surgery 1998 Symposium on Cataract, IOL and Refractive Surgery, San Diego, CA, April 19, 1998.

Course Director, *"Introduction to Retinoscopy for Ophthalmic Technicians,"* Accredited by the Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO). Tucson, AZ, July 25, 1998.

Course Faculty, *"Ocular Pharmacology I & II, Anterior Segment Trauma and Mock Orals,"* The Osler Institute 29th Ophthalmology Board Review Course, San Francisco, CA, October 15, 1998.

Co-Instructor, *"Transscleral Diode Laser Cyclophotocoagulation,"* 1998 Annual Meeting of the American Academy of Ophthalmology, New Orleans, LA, November 8-9, 1998.

Instructor, *"Surgical Pharmacology,"* The Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO) Annual Continuing Education Program for Ophthalmic Médica Personnel, New Orleans, LA, November 9, 1998.

Instructor, *"Pharmacology of Glaucoma Medications,"* The Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO) Annual Continuing Education Program for Ophthalmic Medical Personnel, New Orleans, LA, November 9, 1998.

Instructor, *"Laser Treatment of Glaucoma,"* The Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO) Annual Continuing Education Program for Ophthalmic Medical Personnel, New Orleans, LA, November 9, 1998.

Invited Lecturer, *"Medical Therapy of Glaucoma,"* The California Hispanic-American Ophthalmology Society, San Diego, CA, November 17, 1998.

1999 **Co-Instructor,** "*Anterior Segment Case Presentations and Discussions,"* University of Wisconsin 1999 Winter Symposium, Tucson, AZ, January 16, 1999.

Invited Speaker, "*Selective Laser Trabeculoplasty,"* The Ophthalmological Society of South Africa, Capetown, South Africa, February 16, 1999.

Instructor, "*Pharmacology of Cataract Surgery,"* University of Arizona College of Pharmacy, Tucson, AZ, March 11, 1999.

Instructor, "*Glaucoma Medications,"* University of Arizona College of Pharmacy, Tucson, AZ, March 11, 1999.

Invited Speaker, "*Diabetic Induced Glaucoma,"* The California Hispanic-American Medical Association, San Diego, CA, April 7, 1999.

Invited Speaker, "*New Trends in Glaucoma Therapy,"* San Antonio Ophthalmologic Society, San Antonio, TX, April 17, 1999.

Invited Speaker, "*Glaucoma Topics and Recent Trends,"* Annual Clinical Assembly of the American Osteopathic Colleges of Ophthalmology and Otolaryngology—Head and Neck Surgery, Orlando, FL, April 24, 1999.

Invited Speaker, "*Glaucoma Challenges,"* New England Eye Center, Tufts University School of Medicine, Boston, MA, May 18, 1999.

Invited Lecturer, *"Case Studies in the Management of Glaucoma Patients,"* Perspectives in Glaucoma CME Course, Phoenix, AZ, June 5, 1999.

Invited Lecturer, *"Glaucoma Management and Case Studies,"* Arizona Optometric Association Spring Congress, Tucson, AZ, July 11, 1999.

Course Director, *"Introduction to Contact Lenses for Ophthalmic Technicians,"* Accredited by the Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO). Tucson, AZ, July 14, 1999.

Invited Speaker, *"Cases in Glaucoma Management,"* Barnett & Dulaney Eye Center, Phoenix, AZ, July 27, 1999.

Visiting Professor, *"Trends in the Medical Management of Glaucoma,"* Grand Rounds Conference, Oxford Ophthalmology Department, Oxford University, Oxford, England, September 6, 1999.

Co-Instructor, "*Cyclodestruction: The State of the Art,"* 1999 Annual Meeting of the American Academy of Ophthalmology, Orlando, FL, October 24, 1999.

Instructor, *"Laser Treatment of Glaucoma,"* Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO) Annual Continuing Education Program for Ophthalmic Medical Personnel, Orlando, FL, October 24, 1999.

Instructor, "*The Stressless Transition to Topical Clear Cornea Phacoemulsification for Residents and Accomplished Surgeons,"* 1999 Annual Meeting of the American Academy of Ophthalmology, Orlando, FL, October 26, 1999.

2000 **Co-Instructor,** *"Glaucoma Cases,"* University of Wisconsin Mid-Winter CME Symposium, Tucson, AZ, January 15, 2000.

Course Faculty, *"Treatment Goals and Adjunctive Therapy; Current Glaucoma Practice,"* Ocular Drug and Surgical Therapy Update CME Meeting, Laguna Niguel, CA, March 4, 2000.

Visiting Professor, *"Difficult Glaucomas,"* Stanford University Ophthalmology Grand Rounds, Palo Alto, CA, March 6 & 7, 2000.

Instructor, *"Pharmacology of Glaucoma,"* University of Arizona College of Pharmacy, Tucson, AZ, March 9, 2000.

Invited Speaker, *"Re-Thinking Our 1st Line Medical Therapy" and "Difficult Glaucomas,"* Capital Eye Symposium, Washington, DC, April 1, 2000.

Course Faculty, *"A Neuroprotective Therapeutic Paradigm for Vision Sparing in Glaucoma,"* Glaucoma 2000: Evolving Medical Therapy for a Multifactorial Disease, Annenberg Center CME Program, April 11, 2000 and June 7, 2000.

Invited Speaker, *"Current Glaucoma Practice: Treatment Goals and Patterns,"* American Optometric Association 103rd Annual Congress, June 21, 2000.

Invited Speaker, *"Ocular Manifestations in Parkinson's Disease,"* American Parkinson Disease Association, Green Valley Parkinson's support group, Green Valley, AZ, September 1, 2000.

Instructor, *"Laser Treatment of Glaucoma,"* Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO) Annual Continuing Education Program for Ophthalmic Medical Personnel, Dallas, TX, October 24, 2000.

Co-Instructor, *"Cyclodestruction: The State of the Art*," American Academy of Ophthalmology Annual Meeting, Dallas, TX, October 24, 2000.
Instructor, *"The Stressless Transition to Topical Clear Cornea Phacoemulsification for Residents and Accomplished Surgeons,"* American Academy of Ophthalmology Annual Meeting, Dallas, TX, October 25, 2000.
Course Faculty, *"A Neuroprotective Therapeutic Paradigm for Vision Sparing in Glaucoma,"* Glaucoma 2000: Evolving Medical Therapy for a Multifactorial Disease, Annenberg Center CME Program, Charlotte, NC, November 2, 2000.

2001 **Instructor,** *"Glaucoma Cases,"* University Medical Center Ambulatory Care Conference, Tucson, AZ, January 9, 2001.
Invited Speaker, *"New trends in the Treatment of Glaucoma,"* Southern Arizona Optometric Society Meeting, Tucson, AZ, January 9, 2001.
Invited Lecturer, *"Treatment of Glaucoma,"* National Clinical Consulting Meeting, Scottsdale, AZ, February 21, 2001.
Course Faculty, *"Neuroprotection: Connecting Research to Real Practice,"* Ocular Surgery News CME Symposium, Houston, TX, February 22, 2001.
Course Faculty, *"Neuroprotection: Connecting Research to Real Practice,"* Ocular Surgery News CME Symposium, Orlando, FL, March 8, 2001.
Invited Lecturer, *"Evaluation of brimonidine use in elderly patients previously on chronic, non-selective beta blocker therapy for glaucoma,"* The 3rd International Glaucoma Symposium I.G.S., Prague, Czech Republic, March 25, 2001.
Course Faculty, *"Neuroprotection: Connecting Research to Real Practice,"* Ocular Surgery News CME Symposium, San Francisco, CA, April 5, 2001.
Instructor, *"Don't Worry…Go Topical: Transition to Topical Clear Cornea Phacoemulsification,"* American Society of Cataract and Refractive Surgery 2001 Symposium on Cataract, IOL and Refractive Surgery, San Diego, CA, April 29, 2001.
Invited Lecturer, *"Treatment of Glaucoma,"* National Clinical Consulting Meeting, Scottsdale, AZ, August 23, 2001.
Course Faculty, *"Neuroprotection: Connecting Research to Real Practice,"* Ocular Surgery News CME Symposium, Seattle, WA, November 1, 2001.
Instructor, "Lasers in Glaucoma," 105th Annual Meeting of the American Academy of Ophthalmology, New Orleans, LA, November 11, 2001.
Instructor, *"Alternative/Adjunctive Therapies for Glaucoma,"* 105th Annual Meeting of the American Academy of Ophthalmology, New Orleans, LA, November 14, 2001.
Instructor, *"Laser Treatment of Glaucoma,"* Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO) Annual Continuing Education Program for Ophthalmic Medical Personnel, New Orleans, LA, November 14, 2001.

2002 **Guest Speaker,** Current Concepts in Glaucoma Therapy Meeting, El Paso, TX, January 10, 2002.
Course Faculty, *"Effect of Preservatives in Chronic Therapy,"* Slack Incorporated Hawaii 2002 Physicians Program, Waikoloa, HI, January 23, 2002.

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Course Faculty, *"Effect of Preservatives in Chronic Therapy,"* 5th Annual Ocular Drug and Surgical Therapy Update Meeting, Dana Point, CA, February 16, 2002.
Invited Lecturer, *"Treatment of Glaucoma,"* National Clinical Consulting Meeting, Scottsdale, AZ, February 28, 2002.
Course Faculty, *"Neuroprotection,"* 3 Targets for Glaucoma Management Symposium, Los Angeles, CA, March 16, 2002.
Invited Lecturer, *"Advances in the Treatment of Glaucoma,"* Delhi Ophthalmic Society Meeting, Delhi, India, April 6, 2002.
Course Faculty, *"Neuroprotection,"* 3 Targets for Glaucoma Management Symposium, Dallas, TX, April 13, 2002.
Course Faculty, *"Neuroprotection,"* 3 Targets for Glaucoma Management Symposium, San Francisco, CA, May 18, 2002.
Instructor, *"Take the Stress Out: State-of-the-Art Cataract Surgery,"* American Society of Cataract and Refractive Surgery 2002 Symposium on Cataract, IOL and Refractive Surgery, Philadelphia, PA, June 4, 2002.
Course Faculty, *"Neuroprotection,"* 3 Targets for Glaucoma Management Symposium, Raleigh, NC, June 8, 2002.
Course Faculty, *"Neuroprotection,"* 3 Targets for Glaucoma Management Symposium, Pittsburgh, PA, June 29, 2002.
Course Faculty, *"Neuroprotection,"* 3 Targets for Glaucoma Management Symposium, Baltimore, MD, September 14, 2002.
Visiting Professor, *"Where Lumigan fits into Common Clinical Practice,"* University of Alberta Department of Ophthalmology Grand Rounds, October 3, 2002.
Course Faculty, *"Neuroprotection,"* 3 Targets for Glaucoma Management Symposium, Detroit, MI, October 12, 2002.
Instructor, *"Laser Treatment of Glaucoma,"* Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO) Annual Continuing Education Program for Ophthalmic Medical Personnel, Orlando, FL, October 19, 2002.
Co-Instructor, *"Lasers in Glaucoma,"* The Joint Meeting of the American Academy of Ophthalmology and the Pan-American Association of Ophthalmology, Orlando, FL, October 20, 2002.
Instructor, *"Alternative/Adjunctive Therapies for Glaucoma,"* The Joint Meeting of the American Academy of Ophthalmology and the Pan-American Association of Ophthalmology, Orlando, FL, October 21, 2002.

2003 **Course Faculty,** *"Ocular Surface Issues in Chronic Glaucoma Therapy,"* 2003 Royal Hawaiian Eye Meeting, Maui, HI, January 22, 2003.
Course Faculty, *"Effects of Preservatives on the Ocular Surface in Chronic Therapy,"* 6th Annual Ocular Drug and Surgical Therapy Update, Dana Point, CA, February 15, 2003.
Course Faculty, *"What is all the Controversy About?"* Simplifying Glaucoma Management CME Conference, Killington, VT, March 1, 2003.
Invited Lecturer, *"A comparison of the IOP-lowering efficacy of bimatoprost and latanoprost in patients stratified by baseline diagnosis: ocular hypertension vs. glaucoma,"*

4th International Glaucoma Symposium-I.G.S., Barcelona, Spain, March 22, 2002.
Instructor, *"Cannabinoids and Other IOP-Lowering Agents,"* 4th International Glaucoma Symposium-I.G.S., Barcelona, Spain, March 22, 2002.
Instructor, "Remove the Stress and Enjoy the Challenge: Taking the Stress Out of State-of-the-Art Cataract Surgery," American Society of Cataract and Refractive Surgery 2003 Symposium on Cataract, IOL and Refractive Surgery, San Francisco, CA, April 14, 2003.
Course Faculty, *"Current Issues in Glaucoma Therapy,"* Mountain West Council of Optometrists 2003 Congress, Las Vegas, NV, May 18, 2003.
Course Faculty, *"Alpha Adrenergic Agonists" and "Anti-Fibrosis Agents,"* First Annual Ocular Surgery News Symposium on Glaucoma, Las Vegas, NV, June 6-7, 2003.
Course Faculty, *"Major Clinical Trials for Glaucoma,"* Arizona Ophthalmological Society Annual Scientific Meeting, Las Vegas, NV, June 7, 2003.
Course Faculty, *"Current Concepts in the Medical Management of Glaucoma,"* Arizona Ophthalmological Society Annual Scientific Meeting, Las Vegas, NV, June 7, 2003.
Instructor, *"Laser Treatment of Glaucoma,"* Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO) Annual Continuing Education Program for Ophthalmic Medical Personnel (Subspecialty Day), Anaheim, CA, November 15, 2003.
Co-Instructor, *"Lasers in Glaucoma,"* The Annual Meeting of the American Academy of Ophthalmology, Anaheim, CA, November 16, 2003.
Co-Instructor, *"Alternative/Adjunctive Therapies for Glaucoma,"* The Annual Meeting of the American Academy of Ophthalmology, Anaheim, CA, November 18, 2003.
Invited Lecturer, *"Cataract Surgery in the Glaucoma Patient: Anticipation and Preparation,"* New England Ophthalmological Society Meeting, Boston, MA, December 12, 2003.

2004 **Course Faculty,** *"Alternative Therapy for Glaucoma,"* 2004 Royal Hawaiian Eye Meeting, Kauai, HI, January 28, 2003.
Course Faculty, "Bleb Leaks, Blebitis and Endophthalmitis," 2004 Royal Hawaiian Eye Meeting, Kauai, HI, January 28, 2003.
Course Faculty, *"Assessing Ocular Blood Flow,"* 2004 Royal Hawaiian Eye Meeting, Kauai, HI, January 28, 2003.
Scientific Poster Presentation "*Pharmacoeconomic Analysis of a Literature Review of the Lipid Class of Anti-Glaucoma Medications"***,** 2004 AGS Meeting, Sarasota, FL March 06, 2004
Scientific Poster Presentation, *"Pigment dispersion and glaucoma related to in-the-bag placement of the AcrySof® SA60 IOL,"* 2004 AGS Meeting, Sarasota, FL, March 05, 2004
Scientific Poster Presentation, *"A Multicenter, Randomized, Investigator-Masked Comparison of the Efficacy of Bimatoprost 0.03% versus Travoprost 0.004% in African Americans with Glaucoma or Ocular Hypertension,"*2004 AGS Meeting, Sarasota, FL, March 05, 2004
Scientific Poster Presentation, *"Evaluation of the Effect of Various Artificial Tears on Latanoprost-Induced Corneal Toxicity in Rabbits,"* 2004 ARVO Meeting, Fort Lauderdale, FL, April 25, 2004

Scientific Poster Presentation, *"Bimatoprost Affects Hydraulic Conductivity of Outflow Cell Monolayers,"* 2004 ARVO Meeting, Fort Lauderdale, FL, April 28, 2004

Scientific Poster Presentation, *"A Multicenter, Investigator-Masked, Randomized Comparison of the IOP-Lowering Efficacy of Bimatoprost 0.03% versus Travoprost 0.004% in African Americans with Glaucoma or Ocular Hypertension,"* 2004 ARVO Meeting, Fort Lauderdale, FL, April 28, 2004

Scientific Poster Presentation, *"Pressure-Lowering Efficacy of Bimatoprost and Latanoprost: Effect of Baseline Mean Diurnal IOP,"* 2004 ARVO Meeting, Fort Lauderdale, FL, April 28, 2004

Scientific Poster Presentation, *"The effect of topical cyclosporine on latanoprost-induced conjunctival inflammation,"* 2004 ARVO Meeting, Fort Lauderdale, FL, April 29, 2004

Scientific Poster Presentation, *"Penetration of 4th Generation Fluoroquinolones into the Rabbit Aqueous Humor Using a Lidocaine Gel Mixture,"* 2004 ARVO Meeting, Fort Lauderdale, FL, April 29, 2004

Scientific Poster Presentation, *"Aqueous Levels of Moxifloxacin and Gatifloxacin Following Different Pre and Post-Operative Topical Dosing Protocols,"* 2004 ARVO Meeting, Fort Lauderdale, FL, April 29, 2004

Scientific Poster Presentation, *"Comparison of the Effectiveness of Vigamox™ and Zyar™ against Aspergillus fumigatus and Candida albicans,"* 2004 ARVO Meeting, Fort Lauderdale, FL, April 29, 2004

Course Instructor, *"Controversies in Lens Implant Selection for the Aging Eye,"* ASCRS Symposium on Cataract, IOL and Refractive Surgery, San Diego, CA, May 01, 2004

Moderator/Speaker, *"Mechanisms of Selective Laser Trabeculoplasty,"* ASCRS Symposium on Cataract, IOL and Refractive Surgery, San Diego, CA, May 01, 2004

Scientific Poster Presentation, *"Comparison of the Effect of Brimonidine Purite on Rabbit Corneal Epithelium,"* ASCRS Symposium on Cataract, IOL and Refractive Surgery, San Diego, CA, May 01, 2004

Scientific Poster Presentation, *"Incidence of Iris Pigmentation Changes with Latanoprost and Bimatoprost,"* ASCRS Symposium on Cataract, IOL and Refractive Surgery, San Diego, CA, May 01, 2004

Guest Speaker, *"The Effect of Glaucoma Therapy on the Ocular Surface,"* COS Chicago Ophthalmological Society, Navy Pier, Chicago, IL, May 15, 2004

Course Faculty, *"Glaucoma Medications, Alpha Adrenergic Agonists,"* OSN Ocular Surgery News Symposium, The Venetian, Las Vegas, NV, June 06, 2004.

Course Faculty, *"Glaucoma Surgery, Anti-Fibrosis Agents,"* OSN Ocular Surgery News Symposium, The Venetian, Las Vegas, NV, June 07, 2004.

Course Faculty, *"Angle Closure and Other Complicated Glaucomas, Neovascular Glaucoma"* OSN Ocular Surgery News Symposium, The Venetian, Las Vegas, NV, June 11, 2004.

Course Faculty, *"Managing Late Complications of Trabeculectomy, Leaking Bleb,"* OSN Ocular Surgery News Symposium, The Venetian, Las Vegas, NV, June 12, 2004.
Invited Speaker, *"Pressure Lowering Efficacy of Bimatoprost and Latanaprost: Effect o Baseline Mean Diurnal Intraocular Pressur (IOP)."* SEAGIG 2004, Kuala Lumpur Malaysia, August 26, 2004.
Invited Speaker, *"Comparison of The Effect of Brimonidine .02% Vs. Brimonidine Purite® on Rabbit Corneal Epithelium."* SEAGIG 2004, Kuala Lumpur, Malaysia, August 26, 2004.
Course Director, Anterior Segment Update, University of Pittsburgh, Pittsburgh, PA , September 18, 2004
Invited Lecturer, *"New Diagnostic Methods for Glaucoma: OCT and Other Technologies"* Anterior Segment Update, University of Pittsburgh, Pittsburgh, PA September 18, 2004
Invited Lecturer, *"Update on Glaucoma Laser Therapy"* Anterior Segment Update, University of Pittsburgh, Pittsburgh, PA September 18, 2004
Course Instructor, *"Clinical Applications of ECP."* ECP Course, Boston, MA, September 25, 2004.
Invited Speaker, *"Effects of Glaucoma Therapy on the Ocular Surface."* Grand Rounds, University Hospitals of Cleveland, Case Western Reserve University, September 29, 2004.
Course Instructor, *"Strategies to Prevent Disease Progression."* FORGE CME Program, Orlando, FL, October 02, 2004.
Invited Lecturer, *"Neovascular glaucoma: Potential Novel Approaches."* Angiogenesis and it's Inhibition, Herberman Conference Center, Hillman Cancer Center, Pittsburgh, PA, October 09, 2004
Invited Lecturer, *"Patient Perspectives in Glaucoma Management"* CME Symposium "Winds of Change: An Evidence Based Approach" AAO & SOE Joint Meeting, New Orleans, October 22, 2004
Invited Speaker, *"Second-Line Glaucoma Management: Considerations in Selecting Safer, More Effective Adjunctive Agents"* AAO & SOE Joint Meeting, New Orleans, October 22, 2004
Invited Speaker, *"Tips and Techniques for Successful SLT Treatment"* AAO & SOE Joint Meeting, New Orleans, October 22, 2004
Invited Speaker, *"The Truth About Silicone IOLs (biocompatibility, ease of use, use with silicone oils)"* AAO & SOE Joint Meeting, New Orleans, October 22, 2004
Invited Speaker, *"Weight of Evidence: Choosing Medical Therapy in Glaucoma"* Allergan Consultant Meeting, San Diego, CA, November 13, 2004
Invited Speaker, *"FORGE Program "* Allergan Consultant Meeting, Baltimore, MD, November 16, 2004
Invited Speaker, *"SLT Tips for Clinical Success"* Lumenis CORE Meeting, Pittsburgh, PA, November 17, 2004
Invited Speaker, *"SLT Tips for Clinical Success"* Lumenis CORE Meeting, Grand Rapids, MI, November 18, 2004
Invited Speaker, *"SLT Tips for Clinical Success"* Lumenis CORE Meeting,

Alexandria, VA, November 23, 2004

2005 **Invited Speaker,** *"Update on Optic Nerve and Nerve Fiber Layer Imaging,"* Kansas City Society of Ophthalmology and Otolaryngology Annual Clinical Conference, Kansas City, Missouri January 7, 2005.

Invited Speaker, *"Effect of Glaucoma Therapy on the Ocular Surface,"* Kansas City Society of Ophthalmology and Otolaryngology Annual Clinical Conference, Kansas City, Missouri January 7, 2005.

Invited Speaker, *"Role of Endocyclophotocoagulation in Glaucoma Management,"* Kansas City Society of Ophthalmology and Otolaryngology Annual Clinical Conference, Kansas City, Missouri January 7, 2005.

Guest Lecturer, *"FORGE Structural Evaluations,"* CME Symposium, The Royal Hawaiian Eye J Meeting, Hawaii, January 17, 2005.

Guest Lecturer, *"Glaucoma Overview,"* Nursing Program, The Royal Hawaiian Eye Meeting, Hawaii, January 19, 2005.

Guest Lecturer, *"Glaucoma Medications,"* Nursing Program, The Royal Hawaiian Eye Meeting, Hawaii, January 19, 2005.

Guest Lecturer, *"Glaucoma Therapy and the Ocular Surface,"* Nursing Program, The Royal Hawaiian Eye Meeting, Hawaii, January 19, 2005.

Course Director, "*Ophthalmic Technician Education Series: Tonometry and Lensometry,"* Accredited by the Joint Commission on Allied Health Personnel in Ophthalmology (JCAHPO). Pittsburgh, PA February 05, 2005.

Course Director, "*Ophthalmologic Endo-Cyclophotocoagulation,"* Accredited by the Accreditation Council for Continuing Medical Education. Pittsburgh, PA February 19, 2005.

Guest Lecturer, "*A Comparison of ALT and SLT,"* Eye on the Bayou, The 54th Annual Symposium of the New Orleans Academy of Ophthalmology, New Orleans, LA, February 20, 2005

Guest Lecturer, "*What's New in Glaucoma: Cutting Edge Advances"* Seco International, 2005, Atlanta, GA, February 24, 2005

Scientific Poster Presentation "*Evaluation of Bimatoprost 3.33% versus Latanopro 0.005%: A Bilateral Monocular Trial"***,** American Glaucoma Society (AGS) 2005 Annual Meeting, Snowbird, UT, March 03, 2005

Moderator, "FORGE Focusing Ophthalmology on Reframing Glaucoma Evaluation", March 10, 2005

Scientific Poster Presentation "*Evaluation of Bimatoprost 0.03% versus Latanoprost 0.005%: A Paired Comparison Study"***,** ARVO 2005 Annual Meeting, Fort Lauderdale, FL., May 1-5, 2005

Course Director, Anterior Segment Update, University of Pittsburgh, Pittsburgh, PA , May 07, 2005
Scientific Poster Presentation "*Evaluation of Bimatoprost 0.03% versus Lantanoprost 0.005%: A Paired Comparison Study,* ARVO, Fort Lauderdale, FL May 01-06, 2005
Invited Speaker, "Real Efficacy, Breakfast Symposium "SURGE Sound Understanding of REAL Glaucoma Efficacy*"* Annual OSN Glaucoma Symposium, Las Vegas, NV June 17, 2005
Invited Speaker, "Surgical Complication – Grand Rounds, High IOP*"* Third Annual Ocular Surgery News Symposium, OSN Glaucoma Symposium, Las Vegas, NV June 18, 2005
Invited Speaker, "Other Consideration in Glaucoma Surgery, Cyclodestructive Procedures*"* Third Annual Ocular Surgery News Symposium, OSN Glaucoma Symposium, Las Vegas, NV June 18, 2005
Scientific Poster Presentation, "NTG and Bilateral Monocular Trial Study Posters*"* AIGS World Glaucoma Congress, Vienna, Austria July 06-09, 2005
Guest Speaker, "Corneal Pachymetry – How does it help me manage my glaucoma patients?*"* Innovations in Glaucoma and Anterior Segment Therapies, Cape Cod, MA September 17, 2005
Guest Speaker, "Imaging: An Everyday Perspective on OCT, HRT, and GDX" Innovations in Glaucoma and Anterior Segment Therapies, Cape Cod, MA September 17, 2005
Guest Speaker, "Cataract Surgery in the Glaucoma Patient" Innovations in Glaucoma and Anterior Segment Therapies, Cape Cod, MA September 17, 2005
Course Faculty, "SURGE: Sound Understanding of REAL Glaucoma Efficacy" AAO Annual Meeting, Chicago, IL October 15, 2005
Scientific Poster Presentation, "Comparison of the IOP-Lowering Efficacy of Bimatoprost and Travoprost in Black Patients With Glaucoma or Ocular Hypertension" AAO Annual Meeting, Chicago, IL October 16, 2005
Course Instructor, "Lasers in Glaucoma" AAO Annual Meeting, Chicago, IL October 16, 2005
Scientific Poster Presentation, "Improved Nerve Fiber Layer Assessment Using Eye OCT Raster Scanning" AAO Annual Meeting, Chicago, IL October 17, 2005

2006 **Guest Lecturer,** *"Reframing Disease Severity"* SURGE CME Lunch Symposium*,* The Royal Hawaiian Eye Meeting, Hawaii, January 16, 2006
Guest Lecturer, *"Optimization of Patient Therapy"* SURGE CME Lunch Symposium*,* The Royal Hawaiian Eye Meeting, Hawaii, January 16, 2006
Guest Presenter, *"Endoscopic and Transscleral Cyclophotocoagulation,"*, The Royal Hawaiian Eye Meeting, Hawaii, January 18, 2006.
Scientific Poster Presentation, *"Evaluation of Bimatoprost 0.03% versus Latanoprost 0.005%: A Paired-Comparison Study"* The World Congress of Ophthalmology, Sao Paulo, Brazil February 19 – 24, 2006.
Scientific Poster Presentation, *"Efficacy of Brimonidine 0.15% as Adjunctive Therapy with Latanoprost 0.005% in Patients with Open Angle* ASCRS ASOA Symposium & Congress,

San Francisco, CA, March 17-19, 2006.

Scientific Poster Presentation, "*The Effect of Probe Placement on Endoscopic Cyclophotocoagulation Laser Energy Transmission*" ARVO, Fort Lauderdale, FL April 30, 2006

Scientific Poster Presentation, "*Ocular Hypotensive Efficacy of Brimonidine 0.15% as Adjunctive Therapy With Latanoprost 0.005% in Patients With Open-Angle Glaucoma or Ocular Hypertension*" ARVO, Fort Lauderdale, FL April 30, 2006

Scientific Poster Presentation, "*UGH Syndrome Associated With the Acrysof SA60 at Intraocular Lens Following Placement Within the Capsular***"** ARVO, Fort Lauderdale, FL April 30, 2006

Scientific Poster Presentation, "*Morphologic Evaluation Of Bevacizumab (Avastin®) Treated Corneal Stromal Fibroblasts*" ARVO, Fort Lauderdale, FL, May 01, 2006

Scientific Poster Presentation, "*Reproducibility of Retinal Layer Thickness Measurements Using a Novel Macular Segmentation Software***"** ARVO, Fort Lauderdale, FL, May 02, 2006

Scientific Poster Presentation, "*Macular Retinal Segmentation and Composite Retinal Image for Glaucoma Detection***"** ARVO, Fort Lauderdale, FL May 02, 2006

Scientific Poster Presentation, "*Optical Coherence Tomography (OCT) Quality Evaluation Revisited With Common Classification Criteria*" ARVO, Fort Lauderdale, FL May 02, 2006

Scientific Poster Presentation, "*Pilot Study of the Relationship Among Depression and Visual Impairment in Older Adults*" ARVO, Fort Lauderdale, FL May 02, 2006

Scientific Poster Presentation, "*Evaluation of Heidelberg Retina Tomography (HRT 3) in Healthy Eyes"* ARVO, Fort Lauderdale, FL May 02, 2006

Scientific Poster Presentation, "*Heidelberg Retina Tomograph (HRT) II vs. HRT 3: What Is the Difference?***"** ARVO, Fort Lauderdale, FL, May 03, 2006

Scientific Poster Presentation, "*Frequency of Diagnostic Procedures Amongst Patients Diagnosed as Ocular Hypertension, Primary Open Angle Glaucoma, and Glaucoma Suspects in Western Pennsylvania*" ARVO, Fort Lauderdale, FL, May 03, 2006

Scientific Poster Presentation, "*The Utility of Venting Slits and Punctures in Modifying Glaucoma Drainage Device Outflow Facility***"** ARVO, Fort Lauderdale, FL, May 04, 2006

Guest Lecturer, "*Phaco-ECP Technique*" Ocular Surgery News Las Vegas: Improving your Odds 2006 Symposium, Las Vegas, NV June 08, 2006

Course Faculty, "*Glaucoma Therapy: Scratching the Surface*" The 29th Annual Midwest Glaucoma Symposium, Pittsburgh, PA September 15, 2006

Course Faculty, "*Cyclophotocoagulation Then and Now*" The 29th Annual Midwest Glaucoma Symposium, Pittsburgh, PA September 16, 2006

Invited Speaker, "*Current Glaucoma Therapy*" Sino US Joint Symposium on Ophthalmology,
Shanghai, China September 21, 2006

Guest Chair, "Predicting *the Future—The Role of Optic Nerve Imaging in OHTS* " Managing
Glaucoma: A Full Spectrum Approach AAO Annual Meeting, Las Vegas, NV, November 11, 2006

Guest Lecturer, *"Cataract Surgery with Co-Existing Conditions".* 2006 ASORN Annual

Meeting, Las Vegas, NV, November 11, 2006.
Course Instructor, "*Basic Imaging in Ophthalmology*" AAO Annual Meeting, Las Vegas, NV, November 11, 2006
Course Instructor, "*Laser Treatment of Glaucoma*" AAO Annual Meeting, Las Vegas, NV, November 11, 2006
Course Instructor, "*Lasers in Glaucoma*" AAO Annual Meeting, Las Vegas, NV, November 12, 2006

2007 **Guest Lecturer,** *"Glaucoma Testing Options"* Nursing and Allied Health General Session, The Royal Hawaiian Eye Meeting, Hawaii, January 16, 2007
Course Faculty, *"Adherence I n Medical Therapy-Experience with an Electronic Adherence*
Monitor" The Royal Hawaiian Eye Meeting, Hawaii, January 17, 2007
Course Faculty, *"Endoscopic Cyclophotocoagulation - Clinical Experience and Recent Findings"* The Royal Hawaiian Eye Meeting, Hawaii, January 17, 2007
Scientific Poster Presentation, "*Effect of Audible and Visual Reminders on Adherence in Glaucoma Patients Using a Commercially Available Dosing Aid*" AGS, San Francisco, CA, March 2007
Scientific Poster Presentation, "*Brimonidine Purite 0.15% Versus Dorzolamide 2% Used as Adjunctive Therapy to Latanoprost*" AGS, San Francisco, CA, March 2007
Scientific Poster Presentation, "*Clinical Evaluation of a Novel Gold Micro-Shunt for Reduction of IOP in Refractory Glaucomas*" AGS, San Francisco, CA, March 2007
Scientific Poster Presentation, "*Evaluation of Diurnal Control of Intraocular Pressure After a Single Drop of Bimatoprost 0.03% or Travoprost 0.004%*" IGS, Athens, Greece, March, 2007
Scientific Poster Presentation, A Bleb-Free Approach to Reduction of IOP in Treatment of ARVO, Ft Lauderdale, FL, May 2007
Scientific Poster Presentation, *A Multicenter Evaluation of Methods to Promote Patient Acceptance of Hyperemia Associated with Bimatoprost Therapy for Glaucoma or Ocular Hypertension*, World Glaucoma Congress, Singapore, July 2007
Scientific Poster Presentation, *Brimonidine Purite 0.15% versus Dorzolamide 2% Used as Adjunctive Therapy to Latanoprost*, World Glaucoma Congress, Singapore, July 2007
Invited Speaker, Basic Science of Care Course, University of Pittsburgh School of Medicine, September 19, 2007
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* AAO Annual Meeting, Las Vegas, NV, November 11, 2007
Lead Instructor, "*Laser Treatment of Glaucoma*" AAO Annual Meeting, Las Vegas, NV, November 11, 2007
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* Skills Transfer Lab, AAO Annual Meeting, Las Vegas, NV, November 12, 2007
Scientific Poster Presentation, Evaluation *of Microbial Growth in Topical Glaucoma Medications with and without Benzalkonium Chloride*, AAO Annual Meeting, Las Vegas, NV, November 2007

2008 **Guest Lecturer,** *"How to Manage the Progressing Glaucoma Patient*" Hawaiian Eye, CME,

Lunch Symposium*,* The Royal Hawaiian Eye Meeting, Hawaii, January 21, 2008

Invited Speaker *The Glaucoma Patient with Cataract: What's a Surgeon to Do?*, The Royal Hawaiian Eye Meeting, Hawaii, January 23, 2008

Invited Speaker, *Use of Anti-Vegf Agents in Glaucoma*, Nursing and Allied Health Program, The Royal Hawaiian Eye Meeting, Hawaii, January 24, 2008

Scientific Poster Presentation, *Comparison of Post-Operative IOP Control Using Different Polyglactin Sutures for Cinching of Baerveldt Tubes*, American Glaucoma Society, Washington, DC, March 2008

Scientific Poster Presentation, *Intra-Operative Intracameral Dexamethasone Reduces Inflammation in Glaucomatous Eyes*, American Glaucoma Society, Washington, DC, March 2008

Invited Speaker, *Laser Treatment of Glaucoma*, Pittsburgh Ophthalmologic Society, Pittsburgh, PA, March 07, 2008

Invited Speaker, *Novel Strategies in the Therapeutic Management of Glaucoma,* ASCRS-ASOA Chicago, IL, April 06, 2008

Scientific Poster Presentation*, A Descriptive Cross-Sectional Survey Assessing the Demographic Variations in the Prevalence of Complementary and Alternative Medicine Use in Patients visiting UPMC Eye Center* ARVO 2008 Annual Meeting, April 2008

Scientific Poster Presentation*, Reproducibility of Measurements of Aqueous Velocity Within Schlemm's Canal With Spectral Domain Optical Coherence Tomograph,* ARVO 2008 Annual Meeting, April 2008

Scientific Poster Presentation*, Glaucomatous Progression Detection by Perimetry Using Visual Field Index (VFI) and Global Parameters,* ARVO 2008 Annual Meeting, April 2008

Scientific Poster Presentation*, DSAEK Combined With Phacoemulsification: Compensating for the Hyperopic Shift,* ARVO 2008 Annual Meeting, April 2008

Scientific Poster Presentation*, Evaluating Glaucoma Progression Using a Latent Class Model for MD, PSD, AGIS, and VFI With RNFL as Covariate,* ARVO 2008 Annual Meeting, April 2008

Scientific Poster Presentation*,* Automated Extraction of Optic Nerve Head Parameters From Spectral Domain Optical Coherence Tomography, ARVO 2008 Annual Meeting, April 2008

Invited Speaker, Novel Strategies in the Therapeutic Management of Glaucoma, ASCRS 2008 Annual Meeting, Chicago, IL April 06, 2008.

Invited Speaker, Treatment Algorithms for SLT*,* 2nd Biannual European Glaucoma Laser Surgery Symposium, Sardinia, Italy, June 12, 2008

Course Director, *Anterior Segment Update,* Nemacolin Woodlands, Farmington, PA, September 06, 2008

Glaucoma Laser Therapy: Innovations and Advice From the Experts

Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* AAO Annual Meeting, Atlanta, GA, November 8-11, 2008

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Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* Skills Transfer Lab, AAO Annual Meeting, Atlanta, GA, November 8-11, 2008

2009 **Invited Speaker,** *"Imagining in Glaucoma"* Research Study Club of Los Angeles' 77th Mid-Winter Clinical Conference, Lost Angeles, CA January 17, 2009
Invited Speaker, *"Medical & Surgical Treatments or Glaucoma"* Research Study Club of Los Angeles' 77th Mid-Winter Clinical Conference, Lost Angeles, CA January 17, 2009
Invited Speaker, *"Imagining in Glaucoma"* University of Rochester School of Medicine & Dentistry 54th Annual Ophthalmology Conference, Rochester, NY, March 20-21, 2009
Invited Speaker, *"Medical & Surgical Treatments or Glaucoma"* University of Rochester School of Medicine & Dentistry 54th Annual Ophthalmology Conference, Rochester, NY, March 20-21, 2009
Scientific Poster Presentation, *"Long-Term Follow-Up of Suture Versus Fibrin Glue-Assisted Glaucoma Drainage Device Surgery"* American Glaucoma Society, San Diego, CA, March 2009
Scientific Poster Presentation, *"Long-Term Clinical Outcomes of Baerveldt Glaucoma Implant Tube Placement in the Sulcus Versus the Anterior Chamber"* American Glaucoma Society, San Diego, CA, March 2009
Invited Speaker, *"Combined Endoscopic Cyclophotocoagulation"* ASCRS Glaucoma Day Program, ASCRS 2009, San Francisco, April 4-6, 2009
Course Co-Instructor, Innovative Uses of Adhesives in Anterior Segment Surgery ASCRS 2009, San Francisco, April 4-6, 2009
Invited Lecturer, "*How EMR and IT have helped to make quality, safety, and operations better….or worse"* The Basic Science of Care course, Pittsburgh, PA, September 09, 2009
Course Director, *Anterior Segment Update,* Nemacolin Woodlands, Farmington, PA, September 12, 2009
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* AAO Annual Meeting, San Francisco, CA, October 25, 2009
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* Skills Transfer Lab, AAO Annual Meeting, San Francisco, CA, October 25, 2009
Course Director, "*International Teleophthalmology Symposium"*, Pittsburgh, PA October 31, 2009

2010 **Guest Lecturer**, "*Grand Rounds CME Lectures",* USF Eye Institute, Tampa, FL March 18, 2010
Course Faculty, "*Innovative Uses of Adhesives in Anterior Segment Surgery*" AAO Annual Meeting 2010, Chicago, Illinois, 2010.
Scientific Poster Presentation, *"Long-Term Clinical Outcomes of Baerveldt Glaucoma Implant Tube Placement in the Sulcus Versus the Anterior Chamber"* American Glaucoma Society, San Diego, CA, March 2010
Invited Speaker, *"Combined Endoscopic Cyclophotocoagulation"* ASCRS Glaucoma Day Program, ASCRS 2010, San Diego April 4-6, 2010

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Course Co-Instructor, Innovative Uses of Adhesives in Anterior Segment Surgery ASCRS 2009, San Francisco, April 4-6, 2010
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* AAO Annual Meeting, Chicago, Ill, October 25, 2010
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* Skills Transfer Lab, AAO Annual Meeting, Chicago, Ill, October 25, 2010

2011 **Course Director,** "Evaluation of an Outpatient Electronic Health Record System" HIMSS, Orlando , Florida February 2, 2011
Course Faculty, " Use of teleretina program to identify patients with glaucoma and macular degeneration. VA National Teleretina Symposium, February 24, 2011
Course Faculty, *"Endoscopic Cyclophotocoagulation" A*GS Surgery Day Program, AGS 2011, Dana Point, California March 4-6, 2011
Invited Speaker, *"Surgical Disasters"* ASCRS Glaucoma Day Program, ASCRS 2011, San Diego April 4-6, 2011
Course Director, "*Effect of preservatives on the ocular surface*." World Glaucoma Congress, Paris, France, July 2, 2011
Course Faculty, "Complications of gold shunt and canaloplasty surgery." World Glaucoma Congress, Paris, France, July 2, 2011
Course Faculty, "*Selective Laser Trabeculoplasty as primary therapy for glaucoma*." World Glaucoma Congress, Paris, France, July 2, 2011
Invited Speaker, *"Innovations in Glaucoma Surgical Therapy"* Cape Cod National Glaucoma Symposium, Brewster, MA July 26, 2011
Invited Speaker, *"Imaging in Glaucoma Diagnosis and Therapy"* Cape Cod National Glaucoma Symposium, Brewster, MA July 26, 2011
Invited Speaker, *"Innovations in Glaucoma Surgical Therapy"* Connecticut Optometry Society Annual Meeting, Mystic Connecticut, September 15, 2011
Invited Speaker, *"Evaluation of the Optic Nerve" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, October 22, 2011
Invited Speaker, *"Acute Eye Conditions"* St Vincent's Medical Center Grand Rounds, Bridgeport, Connecticut, October 15, 2011
Course Instructor, "Innovative Uses of Adhesives in Anterior Segment Surgery" American Academy of Ophthalmology 2011, Orlando, October 24, 2011
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* AAO Annual Meeting, Orlando Florida, October 25, 2011
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* Skills Transfer Lab, AAO Annual Meeting, Orlano, FL, October 25, 2011
Course Instructor, *"Endscopic Cyclophotocoagulation"* American Academy of Ophthalmology 2011, Orlando, October 24, 2011
Session Moderator, *"Innovations in Glaucoma Treatment" Yale University Annual Glaucoma Symposium,* New Haven, Connecticut, November 4, 2011
Invited Speaker, *"Combined Cataract and Glaucoma Surgery"* OSN New York Annual Ophthalmology Meeting, New York, New York November 16, 2011.

Invited Speaker, *"Innovations in Glaucoma Surgery". Nassau County Ophthalmology Surgical Meeting*, Garden City, NY December 4, 2011.

2012 **Guest Lecturer,** *"Secondary Glaucomas" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, January 19, 2012
Guest Lecturer. *Glaucoma Reveiew" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, March14, 2012
Course Instructor, *"Special Interest Group: Endscopic Cyclophotocoagulation"* American Glaucoma Society Annual Meeting 2012, New York, NY March 5, 2012
Invited Speaker, *"OKAP review" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, March 14, 2012
Invited Speaker, *"Imaging in Glaucoma Diagnosis and Therapy"* Dallas Ophthalmology Society 34th Annual Meeting, Dallas, TX March 30, 2012
Invited Speaker, *"Formulations of glaucoma medications and generics"* Dallas Ophthalmology Society 34th Annual Meeting, Dallas, TX March 30, 2012
Invited Speaker, *"Combined Cataract and Glaucoma Surgery"* Dallas Ophthalmology Society 34th Annual Meeting, Dallas, TX March 30, 2012
Course Co-Director, *"New devices for glaucoma surgery"* Advances in Anterior Segment Surgery Meeting, Fairfield, CT April 10, 2012.
Course Co-Director, *"New adhesive for use in cataract surgery"* Advances in Anterior Segment Surgery Meeting, Fairfield, CT April 10, 2012.
Course Co-Director, *"The Use of Intense Pulsed Light (IPL) for treatment of ocular surface disease"* Advances in Anterior Segment Therapy and Surgery Meeting, Fairfield, CT April 10, 2012.
Invited Speaker, *"Imaging in Glaucoma"* ASCRS Glaucoma Day Program, ASCRS Annual Meeting 2012, Chicago April 20, 2012
Course Instructor, *"Adhesives in Glaucoma Surgery"* ASCRS Annual Meeting 2012, Chicago April 22, 2012
Invited Speaker, *"Optimizing Glaucoma Therapy"* Thailand Ophthalmology Society Semi-Annual Meeting, Bangkok, Thailand May 25, 2012
Invited Speaker, *"Update on Neuroprotection in Glaucoma Therapy"* Thailand Ophthalmology Society Semi- Annual Meeting, Bangkok, Thailand May 25, 2012
Invited Speaker, *"Evolving Role of Brimonidine in Glaucoma Therapy"* Philippines Glaucoma Society, Manila, Philippines May 26, 2012
Invited Speaker, *"Express Minishunt Surgery" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, August 14, 2012
Course Instructor, "Innovative Uses of Adhesives in Anterior Segment Surgery" American Academy of Ophthalmology 2011, 2012, Chicago, IL, November 10-13 , 2012
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* AAO Annual Meeting, Orlando Florida, 2012, Chicago, IL, November 10-13 , 2012
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* Skills Transfer Lab, AAO Annual Meeting, 2012, Chicago, IL, November 10-13 , 2012
Course Instructor, *"Endscopic Cyclophotocoagulation"* American Academy of

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Ophthalmology 2012, Chicago, IL, November 10-13 , 2012
Invited Speaker, "*Minimally Invasive Glaucoma Surgery - Ready or not, here it comes!"* OSN New York Annual Ophthalmology Meeting, New York, New York November 16, 2012.
Invited Speaker, "*Perspectives in Femtosecond Cataract Surgery"* OSN New York Annual Ophthalmology Meeting, New York, New York November 16, 2012.
Invited Speaker, "*Controversies in Ocular Surface Disease Management"* OSN New York Annual Ophthalmology Meeting, New York, New York November 18, 2012.
Featured Speaker, "Management of Complex Refractive IOL Cases", NASSAU SURGICAL SOCIETY CLINIC DAY, December 5, 2012.
Featured Speaker, "Update on Microinvasive Glaucoma Devices", NASSAU SURGICAL SOCIETY CLINIC DAY, December 5, 2012.
Featured Speaker, "Glaucoma Case Studies", NASSAU SURGICAL SOCIETY CLINIC DAY, December 5, 2012.
Featured Speaker, "Glaucoma Update: Detection and Monitoring of Glaucoma Progression", Wills Eye Hospital Glaucoma Symposium, December 15, 2012.

2013 **Guest Lecturer,** *"Laser Treatment of Glaucoma" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, January 17, 2013
Guest Lecturer, *"OKAP Review Course" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, March 19, 2013
Invited Speaker, "Insights on the Risk of Glaucoma Progression″ Phoenix Ophthalmology Society Meeting, Phoenix, Arizona, April 4, 2013.
Invited Speaker, "*ECP and Cataract Surgery – PRO"* ASCRS Glaucoma Day Program, ASCRS 2013, San Fancisco, CA April 19, 2013
Invited Speaker, "*Controversies in Medical and Laser Treatment"* ASCRS Glaucoma Day Program, ASCRS 2013, San Fancisco, CA April 19, 2013
Invited Speaker, "*Minimally Invasive Glaucoma Surgery"* Cape Cod Innovations in Ophthalmology Meeting, Brewster, MA May31-June2, 2013.
Invited Speaker, "*Use of Adhesives in Glaucoma Surgery"* Cape Cod Innovations in Ophthalmology Meeting, Brewster, MA May 31-June 2, 2013.
Invited Speaker, "*Shunts, Tubes and Trabs"* Cape Cod Innovations in Ophthalmology Meeting, Brewster, MA May 31-June 2, 2013.
Featured Speaker, *"Current Role of Lasers in Glaucoma Therapy" Yale University Ophthalmology Annual Research Day*, New Haven, Connecticut, June 21, 2013
Featured Speaker, *"Evolving advances in Glaucoma Surgery" Yale University Ophthalmology Annual Research Day*, New Haven, Connecticut, June 21, 2013
Featured Speaker, *"Update on Eyelid Lesions and Procedures" Connecticut Optometry Society Meeting*, Rocky Hill, Connecticut, May 23, 2013.
Featured Speaker, *"Update New Office Technologies" Connecticut Optometry Society Meeting*, Fairfield, Connecticut, June 9, 2013.
Featured Speaker, *"Update New Office Technologies" Connecticut Optometry Society Meeting*, Fairfield, Connecticut, June 23, 2013.
Featured Speaker, "Update on Microinvasive Glaucoma Devices", St. Luke's Annual

Ophthalmology Meeting, Manila, Phillipines August 24-25, 2013.
Featured Speaker, "Update on Imaging in Glaucoma", St. Luke's Annual Ophthalmology Meeting, Manila, Phillipines August 24-25, 2013.
Featured Speaker, "ECP for Glaucoma Therapy", St. Luke's Annual Ophthalmology Meeting, Manila, Phillipines August 24-25, 2013.
Featured Speaker, "Adhesives for Glaucoma Surgery", St. Luke's Annual Ophthalmology Meeting, Manila, Phillipines August 24-25, 2013.
Featured Speaker, "Update on Microinvasive Glaucoma Devices", St. Luke's Annual Ophthalmology Meeting, Manila, Phillipines August 24-25, 2013.
Featured Speaker, "Update on Lasers for Glaucoma", St. Luke's Annual Ophthalmology Meeting, Manila, Phillipines August 24-25, 2013.
Featured Speaker, "New Glaucoma Drainage Device Technique. St. Luke's Annual Ophthalmology Meeting, Manila, Phillipines August 24-25, 2013.
Invited Speaker, "*Treatment of Glaucoma and Cataract"* OSN New York Annual Ophthalmology Meeting, New York, New York September 6-8, 2013.
Invited Speaker, "*Challenging Cases in Glaucoma"* OSN New York Annual Ophthalmology Meeting, New York, New York September 6-8, 2013.
Invited Speaker, "*Hot Topics in Glaucoma"* OSN New York Annual Ophthalmology Meeting, New York, New York September 6-8, 2013.
Invited Speaker, "*Controversies in Ocular Surface Disease Management"* OSN New York Annual Ophthalmology Meeting, New York, New York September 6-8, 2013.
Guest Faculty,*"Comprehensive ECP"* 36th Annual Midwest Gluacoma Symposium, Pittsburgh, PA , September 27-28, 2013
Course Instructor, "Innovative Uses of Adhesives in Anterior Segment Surgery" American Academy of Ophthalmology 2013, New Orleans, LA, October 18-21 , 2013
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* New Orleans, LA, October 18-21 , 2013
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* Skills Transfer Lab, AAO Annual Meeting, New Orleans, LA, October 18-21 , 2013
Course Instructor, *"Endscopic Cyclophotocoagulation"* American Academy of Ophthalmology New Orleans, LA, October 18-21 , 2013
Invited Speaker, "*Selective Laser Trabeculoplasty in Clinical Practice"* Russian Ophthalmology Society Meeting, Moscow, Russia December 5-8, 2013.

2014 **Guest Lecturer,** *"Laser Treatment of Glaucoma" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, January 18, 2014
Guest Lecturer, *"OKAP Review Course" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, March 20, 2014
Invited Speaker, "*ECP Pearls"* American Glaucoma Society Program, Washington DC, February 28, 2014
Invited Speaker, "*What Technology is Currently Available and What will be approved shortly"* ASCRS, REACT program New York, New York, March 1, 2014
Invited Speaker, "*How to implant a trabecular microbypass"* ASCRS, REACT program

New York, New York, March 1, 2014
Instructor, "*MIGS and Cataract Surgery wet lab"* ASCRS, REACT program New York, New York, March 1, 2014
Invited Speaker, "*Minimally Invasive Glaucoma Surgery"* Pittsburgh Ophthalmology Society Meeting March 21, 2014.
Invited Speaker, "*Formulation Issues in Ophthalmic Medications"* Pittsburgh Ophthalmology Society Meeting March 21, 2014.
Invited Speaker, "*Laser Assisted Cataract Surgery in the Glaucoma Patient"* Pittsburgh Ophthalmology Society Meeting March 21, 2014.
Featured Speaker, "*Neuroprotection in Glaucoma Therapy"* Review of Ophthalmology Meeting Chicago, Illinois March 24, 2014.
Invited Speaker, "*Filtering Surgery in Glaucoma"* New England Ophthalmology Society Meeting, Boston, MA April 11, 2014.
Invited Speaker, "*Iridoplasty- Forgotten Friend"* Glaucoma Subspecialty Day, ASCRS Annual Meeting, Boston, MA April 25, 2014.
Course Director, " ASCRS Course: Ultimate MIGS Triple Procedure 26-305" ASCRS Annual Meeting, ASCRS 2014, Boston, MA April 26, 2014
Course Faculty ASCRS Course: Innovative Uses of Adhesives in Anterior Segment Surgery 28-401 ASCRS Annual Meeting 2014, Boston, MA April 26, 2014
Featured Speaker, "*Steroids and Glaucoma"* Review of Ophthalmology CME Symposium, New York, New York, May 14, 2014
Invited Speaker, "*Selective Laser Trabeculoplasty in Clinical Practice"* New England Ophthalmology Society Meeting, Boston, MA May 30, 2014.
Featured Speaker, *"Update on Laser Treatment of Glaucoma" SUNY Downstate Ophthalmology Annual Research Day*, Brooklyn, New York June 12, 2014
Featured Speaker, *"Update on MIGS Procedures"" SUNY Downstate Ophthalmology Annual Research Day*, Brooklyn, New York June 12, 2014
Featured Speaker, *"Update on Imaging" SUNY Downstate Ophthalmology Annual Research Day*, Brooklyn, New York June 12, 2014
Course Faculty, "*Micropulse Laser Treatment of Glaucoma"* European Society of Cataract and Refractive Surgery Meeting, London, England September 13, 2014.
Featured Speaker, *"Current anterior segment and glaucoma surgery" Association of Veterinary Ophthtalmologists Annual Meeting*, Fort Worth, Texas October12, 2014
Course Instructor, "Innovative Uses of Adhesives in Anterior Segment Surgery" American Academy of Ophthalmology Chicago, Illinois, October 18-21, 2014
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* American Academy of Ophthalmology Chicago, Illinois, October 18-21, 2014
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* Skills Transfer Lab, American Academy of Ophthalmology Chicago, Illinois, October 18-21, 2014
Course Instructor, *"Endscopic Cyclophotocoagulation"* American Academy of Ophthalmology Chicago, Illinois, October 18-21, 2014.
Invited Speaker, "*Top 3 Pearls for Cataract Surgery in Glaucoma Patients"* OSN New

York Annual Ophthalmology Meeting, New York, New York November 15, 2014
Invited Speaker, "*Top 3 Pearls for Adopting MIGS"* OSN New York Annual Ophthalmology Meeting, New York, New York November 15, 2014
Invited Speaker, "*Glaucoma Case Conference"* OSN New York Annual Ophthalmology Meeting, New York, New York November 15, 2014
Invited Speaker, "*Top 3 Pearls for Successful Filtering Surgery"* OSN New York Annual Ophthalmology Meeting, New York, New York November 15, 2014
Invited Speaker, "*Controversies in Ocular Surface Disease Management"* OSN New York Annual Ophthalmology Meeting, New York, New York November 16, 2014

2015 **Guest Lecturer,** *"***Course Faculty,** "*Micropulse Laser Treatment of Glaucoma"* Hawaiian Eye Symposium*,* The Royal Hawaiian Eye Meeting, Hawaii, January 16, 2015
Guest Lecturer, *"OKAP Review Course" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, February 9, 2015.
Invited Speaker, "*Istent and cataract surgery"* New England Ophthalmology Society Meeting, Boston, MA April 11, 2015.
Invited Speaker, "*ECP Symposium"* ASCRS Annual Meeting 2015 San Diego, CA April 21, 2015.
Course Faculty ASCRS Course: Innovative Uses of Adhesives in Anterior Segment Surgery ASCRS Annual Meeting 2015 San Diego, CA April 21, 2015.
Invited Speaker, "*SLT in Clinical Practice"* New England Ophthalmology Society Meeting, Boston, MA April 11, 2015.
Guest Lecturer, *"Glaucoma Surgery Wet Lab" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, July 20, 2015.
Moderator, "*Pharmacology"* New England Ophthalmology Society Meeting, Boston, MA September 11, 2015.
Invited Speaker, "*Femto Laser Applications"* OSN New York Annual Ophthalmology Meeting, New York, New York October 25, 2015.
Invited Speaker, "*Adopting MIGS Refining Tubes and Trabs"* OSN New York Annual Ophthalmology Meeting, New York, New York October 25, 2015.
Invited Speaker, "*Video Case Conference"* OSN New York Annual Ophthalmology Meeting, New York, New York October 25, 2015.
Invited Speaker, "*Challenges in Ocular Surface Disease"* OSN New York Annual Ophthalmology Meeting, New York, New York October 25, 2015.

2016 **Guest Lecturer,** *"Laser Treatment of Glaucoma" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, January 18, 2016
Guest Lecturer, *"OKAP Review Course" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, March 20, 2016
Invited Speaker, "*ECP Pearls"* American Glaucoma Society Meeting, Fort Lauderdale Florida March 3-6, 2016
Invited Speaker, "*MIGS and Cataract Surgery"* ASCRS, YES program New York, New York, March 1, 2016

Instructor, "*MIGS and Cataract Surgery wet lab"* ASCRS, YES program New York, New York, March 1, 2016
Invited Speaker, "*Transforming Ophthalmic Care with Sustained Therapies"* Ocular Therapeutics Investor Program program New York, New York, April 6, 2016
Invited Speaker, "*Filtering Surgery in Glaucoma"* New England Ophthalmology Society Meeting, April 11, 2016
Invited Speaker *"Electrophysiology PERG"* ASCRS Glaucoma Subspecialty Day, Boston, MA May 6, 2016
Panel Member *"OCT vs UBM: Which Technology, When?"* ASCRS Glaucoma Subspecialty Day, Boston, MA May 6, 2016
Invited Speaker *"The lighter side of Cyclodestruction: MP3CPC and ECP"* ASCRS Glaucoma Subspecialty Day, Boston, MA May 6, 2016
Course Faculty ASCRS Course: Innovative Uses of Adhesives in Anterior Segment Surgery 28-401 ASCRS Annual Meeting, Boston, MA May 7, 2016
Invited Speaker, "*Selective Laser Trabeculoplasty in Clinical Practice"* New England Ophthalmology Society Meeting, Boston, MA May 30, 2016
Invited Speaker *"Micropulse Technology in Glauocma"* The Manhattan Glaucoma Symposium 2016, New York, New York, June 1, 2016
Course Instructor, "Innovative Uses of Adhesives in Anterior Segment Surgery" American Academy of Ophthalmology October 18-21, 2016
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* American Academy of Ophthalmology October, 2016
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* Skills Transfer Lab, American Academy of Ophthalmology October 18-21, 2016
Course Instructor, *"Endscopic Cyclophotocoagulation"* American Academy of Ophthalmology October 18-21, 2016
Invited Speaker, "*Treatment of Glaucoma"* OSN New York Annual Ophthalmology Meeting, New York, New York November 15, 2016
Invited Speaker, "*Challenging Cases in Glaucoma"* OSN New York Annual Ophthalmology Meeting, New York, New York November 15, 2016
Invited Speaker, "*Controversies in Ocular Surface Disease Management"* OSN New York Annual Ophthalmology Meeting, New York, New York November 16, 2016

2017 **Guest Lecturer,** *"Treatment Options for Glaucoma"*, Connecticut Society for Eye Physicians Annual Scientific Meeting, Plainville, Connecticut, January 13, 2017
Guest Lecturer, *"Laser Treatment of Glaucoma" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, January 18, 2017
Guest Lecturer, *"OKAP Review Course" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, March 20, 2017
Invited Speaker, "*ECP Pearls"* American Glaucoma Society Program,, February 28, 2017
Invited Speaker, "*MIGS and Cataract Surgery"* ASCRS, YES program New York, New York, March 1, 2017
Invited Speaker, "*MIGS and Cataract Surgery wet lab"* ASCRS, YES program New York,

New York, March 1, 2017
Invited Speaker, "*Filtering Surgery"* Glaucoma Subspecialty Day, ASCRS Annual Meeting, April 25, 2017
Course Director, " ASCRS Course: Ultimate MIGS Triple Procedure 26-305" ASCRS Annual Meeting, ASCRS 2014, April 26, 2017
Course Faculty ASCRS Course: Innovative Uses of Adhesives in Anterior Segment Surgery 28-401 ASCRS Annual Meeting 2014, April 26, 2017
Invited Speaker, "*Surgical Advances in Glaucoma Therapy"* 14th Annual National Glaucoma Symposium, Cap Cod, MA July 29, 2017
Invited Speaker, "*Glaucoma Surgery Grand Rounds"* 14th Annual National Glaucoma Symposium, Cap Cod, MA July 30, 2017
Invited Speaker, "*Controversies in Glaucoma"* 14th Annual National Glaucoma Symposium, Cap Cod, MA July 30, 2017
Invited Speaker, "*Selective Laser Trabeculoplasty in Clinical Practice"* New England Ophthalmology Society Meeting, Boston, MA September 10, 2017
Course Instructor, "Innovative Uses of Adhesives in Anterior Segment Surgery" American Academy of Ophthalmology October 18-21, 2017
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* American Academy of Ophthalmology October 18-21, 2017
Course Director, "*Glaucoma Laser Therapy: Innovations and Advice From the Experts"* Skills Transfer Lab, American Academy of Ophthalmology October 18-21, 2017
Course Instructor, *"Endscopic Cyclophotocoagulation"* American Academy of Ophthalmology October 18-21, 2017
Invited Speaker, "*Treatment of Glaucoma"* OSN New York Annual Ophthalmology Meeting, New York, New York November 15, 2017
Invited Speaker, "*Challenging Cases in Glaucoma"* OSN New York Annual Ophthalmology Meeting, New York, New York November 15, 2017
Invited Speaker, "*Controversies in Ocular Surface Disease Management"* OSN New York Annual Ophthalmology Meeting, New York, New York November 16, 2017

2018 **Course Faculty, "***Sub-cyclo concept: technology and mechanism of action" The* Royal Society, London, England January 11, 2018.
Guest Lecturer, *"Laser Treatment of Glaucoma" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, January 18, 2018
Guest Lecturer, *"OKAP Review Course" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, March 20, 2018
Invited Speaker, Innovative Uses of Adhesives in Anterior Segment Surgery ASCRS Annual Meeting April 26, 2018
Course Faculty, "*Micropulse Laser Treatment of Glaucoma"* Yale Glaucoma Symposium New Haven, CT, September 10, 2018.
Course Faculty, "*Cypass Glaucoma Drainage Device Update"* Yale Glaucoma Symposium New Haven, CT, September 10, 2018.
Invited Speaker, "*Treatment of Glaucoma"* OSN New York Annual Ophthalmology Meeting, New York, New York November 15, 2018

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Invited Speaker, "*Challenging Cases in Glaucoma"* OSN New York Annual Ophthalmology Meeting, New York, New York November 15, 2018
Invited Speaker, "*Controversies in Ocular Surface Disease Management"* OSN New York Annual Ophthalmology Meeting, New York, New York November 16, 2018

2019 **Guest Lecturer,** *"Laser Treatment of Glaucoma" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, January 18, 2019
Invited Faculty, "*Current techinques and devices for angle surgery in glaucoma" Congreso Anual de Oftalmología,* Bogota, Colombia, February 8, 2019.
Invited Faculty, "*Ocular surface disease and preservatives" Congreso Anual de Oftalmología,* Bogota, Colombia, February 8, 2019.
Invited Faculty, "*Micropulse laser treatment in glaucoma" Congreso Anual de Oftalmología,* Bogota, Colombia, February 8, 2019.
Invited Faculty, "*Femtolaser assisted cataract surgery in the glaucoma patient" Congreso Anual de Oftalmología,* Bogota, Colombia, February 8, 2019.
Invited Faculty, "*MIGS: Pros y Contras" Congreso Anual de Oftalmología,* Bogota, Colombia, February 8, 2019.
Invited Faculty, "*Current techinques and devices for angle surgery in glaucoma" Congreso Anual de Oftalmología,* Bogota, Colombia, February 8, 2019.
Invited Faculty, "*Progression of glaucoma on OCT or not?" Congreso Anual de Oftalmología,* Bogota, Colombia, February 8, 2019.
Invited Faculty, "*Current concepts in combined cataract and glaucoma surgery" Congreso Anual de Oftalmología,* Bogota, Colombia, February 9, 2019.
Guest Lecturer, *"OKAP Review Course" Yale University Ophthalmology Resident Lecture Series*, New Haven, Connecticut, March 20, 2019
Invited Speaker, "*Laser Cyclophotocoagulation" Manhattan Eye and Ear Glaucoma Symposium* New York, April 25, 2019.
Featured Speaker, "*Pro- Laser Cyclophotocoagulation in Mild to Moderate Glaucoma"* ASCRS Subspecialty Day. San Diego California May 10, 2019
Moderator, "*Medications and Lasers"* ASCRS Subspecialty Day. San Diego California May 10, 2019
Featured Lecturer, "*Glaucoma Update"* National Glaucoma Society Annual Meeting, Newport Beach, CA October 20, 2019
Featured Lecturer, "*Glaucoma Surgery Grand Rounds"* National Glaucoma Society Annual Meeting, Newport Beach, CA October 20, 2019
Invited Speaker, "*Update on medications in Glaucoma"* OSN New York Annual Ophthalmology Meeting, New York, New York November 15, 2019
Invited Speaker, "*Controversies in Ocular Surface Disease Management"* OSN New York Annual Ophthalmology Meeting, New York, New York November 16, 2019

2020 **Invited Speaker, "***Learning Surgery from YouTube- Pearls and Pitfalls" MIGS- travaganza 2020: A New Hope. A Glaucoma Symposium* Bascom Palmer Eye Institute, Miami, Florida, January 25, 2020.
Invited Speaker, "*Mistakes I have made and how not to repeat them" MIGS- travaganza*

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2020: A New Hope. A Glaucoma Symposium Bascom Palmer Eye Institute, Miami ,Florida, January 25, 2020.
Panel Member, "*Use the Force of an Expert Panel Case Presentations" MIGS- travaganza 2020: A New Hope. A Glaucoma Symposium* Bascom Palmer Eye Institute, Miami, Florida, January 25, 2020.
Instructor, "*Power up your Lightsabers Wet Lab" MIGS- travaganza 2020: A New Hope. A Glaucoma Symposium* Bascom Palmer Eye Institute, Miami Florida, January 25, 2020.
Invited Speaker, *"Experience and Pearls using the Hydrus Trabecular microbypass"* Hartford Hospital Eye Surgery Center, Newington Connecticut, February 11, 2020.
Expert Panelist, *"The coming era for advancements in glaucoma therapies"* Ophthalmology Innovation Summit at SECO, March 4, 2020.
Featured Lecturer, "*Update on diagnosis and management of Glaucoma "* National Glaucoma Society Lecture Series, Fairfield, CT June 14, 2020
Course Instructor, *"An Overiew of Ab-Interno iTrack™ Canal-BasedGlaucoma Surgery"*, World Glaucoma Congress, Capetown, South Africa, June 20, 2020.

2021

2022 **Invited Faculty,** *"Paracentesis for IOP redcution"*, Connecticut Optometry Society, Fairfield, CT. March 31, 2022.
Invited Speaker, *"Endoscopic and Transscleral Laser Therapy"*, Association of Cataract and Refractive Surgery Annual Meeting, Glaucoma Sub-Specialty Day, Washington, DC. April 22-26, 2022.
Course Faculty, *"Posterior Segment OCT"*, Basic Skills Section, Association of Cataract and Refractive Surgery Annual Meeting, Washington, DC. April 22-26, 2022.
Course Instructor, *"Endoscopic Cyclophotocoagulation"*, Association of Cataract and Refractive Surgery Annual Meeting, Washington, DC. April 22-26, 2022.
Course Instructor, *"MIGS Skills Transfer Laboraratory Session"*, Association of Cataract and Refractive Surgery Annual Meeting, Washington, DC. April 22-26, 2022.

SYMPOSIA
Selective Laser Trabeculotherapy: An Innovative Treatment for Glaucoma. Ocular Surgery News symposium at the 1999 Annual Meeting of the American Academy of Ophthalmology. October 24, 1999.

Chemical Injury. Traumatic Glaucoma: Mechanisms and Management. The Joint Meeting of the American Academy of Ophthalmology and the Pan-American Association of Ophthalmology. October 21, 2002.

Glaucoma Trials: What are the Key Findings? Simplifying Glaucoma Management: Medical Approaches for Busy Practices. EyeWorld Educational Symposium at the American Society of Cataract and Refractive Surgeons Symposium on Cataract, IOL and Refractive Surgery. April 12, 2003.

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Making Sense of the Signs in Glaucoma: Management Strategies That Work. Health Answers Symposium sponsored by the FCG Institute for Continuing Education. New York City, NY. June 20, 2003.

In which patients can UBM be helpful?; The hypotensive lipids maze: Is there a difference in how they work?; Trabeculectomy: One procedure, so many variations…Why?. 7th Annual Yale Glaucoma Symposium, Westbrook, CT. September 26, 2003.

Making Sense of the Signs in Glaucoma: Management Strategies That Work. Health Answers Symposium sponsored by the FCG Institute for Continuing Education.
Newport, RI. October 18, 2003

FORGE: Focusing Ophthalmology on Reframing Glaucoma Evaluation, Las Vegas, NV, June 12, 2004

"Focusing on Reframing Glaucoma Evaluation" SEAGIG Young Ophthalmologist Symposia, SEAGIG 2004, Kuala Lumpur Malaysia, August 25, 2004.

"Glaucoma: The Importance of Low Intraocular Pressure (IOP). How To Get There and Maintain The Health of the Eye." SEAGIG 2004, Kuala Lumpur Malaysia, August 26, 2004.

"*ECP and Cataract Surgery Symposium"*, ASCRS 2013, San Fancisco, CA April 19, 2013

MIGS symposia with FDA, American Glaucoma Society Pre-meeting. Washington, DC February 28, 2014.

Surviving the Learning Curve : Introducing New Procedures into Your Clinical Practice. American Glaucoma Society Annual Meeting, Washington, DC, February 27, 2014.

ASCRS Panel Glaucoma Surgical 2-L, ASCRS Annual Meeting, Boston, MA April 27, 2104

Pharmacology of Ophthalmology. Session Moderator. New England Ophthalmology Meeting, Boston, MA, September 11, 2015.

Innovation in Access to Branded Therapy. Expert Panelist. American Glaucoma Society Meeting, Washington, DC, February 28, 2020.

The Coming Era for Advancements in Glaucoma Therapies. Expert Perspectives. OIS Ophthalmic Summit at SECO, Atlanta, Georgia. March 4, 2020.

"Best Papers of ASCRS Annual Meeting 2022", Expert Panelist. Association of Cataract and Refractive Surgery Annual Meeting, Washington, DC. April 26, 2022.

CURRENT GRANT SUPPORT
Glaukos Evaluation of Aqueous Shunt to Decrease IOP (Principal Investigator)
Santen, Evaluaton of Aqueous Shunt to Decrease IOP (Principal Investigator)
Iridex, Evaluation of Micropulse Technology for Glaucoma

PRIOR GRANT SUPPORT
Advanced Medical Optics Surgical Technique Videos. (Principal Investigator)
Merck Imaging of retina and optic nerve in Alzheimers patients (Principal Investigator)
Iridex Histopathology of Laser Trabeculoplasty (Principal Investigator)
Advanced Medical Optics Teaching Novel Techniques for Seton Implantation (Principal Investigator)
eRecord Enterprise Services/CLIQS - Evaluation of Powerchart for Operative Report Dictation in Ophthalmology (Principal Investigator)
Glaukos Evaluation of Shunt to Decrease IOP (Principal Investigator)
Alcon Evaluation of Glaucoma Medications on Ocular Surface (Co-Investigator)
Merck/Alzheimer Effects of Glaucoma Medications on the Ocular Surface (Co-Investigator)
Allergan A Multicenter, Masked, Randomized, Sham-controlled, Parallel-group, 6-Month (Plus 6-Month Extension) Study to Evaluate the Safety and Effects on Visual Function of Brimonidine Tartrate Posterior Segment Drug Delivery System (Brimonidine Tartrate PS DDS) Applicator System in Patients with Primary Open-Angle Glaucoma (Principal Investigator)
Coherent Laser Use of Double Frequency Nd:YAG for Selective Laser Trabeculoplasty (Principal Investigator)
Merck Sharp & Dohme Addition of Trusopt versus Pilocarpine to Timoptic XE for Treatment of Glaucoma (Co-Investigator)
Allergan Corp. Assessment of Increased Iris Pigmentation through Video Monitoring (Principal Investigator)
Pharmacia & Upjohn A 1-year, double-masked, randomized, 3-arm parallel group study comparing the effect of 0.005% latanoprost (Xalatan) and fixed combination 0.005% latanoprost 0.5% timolol eye drops to 0.5% timolol on corneal endothelial cell counts and corneal thickness in patients with open angle glaucoma or ocular hypertension. (Principal Investigator)
Allergan Corp. Evaluation of Refresh Tears on Tear Film Break-Up Time and Effect of Artificial Teardrops on Corneal Epithelial Healing following Excimer Laser Ablation. (Principal Investigator)
Allergan Corp. Evaluation of Artificial Tear Solutions on the Corneal Epithelium (Principal Investigator)
Allergan Corp. Evaluation of Alphagan versus Trusopt in the Treatment of Glaucoma or Ocular Hypertension in Mexican-Americans (Principal Investigator)
American Health Assistance Foundation, National Glaucoma Research. A Tissue Engineered Aqueous Drainage Device (Co-Investigator)
Pharmacia & Upjohn A Randomized, 5-year Postmarketing Safety Study of Xalatan Compared to "Usual Care" in Patients with Open Angle Glaucoma or Ocular Hypertension (Principal Investigator)
Allergan Corp. Evaluation of Alphagan in Elderly Glaucoma Patients Stabilized on Chronic

(6 mos) Beta Blocker Therapy (Principal Investigator)
Allergan Corp. A Multi-Center, Double-Masked, Randomized, Parallel, Three-Month Study (with treatment extended to one year) of the Safety and Efficacy of AGN 192024 0.03% Ophthalmic Solution, Administered Once-Daily or Twice-Daily Compared with Timolol 0.5% Ophthalmic Solution Administered Twice-Daily, in Subjects with Glaucoma or Ocular Hypertension (Principal Investigator)
Allergan Corp. A Multi-Center, Double-Masked, Randomized, Split-Parallel Group Comparison of an Artificial Tear to Cyclosporine 0.1% Ophthalmic Emulsion used Twice Daily for up to Six Months in Patients with Mild to Moderate Keratoconjunctivitis Sicca. (Principal Investigator)
Atrium Medical Corp. Ocular Shunt for Glaucoma Treatment. (Co-Investigator)
Allergan Corp. A Multi-Center, Double-Masked, Randomized, Parallel Study of the Safety and Efficacy of 0.2% Brimonidine Tartrate/0.5% Timolol Combination Ophthalmic Solution Twice-Daily or Alphagan Three-Times-Daily for Three Months (Plus 9-Month, Masked Extension) in Patients with Glaucoma or Ocular Hypertension. (Principal Investigator)
Merck A Parallel, Randomized, Observer-Masked, Multi-Center Study Comparing the Ocular Hypotensive Effect of 2% Dorzolamide Hydrochloride/0.5% Timolol Maleate Ophthalmic Solution to the Concomitant Administration of 0.2% Brimonidine Tartrate Ophthalmic Solution and 0.5% Timolol Maleate Ophthalmic Solution in Patients with Ocular Hypertension or Primary Open Angle Glaucoma. (Principal Investigator)
Valley Forge A One-Year, Multi-Center, Double-Masked, Placebo-Controlled, Parallel, Safety and Efficacy Study of 2% Pirenzepine Ophthalmic Gel in Children with Myopia. (Principal Investigator)
Akorn Evaluation of PIROXICAM (0.3%) Ophthalmic Solution Versus Placebo in Inhibition of Intraoperative Miosis During Cataract Extraction. (Principal Investigator)
Whitaker Foundation Imaging the Healing Response of Glaucoma Implants. (Co-Investigator)
Allergan A Multicenter, Investigator-Masked, Randomized, Parallel Study of the Efficacy and Safety of AGN 192024 0.03% Ophthalmic Solution (QD) Compared with Latanoprost 0.005% Ophthalmic Solution (QD) in Patients with Glaucoma or Ocular Hypertension for 3 Months of Treatment (with Treatment Extended to Month 6). (Principal Investigator)
Allergan A Multicenter, Double-Masked, Randomized, Parallel, Extension Study Evaluating the Safety and Efficacy of AGN 192024 0.03% Ophthalmic Solution Compared with Timolol 0.5% Ophthalmic Solution, in Patients with Glaucoma or Ocular Hypertension.
Allergan Corp. Evaluation Refresh – Endura Tears in patients with dry eyes.. (Principal Investigator)
Valley Forge Use of pirenzpine for retardation of Myopic Progression in Children – Extension. (Principal Investigator)
Valley Forge Use of pirenzipine for retardation of Myopic Progression in Children – Open Label. (Principal Investigator)
Biogen ABI-007, Bone Marrow, Irofulven, IROF-007, Leukemia, Lung, OSI, Pancreatic. (Sub-Investigator)
Allergan Corp. Comparison of Bimatoprost and Latanoprost in the Treatment of Normal Tension Glaucoma. (Principal Investigator)
Allergan Corp. Efficacy of Brimonidine Purite 0.15% in Patients Presently on Latanoprost

Monotherapy. (Principal Investigator)
Allergan Corp. Hypotensive Lipids – EXT2. (Principal Investigator)
Allergan Corp. 48 Month trial for Memantine. (Principal Investigator)
Allergan Corp. Travatan versus Lumigan in African-Americans. (Principal Investigator)
Genentech Macular degeneration study (Marina) rhu Fab V2 vs Sham injection (Sub-investigator)
Genentech Macular degeneration study (Anchor) rhu Fab V2 vs Visudyne. (Sub-Investigator)
University of Arizona/RPB Genetic linkage study of primary open angle glaucoma in Mexican Americans (Principal Investigator)
University of Arizona/RPB Selenium levels in Glaucoma Patients. (Principal Investigator)
Lumenis SLT/Med Trial. (Principal Investigator)
University of Arizona/RPB Tear lactoferrin levels on glaucoma patients. (Principal Investigator)
Pharmacia (Pfizer) Xalatan –5 year safety study. (Principal Investigator)
Allergan IOP lowering efficacy of Bimatoprost and Latanoprost as adjunctive agents in subjects presently using Brimonidine. (Principal Investigator)
Valley Forge/Novartis Pirenzipine for Myopia – Open Label study 2nd year (Principal Investigator)
Merck Safety of Experimental Cardiovascular M132-03 Heart Study (Sub-Investigator)
Lumenis Evaluation of IPL for treatment of meibomian gland disease (Principal Investigator)
Ocular Therapeutics Evaluation of an Ocular Sealant in Cataract Surgery (Principal Investigator)
Aquesys/Allergan, Evaluaton of Aqueous Shunt to Decrease IOP (Principal Investigator)
Innfocus/Santen, Evaluation of IMS Aqueous Shunt to Decrease IOP (Principal Investigator)
Glaukos, Evaluation of microbypass shunt combined with cataract surgery to lower IOP in patients with glaucoma (Principal Investigator)

MEDICAL MONITOR
Lumenis November 2006- December 2008.
Ocular Therapeutics September 2011- 2017
SOLX, June 2012- 2017

SCIENTIFIC ADVISORY BOARDS
Inotek, November, 2104- 2018
EndoOptiks 2001-present

MEDICAL DIRECTOR
ISP Surgical Inc., 2016- present
Tula Medical, Inc 2017- present

PEER-REVIEWED JOURNAL ARTICLES

1. Kost J, Noecker R, Kunica E, Langer R. Magnetically controlled release systems: Effect of polymer composition. *J Biomedical Materials Research 19:935-940*; 1985.
2. Cowden K, Giammara B, Georgiade N, Noecker R, Hanker J. "Effects of Compression

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During Formation on the Mechanical Strengths and Physical Properties of Composite Hydroxyapatite/Plaster Implants for Bone Reconstruction. *Materials Research Society Symposium Proceedings 110:263-268;* 1987.

3. Noecker R, Branner W, Cohen K. Intraocular Lens Explantation with and without Penetrating Keratoplasty. *Ophthalmic Surgery 20:849-854;* 1989.
4. Cohen K, Tripoli N, Noecker R. Prospective Analysis of Photokeratoscopy for Arcuate Keratotomy to Reduce Postkeratoplasty Astigmatism. *Refractive and Corneal Surgery 5:388-393*; 1989.
5. Noecker RJ, Cohen KL. Contact lens related corneal ulcers. *NCMJ 51:269-271;* 1990.
6. Schuman JS, Jacobson JJ, Puliafito CA, Noecker RJ, Reidy WT. Experimental use of semiconductor diode laser in contact transscleral cyclophotocoagulation in rabbits. *Arch Ophthalmol 108(8):1152-1157;* 1990.
7. Schuman JS, Noecker RJ, Puliafito CA, Jacobson JJ, Shepps GJ, Wang N. Energy levels and probe placement in contact transscleral semiconductor diode laser cyclophotocoagulation in autopsy human eyes. *Arch Ophthalmol 109(11):1534-1538;* 1991.
8. Cook RL, Noecker RJ, Suits GW. Time allocation of students in a traditional curriculum. *Acad Med 67(4):279-281*; 1992.
9. Allinson RW, Metrikin DC, Fante R, Noecker R. Phacoemulsification by residents. *Ophthalmology 99:1481-2*; 1992.
10. Hodes BL, Noecker RJ, Prendiville, K. Autosomal dominant inheritance of iridogonio-dysgenesis and cataract. *Ophthalmology 100(2):168-172*;1993.
11. Noecker RJ, Allinson RW, Snyder RW. Resident phacoemulsification experience using the in situ nuclear fracture technique. *Ophthalmic Surg 25(4):216-21*; 1994.
12. Noecker RJ, Kramer TR, Ellsworth LG, Snyder RW. Endolenticular Phacovaporization of the lens in human autopsy eyes using the erbium:YAG laser: A histopathologic study. *SPIE Ophthalmic Technologies IV 2126:315-322;* 1994 .
13. Kramer TR, Noecker RJ, Ellsworth LG, Yarborough JM, Snyder RW. Laser trabecular ablation on human autopsy eyes using the erbium:YAG laser. *SPIE Ophthalmic Technologies IV 2126:242-250;* 1994.
14. Ellsworth LG, Kramer TR, Noecker RJ, Yarborough JM, Snyder RW. Retinotomy using erbium:YAG laser equipped with a contact probe on human autopsy eyes. *SPIE Ophthalmic Technologies IV 2126:101--108;* 1994.
15. Kramer TR, Noecker RJ, Miller JM, Clark MC. Langerhans cell histiocytosis with orbital involvement. *Am J Ophthalmol* 124(6):814-824; 1997.
16. Roh SY, Noecker RJ, Schuman JS. Evaluation of coexisting optic nerve head drusen and glaucoma with optical coherence tomography. *Ophthalmology 104(7):1138-1144*; 1997.
17. Latina MA, Sibayan SA, Shin DH, Noecker RJ, Marcellino G. Q-Switched 532 nm Nd:YAG laser trabeculoplasty (selective laser trabeculoplasty): a multicenter pilot, clinical study. *Ophthalmology 105(11):2082-2088; 1998.*
18. Roh SY, Noecker RJ, Schuman JS. Effect of optic nerve head drusen on nerve fiber layer thickness. *Ophthalmology 105(5):878-885; 1998.*
19. Boswell CA, Noecker RJ, Mac M, Snyder RW, Williams SK. Evaluation of an aqueous drainage glaucoma device constructed of ePTFE. *J Biomed Mater Res (Appl Biomater)*

48(5):591-595; 1999.
20. Noecker RJ, Golightly SF. Pharmacology of ocular surgery. *J Ophthalmic Nurs Technol, 18(3):101-108; May/June 1999.*
21. Noecker RJ. Changing the paradigm for first-line treatment may result in healthier, happier patients. *J Ophthalmic Nurs Technol 19(2):96-98; March/April 2000.*
22. Noecker RJ, Kramer TR. Comparison of the acute morphologic changes after selective laser trabeculoplasty and argon laser trabeculoplasty in human eye bank eyes. *Ophthalmology 108:773-779; 2001.*
23. Morgan P, Proniuk S, Blanchard J, Noecker RJ. Effect of temperature and light on the stability of latanoprost and its clinical relevance. *Journal of Glaucoma 10:401-405; 2001.*
24. Noecker R. Effects of common ophthalmic preservatives on ocular health. *Advances in Therapy 18(5):205-215; 2001.*
25. Stamer WD, Golightly SF, Hosohata Y, Ryan EP, Porter AC, Varga E, Noecker RJ, Felder CC, Yamamura HI. Cannabinoid CB_1 receptor expression, activation and detection of endogenous ligand in trabecular meshwork and ciliary process tissues. *European Journal of Pharmacology 431:277-286; 2001.*
26. Noecker RJ, et al. Brimonidine 0.2% as a replacement for beta blockers in geriatric patients with glaucoma. *Advances in Therapy 19(2):91-97; 2002.*
27. Noecker RJ, Dirks MS, Choplin NT, Bernstein P, Batoosingh AL, Whitcup SM. A six-month randomized clinical trial comparing the intraocular pressure-lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma. *Amer J Ophthalmol 135(1):55-63; 2003.*
28. Noecker RJ, Earl ML, Mundorf T, Peace J, Williams RD. Bimatoprost 0.03% versus travoprost 0.004% in black Americans with glaucoma or ocular hypertension. *Advances in Therapy 20(2):121-128; March/April 2003.*
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113. Lee D, Noecker, R. Combined ECP With Femtosecond Laser–Assisted Cataract Surgery in Patients With Glaucoma and Cataracts. ASCRS annual meeting, San Diego, CA April 20, 2015.
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LETTER/REPLIES TO COMMENTS

1. Noecker RJ: A six-month randomized clinical trial comparing the intraocular pressure-lowering efficacy of bimatoprost and latanoprost in patients with ocular hypertension or glaucoma (author's reply).
2. Noecker RJ, Dirks MS, Choplin N: Parrish et al. A comparison of latanoprost, bimatoprost and travoprost in patients with elevated intraocular pressure: a 12-week, randomized, masked-evaluator multicenter study (comment letter).
3. Noecker RJ, Dirks MS, Choplin NT, et al. 6-month comparison of bimatoprost and latanoprost (author's reply).

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Appendix B

APPENDIX B

LISTING OF MATERIALS CONSIDERED

EXHIBIT	DESCRIPTION
	Petition for *Inter Partes* Review (IPR2022-00142)
1001	U.S. Patent No. 8,293,742 (filed July 27, 2009) (issued Oct. 23, 2012) ('742 Patent)
1002	Expert Declaration of Neal A. Sher, M.D. (Sher) and the materials cited therein
1003	Expert Declaration of Paul A. Laskar, Ph.D. (Laskar) and the materials cited therein
1004	U.S. Patent No. 6,294,553 (filed Feb. 14, 2001) (issued Sep. 25, 2001) ('553 patent)
1005	Walters, Thomas R., et al. "A Pilot Study of Life Efficacy and Safety of AGN 190342-Lf 0.02% And 0.08% In Patients with Elevated Intraocular Pressure." Association for Research in Vision and Ophthalmology, vol. 32, no. 4, 15 Mar. 1991, p. 988 (Walters 1991)
1006	Norden, Richard A. "Effect of Prophylactic Brimonidine or Bleeding Complications and Flap Adherence after Laser in Situ Keratomileusis." Journal of Refractive Surgery, vol. 18, no. 4, 2002, pp. 468–471 (Norden 2002)
1007	U.S. Patent 6,242,442 (filed Dec. 7, 1999) (issued June 5, 2001) ('442 patent)
1008	"ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.2%." Physicians' Desk Reference, 52th ed., Medical Economics Company, Inc., 1998, p. 487 (Alphagan® Label 1998)
1009	53 Fed. Reg. 7076-7093 (Mar. 4, 1988) (Federal Register 1988)
1016	Griffith, Robert K. "Adrenergics and Adrenergic- Blocking Agents." Burger's Medicinal Chemistry and Drug Discovery, edited by Donald J. Abraham, 6th ed., vol. 6, John Wiley & Sons, Inc., New York, NY, 2003, pp. 2–37 (Griffith 2003)

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