

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

IN RE LUMIFY

Civil Action No. 21-16766 (RK) (RLS)
(CONSOLIDATED)

Document Electronically Filed

**DECLARATION OF DR. WILLIAM B. TRATTler IN
SUPPORT OF PLAINTIFFS' OPENING MARKMAN BRIEF**

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I. QUALIFICATIONS

1. I, William B. Trattler, M.D., submit this declaration at the request of Plaintiffs Bausch & Lomb, Inc. and Bausch & Lomb Ireland Limited and Eye Therapies, LLC, as a medical expert in the field of ophthalmology, including cataract, corneal and refractive surgery. My qualifications in these areas, as well as other areas, are established below and by my curriculum vitae, which is attached as Appendix A.

2. I am an ophthalmologist specializing in refractive, corneal and cataract eye surgery at the Center for Excellence in Eye Care in Miami, FL, where I have practiced since July 1997. I perform a wide variety of cataract and refractive surgeries, including photorefractive keratectomy (“PRK”), all laser LASIK, and no-injection sutureless cataract surgery as well as laser cataract surgery.

3. I received my Bachelor of Arts degree in biology from Dartmouth College in 1988 and my M.D. degree, with research distinction, from the University of Miami School of Medicine in 1992. I completed an internal medicine internship at Mount Sinai Medical Center in June 1993, an ophthalmology residency at the University of Pennsylvania Scheie Eye Institute in July 1996, and a cornea and external disease fellowship from the University of Texas-Southwestern Medical Center in 1997. I received board certification in ophthalmology in October 1998, and in January 2009 I was recertified through 2018.

4. While practicing at the Center for Excellence in Eye Care, I also served on the surgical staff of the V.A. Hospital in Miami from July 1997 through July 2001, supervising University of Miami ophthalmology residents in surgery and in the clinic. I additionally assisted at the Bascom Palmer Eye Institute on a part-time basis from July 2002 through July 2006, supervising residents in the eye emergency department and instructing residents in cataract and

corneal surgery. From 2002 to the present, I also have worked as a volunteer for the Good News Care Center in Miami, which provides free medical services to uninsured low-income patients regardless of race, occupation, national origin or immigrant status. In this role, I have provided between 50 and 100 free examinations and 5 to 10 free surgeries to low-income patients each year.

5. I also have held multiple academic appointments during my career as an ophthalmologist. From July 2000 through 2017, I have been a Volunteer Assistant Professor of Ophthalmology at the Bascom Palmer Eye Institute. From January 2012 through the present, I have been a volunteer faculty member in the Department of Ophthalmology at the Herbert Wertheim College of Medicine at Florida International University. I have also served on the Volunteer Faculty for the Larkin Hospital Ophthalmology Residency Program.

6. I have received numerous awards and honors over the course of my professional career, including an Achievement Award and Senior Achievement Award from the American Academy of Ophthalmology, the Curtis D. Benton, Jr., M.D. Outstanding Young Ophthalmologist Leadership Award presented by the Florida Society of Ophthalmology, and the Scheie Eye Institute Teaching Award on two separate occasions. I have been qualified and listed as a Trusted LASIK Surgeon, a LASIK directory service that screens surgeons based on experience, premier patient care and professional credentials. I also have been voted by readers of the publication *Cataract and Refractive Surgery Today* as a top 50 opinion leader in the field of cataract and refractive surgery. I have received a Patient Choice Award and, for the past several years, have been elected to Best Doctors in America. I also have been selected by my peers as a Florida Super Doctor for South Florida, a distinction bestowed upon the top 5% of South Florida doctors, based on peer nominations as well as a panel review process and independent research on candidates. A full list of awards and honors I have received can be found in my curriculum vitae.

7. I have conducted research in the field of ophthalmology for over 30 years and have been an investigator on approximately 70 clinical trials for ophthalmic products, a full list of which can be found in my curriculum vitae. I have conducted clinical trials for ophthalmic formulations that led to their approval by the U.S. Food and Drug Administration (“FDA”).

8. I have authored scores of publications in both peer-reviewed and non-peer reviewed journals, and I have co-authored five textbooks and two chapters in textbooks. I also have co-authored chapters in four different online textbooks. A full list of my publications can be found in my curriculum vitae.

9. I regularly attend a variety of scientific meetings in the field of ophthalmology and have given hundreds of presentations at these meetings. I also have served on a number of scientific panels, as both a panelist and moderator. I have given numerous lectures to local ophthalmology and medical groups. A full list of these activities can be found in my curriculum vitae.

10. I have served as a reviewer for the American Academy of Ophthalmology, and I currently serve as a peer reviewer for five journals: *Ophthalmology*, *Journal of Cataract and Refractive Surgery*, *Cornea*, *American Journal of Ophthalmology*, and *Ophthalmic Research*. I also have served on the editorial boards for several publications, which are listed in my curriculum vitae.

11. I have been a member of several professional associations for many years. I have been a member of the American Academy of Ophthalmology since 1996 and have served in various capacities, including on the Annual Meeting Program Committee for Refractive Surgery, on the Ophthalmic Technology Assessment Committee Refractive Surgery Panel, and as Chairperson of the Refractive Management/Intervention Panel. Since 1997 I have been a member of the American Society of Cataract and Refractive Surgery, as well as the Miami Ophthalmology

Society, for which I served as Secretary in 2004, Treasurer in 2005 and President in 2006. Since 2000 I have been a member of the Florida Society of Ophthalmology, and since 2007 I have been a member of The Cornea Society. I also have been a member of the International Society of Refractive Surgery since 2007 and was appointed to the Executive Board in 2011. I am a founding board member of the American-European Congress of Ophthalmic Surgery and a founding member of CEDARS, which stands for Cornea, External Disease and Refractive Surgeons. A full list of these activities can be found in my curriculum vitae.

12. I routinely see patients with eye redness (ocular hyperemia) caused from various conditions and treatments. I am familiar with the well-known commercial redness relievers like VISINE and others that existed before the earliest filing date of the patent that is the subject of this matter (U.S. Patent No. 11,596,600 (“the ’600 patent”)) and the development of the product known as Lumify. I have worked with Lumify in my practice and have recommended it patients presenting with eye redness.

13. 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.

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

II. DOCUMENTS AND INFORMATION CONSIDERED

15. In preparing my declaration accompanying Plaintiffs’ Opening *Markman* Brief, dated December 1, 2023, I have in particular considered the ’600 patent, including its claims and written description (i.e., the patent specification) as well as the public record of the ’600 patent’s examination before the U.S. Patent and Trademark Office (“USPTO”), also referred to as the

prosecution history. I have also relied on my professional and academic experience in the area of ophthalmology.

III. STATEMENT OF OPINIONS EXPRESSED AND BASES AND REASONS THEREFOR

A. Legal Standard

16. I have no formal legal training, but I have been informed by Plaintiffs' counsel about the appropriate legal standards as set forth below. In the event there are any modifications to the legal standards applicable to this declaration, I reserve the right to supplement my declaration to take into account any such modifications.

17. I have been informed and understand that a patent includes a specification containing the written description of one or more embodiments of the invention, drawings, and figures, as well as one or more claims that point out and claim the subject matter of the invention. The claims set forth the bounds of a patented invention's scope. Each claim defines a separate invention. I have also been informed and understand that a dependent claim incorporates each and every element of the claim from which it depends.

18. I have been informed and understand that the patent claims, and their terms and phrases, are interpreted by the Court according to their ordinary and customary meaning to a person of ordinary skill in the art at the time the application for patent was filed. 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 language of other claims, the patent specification and the prosecution history. I understand the claims, specification and prosecution history form the intrinsic record for purposes of claim construction.

19. I have been informed that for claim construction purposes the specification can act as a dictionary, explaining the invention and how terms may be used in the claims. A construction

of a term should be consistent with the specification and should most naturally align with the specification's description of the invention. I have also been informed that the prosecution history is also important in construing patent claims. It represents the result of a negotiation between the USPTO examiner and the patent applicant, and culminates in allowable subject matter covered by the claims of the issued patent. I understand it often happens that originally filed claims become narrowed during prosecution as part of that negotiation process, possibly informing the meaning of claim language by demonstrating how the inventor understood the invention as different, for example, from the prior art. As such, express representations made by the applicant to the examiner to convince the examiner of patentability and induce the patent grant can impact the claim scope.

20. I understand that evidence extrinsic to the patent and its prosecution history may also be consulted, so long as it is not inconsistent with the claim language, the patent specification and the prosecution history. Such extrinsic evidence can include expert testimony. It can be useful to a court to provide background on the technology to which the invention pertains, how the invention works, to ensure that the court's understanding of the technical aspects of the patent is consistent with that of a person of ordinary skill in the art, or to establish that a term in a patent has a particular meaning in the pertinent field.

B. Person of Ordinary Skill in the Art

21. I have reviewed the '600 patent and the prosecution history of the '600 patent. I understand that the '600 patent claims priority to a provisional application filed on August 1, 2008. Based on my review of the '600 patent and its file history, I have considered the qualifications of a person of ordinary skill in the art ("POSA") at the time of the August 1, 2008, priority date of the '600 patent.

22. The field to which the '600 patent pertains is interdisciplinary. The POSA 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. The POSA would also have had access to team members 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.

23. I understand that Defendants have proposed that the POSA “was a composite person (or team) that included a medical doctor and a pharmaceutical formulator. The 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. The 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.” While I disagree with this definition, regardless of which definition is applied, my opinions with respect to the ’600 patent would not change.

24. As of the filing date of the ’600 patent (August 1, 2008), I would have been considered at least a person of ordinary skill in the art to which the invention of the ’600 patent pertains, under both Plaintiffs’ and Defendants’ definitions.

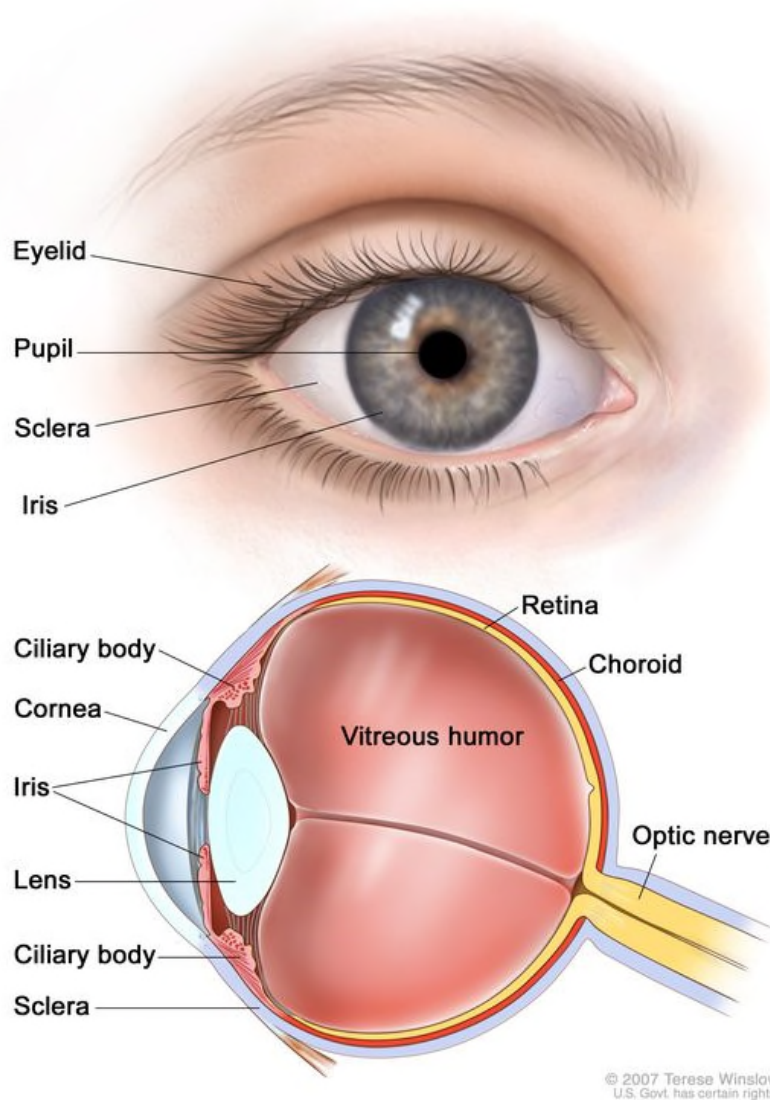
C. Technical Background

1. The Field to Which the ’600 Patent Pertains

25. The field to which the invention of the ’600 patent pertains involves ophthalmic products topically administered to reduce eye redness or ocular hyperemia. Ex.¹ 1 (’600 patent) at 4:40-5:6, 5:51-61, 7:24-33, 14:21-29. Such ophthalmic products target parts of the eye known as

¹ The exhibits referenced herein are attached to the Declaration of Bryan C. Diner in Support of Plaintiffs’ Opening *Markman* Brief.

the conjunctiva, the episclera, and the sclera, which can be seen in the illustration below. *Id.* at 1:23, 14:21-23, 30-36.



26. As seen in this illustration of parts of a human eye, the sclera is the visible “white” of the eye that provides a protective covering of the eyeball. The conjunctiva is a clear, thin tissue that covers the sclera. The sclera consists of several layers, including the episclera, which is a thin tissue resting on the outer surface of the eyeball. The conjunctiva, episclera, and sclera all have blood vessels, which, when dilated, present as eye redness.

27. Eye redness or hyperemia refers to an ocular condition caused by vasodilation—an increase in the diameter of the blood vessels due to the influx of blood. Ex. 1 ('600 patent) at 1:20-25. The dilated blood vessels become congested and engorged with blood, making the eyes appear red or hyperemic. *Id.* at 4:49-51. Conversely, constricting dilated ocular blood vessels will decongest them, which on the surface can reduce redness and make the eyes appear whiter but can also cause an ischemic condition. *Id.* at 4:55-61. This is known as vasoconstriction.

28. Ocular vasodilation and vasoconstriction are mediated by the alpha-adrenergic receptors, which are complex and present different effects depending on which tissue is being considered. Although there are multiple subtypes of alpha-adrenergic receptors, for simplicity, I will focus on two major subtypes in the eye: α -1 and α -2 (which have their own subtypes themselves). Ex. 1 ('600 patent) at 1:29-31, 2:5-7, 11-14, Ex. 2 (Derick 1995) at 2. Agents that activate these α -receptors, respectively, are known as α -1 and α -2 agonists. *Id.* In 2008, it was understood that α -1 agonists trigger an excitatory response (so-called “fight or flight” response) that contracts smooth muscles, thereby constricting blood vessels and reducing eye redness. Ex. 3 (Griffith 2003) at 12-13; Ex. 4 (Burke 1996) at 2. This is known as an “ α -1 effect.” By contrast, α -2 agonists were typically known to trigger a relaxation response that decontracts smooth muscles, thereby dilating blood vessels and causing eye redness. *Id.*; Ex. 5 (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. 4 (Burke 1996) 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”). This is known as an “ α -2 effect.”

29. Alpha-adrenergic receptor agonists fall into three categories: selective α -1, mixed α -1/ α -2, and selective α -2. Whether a particular agonist interacts with an α -1 or α -2 receptor depends on its selectivity, which refers to the propensity of a drug to interact with a specific receptor subtype. If a compound is 100% selective, it would only interact with the receptor for which it is selective. But sometimes a compound may be a “highly selective” agonist at a level of, e.g., 99.9%, such that at high concentrations it may interact with the other receptor. For example, high concentrations of a selective α -2 agonist may trigger a low α -1 effect and cause vasoconstriction. Brimonidine is a highly selective α -2 agonist and is at least **1000-fold more selective** for the α -2 receptors than the α -1 receptors. Ex. 1 ('600 patent) at 11:66-12:1; Ex. 4 (Burke 1996) at 2, Fig. 1.

2. Prior Commercial Redness Relievers

30. Because reduction in redness was recognized in the art as an α -1 effect, all FDA-approved redness relievers before the filing of the '600 patent contained either selective α -1 receptor agonists or mixed α -1/ α -2 receptor agonists—including the VISINE products (tetrahydrozoline), All Clear (naphazoline), and Ocu-Clear (oxymetazoline). In general, eyecare professionals, including myself, did not recommend these products to patients because of common side effects, such as rebound hyperemia and tachyphylaxis, but they knew that patients used these OTC eye redness relievers and accepted them as the standard of care for eye redness due to the lack of better options available at the time.

31. Unfortunately, despite being the standard of care and accepted by consumers, these OTC redness relievers suffered from frequent adverse side effects, including rebound hyperemia and tachyphylaxis. Ex. 1 ('600 patent) at 16:2-7. Rebound hyperemia occurs, for example, after the vasoconstrictive effects of the redness reliever wear off and compensatory vasodilation occurs to flood/engorge the vessels with blood to bring in the needed oxygen. Eyes with rebound

hyperemia thus present with more redness than before instillation of the redness reliever. *Id.* at 4:46-51. Tachyphylaxis is a medical condition that manifests as a rapid decrease in drug effectiveness after repeated uses over time. It could prompt consumers to instill more drops more frequently to obtain the same level of whitening, unwittingly leading to misuse and overuse of the drug. The continued overuse of the drug could lead to ocular toxicity as well as chronic swelling and redness (medicamentosa) even after discontinuation. *Id.* at 4:52-54.

32. This changed when Lumify launched. Eyecare professionals, including myself, were surprised by the lack of side effects that were once thought to be inevitable results of using an eye redness reliever and started recommending Lumify to patients.

3. **Brimonidine was Previously Approved to Treat Glaucoma and Reduce Intraocular Pressure**

33. Brimonidine tartrate is the active ingredient in various FDA-approved Alphagan products for treating glaucoma and reducing intraocular pressure (IOP): Alphagan (0.5% and 0.2% brimonidine) and Alphagan P (0.15% and 0.1% brimonidine). As discussed, brimonidine is a highly selective α -2 receptor agonist and is at least **1000-fold more selective** for the α -2 receptors than the α -1 receptors. Ex. 1 ('600 patent) at 1:63-64, 2:14-16; 10:52-58; 11:66-12:1; Ex. 6 (Scruggs 2000) at 5; Ex. 4 (Burke 1996) at 2, Fig. 1. Due to brimonidine's disproportionately high selectivity for the α -2 receptor, it was also known to cause ocular vasodilation and thus hyperemia. '600 patent, 2:14-17. Although at high concentrations, brimonidine could vasoconstrict because such concentrations could trigger brimonidine's low α -1 effect. 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. 7 (Alphagan® Label 1998) at 3; Ex. 8 (Alphagan® Label 2001) at 9, 14.

D. The '600 Patent

1. Asserted Claims

34. I understand that the claims at issue for the '600 patent are claims 12 and 28. Both claims depend from claim 1. Claim 12 further limits claim 1 by reciting that “the eye redness of said human is not associated with an ocular disease or the result of a surgical procedure on the eye.” Written in independent form, claim 12 reads as follows:

12. A method for reducing eye redness in a human subject having ocular hyperemia, comprising topically administering to an eye of said human in need of said reduction of eye redness an ocular drop comprising about 0.025% weight by volume brimonidine as the sole active ingredient, wherein the ocular drop has a pH between 5.5 to 6.5, and wherein the eye redness of said human is not associated with an ocular disease or the result of a surgical procedure on the eye.

Ex. 1 ('600 patent) at 22:34-39, 23:1-3.

35. Claim 28 further limits claim 1 by reciting that the amount of brimonidine administered in the method of claim 1 is 0.025%, and when written in independent form reads as follows:

28. A method for reducing eye redness in a human subject having ocular hyperemia, comprising topically administering to an eye of said human in need of said reduction of eye redness an ocular drop comprising 0.025% weight by volume brimonidine as the sole active ingredient, wherein the ocular drop has a pH between 5.5 to 6.5, and wherein the weight by volume brimonidine is 0.025%.

Ex. 1 ('600 patent) at 22:34-39, 24:22-23.

2. Specification

36. The '600 patent describes administering low-concentration brimonidine to achieve more effective vasoconstriction and reduce eye redness with significantly less rebound hyperemia compared to prior art redness relievers. Ex. 1 ('600 patent) at 2:43-55; 4:40-54, 4:62-5:6. The first

substantive paragraph of the specification identifies eye redness with conjunctival hyperemia. *Id.* at 1:23 (referring to “eye redness (conjunctival hyperemia)”). A POSA would appreciate that reducing eye redness in the conjunctiva, sclera and episclera makes the eyes appear whiter. Indeed, the '600 patent specification describes inventive methods of using brimonidine to achieve “a more effective scleral whitening (i.e., whiter shades of scleral color) than possible with prior art compositions and methods, as a result of more effective vasoconstriction....” *Id.* at 14:30-36. It discloses, moreover, several clinical studies substantiating this claim (e.g., Examples 1, 4, and 5 and the studies embodied in Figures 5A-C.)

37. The low-concentration brimonidine used in the compositions of the methods for reducing redness can range from about 0.0001% to about 0.05% (3:60-65), and the specification identifies various preferred amounts including about 0.025%, which it identified as preferred over twenty times, either alone or as part of a range. *See, e.g.*, Ex. 1 ('600 patent) at 4:8-13, 5:65-67, 6:8-11, 7:19-23, 8:26-30, 11:47-52. The specification discloses various inventive embodiments, some of which dose brimonidine in combination with other active ingredients (*See, e.g., id.* at 9:53-55, 15:61 to 17:3, 16:57-58 and 65-66) and others that dose brimonidine as the sole active ingredient, *see id.* at 7: 34-40, 8:19-25, 9:46-49, 10:21-26, Examples 1, 4, and 5 and the studies embodied in Figures 5A-C.

38. In Example 1 (col. 20), a patient having ocular hyperemia, as shown by the patient's baseline eye redness in Fig. 4A, was treated in the left eye with various low-doses of brimonidine as the sole active ingredient in accordance the invention disclosed in the '600 patent. Ex. 1 ('600 patent) at 20:36-67. In the patient's right eye, for comparative purposes, 0.05% tetrahydrozoline was initially instilled. After three hours, Fig. 3B visibly shows that 0.01% brimonidine reduced the patient's ocular hyperemia much more effectively than 0.05% tetrahydrozoline. A similar

experiment was done to compare 0.025% oxymetazoline with 0.02% brimonidine, and the results in Fig. 4C demonstrated the superiority of 0.02% brimonidine to reduce the patient's hyperemia after 4 hours than 0.025% oxymetazoline. The same results occurred when 0.2% brimonidine was compared against 0.033% naphazoline, as visibly shown in Fig. 4D. Example 1 concludes that these "results clearly demonstrate significant scleral whitening brightening effects of treatment with brimonidine as compared with treatment with prior art compositions." *Id.* at 20: 41-43.

39. Example 4 of the '600 patent is another clinical study that compared the eye redness reducing ability in fifteen patients between 0.018% brimonidine, administered as the sole active ingredient in one eye, and VISINE Original® (tetrahydrozoline) administered as the sole active ingredient in the other eye of each patient. Ex. 1 ('600 patent) at 21:57 to 22:19. After a single application, 0.018% brimonidine exhibited a reduction in redness score of 68.71% compared to 31.06% for VISINE Original®. *Id.* at 22:1-6. Additionally, when brimonidine was administered at 0.05% to fifteen patients as the sole active ingredient, only one patient experienced rebound hyperemia (6.6%), whereas 26.6% of those patients experienced rebound hyperemia with VISINE Original®. *Id.* at 22:7-10.

40. Example 5 is a clinical study involving seven patients with chronic red eyes. Ex. 1 ('600 patent) at 22:21-31. One of the patients was treated with 0.015% brimonidine alone, while the eye received Naphcon-A®. *Id.* In a patient satisfaction assessment, all patients reported reduced redness with 0.015% brimonidine and 42% of them preferred brimonidine, whereas none preferred Naphcon-A®. *Id.* 22:27-31.

3. File History

41. I have reviewed the file history of the '600 patent before the U.S. Patent and Trademark Office ("USPTO"). I summarize the relevant parts bearing on the claim construction issues on which I have been asked to provide my opinion. The application that became the '600

patent was filed on January 22, 2022. It was allowed on November 4, 2022, and granted as the '600 patent on March 7, 2023. Between the filing of the application and its allowance, two substantive office actions were issued by the USPTO Patent Examiner to which the Patentee submitted two corresponding responses.

42. As filed, application claim 1 read as follows:

1. A method for reducing eye redness in a human subject resulting from an ocular condition, comprising topically administering to an eye of said human an ocular drop comprising about 0.025% weight by volume brimonidine as the sole active ingredient, wherein the ocular drop has a pH between 5.5 to 6.5.

Ex. 1 ('600 patent) at 22:34-39.

43. The first office action issued on August 5, 2022. I understand that the Patent Examiner rejected all pending claims in the application, including claim 1, for reasons relating to the clarity of the claims under, as I am informed, 35 U.S.C. § 112(b). Ex. 9 ('600 patent file history, August 5, 2022 Office Action at 4). I also understand that the Patent Examiner issued two rejections of claim 1 for obviousness under, as I am informed, 35 U.S.C. § 103 in view of several prior art documents, including Ex. 15 (U.S. Patent Application No. 2001/0031754 to Gil et al. ("Gil")), Ex. 10 (U.S. Patent No. 6,242,442 to Dean et al. ("Dean")), and Ex. 16 (U.S. Patent Application No. 2004/0219219 to Graham et al ("Graham")). *Id.* at 9, 16.

44. Regarding the clarity rejection, which I have been informed can also be referred to as an indefiniteness rejection, the Patent Examiner alleged that "eye redness" resulting from "an ocular condition" was indefinite. Ex. 9 ('600 patent file history, August 5, 2022 Office Action at 4). In the November 4, 2022 Response to Office Action, the Patentee amended claim 1 to delete "resulting from an ocular condition" and to more particularly describe the human subject as "having ocular hyperemia" and, relatedly, as being "in need of said reduction of eye redness." As amended, claim 1 read as follows (deletions in strikethrough and additions in underline):

1 (Amended). A method for reducing eye redness in a human subject having ocular hyperemia ~~resulting from an ocular condition~~, comprising topically administering to an eye of said human in need of said reduction of eye redness an ocular drop comprising about 0.025% weight by volume brimonidine as the sole active ingredient, wherein the ocular drop has a pH between 5.5 to 6.5.

Ex. 17 ('600 patent file history, November 4, 2022 Response to Office Action at 2).

45. The Patentee addressed this rejection and the claim amendments in the “Remarks” section of the November 2022 response. *Id.* at 7. The Patentee stated that “[c]laim 1 has been amended to recite that the human has ocular hyperemia, which is eye redness caused by dilation of intact blood vessels in the conjunctiva, episclera and sclera, where such redness can be reduced by vasoconstriction of those blood vessels.” *Id.* It also emphasized that eye redness as used in the claim 1 of the application (i.e., ocular hyperemia) is different from eye redness resulting from subconjunctival hemorrhage. The Patentee specifically stated “[o]cular hyperemia is different than eye redness caused by subconjunctival hemorrhage, which is typically the result of trauma that breaks the ocular blood vessels, resulting in blood pouring out and settling beneath the conjunctiva. (citation omitted.) Redness resulting from subconjunctival hemorrhage cannot be reduced by vasoconstriction of the broken blood vessels.” *Id.* The amendment and related arguments obviated the rejection, as the Patent Examiner did not reassert it in the next office action.

46. In the first obviousness rejection, the Patent Examiner alleged that the method of claim 1, among other claims, was obvious in view of Gil and Dean. In the second obviousness rejection, the Patent Examiner asserted that the claim 1 method was obvious in view of Dean, Gil, and Graham. Ex. 9 ('600 patent file history, August 5, 2022 Office Action at 16). The Patentee argued that the Patent Examiner’s combination of Gil and Dean was fatally defective. Ex. 17 ('600 patent file history, November 4, 2022 Response to Office Action at 12-14). The arguments made to distinguish Dean are particularly relevant.

47. Specifically, the Patentee argued that “Dean is not directed to treating eye redness, nor does it suggest using brimonidine, let alone low-dose brimonidine as the sole active ingredient, to affirmatively reduce eye redness in a patient having ocular hyperemia. Rather, Dean is directed to **combinations** of brinzolamide and brimonidine for treating a different condition, i.e., lowering intraocular pressure (IOP).” *Id.* at 12 (emphasis in original). The Patentee further argued that Dean is “far from guiding the skilled artisan to about 0.025% as the **sole active ingredient** to affirmatively reduce redness in a person having ocular hyperemia...” and that “[t]his preferred range would have led the skilled person, if anywhere, to concentrations much higher than the instantly claimed concentrations of about 0.025% as the sole active.” *Id.* at 13.

48. The Patentee continued to distinguish Dean, further characterizing how the claimed invention should be understood by a POSA: “At bottom, while Dean hypothesizes that lowering the dose of brimonidine could reduce the *incidence* of hyperemia, it does not teach or suggest that low dose brimonidine as the sole active can reduce redness,” and “[t]he invention here demonstrates that low-dose brimonidine, used on a human subject having ocular hyperemia, affirmatively *reduces* eye redness: whereas Dean suggests that lowering the dose of brimonidine *my induce* less redness (as a side effect), but does not teach or suggest *reducing redness* in a subject *having* ocular hyperemia.” *Id.* (emphasis in original).

49. In the second Office Action of December 1, 2022, the Patent Examiner stated that rejections not repeated from the previous office action were withdrawn. Ex. 18 (’600 patent file history, December 1, 2022 Office Action at 2-3). The clarity rejection was not repeated. Nor did the Patent Examiner repeat the two obviousness rejections. Thus, all of these rejections were withdrawn in view of the Patentee’s amendments and arguments. The Patent Examiner maintained a previous rejection under obviousness-type double patenting in view of several related patents.

Id. at 4-6. I understand that the Patentee filed a terminal disclaimer to remove this obviousness-type double patenting rejection, and the application was allowed. Afterwards, I understand that the Patentee paid a USPTO fee to have the application issue as a patent, and the '600 patent subsequently issued on March 7, 2022.

E. Disputed Phrase: “[human] in need of said reduction of eye redness” (Claims 12 and 28)

50. I understand that Defendants dispute the meaning of the claim phrase “human in need of said reduction of eye redness” recited in claim 1, which I understand is incorporated in claims 12 and 28 because they each depend from claim 1. The parties’ proposed constructions for this phrase are shown below.

Plaintiffs’ Construction	Defendants’ Construction
“a human having ocular hyperemia, where such hyperemia is reduced by vasoconstriction.”	“having ocular hyperemia”

51. Based on my review of the claims, the specification, and the prosecution history, I believe that a POSA would have understood this phrase to mean “a human having ocular hyperemia, where such hyperemia is reduced by vasoconstriction,” as Plaintiffs have proposed.

52. As an initial matter, a POSA would have understood “eye redness” in the disputed phrase to mean ocular hyperemia. That is clear from what I understand is called the “preamble” of the claim, which defines the human subject as one with ocular hyperemia. This understanding is consistent with the specification, which identifies eye redness with conjunctival hyperemia (Ex. 1 ('600 patent) at 1:23 (...“eye redness (conjunctival hyperemia)...”) and notes several conditions that will make the eyes appear red or hyperemic. *Id.* at 2:27-30. The prosecution history similarly supports this understanding, where the Patentee equated eye redness with ocular hyperemia to address the indefiniteness rejection relating to “eye redness” resulting from an “ocular condition.”

Specifically, the Patentee stated “[c]laim 1 has been amended to recite that the human has ocular hyperemia, which is eye redness” Ex. 17 (’600 patent file history, November 4, 2022 Response to Office Action at 7).²

53. Thus, the object of the human subject’s “need” as recited in disputed phrase is to reduce the person’s eye ocular hyperemia (i.e., eye redness). Reading the disputed phrase in context of the administering step of which it is part together with the ’600 patented method generally, a POSA would have understood that human subject’s hyperemia is reduced by vasoconstriction. Both the specification and the prosecution support this understanding.

54. The specification describes a key discovery of the invention as ***achieving*** significantly reduced hyperemia with more effective vasoconstriction. Ex. 1 (’600 patent) at 2:50-55 (“One of the key discoveries of the present invention lies in using low doses of highly selective α -2 adrenergic receptor agonists to achieve vasoconstriction with significantly reduced hyperemia.”) It teaches inventive methods of using brimonidine to achieve “a more effective scleral whitening (i.e., whiter shades of scleral color) than possible with prior art compositions and methods, as a result of more effective vasoconstriction....” *Id.* at 14:30-36. It discloses, moreover, several clinical studies substantiating this teaching with low-concentration brimonidine. *See, e.g., id.* at Examples 1, 4, and 5 and the studies embodied in Figures 5A-C.

² Relatedly, a POSA would understand that eye redness as used in claim 1 is not the type of red eye that may result from subconjunctival hemorrhage. They are completely different ocular conditions. Ocular hyperemia can be reduced by vasoconstriction of dilated blood vessels, as the prosecution history correctly points out. Ex. 17 (’600 patent file history, November 4, 2022 Response to Office Action at 7). Once it occurs, subconjunctival hemorrhage cannot be reduced by vasoconstriction. This is because, as the prosecution history explains and as a POSA would fully appreciate, subconjunctival hemorrhage occurs when ocular blood vessels are broken, resulting in blood pouring out and settling beneath the conjunctiva. *Id.* Vasoconstriction of the broken blood vessels will not reverse or reduce the hemorrhage. *Id.* Subconjunctival hemorrhage will only dissipate with the passage of time.

55. The prosecution history provides further support. In overcoming the indefiniteness rejection, the Patentee amended the claim “to recite that the human has ocular hyperemia, which is eye redness ..., where such redness can be reduced by vasoconstriction of blood vessels.” Ex. 17 (’600 patent file history, November 4, 2022 Response to Office Action at 7). It further argued in distinguishing Dean that “[t]he invention here demonstrates that low-dose brimonidine, used on a human subject having ocular hyperemia, affirmatively *reduces* eye redness....” *Id.* at 13 (emphasis in original). The Patentee continues to emphasize that the claimed method requires achieving redness reduction: “[N]or does [Dean] suggest using brimonidine, let alone low-dose brimonidine as the sole active ingredient, ***to affirmatively reduce eye redness in a patient having ocular hyperemia.***” *Id.* (emphasis added). And Dean is “far from guiding the skilled artisan to about 0.025% as the sole active ingredient ***to affirmatively reduce redness in a person having ocular hyperemia...***” *Id.* (emphasis added).

56. In view of the claims, the specification, and the prosecution history, therefore, it is my opinion that a POSA would have understood “human in need of said eye redness reduction” to mean “a human having ocular hyperemia, where such hyperemia is reduced by vasoconstriction.”

57. I disagree with Defendants’ interpretation of this phrase because their proposal seems to just interpret what eye redness means, that is, ocular hyperemia. But that is already stated in the preamble, rendering Defendants’ interpretation entirely duplicative of separate language in the claim. Further, Defendants’ proposed construction does not seem to address the “in need of” language that is integral to the disputed phrase and part of the administering step. Defendants’ proposal also seems to ignore both the specification and the prosecution history, which, in my opinion, clearly inform a POSA that the human subject of the ’600 patent methods has ocular hyperemia and that that person’s hyperemia is reduced by vasoconstriction.

F. Disputed Phrase: “as the sole active ingredient” (Claims 12 and 28)

58. I understand that Defendants dispute the meaning of the claimed phrase “as the sole active ingredient” recited in claim 1, which is incorporated in claims 12 and 28 as they depend from claim 1. Below I provide Plaintiffs’ and Defendants’ constructions for this phrase.

Plaintiffs’ Construction	Defendants’ Construction
“[administering brimonidine] as the only active ingredient to affirmatively reduce redness in a person having ocular hyperemia.”	“without any other active ingredient in the ocular drop”

59. Reviewing the disputed phrase in context of the ’600 patented method generally and with benefit of the specification and prosecution history, it is my opinion that a POSA would have understood “as the sole active ingredient” to mean “administering brimonidine as the only active ingredient to affirmatively reduce redness in a person having ocular hyperemia.”

60. In the claims, the reference to brimonidine as the sole active ingredient would have been read and understood by a POSA as pertaining to the claimed method as a whole. The POSA would have understood the “ocular drop” as merely the vehicle for administering brimonidine as the sole active agent in the claimed method. As such, whether one or multiple ocular drops are topically administered to reduce a person’s ocular hyperemia according to the ’600 patented method, a POSA would have understood all administered medicated drops to contain brimonidine as the lone active ingredient. That understanding is consistent with the specification and prosecution history.

61. A POSA would have read the prosecution history and understood the Patentee to clearly convey that brimonidine is the sole active ingredient used in the claimed invention. In fact, the Patentee distinguished the invention from Dean on this very basis. Specifically, Dean taught combining brimonidine and brinzolamide in the same dosage protocol, either together or

sequentially, to treat diseases like glaucoma and diabetic retinopathy. Ex. 10 (Dean) at 2:55-57 (“When two separate formulations of brinzolamide and brimonidine are used, the preferred administration sequence is brimonidine first and brinzolamide second.”). The Patentee consistently argued that “Dean is not directed to treating eye redness, nor does it suggest using brimonidine, ***let alone low-dose brimonidine as the sole active ingredient***, to affirmatively reduce eye redness in a patient having ocular hyperemia.” Ex. 17 (’600 patent file history, November 4, 2022 Response to Office Action at 13) (emphasis added). “Rather, Dean is directed to ***combinations*** of brinzolamide and brimonidine for treating a different condition, i.e., lowering intraocular pressure (IOP).” *Id.* (emphasis in original). And Dean is “far from guiding the skilled artisan to about 0.025% ***brimonidine as the sole active ingredient*** to affirmatively reduce redness in a person having ocular hyperemia.” *Id.* (emphasis added). “At bottom, while Dean hypothesizes that lowering the dose of brimonidine could reduce the *incidence* of hyperemia, it does not teach or suggest that ***low dose brimonidine as the sole active*** can reduce redness....” *Id.* (emphases added).

62. A POSA would have similarly understood the specification to correspondingly disclose embodiments with low-dose brimonidine as the sole active ingredient. In fact, the specification discloses embodiments that dose brimonidine with other active ingredients, *see, e.g.*, Ex. 1 (’600 patent) at 9:53-55, 15:61-17:3, 16:57-58, 65-66, and others that dose brimonidine as the sole active ingredient, *see, e.g., id.* at 7:34-40, 8:19-25, 9:46-49, 10:21-26, Examples 1, 4, and 5 and the studies embodied in Figures 5A-C. Consistent with the arguments made during prosecution to distinguish Dean, a POSA would have simply understood that the Patentee claimed in the ’600 patent certain embodiments described in the specification wherein brimonidine is administered as the sole active ingredient as opposed to with other active ingredients.

63. I disagree with Defendants' proposed interpretation. I do not believe a POSA would have read the claims together with the specification and prosecution and understood "as the sole active ingredient" as they propose. Defendants' interpretation would permit administering separate drops that can contain other active ingredients. As explained above, that is clearly not how the Patentee described and characterized its invention to distinguish Dean, which specifically disclosed sequential administration of separate formulations of brimonidine in one formulation and brinzolamide in another.

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

DATED: December 1, 2023

A handwritten signature in cursive script, reading "William B. Trattler M.D.", positioned above a horizontal line.

William B. Trattler, M.D.