

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

DR. REDDY'S LABORATORIES S.A. AND
DR. REDDY'S LABORATORIES, INC.,
Petitioners,

v.

EYE THERAPIES, LLC,
Patent Owner

U.S. Patent No. 11,833,245

Title: VASOCONSTRICTION COMPOSITIONS AND METHODS OF USE

Inter Partes Review No. IPR2024-00467

**DECLARATION OF JOHN C. GALANIS, MD, FACS
IN SUPPORT OF PETITIONERS' REPLY**

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I, John C. Galanis, MD, FACS, declare as follows:

I. INTRODUCTION

1. I am the same John C. Galanis, MD, FACS, who submitted the Declaration of John C. Galanis, MD, FACS (EX-1014, “Opening Declaration”) dated January 24, 2024, in support of Dr. Reddy’s Laboratories S.A. and Dr. Reddy’s Laboratories, Inc.’s (collectively, “DRL” or “Petitioners”) petition for *inter partes* review of U.S. Patent No. 11,833,245 (EX-1001, “the ’245 patent”).

2. I understand that the Board has instituted *inter partes* review of claims 1, 2, 4–9, 11–17, 20–22, 25, and 27 (“the challenged claims”) of the ’245 patent and that Patent Owner (“PO”) has filed a Patent Owner’s Response (“POR”), together with the Declarations of Robert J. Noecker, M.D., MBA (EX-2223, “Noecker Declaration”), Eric D. Donnenfeld, M.D. (EX-2224, “Donnenfeld Declaration”), and W. Daniel Stamer, Ph.D. (EX-2225, “Stamer Declaration”), among others, in support of the POR.

3. I provided in my Opening Declaration the details of my compensation for my work on this matter. My compensation is not contingent upon, and in no way related to, the outcome of this proceeding or the testimony that I give.

4. I also provided in my Opening Declaration a summary of my qualifications and background, including my education and experience, as well as a copy of my *curriculum vitae*.

5. I discussed in my Opening Declaration my understanding of the relevant legal standards as provided by counsel. My understanding of these legal standards has not changed since I submitted my Opening Declaration.

II. MATERIALS CONSIDERED

6. In preparing this reply declaration, I considered the Board's Institution Decision; the POR; Dr. Noecker's Declaration and materials cited therein; Dr. Donnenfeld's Declaration and materials cited therein; Dr. Stamer's Declaration and materials cited therein; and any materials identified in this reply declaration. I have listed the materials I considered in Exhibit C to this Reply Declaration. I also considered my Opening Declaration and the materials listed in Exhibit B thereto. I have considered all these materials in light of the knowledge and experience I have accumulated over decades of practicing ophthalmology.

III. PERSON OF ORDINARY SKILL IN THE ART

7. In paragraph 60 of my Opening Declaration, I provided my opinion regarding the qualifications of the person of ordinary skill in the art ("POSA") with respect to the '245 patent. In paragraph 24 of his declaration, Dr. Noecker states that he "prefer[s] Patent Owner's definition" of the POSA, which differs from mine in that Patent Owner's POSA appears to be less skilled. Although I disagree with Patent Owner's definition, my opinions expressed in my Opening Declaration and in this Reply Declaration would not change if Patent Owner's definition were

applied instead of mine.

IV. THE CLAIMED METHOD IS NOT LIMITED TO A SINGLE DROP

8. Dr. Noecker, referring to claim 1, opines that “the phrase ‘*consisting of*’ topically administering to an eye ... a composition in the form of *an ocular drop* consisting of 0.025% weight by volume brimonidine as the sole active ingredient’ limits the claimed method to ocularly topically administering a single drop of 0.025% brimonidine as the only active ingredient in a single step, in which the single step is the only step taken to reduce eye redness.” EX-2223 (Noecker Decl.) ¶ 62 (emphases in original). I disagree that claim 1 and its dependent claims¹ are limited to administration of “a single drop” of 0.025% brimonidine.

9. As an initial matter, I understand from counsel that the transitional phrase “consisting of” does not necessarily limit each subsequent indefinite article (“a” or “an”) in the claim to its singular sense. In my opinion, the plain language of claim 1, specification, and prosecution history support that claim 1 and its dependent

¹ Dr. Noecker’s “single drop” interpretation would apply only to claim 1 and its dependent claims. Unlike claim 1, claim 8 (and its dependent claims) is directed to a method “comprising” topically administering brimonidine. I understand from counsel that the transitional phrase “comprising” means the claim is “open” to (i.e., does not exclude) steps or elements not explicitly recited in the claim.

claims are not limited to administration of a single drop of brimonidine.

A. The Language of Claim 1

10. In my opinion, the POSA reading the plain language of claim 1 would have understood the phrase “consisting of” to be limiting “a composition,” not “an ocular drop.” In his declaration, Dr. Noecker incorrectly states that “the method explicitly recites a single step: ‘topically administering to an eye ... an ocular drop consisting of 0.025% weight by volume brimonidine as the sole active ingredient.’” EX-2223 (Noecker Decl.) ¶ 63. But this is *not* what claim 1 says. Claim 1 recites a method for reducing eye redness “***consisting of*** topically administering to an eye of said human in need of said reduction of eye redness ***a composition*** in the form of an ocular drop consisting of 0.025% weight by volume brimonidine as the sole active ingredient.” EX-1001 (’245 Patent) at 22:37–41. A POSA would understand that the term “ocular drop” refers to the form of the composition being administered. Compositions formulated for topical administration to an eye come in several different forms. For example, these compositions can be formulated as an ocular drop, ocular ointment, gel, or cream. *Id.* at 17:16–17. In claim 1, the phrase “an ocular drop” does nothing more than specify the form in which the composition must be administered—the form of an ocular drop.

B. The Specification of the ’245 Patent

11. Dr. Noecker opines that “[n]umerous examples in the specification

further demonstrate administering a single drop of brimonidine in a single step as a means for reducing redness,” stating that “Examples 1, 4, and 5, and Figures 5A-C all use a single drop of low-dose brimonidine to redness better than prior art redness relievers.” EX-2223 (Noecker Decl.) ¶ 65. I disagree with Dr. Noecker’s interpretation of the specification.

12. As an initial matter, when the specification uses the phrase “an ocular drop,” it is always referring to the dosage form of a composition, not the number of drops administered. *See, e.g.*, EX-1001 (’245 Patent) at 6:20–21 (“wherein said composition is formulated as an ocular drop”); *id.* at 6:27–28 (same); *id.* at 7:32–33 (same); *id.* at 9:51–52 (same); *id.* at 9:59–60 (same); *id.* at 10:25–26 (same); *id.* at 10:34–35 (same). This is consistent with my understanding that the reference to “an ocular drop” in claim 1 describes the dosage *form*, not the dose.

13. In my opinion, the specification never suggests that administering only a single drop of brimonidine is an important or necessary feature of the claimed methods. Further, the specification never suggests that administering more than one drop of brimonidine would materially impact the results of the claimed methods. In fact, the specification never explicitly discloses a single-drop method of administering brimonidine, and none of the Examples or Figures are expressly limited to administration of a single drop of brimonidine.

14. Example 1 discloses multiple administrations of brimonidine to a single

patient, but Example 1 is silent on the number of drops per administration—it discloses only that “a patient was treated with brimonidine at claimed concentrations.” *Id.* at 20:41–42. The results of Example 1 are shown in Figures 4A-4E, and the description of those figures is likewise silent on the number of drops per administration. Figure 4B shows “the left eye was treated with brimonidine at 0.01%”; Figures 4C and 4D show “the left eye was treated with brimonidine at 0.02%”; and Figure 4E shows “the effect of brimonidine at 0.033% on the left eye only.” *Id.* at 20:48–63. Importantly, Figure 4D shows a comparison of the patient’s left and right eyes “after a further four hours,” which a POSA would interpret to mean four hours after the photograph in Figure 4C. *Id.* at 20:56–57; EX-1047 (Noecker ’245 IPR Dep. Tr.) at 40:12–18. Figure 4E “shows the effect of brimonidine 0.033% on the left eye only, 4 hours after the effect shown in FIG. 4D (showing the **third application** to be without rebound hyperemia).” *See* EX-1001 (’245 Patent) at 20:60–63 (emphasis added). Thus, Example 1 discloses multiple administrations of at least one drop of brimonidine, including the administration of at least three drops of low-concentration brimonidine over a 12-hour period in the same eye of the same patient. *See* EX-1044 (Donnenfeld ’245 IPR Dep. Tr.) at 27:15–20 (Dr. Donnenfeld agreeing that “there were at least three administrations of brimonidine to this patient”). Example 1 concludes that “the results show that compositions of the present invention may be used every three to four hours with

low incidence of hyperemia.” EX-1001 (’245 Patent) at 21:1–3.

15. Example 2, which Dr. Noecker neglects to discuss in his declaration, discloses “[t]reatment of 200 patients via the intralase femtosecond laser with no pretreatment for vasoconstriction.” *Id.* at 21:9–10. The patients were divided into three treatment groups, two of which were treated with brimonidine. *Id.* at 21:16–47. Patients in Treatment Group 2 were administered 0.02% brimonidine, but the number of drops is not specified. *Id.* at 21:24–30. Patients in Treatment Group 3, on the other hand, were administered 0.02% brimonidine “applied topically *[i]-ii gtts per eye.*” *Id.* at 21:31–32 (emphasis added). The abbreviation “gtts” means “drops,” from the Latin word “guttae.”² See EX-1058 (ARVO Glossary) at 7; EX-1044 (Donnenfeld ’245 IPR Dep. Tr.) at 36:11–37:8 (Dr. Donnenfeld agreeing that “gtts” means plural “drops”). The POSA would have understood the lowercase Roman numerals “i-ii” means “one to two.” See EX-1059 (Understanding Pharmacy Abbreviations) at 3 (“i, ii, iii and iiiv medical abbreviations indicate dose size and equate to 1, 2, 3 and 4”). Thus, patients in Treatment Group 3 were administered one to two drops per eye. Example 2 therefore explicitly discloses multiple-drop administration of 0.02% brimonidine.

² The singular form of this abbreviation is “gtt,” which means “drop,” from the Latin word “gutta.”

16. Example 4 is silent on the number of drops administered—it discloses only that “[e]ighteen patients having a red eye condition were treated with a composition of the present invention (i.e., brimonidine at 0.018%) and with VISINE Original®.” EX-1001 (’245 Patent) at 21:64–66. Example 4 mentions that redness reduction was calculated “after administration of a single dose of brimonidine at 0.018%,” but a “single dose” is not equivalent to a “single drop” because a dose could be one drop, two drops, etc. *See, e.g.*, EX-2170 (DailyMed Visine Drug Info) at 2 (instructing dose of “1 to 2 drops in the affected eye(s) up to 4 times daily”); EX-2224 (Donnenfeld Decl.) ¶ 47 n.3 (Dr. Donnenfeld asserting Norden administered “a dose” of 0.4% brimonidine because Norden administered two drops 0.2% brimonidine within a 10-minute period). Example 4 appears to disclose multiple administrations of brimonidine, as the Example refers to patients being measured for redness “prior to each administration” as well as “10 min after each dose.” EX-1001 (’245 Patent) at 22:1–3. The Example also calculated “three week scores” over the “length of the study,” indicating that patients were administered brimonidine multiple times (and thus were administered multiple drops) over the course of the study. *Id.* at 22:14–19.

17. Example 5 discloses treatment of “[s]even patients with chronic red eyes” with “extreme low dose (eld) brimonidine at 0.015%,” the treatment being “drops twice a day for three to five weeks.” *Id.* at 22:26–30. A POSA would have

understood the phrase “drops twice a day” could mean multiple drops (e.g., two drops) twice a day. The description is unclear as to how many drops the patients were administered twice a day, but Patent Owner’s expert Dr. Donnenfeld believes that multiple drops were administered twice a day. *See* EX-1044 (Donnenfeld ’245 IPR Dep. Tr.) at 34:14–18 (Dr. Donnenfeld agreeing that Example 5 discloses “multiple drops were administered twice a day”).

18. Figures 5A-5C disclose a comparison of a patient’s eyes after treatment with “a composition of the present invention comprising brimonidine at 0.015%” and/or VISINE Original® (tetrahydrozoline HCl 0.05%). EX-1001 (’245 Patent) at 20:4–32. Figure 5B shows the patient’s eyes, with an annotation above each eye: “ii gtts tid, day 2 1st instillation.” *Id.* at Fig. 5B. As explained above, “ii gtts” means “two drops.” The abbreviation “tid” means “three times per day.” *See* EX-1058 (ARVO Glossary) at 15; EX-1044 (Donnenfeld ’245 IPR Dep. Tr.) at 38:21–39:2. Thus, the POSA would have understood the annotation in Figure 5B to mean that each eye was receiving either two drops of brimonidine or two drops of tetrahydrozoline three times per day. Figure 5C shows the patient after being treated with two drops—the left eye was treated with two drops of 0.015% brimonidine, and the right eye was treated with one drop of VISINE Original® and then one drop of 0.015% brimonidine. EX-1001 (’245 Patent) at 20:19–26. Consistent with this, the annotation in Figure 5C itself again shows “ii gtts” above both the left and right eyes

of the patient. *Id.* at Fig. 5C. The POSA would have understood this to mean that Figure 5C was showing the results after administration of “two drops” as described in the text of the Figure.

C. The Prosecution History of the '245 Patent

19. Dr. Noecker opines that the prosecution history supports the single-drop construction. *See* EX-2223 (Noecker Decl.) ¶ 64. I disagree with his interpretation of the prosecution history.

20. I understand the claim that eventually issued as claim 1 of the '245 patent was originally filed as claim 29 of U.S. Patent Application No. 18/103,404 (the application that issued as the '245 patent). This original claim 29 recited a method for reducing eye redness “comprising topically administering ... an ocular drop comprising about 0.025% weight by volume brimonidine”:

29. (New) 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, wherein the ocular drop is preservative free.

EX-1010 ('245 Patent File History) at 4.

21. Thus, as originally filed, claim 29 was “open” to other elements or steps not explicitly recited in the claim. I understand the applicant subsequently amended the claim to replace “comprising” with “consisting of”:

29. (Currently Amended) A method for reducing eye redness in a human subject having ocular hyperemia, ~~comprising consisting of~~ 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 brimonidine is administered in the form of an ocular drop having the ocular drop has a pH between 5.5 to 6.5, wherein the ocular drop is preservative-free further comprises benzalkonium chloride, and wherein the ocular hyperemia is reduced.

Id. at 185. In its remarks, the applicant explained that, by replacing “comprising” with “consisting of,” the applicant “meant that brimonidine is the sole active ingredient administered in the method” and “it is clear that other active ingredients ... would be excluded.” *Id.* at 189. In my opinion, the POSA would have understood the applicant to be referring only to whether administration of other active ingredients would be excluded by the method, not whether the method is limited to administration of a particular number of drops of brimonidine.

22. Claim 29 was amended once more, finally reading as it would eventually issue as claim 1:

29. (Currently Amended) A method for reducing eye redness in a human subject having ocular hyperemia, consisting of topically administering to an eye of said human in need of said reduction of eye redness a composition in the form of an ocular drop consisting of 0.025% weight by volume brimonidine as the sole active ingredient, and one or more non-therapeutic components including benzalkonium chloride, wherein the brimonidine is administered in the form of an ocular drop having has a pH between 5.5 to 6.5, wherein the ocular drop further comprises benzalkonium chloride, and wherein the ocular hyperemia is reduced.

Id. at 283. In this final amendment, the applicant inserted the phrase “a composition

in the form of an ocular drop” after the first instance of “consisting of” such that the claim became directed to a method for reducing eye redness “consisting of topically administering ... a composition in the form of an ocular drop consisting of 0.025% weight by volume brimonidine.” *Id.* As explained above, in my opinion, a plain reading of this final version of the claim is that “consisting of” modifies “a composition,” not “an ocular drop.” The phrase “an ocular drop” specifies only the form of the composition—it does not specify the number of drops administered.

V. ALL CHALLENGED CLAIMS WOULD HAVE BEEN OBVIOUSNESS TO A POSA

23. In my opinion, all of the challenged claims of the '245 patent would have been obvious to the POSA, and nothing in the declarations of Dr. Noecker, Dr. Donnenfeld, or Dr. Stamer demonstrates otherwise.

24. As I explained in my Opening Declaration, a POSA would have been motivated to administer brimonidine (a known vasoconstrictor) to reduce eye redness (a known result of vasoconstriction). Eyecare professionals were *already* doing this at the time of the invention in 2008.³ See EX-1014 (Opening Decl.) ¶

³ PO's expert Dr. Noecker cites Fudenberg (EX-2028) as allegedly evidencing the state of the art at the time of the invention, pointing out that Fudenberg does not explicitly mention that brimonidine can be used a redness reliever. See EX-2223 (Noecker Decl.) ¶ 111. But Fudenberg is about brimonidine's “role in glaucoma

121; EX-1006 (Norden) at 4; *see also* EX-1131 (Desco) at 1 (stating “Norden concluded that brimonidine administered before LASIK may significantly reduce the amount of hyperemia” and noting “[n]owadays many refractive surgeons administer [brimonidine] prophylactically to reduce postoperative subconjunctival hemorrhage or hyperemia”). Indeed, by 2008 I had been regularly administering brimonidine (in the form of Alphagan 0.2%) prophylactically to my LASIK patients because I knew—as did the LASIK surgeon community generally—that brimonidine was a vasoconstrictor that would effectively reduce the amount of my patients’ post-operative hyperemia and hemorrhage. This was a very common

management.” EX-2028 (Fudenberg) at Abstract. It was written for an audience who would have been focused on that role of brimonidine. Although I do not personally know the Fudenberg authors, I know they are glaucoma specialists. *See* EX-1047 (Noecker ’245 IPR Dep. Tr.) at 121:2–122:20 (Dr. Noecker agreeing that all Fudenberg authors are glaucoma specialists who work in the glaucoma department of the Willis Eye Institute). I reviewed Fudenberg, and nowhere does the article claim to be exhaustively listing all known uses of brimonidine. Further, I note that Fudenberg does not cite to Norden, Gil, or Dean. *Id.* at 122:21–123:10 (Dr. Noecker admitting Fudenberg does not cite to Norden or any reference that cites to Norden, including Desco (EX-1131) and Hong (EX-1064)).

practice in 2008.

25. PO's experts' opinions that the POSA would not have used brimonidine to reduce redness contradicts not only my own clinical experience but also the explicit teachings of the prior art. As a result, PO's experts' opinions do not change any of the opinions set forth in my Opening Declaration. In my opinion, the POSA would have been motivated to use low-concentration brimonidine given the express teachings of, e.g., Norden, Gil, and Dean. Further, the POSA seeking to develop a redness reliever would have been motivated more generally to determine the minimum effective concentration—the concentration at which the intended effect of redness reduction (i.e., vasoconstriction) is achieved while minimizing side effects. *See* EX-1045 (Stamer '245 IPR Dep. Tr.) at 21:13–22:7 (Dr. Stamer agreeing that “the goal of drug development” is to determine “the concentration where you achieve the intended therapeutic effect with minimal off-target effect”). The POSA would have known that lower concentrations cause less pronounced side effects. *See, e.g.,* EX-2002 (Jan. 23, 2024, PI Hearing Tr.) at 84:22–24 (Dr. Noecker testifying that “the concentration [of Alphagan 0.5%] was dropped to [Alphagan 0.2%] in an effort to get rid of some of these side effects – less hyperemia, less allergic reactions – and that was successful”); *see also id.* at 92:20–93:2 (Dr. Noecker agreeing that “scientifically ... when the concentration [of Alphagan] went down” the patient was “exposed to less drug and, therefore, the negative side effect

of hyperemia [was] reduced”); *see also* EX-2009 (Jan. 24, 2024, PI Hearing Tr.) at 108:22–23 (Dr. Gil testifying that “if you go to a higher dose, [brimonidine] may start having side effects”); *see also* EX-2006 (Jan. 26, 2024, PI Hearing Tr.) at 383:24–384:2 (Dr. Noecker testifying “Alphagan P, which has a lower concentration of the active ingredient brimonidine, and we see that the hyperemia/allergy reactions are lower. So with the decreasing dose, you see less of those eye redness side effects.”).

A. The POSA Would Have Been Motivated to Combine the Teachings of Norden, Gil, and Dean When Evaluating Brimonidine as an Eye-Redness Reducer

26. PO’s experts opine that a POSA would not have looked to the teachings of Norden, Gil, and Dean to develop a redness-reducing ocular drop. I disagree.

27. PO’s experts ignore the common thread in Norden, Gil, and Dean—each expressly directs the POSA to brimonidine’s role as a vasoconstrictor. It is this mechanism of action—vasoconstriction—that is responsible for reducing redness in the front of the eye (making the blood vessels less visible), and this was common knowledge by 2008. *See, e.g.*, EX-1044 (Donnenfeld ’245 IPR Dep. Tr.) at 59:10–15 (Dr. Donnenfeld agreeing that “in 2008, the POSA would have understood that redness relievers generally work by narrowing blood vessels in the front of the eye”).

28. Norden explicitly identifies brimonidine as a “strong vasoconstrictor.” EX-1006 (Norden) at 4. PO’s expert Dr. Donnenfeld agreed that brimonidine was

known as a “strong vasoconstrictor” by 2008. EX-2009 (Jan. 24, 2024, PI Hearing Tr.) at 80:24–81:1 (“Okay. And you would agree that as of 2002, brimonidine, this alpha-2 agonist, was known to be a strong vasoconstrictor? A. Yes.”). Norden concludes that his data—the results of a “prospective, double-masked, single-surgeon study”—showed that “brimonidine administered before LASIK may significantly reduce subconjunctival hemorrhage and *reduce the amount of hyperemia.*” EX-1006 (Norden) at 7. Specifically for hyperemia, Norden’s data showed that “[t]he amount of hyperemia ... was notably lower in eyes treated prophylactically with brimonidine (Fisher’s exact $P < .0001$).” *Id.* at 6. In other words, Norden’s data demonstrated a *statistically significant* difference (p-value < 0.0001) between the treatment groups, meaning that it was very likely that the reduced redness in the brimonidine group was due to brimonidine and not random chance.

29. Gil and Dean also highlight for the POSA brimonidine’s role as a vasoconstrictor. Gil teaches that brimonidine is effective in reducing “neurogenic responses” in the eye, which were defined to include “redness.” EX-1004 (Gil) at 5:38–40. And Dean teaches that “brimonidine causes vasoconstriction in scleral vessels.” EX-1007 (Dean) at 2:30–36.

30. A POSA seeking to develop a redness reliever would look to drugs that act as vasoconstrictors, as it was well known by 2008 that redness relievers work

precisely because they are vasoconstrictors. EX-1009 (Federal Register) at 7 (“the term ‘eye redness reliever’ is a complete and accurate description of the principal action of an OTC ophthalmic vasoconstrictor ingredient, which is used to relieve redness in the eye”); EX-2223 (Noecker Decl.) ¶ 123 (Dr. Noecker opining that, “[w]hen developing a new drug product, a POSA would first consider existing drugs approved by the FDA for the particular condition sought to be treated,” which, for redness relief, were “ocular vasoconstrictors”).

31. PO’s experts assert that the POSA would not look to Norden and Gil because they teach administration of brimonidine in connection with “surgical trauma models.” EX-2223 (Noecker Decl.) ¶¶ 114, 120, 143; EX-2224 (Donnenfeld Decl. ¶¶ 48–51. I disagree that the *cause* of the redness would impact the conclusions the POSA would draw from the data. The POSA would have understood that the *cause* of the eye redness in Norden and Gil is separate and apart from how brimonidine works to reduce the redness. Norden and Gil use brimonidine according to its known mechanism of action—vasoconstriction. And both references teach brimonidine’s effectiveness in reducing eye redness, regardless of the underlying cause of the redness. In Norden, the redness was caused by the LASIK procedure. In Gil, the redness was caused by the radial keratotomy procedure (Example 1) or “ocular surface sensory challenge such as topical capsaicin, potassium chloride or fine hairs” (Example 4). The POSA would have

known that brimonidine did not *become* a vasoconstrictor in Norden and Gil simply because “trauma” was introduced. Rather, the POSA would have known that brimonidine’s innate vasoconstrictive activity is context-independent—it acts as a vasoconstrictor no matter whether it is administered to a traumatized eye or a healthy eye. Thus, the POSA would have understood Norden and Gil to teach that brimonidine acts as a vasoconstrictor in the front of the eye, i.e., that brimonidine works to reduce eye redness.

32. I also note that PO’s experts’ suggestion that the POSA would not look to “trauma models” to evaluate a redness reliever cannot be reconciled with the specification of the ’245 patent. For example, the specification clearly states that the claimed method can be used in connection with not only LASIK but also other surgeries. *See, e.g.*, EX-1001 (’245 Patent) at 7:42–44, 10:36–38; *see also id.* at 12:11–41 (listing ocular conditions “the present invention potentially ha[s] application in treating,” including “ocular vascular congestion after Lasik surgery; prophylactic intraoperative and postoperative reduction of hemorrhage and hyperemia after Lasik surgery; preoperative hemorrhage and hyperemia prophylaxis prior to Lasik surgery”); *id.* at 13:5–8 (“The methods and compositions of the present invention can be used with other ocular procedures, particularly cataract surgery, retinal surgery, pterygiae removal, and motility surgery.”). The specification even provides working examples of the claimed methods in connection with LASIK.

Example 2 discloses administration of 0.02% brimonidine (one to two drops per eye) to hundreds of patients undergoing the LASIK procedure. *Id.* at 21:5–47. Example 2 states that “no or only trace hyperemia [was] found” in the majority of the patients treated with brimonidine. *Id.* at 21:39–40. PO’s experts provide no explanation why it would be improper for the POSA to look to “trauma models,” such as LASIK, to evaluate brimonidine’s ability to reduce hyperemia when the ’245 patent itself does just that.

33. Likewise, PO’s experts argue that Dean does not address redness reduction, let alone redness reduction in patients with hyperemia. *See, e.g.*, EX-2223 (Noecker Decl.) ¶ 117. Again, PO’s experts miss the point. The POSA would have understood Dean to teach using brimonidine *as a vasoconstrictor*—“to constrict ocular vessels and thereby reducing the flux of blood through the anterior portion of the eye.” EX-1007 (Dean) at 2:55–65. The “anterior” portion of the eye includes the conjunctiva. That is the primary purpose of the brimonidine in Dean—to constrict the blood vessels in the front of the eye to improve the bioavailability of a second drug, the IOP-lowering brinzolamide. The POSA seeking to develop a redness reducer would have readily appreciated that Dean’s use of brimonidine—to vasoconstrict in the front of the eye—could be applied in the context of an everyday redness reducer because the mechanism of action is the same in both contexts. The POSA would have known that vasoconstriction in the front of the eye reduces the

visibility of the blood vessels in the front part of the eye, which is exactly what is needed to reduce eye redness. Thus, the POSA's takeaway from Dean is that low-dose brimonidine reduces redness through its vasoconstrictive property.

B. Norden, Gil, and Dean Explicitly Teach Brimonidine Is a Vasoconstrictor and Reduces Hyperemia

34. In my opinion, Norden, Gil, and Dean explicitly teach that brimonidine is a vasoconstrictor and reduces hyperemia.

1. Norden

35. PO's experts opine that Norden's reference to "hyperemia" does not actually refer to "hyperemia," but rather something PO's experts call "micro-vessel hemorrhage." EX-2223 (Noecker Decl.) ¶ 106; EX-1047 (Noecker '245 IPR Dep. Tr.) at 95:17–96:4; EX-2224 (Donnenfeld Decl.) ¶¶ 50–51. I disagree with this interpretation of Norden.

36. First and foremost, there is simply no evidence to support that Norden actually meant "micro-vessel hemorrhage" when he said "hyperemia." The only basis for this interpretation is unsupported statements from PO's experts. *See* EX-2224 (Donnenfeld Decl.) ¶ 51. For example, to support his opinion, Dr. Donnenfeld cites a single publication—the Doshi reference (EX-2082). I reviewed this reference, and it does not mention "micro-vessel hemorrhage." *See* EX-1054 (Donnenfeld PI Dep. Tr.) at 105:2–5 (Dr. Donnenfeld admitting that Doshi "does not specifically use the word micro-vessel hemorrhages"). Doshi says that

“Subconjunctival Hemorrhage ... can appear as diffusely hyperemic,” but that does mean that “hyperemia” is equivalent to “micro-vessel hemorrhage.” The phrase “micro-vessel hemorrhage” does not even appear in that sentence—it mentions only “subconjunctival hemorrhage,” which is plainly not the same as “hyperemia.” Additionally, to the extent that Dr. Donnenfeld and Dr. Noecker suggest that “hyperemia” actually means “micro-vessel hemorrhage” specifically in the LASIK context, I would note that Doshi is not a paper about LASIK—it is a general discussion of subconjunctival hemorrhage. *See generally* Doshi (EX-2082); *see also* EX-1054 (Donnenfeld PI Dep. Tr.) at 113:13–18 (Dr. Donnenfeld admitting he is “not aware of any articles” that would “support that clinicians performing LASIK use the term hyperemia in the way [Dr. Donnenfeld] described [i.e., micro-vessel hemorrhage]”).

37. I have been practicing ophthalmology for over three decades. I have performed thousands of LASIK procedures in my career, and I have been intimately involved with the LASIK surgeon community for the entirety of my career. Never once in my decades of practice have I heard a LASIK surgeon use the term “hyperemia” to describe “micro-vessel hemorrhage.” In my opinion, trained ophthalmologists would not mistake hyperemia for micro-vessel hemorrhage. This would be especially true in the LASIK context. After the LASIK procedure is complete, the surgeon typically observes the patient’s eyes under high magnification

using a technique called slit-lamp microscopy. Norden examined his patients specifically using this technique after LASIK. EX-1006 (Norden) at 5 (“Slit-lamp microscopy was performed 5 minutes postoperatively.”). At this high level of magnification, the surgeon can observe *individual red blood cells*, and it is simply not possible to mistake hyperemia (dilation of intact blood *vessels*) for micro-vessel hemorrhage (what Dr. Donnenfeld describes as “leaking of a few scattered red blood *cells*” (EX-2224 (Donnenfeld Decl.) ¶ 51)).

38. I note that the scientific literature interpreted Norden’s conclusion at face value (i.e., hyperemia means hyperemia), repeatedly discussing Norden’s findings as relevant to redness (i.e., hyperemia), separate and apart from any sort of hemorrhage. EX-1144 (Hosten) at 3 (citing Norden and stating “use of brimonidine prior to [LASIK] ... demonstrated that brimonidine was effective at reducing subconjunctival hemorrhage *and ocular redness*”); EX-2101 (Üretmen); EX-1062 (Aslanides 2005) at 1; EX-1063 (Aslanides 2006) at 4; EX-1131 (Desco) at 1.

39. PO’s experts assume that Norden measured “hyperemia” only during the second examination the following day. *See* EX-2224 (Donnenfeld Decl.) ¶ 54 (Dr. Donnenfeld asserting that Norden evaluated hyperemia “the next morning after

surgery”).⁴ Although Norden does not explicitly state whether he examined his patients for hyperemia during the first examination (five minutes post-operation), the second examination (the next morning), or both, it is my opinion that the POSA would have understood Norden measured hyperemia during only the first examination, when he performed slit-lamp microscopy five minutes after the surgery was complete. EX-1006 (Norden) at 5; *see also* EX-1054 (Donnenfeld PI Dep. Tr.) at 123:16–20 (Dr. Donnenfeld agreeing that Norden “doesn’t say whether

⁴ I note that Dr. Donnenfeld was not always so convinced that Norden evaluated hyperemia the morning after surgery. Dr. Donnenfeld previously testified that he “[does not] know the answer” to the question of whether “the results reported in Norden are the results from only a morning-after examination and did not contain any data from the five-minute post-op examination.” EX-1054 (Donnenfeld PI Dep. Tr.) at 124:20–125:1. Dr. Donnenfeld further testified that “it’s not written in [Norden] on whether the results were described for that day or the next day” and that “[i]t is not written whether the findings that he presents here are recorded from five minutes postoperatively or the next day” *Id.* at 125:3–15; *see also id.* at 125:25–126:4 (“And I cannot tell you exactly what the bleeding that took place here, whether it took place or was described at five-day [sic] or the next day. It just – that data is just not there.”).

hyperemia, hemorrhage, or bleeding were measured in the five-minute post-op examination, or in the morning-after examination”). The reason Norden took these measurements during only the first examination is straightforward—brimonidine’s effect on hyperemia (i.e., its vasoconstrictive effect) could only be observed shortly after surgery because brimonidine’s half-life is only about four to six hours. Norden, and the POSA, would have known that the greatest effect of brimonidine on hyperemia would have been immediately after surgery. Notably, PO’s experts have not presented even a single scientific paper or article suggesting that Norden’s study was flawed because it did not specify when hyperemia was measured.

40. Norden did conduct a second examination—“[f]or purposes of this study, eyes were examined *again* the next morning.” EX-1006 (Norden) at 5. In my opinion, the reason Norden conducted this second examination was to check for flap slippage. The LASIK procedure requires a “flap” to be peeled back, making way for the laser to reshape the cornea underneath. After the treatment is complete, the surgeon gently puts that flap back in place. A common problem with LASIK is that sometimes the flap does not remain in place right away, i.e., it “slips.” This is a significant complication that surgeons want to avoid. The flap is particularly vulnerable to slipping during the first few days following the procedure, but flap slippage typically does not occur immediately (i.e., within a few minutes) after surgery. It is common practice to examine LASIK patients the day *after* surgery—

the primary purpose being to check for flap slippage. Thus, the purpose of Norden's second examination was to check his patients' eyes for flap slippage. Indeed, Norden's major finding was that brimonidine did not increase the chances of flap slippage after LASIK. *Id.* at 7.

41. I remember when the Norden paper was published. It was a big deal in the LASIK community, but, ironically, not for the finding that brimonidine reduced hyperemia and hemorrhage after LASIK. Before Norden's paper, LASIK surgeons had already been using brimonidine prophylactically as a vasoconstrictor to reduce redness (hyperemia and hemorrhage). Many surgeons, myself included, were doing this. *See id.* at 4 ("There are many anecdotal reports that the use of topical brimonidine before laser in situ keratomileusis (LASIK) can help prevent bleeding-related problems in the anterior segment, and some refractive surgeons now administer it prophylactically to reduce subconjunctival hemorrhage and improve the postoperative appearance."). Norden conducted his study because there was some concern in the LASIK community that the brimonidine surgeons had already been using to reduce redness was also inadvertently increasing the likelihood of flap slippage. Of course, surgeons and patients alike preferred to have reduced redness and improved post-operative appearance of their eyes, but not at risk of causing a major complication like flap slippage. Norden's study confirmed what we in the LASIK community already knew—that brimonidine reduced redness—but his

major contribution was finding that brimonidine did not increase flap slippage. This reassured surgeons that they could continue using brimonidine to reduce redness in their LASIK patients and alleviated any concerns about flap slippage.

42. PO's experts also criticize Norden because the patients received the corticosteroid prednisolone, which PO's experts allege would have resolved any vasodilation and normalized vessel diameter at the time of examination, which PO's experts allege would have been the second examination (the morning after surgery). But as I explained above, a POSA would have understood that Norden measured for hyperemia during the first examination (five minutes post-operatively). Thus, whether prednisolone resolved any vasodilation by the next morning would have no impact on Norden's results. In any event, PO's experts are incorrect that the prednisolone would have in fact resolved any hyperemia by the second examination. I have conducted thousands of LASIK procedures in my career and have observed the vast majority of those patients within 24 hours after the procedure, and those patients nearly always have at least some residual hyperemia the following day despite the prednisolone.

43. PO's experts also opine that Norden does not teach using brimonidine as the sole active ingredient because the brimonidine is administered with other active ingredients (e.g., an antibiotic). EX-2223 (Noecker Decl.) ¶¶ 130–32; EX-2224 (Donnenfeld Decl.) ¶¶ 47, 58–59. I disagree that the use of other drugs Norden

would impact the conclusions the POSA would draw from Norden’s express teachings. As I explained in my Opening Declaration, the POSA would have understood that brimonidine *alone* was responsible for the reduced hyperemia because that was the *only* difference between the two groups in the study. *See* EX-1014 (Opening Decl.) ¶¶ 82–83. Even if other drugs somehow impacted the amount of redness in the patients’ eyes, the impact of the other drugs would have been the same on both treatment groups—it could not explain the reduced hyperemia in the brimonidine-treated group.

44. I note that PO’s experts have not cited a single scientific paper or other reference demonstrating that anyone (other than PO’s experts themselves) interpreted Norden’s results to mean that brimonidine’s ability to reduce redness depended on any of the other drugs that were administered as part of the LASIK procedure. The POSA reading Norden would have reached (to the extent it is even a reach) the logical conclusion that brimonidine alone works to reduce redness. *See* EX-1054 (Donnenfeld PI Dep. Tr.) at 97:4–16 (Dr. Donnenfeld admitting that, in 2008, “a POSA would have accepted that a vasoconstrictor did not necessarily require other medications to be effective”) (cleaned up).

2. Gil

45. PO’s experts also dispute whether Gil teaches that brimonidine reduces redness. But the plain language of Gil is clear: “[b]rimonidine is effective in

reducing such neurogenic response[s],” which Gil defines to include “redness.” EX-1004 (Gil) at 5:38–45. Even if PO’s experts are correct that Gil is primarily directed to using brimonidine to treat ocular pain, that does not mean that Gil does not also disclose using brimonidine to reduce redness. The POSA—who is seeking to develop a *redness reliever*—would have read Gil in its *entirety* and would have taken Gil’s disclosures at face value. PO’s experts have not explained why the POSA would blatantly ignore the express teachings of Gil regarding brimonidine being “effective in reducing ... neurogenic response[s],” such as “redness.” *Id.*

46. With respect to Gil, PO’s experts focus exclusively on Gil’s disclosures related to the use of brimonidine to treat ocular pain. As I explained in my Opening Declaration, however, Gil’s disclosures relate to more than just the administration of brimonidine to treat ocular pain. *See* EX-1014 (Opening Decl.) ¶¶ 135–36, 152.

47. PO’s experts suggest the POSA would not have been motivated to arrive at the claimed invention based on Gil’s Example 1 because the patients received multiple administrations of brimonidine. *See, e.g.,* EX-2223 (Noecker Decl.) ¶ 140. I note Example 1 teaches administration of a single drop of 0.03% brimonidine—“[e]ach patients receives *one drop* of the assigned study medication”—albeit there are multiple administrations discussed in Example 1. *See* EX-1004 (Gil) at 5:54–55 (emphasis added). In any event, as explained above, it is my opinion that the claimed methods are *not* limited to administration of a single

drop of brimonidine, so the fact that Gil's Example 1 includes multiple administrations of that single drop of brimonidine is irrelevant.

48. PO's experts also argue that Example 1 requires multiple "steps"—apparently believing that every single administration of a single drop of brimonidine is a separate "step" in the method. *See, e.g.*, EX-2223 (Noecker Decl.) ¶ 140 (Dr. Noecker opining that "one drop of brimonidine every four hours while awake for 14 days" is "an additional 56 administrations/steps"). But PO's experts offer no principled reason for why this would be the case. Even if Example 1 were strictly about managing ocular pain, that does not mean that each administration (66 total administrations, according to Dr. Noecker) is part of a unitary method wherein every administration is necessary for brimonidine to have an effect. Rather, the POSA would understand that brimonidine has a half-life of 4-6 hours, and Example 1 is mindful of this half-life when it teaches the repeat administrations (of a single drop of 0.03% brimonidine) spaced every four hours apart. This is simply administering an additional drop of brimonidine once the effects of the previous drop have dissipated—nothing in Gil suggests that brimonidine must be administered 66 times to achieve the intended effect. *See* EX-2223 (Noecker Decl.) ¶ 248 (Dr. Noecker opining that "[t]he Lumify label instructs users to 'instill 1 drop in the affected eye(s) every 6-8 hours.'") (quoting EX-2050 (Lumify Label) at 2); *see also* EX-1047 (Noecker '245 IPR Dep. Tr.) at 79:21–80:3 (Dr. Noecker admitting the Lumify

label's "instruction [to instill 1 drop every 6-8 hours] is based on the half-life of the drug being gone or basically that the useful half – the useful amount of the drug being gone due to its known half-life in the human body").

49. PO's experts also argue that Gil's Example 4 does not teach using brimonidine alone in a single step method for reducing human eye redness. *See, e.g.,* EX-2223 (Noecker Decl.) ¶ 145. Once again, PO's experts ignore the clear teachings of Gil: "[b]rimonidine is effective in reducing such neurogenic responses," referring to "[o]cular responses characteristic of neurogenic inflammation, including redness." EX-1004 (Gil) at 5:38-45. I also note that Example 4 does *not* require administration of multiple drops. In my opinion, the POSA would have understood that Example 4 includes at least administration of a single drop of brimonidine over the disclosed concentration range. Thus, the POSA reading Example 4 would have reasonably inferred that a single drop of low-concentration brimonidine (the sole active ingredient) would be effective in reducing redness (in a single step).

3. Dean

50. PO's experts also suggest Dean does not teach "administering brimonidine as the only active ingredient in a single step for reducing eye redness." EX-2223 (Noecker Decl.) ¶ 151. In doing so, PO's experts take an overly narrow view of Dean's disclosures and what they would reasonably suggest to the POSA. The POSA reading Dean would have understood the *how* Dean uses brimonidine.

Dean teaches using brimonidine *as a vasoconstrictor*. Dean explicitly explains the reason for this—constricting the blood vessels in the front of the eye would improve the bioavailability of a second drug, brinzolamide:

When two separate formulations of brinzolamide and brimonidine are used, the preferred administration sequence is brimonidine first and brinzolamide second. In this case, brimonidine serves to constrict ocular vessels and thereby reducing the flux of blood through the anterior portion of the eye. When brinzolamide is administered the reduced circulation in the eye should result in an increase in the bioavailability of the [carbonic anhydrase inhibitor, brinzolamide].

EX-1007 (Dean) at 2:55–62. That is the primary purpose of brimonidine in Dean’s method. The POSA reading Dean would have readily appreciated the role brimonidine is playing in Dean and would have reasonably inferred that brimonidine alone could act as the sole active ingredient to induce vasoconstriction in the front part of the eye (which is how redness relievers work).

51. PO’s experts suggest the POSA would have understood Dean as relating only to using brimonidine in combination with brinzolamide to treat glaucoma. *See, e.g.*, EX-2223 (Noecker Decl.) ¶ 152. I disagree. I understand that the POSA is a person of ordinary creativity and is capable of making reasonable inferences from the prior art. In my opinion, the POSA reading Dean would understand how brimonidine is used in Dean (i.e., as a vasoconstrictor) and would have been able to apply this understanding to contexts outside of brinzolamide combination treatments for glaucoma. Further, PO’s experts have presented no

compelling reason why the POSA would have believed that brimonidine's ability to work as a vasoconstrictor would have somehow depended on the presence of brinzolamide. *See* EX-1054 (Donnenfeld PI Dep. Tr.) at 97:4–16 (Dr. Donnenfeld admitting that, in 2008, “a POSA would have accepted that a vasoconstrictor did not necessarily require other medications to be effective”) (cleaned up).

52. PO's experts also suggest that Dean does not teach that the vasoconstrictive effects would have been sufficient to reduce eye redness at lower concentrations. EX-2223 (Noecker Decl.) ¶ 164. I disagree. Vasoconstriction *is* redness reduction. Any amount of vasoconstriction will necessary result in redness reduction because by definition the blood vessels have become smaller and are therefore less visible. Of course, vasoconstriction and redness reduction exist on a spectrum—a small amount of vasoconstriction would result in only a small amount of redness reduction, and, at the other end of the spectrum, a large amount of vasoconstriction could even result in extreme events such as blanching. But PO's experts have presented no evidence, and the POSA would not have understood, that there is some threshold level of vasoconstriction (e.g., blood vessel must be constricted by 20%) before redness reduction is observed. Even Dr. Noecker admits that “constricting dilated ocular blood vessels, known as vasoconstriction, can ‘decongest’ them, which on the surface can reduce redness and make the eyes appear whiter.” EX-2223 (Noecker Decl.) ¶ 26. The POSA would have understood that

vasoconstriction reduces redness and makes the eyes appear whiter, and there is no threshold level of vasoconstriction that much be reached before the eyes begin to appear less red.

53. PO's experts also suggest that Dean does not teach using a single drop of 0.025% brimonidine to reduce eye redness. EX-2223 (Noecker Decl.) ¶ 163. I disagree. Dean discloses a concentration range of 0.01% to 0.2% brimonidine. EX-1007 (Dean) at 5:21–23. This range encompasses the claimed range of 0.025% brimonidine. And Dean explicitly discloses administration of a single drop of brimonidine: “for topical presentation *1-3 drops* ... would be delivered ... 1-4 times a day *according to the routine discretion of a skilled clinician.*” *Id.* at 15:24–27 (emphasis added). The POSA would have understood the disclosed concentration range of 0.01% to 0.2% brimonidine was the range of concentrations at which Dean expected brimonidine to work for its primary intended purpose in Dean—to achieve vasoconstriction in the blood vessels of the front of the eye in order to improve the bioavailability of brinzolamide. Again, the POSA would have readily appreciated brimonidine's role in Dean as a vasoconstrictor. Dean makes this explicit. On the other hand, the POSA would *not* have thought that the brimonidine in Dean was intended to be used for its IOP-lowering effects because the POSA would have recognized that the lower end of the concentrations disclosed in Dean would not be effective to lower IOP. *See* EX-2085 (Galanis '245 IPR Dep. Tr.) at 44:1–45:5. The

POSA would not have understood Dean to be using low-concentration brimonidine to directly treat glaucoma by harnessing brimonidine's IOP-lowering effects; rather, the POSA would have understood low-concentration brimonidine to be used as a vasoconstrictor to improve the bioavailability of brinzolamide, which is the primary IOP-lowering active ingredient in Dean. Thus, the POSA would have understood the lower brimonidine concentrations in Dean to be concentrations of brimonidine sufficient to achieve vasoconstriction.

4. PO's Experts' Opinions Regarding the Number of Drop Administered Are Misplaced

54. PO's experts opine that the number of drops of brimonidine administered in Norden, Gil, and Dean would impact the POSA's conclusions about brimonidine's ability to act as a vasoconstrictor and reduce hyperemia. *See, e.g.,* EX-2223 (Noecker Decl.) ¶¶ 156, 179. In my opinion, the POSA would have focused on the *concentration* of brimonidine in the drop, not the number of drops administered. It is the *concentration* that is of primary concern to the POSA, and with good reason.

55. Ocular drops are unlike many other drug forms, such as oral tablets, in that the dose of an ocular drop does not specify the absolute amount of drug administered, instead referring only to the concentration of drug in the drop that is topically applied to the eye. This is partly due to the nature of ocular drops, which are dispensed as a liquid from a dropper.

56. The volume of a “drop” is not standard. *See* EX-1069 (Sklubalova 2005) at Abstract (“application of eye drops is known to be problematic due to the high variability of eye drop volume”); EX-1070 (Sklubalova 2006) at Abstract (“application of eye drops from flexible dropper bottles fitted with different types of dropper tips is associated with the high variability of eye drop weights”). The POSA would have known that different volumes of drops would result in more or less drug being administered. *See* EX-1045 (Stamer ’245 IPR Dep. Tr.) at 40:9–14 (Dr. Stamer admitting that “more [brimonidine] would be in a bigger drop” and less in a smaller drop). This is why, in the field of ophthalmology, eye drops are typically described in terms of their *concentration*—not the milliliters of solution in each drop or the milligrams of the drug in each drop.

57. This is why the prior art refers to the amount of brimonidine administered in terms of the concentration of the drop, often not specifying the number of drops administered and never specifying the volume of the drops. For example, Gil’s Example 4 teaches “an ophthalmic solution of brimonidine at concentrations ranging from 0.01% to 0.5%” but does not specify the number of drops. EX-1004 (Gil) at 5:41–42. Even without specifying the number or volume of the drops, Gil’s Example 4 concludes that “[b]rimonidine is effective in reducing ... neurogenic responses,” including “redness.” *Id.* at 5:44–45. Each of Norden, Gil, and Dean refer to their brimonidine formulations by concentration, and none of

them disclose the drop volume. Indeed, it would make little sense to refer to the number or volume of drops of brimonidine without specifying the concentration of the drops, but the reverse is not true—the prior art often refers to the brimonidine concentration without specifying the number of drops, and the prior art never specifies the drop volume.

58. Additionally, as I explained in my Opening Declaration, the POSA would have been motivated to find the minimum effective dose—to achieve the redness reduction while minimizing side effects. EX-1014 (Opening Decl.) ¶ 85. Further, the POSA would have had a reasonable expectation of success in determining the minimum effective dose because doing so would have been a matter of routine optimization. *Id.*; *see also* EX-1004 (Gil) at 3:49–51 (“The determination of the effective dose for any selected compound is well within the skill of an ordinary skilled physician.”). The POSA would have readily determined the appropriate number and volume of drops of brimonidine sufficient achieve redness reduction while minimizing side effects.

59. In determining the minimum effective dose, the POSA would have also considered that redness relievers are often used on a daily basis, with some users administering the redness reliever multiple times per day. This is further motivation for the POSA to use a lower dose (the lowest effective dose, i.e., concentration and number of drops) of brimonidine, because the POSA would have known that any

side effects could be exacerbated if higher concentrations were used multiple times per day. *See* EX-2002 (Jan. 23, 2024, PI Hearing Tr.) at 84:19–24 (Dr. Noecker testifying that Alphagan 0.2% “was developed for more long-term use, ... [s]o the concentration was dropped ... in an effort to get rid of some of these side effects – less hyperemia, less allergic reactions – and that was successful”). The POSA would have appreciated the differences between administering brimonidine in a single-use context, such as LASIK, and a multiple-use-per day context, such as daily redness relief. This is common sense—the more frequently a drug is expected to be administered, the more concerned the POSA would be about the drug’s side effects. *See id.*

60. I note that, in their opinions regarding the number of drops, PO’s experts ignore Hong (EX-1064). Hong followed a similar protocol to Norden, administering brimonidine prophylactically to reduce redness in patients undergoing strabismus surgery. *See* EX-1064 (Hong) at 1–2. Hong deviated from Norden’s protocol, however, in important ways—Hong administered a single drop (as opposed to Norden’s two drops) of 0.15% brimonidine (lower than Norden’s 0.2% brimonidine). *Id.* at 1. Hong successfully used this single drop of 0.15% brimonidine to induce vasoconstriction prophylactically, resulting in less subconjunctival hemorrhage in his patients. *Id.* at 2. The reduced hemorrhage is a direct result of brimonidine’s narrowing of the blood vessels pre-operatively. *Id.*

C. The Alphagan Blanching Reports Do Not Undercut the Reasonable Expectation of Success

61. PO's experts suggest that the POSA would not have had a reasonable expectation of success in achieving the claimed invention because the blanching reported in the Alphagan labels taught away from administering lower concentrations of brimonidine. *See, e.g.*, EX-2223 (Noecker Decl.) ¶ 185. I disagree that this information would have impacted a POSA's motivation to use low-dose brimonidine as a redness reducer.

62. As an initial matter, PO's experts ignore that the prior art—both Gil and Dean—explicitly teach concentrations ranges that encompass the claimed concentration of 0.025% brimonidine. *See* EX-1004 (Gil) at 3:46–49, 3:63–66, 5:31–34 (disclosing concentration range of 0.01% to 0.5% brimonidine); EX-1007 (Dean) at 5:20–23 (disclosing concentration range of 0.01% to 0.2% brimonidine). In my opinion, the POSA would have easily determined which brimonidine concentrations within these ranges would have achieved redness reduction while minimizing side effects, as this would have been a routine exercise for the POSA. *See* EX-1045 (Stamer '245 IPR Dep. Tr.) at 24:13–25:7 (“They take a drug and they expose humans to different doses and look at both the therapeutic effects and the off-target effects. So that’s pretty standard in drug development.”). This is always the goal of dose optimization—finding the minimum effective dose or concentration. Of course, the POSA would have known that there is some minimum amount of

brimonidine needed to induce any vasoconstriction at all, but ascertaining that minimum threshold would have been a routine exercise for the POSA. EX-2016 (Jan. 25, 2024, PI Hearing Tr.) at 142:10–12 (Dr. Gil admitting that the “dose finding process” is a “routine part of pharmacology”).

63. In any event, in my opinion, PO’s experts give far too much weight to the very limited information reported in the Alphagan labels. The POSA would have given little weight, if any, to the Alphagan labels, as they provide nothing more than vague “data” regarding brimonidine’s vasoconstrictive effects vis-à-vis the reported rates of the undefined adverse event of “blanching” across different clinical trials that were designed to evaluate different products for different therapeutic purposes for different lengths of time. Put simply, PO’s experts are comparing apples to oranges.

64. For Alphagan 0.5%, the clinical studies were designed to test whether “Alphagan 0.5% ophthalmic solution was significantly more effective in decreasing the incidence of post-operative IOP elevations ... than was the vehicle at one, two and three hours post-argon laser trabeculoplasty.” EX-1067 (Alphagan Labels) at 4. For Alphagan 0.2%, the clinical studies were designed to test something completely different—“the IOP lowering effect” of Alphagan 0.2%, dosed twice a day for “up to one year,” in patients with open-angle or ocular hypertension. *Id.* at 7. And for Alphagan P 0.15%, the clinical studies were designed to test the IOP-lowering effect

of Alphagan P 0.15% “administered three-times-daily” for an undisclosed length of time in patients with open-angle glaucoma or ocular hypertension. *Id.* at 12. Notably, none of these studies tested 0.025% brimonidine. In my opinion, there are simply too many variables among and too little information about these different clinical studies such that the POSA would not have drawn from them any firm conclusions regarding the ability of 0.025% brimonidine to reduce redness. For example, the labels do not include any grading scale that may have been used (if one was used at all) to evaluate “blanching,” let alone any precise description of each grade on that scale. And the labels report nothing about the actual grading scale score(s) of the patients who experienced “blanching,” so the POSA would have had no idea whether the majority of the patients were experiencing, e.g., extreme, moderate, or mild “blanching.”

65. The Alphagan clinical trials were not designed to precisely determine brimonidine’s ability to reduce redness at different concentrations. I understand Dr. Noecker agreed with this in his testimony during the IPR concerning the ’742 patent. EX-1053 (Noecker ’742 IPR Dep. Tr.) at 68:15–19 (Dr. Noecker admitting that the Alphagan 0.2% “study design was ... not to evaluate or do statistical analysis on redness”). Compared to Norden, where one of the expressly stated objectives of the clinical study was to determine whether brimonidine reduced “hyperemia,” the POSA would have given the adverse reactions “data” from the Alphagan clinical

trials (whose primary purpose was to evaluate brimonidine's effects on IOP) very little weight. The POSA would have been highly motivated to find the minimum effective concentration of brimonidine for purposes of developing a redness reliever, and the POSA simply would not have been dissuaded by the Alphagan labels from testing lower concentrations and confirming (as suggested by, e.g., Gil and Dean) that lower concentrations would still induce vasoconstriction and reduce redness.

66. I note the stark contrast between PO's experts' treatment Norden versus the Alphagan labels. PO's experts treat Norden's data—collected from a double-masked, clinical trial complete with fulsome descriptions of the study objectives, protocol, results, and statistical analysis—as if it could not possibly teach the POSA *anything* about brimonidine's ability to reduce redness. Yet PO's experts treat the Alphagan labels—utterly devoid of meaningful descriptions of how the study defined, graded, and reported “blanching”—as if it were conclusive evidence that brimonidine had no ability to reduce redness at a concentration not even tested anywhere in the labels. If PO's experts were to apply the same rigor to the Alphagan labels that they purportedly apply to Norden, they would not make such broad pronouncements about what the adverse reactions sections of the labels would have reasonably suggested to the POSA.

67. I further note that PO's experts have still not provided any actual protocol that was used in the Alphagan clinical studies. PO's experts speculate about

what may have been included in those protocols, but they do not present any direct evidence to substantiate their claims. *See* EX-1044 (Donnenfeld '245 IPR Dep. Tr.) at 44:10–13 (Dr. Donnenfeld admitting he still has not “seen the actual study protocol from any Alphagan clinical study”). For example, there is still no evidence demonstrating whether a specific definition of “blanching” was used in any grading scale (to the extent a grading scale was even applied to “blanching”). There is still no data showing *when* and how *frequently* patients in the Alphagan studies experienced “blanching,” and, if it were graded on a scale, what severity grades each patient experienced in the studies—some of which lasted only a single day, and some of which lasted up to one year.

68. PO’s experts suggest that “blanching” was measured using a scale in *all* of the Alphagan and Alphagan P clinical trials because one of the NDAs for one of those drugs—the Alphagan 0.2% NDA—states that “[a]ny adverse event occurring during the study was recorded” and “graded for severity (trace, mild, moderate, or severe).” EX-2223 (Noecker Decl.) ¶ 198; EX-2224 (Donnenfeld Decl.) ¶ 44. I do not agree that this necessarily means that moderate redness reduction was affirmatively observed, recorded, and reported as “blanching” in what was eventually published as the Alphagan labels.

69. The Alphagan NDA states that the adverse event reports included the “number and percentage of subjects with at least one severity grade *increased* from

baseline at one or more follow-up visits.” EX-1030 (Alphagan 0.2% NDA) at 52. It is unclear—and PO’s experts have presented no clarifying evidence—whether severity grade *decreases* from baseline would have been observed, recorded, and eventually reported in the labels. For example, it is unclear whether a decrease from moderate hyperemia to trace hyperemia would have been observed, recorded, and eventually reported as a “blanching” event. In my opinion and experience, it is possible that moderate redness reductions—a *decrease* in the adverse event of hyperemia—would not have been recorded as “blanching,” as this would not have represented a severity grade *increase* in “blanching.”

70. At bottom, the POSA would have been motivated, regardless of the “blanching” data in the Alphagan labels, to balance brimonidine’s desired vasoconstrictive effects with its undesired side effects, i.e., to find the “sweet spot”—the concentration at which brimonidine achieves vasoconstriction (i.e., redness reduction) with minimized side effects. *See* EX-1045 (Stamer ’245 IPR Dep. Tr.) at 21:13–22:7 (Dr. Stamer agreeing that “the goal of drug development” is to determine “the concentration where you achieve the intended therapeutic effect with minimal off-target effect”). The POSA would have needed much more information than what was provided in the Alphagan labels to reach any conclusions about what concentrations of brimonidine would be effective in reducing redness. The vague data provided in the labels simply would not have dissuaded the POSA

from using low-concentration brimonidine.

71. I note that PO's experts' opinions hinge on their assertion that "blanching" is synonymous with redness reduction. As I explained in my Opening Declaration, this is incorrect. *See* EX-1014 (Opening Decl.) ¶¶ 131–32. Further, in my opinion, the reason that "blanching" is listed as an adverse reaction in the Alphagan and Alphagan P labels is because it was in fact *adverse*, i.e., undesired. I understand that PO's expert Mr. Karst has opined that "FDA's prescription drug labeling regulations require that Section 6 of the Prescribing Information contain certain information on adverse reactions—i.e., '*an undesirable effect*, reasonably associated with use of a drug....'" EX-2228 (Karst Decl.) ¶ 88 (emphasis added). I agree that "blanching" was reported in the Alphagan and Alphagan P labels because it was an "undesirable effect"—*not* moderate redness reduction, which would have been a welcome effect for patients with red eyes.

72. PO's experts also cite to the Federal Register's statement that the "action of a vasoconstrictor when applied to the surface of the eye is described in the literature as blanching, bleaching, and whitening of reddened conjunctiva." EX-2223 (Noecker Decl.) ¶ 189; EX-1009 (Federal Register) at 9. In my opinion, the POSA would have read this statement as merely describing the spectrum of effects that a vasoconstrictor can have—ranging from something more moderate, like "whitening of reddened conjunctiva," to something more extreme, like "blanching"

or “bleaching.”

73. PO’s experts also suggest that the Alphagan labels support their opinion that the POSA would have thought that high concentrations were needed to achieve vasoconstriction because brimonidine is selective for alpha-2. In PO’s experts’ view, the POSA would have thought the high dose was needed to achieve any activation of alpha-1 receptors, which PO’s experts’ suggest was solely responsible for inducing vasoconstriction. *See, e.g.*, EX-2223 (Noecker Decl.) ¶ 75 (Dr. Noecker suggesting “high concentrations” were needed “to trigger sufficient $\alpha 1$ activity” to reduce redness). I disagree. As I explained in my Opening Declaration, the POSA would have known that alpha-2 can also induce vasoconstriction, and so a high dose of a selective alpha-2 agonist would have been unnecessary. The prior art explicitly teaches that alpha-2 agonists can achieve vasoconstriction *without* activating alpha-1 receptors. Norden states that “the alpha-2 adrenergic agonist drugs *as a class* are also considered to be *strong vasoconstrictors*.” EX-1006 (Norden) at 4. Üretmen, citing approvingly to Norden, states “[w]e agree that brimonidine can be considered a strong vasoconstrictor *based on alpha-2-adrenergic agonist activity*.” EX-2101 (Üretmen). Robin states—at least *ten years* before the invention—that “*even without $\alpha 1$ activation, $\alpha 2$ receptor activation can produce vasoconstriction*.” EX-1023 (Robin) at 3. Thus, contrary to PO’s experts’ testimony, the POSA would have known that brimonidine could still achieve vasoconstriction at lower concentrations

precisely *because* brimonidine is selective for alpha-2.

VI. NO UNEXPECTED RESULTS

74. Dr. Noecker opines that unexpected results support the non-obviousness of the claims of the '245 patent. *See, e.g.*, EX-2223 (Noecker Decl.) ¶ 213. As I explained in my Opening Declaration, however, Dr. Noecker fails to compare the alleged invention to the closest prior art, which is Gil. EX-1014 (Opening Decl.) ¶ 150. Further, Dr. Noecker's evidence of unexpected results derives from the aspects of the challenged claims that had already been disclosed and described in the prior art. *Id.* ¶ 148. Even if Dr. Noecker were correct that Visine and other non-brimonidine prior art redness relievers are the closest prior art, the results produced by Lumify compared to the non-brimonidine prior art redness relievers demonstrate differences only in degree, not in kind., which I understand from counsel means that these differences do not support a conclusion of non-obviousness. For example, Dr. Noecker opines that brimonidine demonstrated superior redness reduction compared to the prior art, but that is not a difference in *kind*—it is merely a difference in degree (one alpha-agonist allegedly reducing redness better than another).

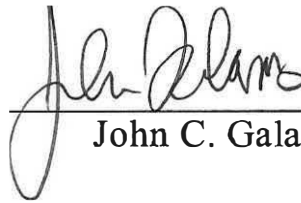
VII. CONCLUSION

75. For the reasons discussed above, it is my opinion that the challenged claims of the '245 patent are invalid for obviousness.

I declare that all statements made herein of my knowledge are true, that all statements made herein on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Respectfully submitted,

Dated: February 25, 2025



John C. Galanis, MD, FACS

EXHIBIT C

List of Materials Considered

Exhibit	Description
1001	U.S. Patent No. 11,833,245 (filed on January 30, 2023) (issued Dec. 5, 2023) ('245 Patent)
1004	U.S. Patent No. 6,294,553 (filed Feb. 14, 2001) (issued Sep. 25, 2001) ('553 Patent) (Gil)
1006	Norden, R., "Effect of Prophylactic Brimonidine or Bleeding Complications and Flap Adherence after Laser in Situ Keratomileusis," <i>Journal of Refractive Surgery</i> , vol. 18, no. 4, July/ Aug. 2002 at 468–471 (Norden)
1007	U.S. Patent 6,242,442 (filed Dec. 7, 1999) (issued June 5, 2001) (Dean)
1009	53 Fed. Reg. 43, 7076-7093 (Mar. 4, 1988) (Federal Register)
1010	File Wrapper, U.S. Application for 18/103,404 filed January 30, 2023, downloaded from Patent Center.
1014	Declaration of John Galanis MD, FACS
1023	Robin, A. L., and Burnstein, Y, "Selectivity of Site of Action and Systemic Effects of Topical Alpha Agonists." <i>Current Opinion in Ophthalmology</i> , vol. 9, no. 2, 1998, pp. 30–33 (Robin)
1030	United States, Center for Drug Evaluation and Research, and Joanne Holmes. NDA 20-613 Alphagan™ (Brimonidine Ophthalmic Solution) 0.2% Sterile, vol. 1, U.S. Food and Drug Administration, 1985, pp. 1–286 (Alphagan NDA)
1044	<i>Dr. Reddy's Laboratories, S.A., et al. -v- Eye Therapies, LLC (PTAB)</i> IPR2024-00563, Deposition Transcript of Eric D. Donnenfeld, M.D. dated February 6, 2025. (Donnenfeld '245 IPR Dep. Tr.)
1045	<i>Dr. Reddy's Laboratories, S.A., et al. -v- Eye Therapies, LLC (PTAB)</i> IPR2024-00563, Deposition Transcript of Daniel Stamer, Ph.D. dated February 13, 2025. (Stamer '245 IPR Dep. Tr.)
1047	<i>Dr. Reddy's Laboratories, S.A., et al. -v- Eye Therapies, LLC (PTAB)</i> IPR2024-00563, Deposition Transcript of Robert J. Noecker, M.D. dated February 19, 2025. (Noecker '245 IPR Dep. Tr.)
1054	IN RE LUMIFY C.A. No. 21-16766 (RK) (RLS) (CONSOLIDATED) Preliminary Injunction Deposition Transcript of Eric D. Donnenfeld, M.D. dated Jan 21, 2024. (Donnenfeld PI Dep. Tr)

1058	ARVO Glossary, Eye and Vision Acronyms
1059	Carrington College, Decoding Your Prescriptions: Understanding Pharmacy Abbreviations, dated February 24, 2015 (Understanding Pharmacy Abbreviations)
1062	Aslanides I.M., et al., “Letter to the Editor,” <i>Ophthalmology</i> , vol. 112, no. 12, Dec. 2005, pp. 2238.e8-2238.e9 (Aslanides 2005)
1063	Aslanides I.M., et al., “The Effect of Topical Apraclonidine on Subconjunctival Hemorrhage and Flap Adherence in LASIK Patients,” <i>Journal of Refractive Surgery</i> , vol. 22, Jun. 2006, pp. 585-588 (Aslanides 2006)
1064	Hong, S., et al., “Effect of Prophylactic Brimonidine Instillation on Bleeding During Strabismus Surgery in Adults,” <i>American Journal of Ophthalmology</i> , vol. 144, no. 3, Sept. 2007 pp. 469-470 (Hong)
1067	ALPHAGAN® (brimonidine tartrate ophthalmic solution) 0.5% Label (Dec. 2001), https://www.accessdata.fda.gov/drugsatfda_docs/label/2001/21262s61b1.pdf (Alphagan Label 2001) (Alphagan Labels)
1069	Z. Sklubalova, et al. <i>Systematic study of factors affecting eye drop size and dosing variability</i> . Pharmazie 60: 917–921 (2005) (Sklubalova 2005)
1070	Z. Sklubalova, et al., <i>Study of Eye Drops Dispensing and Dose Variability by Using Plastic Dropper Tips</i> . Drug Development and Industrial Pharmacy, 32:197–205, 2006 (Sklubalova 2006)
1131	Desco, M.C., et al., “Effect of Prophylactic Brimonidine on Bleeding Complications After Cataract Surgery,” <i>European Journal of Ophthalmology</i> , vol. 15 no. 2, 2005, pp. 228-232 (Desco)
1144	Hosten, L., Snyder C., “Over-the-Counter Ocular Decongestants in the United States – Mechanisms of Action and Clinical Utility for Management of Ocular Redness,” <i>Clinical Optometry</i> ; vol. 12, 2020, pp. 95-105 (Hosten)
2002	IN RE LUMIFY C.A. No. 21-16766 (RK) (RLS) (CONSOLIDATED) Preliminary Injunction Science Day Transcript, dated Jan 23, 2024.
2006	IN RE LUMIFY C.A. No. 21-16766 (RK) (RLS) (CONSOLIDATED) Preliminary Injunction Noecker PI Transcript, dated Jan 26, 2024.
2009	IN RE LUMIFY C.A. No. 21-16766 (RK) (RLS) (CONSOLIDATED) Preliminary Injunction Hearing Transcript - Vol. 1, dated Jan 24, 2024.
2016	IN RE LUMIFY C.A. No. 21-16766 (RK) (RLS) (CONSOLIDATED) Preliminary Injunction Hearing Transcript - Vol. 2, dated Jan 25, 2024.

2028	Fudenberg, S <i>et al</i> , “Efficacy, safety, and current applications of brimonidine,” <i>Expert Opinion on Drug Safety</i> , 7:6, 2008, 795-799.
2050	Lumify Label
2082	Doshi, Subconjunctival Hemorrhage StatPearls NCBI Bookshelf (Feb 2023) https://www.ncbi.nlm.nih.gov/books/NBK551666/?report=printable (Doshi)
2085	<i>Dr. Reddy's Laboratories, S.A., et al. -v- Eye Therapies, LLC (PTAB)</i> IPR2024-00467, Declaration of John C. Galanis, MD, and materials cited therein (Galanis '245 IPR Dep. Tr.)
2101	Üretmen et al., “Prophylactic Brimonidine Before LASIK,” <i>Journal of Refractive Surgery</i> (2003) (Üretmen)
2170	DailyMed Visine Drug Info
2223	<i>Dr. Reddy's Laboratories, S.A., et al. -v- Eye Therapies, LLC (PTAB)</i> IPR2024-00467, Declaration of Robert J. Noecker, M.D., MBA (FINAL UNDER SEAL)
2224	<i>Dr. Reddy's Laboratories, S.A., et al. -v- Eye Therapies, LLC (PTAB)</i> IPR2024-00467, Declaration of Eric D. Donnenfeld, M.D.
2225	<i>Dr. Reddy's Laboratories, S.A., et al. -v- Eye Therapies, LLC (PTAB)</i> IPR2024-00467, Declaration of Daniel Stamer, Ph.D.