

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.

Case IPR2024-00467
Patent 11,833,245

PATENT OWNER'S SUR-REPLY

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TABLE OF ABBREVIATIONS

Abbreviation	Description
Reply	Petitioners' Reply (Paper 58)
POR	Patent Owner's Response (Paper 25)
PO	Patent Owner
Noecker ¶	EX2223, Declaration of Robert J. Noecker, M.D., MBA
Donnenfeld ¶	EX2224, Declaration of Eric D. Donnenfeld, M.D.
Stamer ¶	EX2225, Declaration of W. Daniel Stamer, Ph.D.
Gil ¶	EX2227, Declaration of Daniel W. Gil, Ph.D.

I. Introduction

Petitioners' focus on concentration rather than dose is fatal to their position as POSAs would have understood that the therapeutic effect and safety of a drug depend on the *amount (i.e., the dose)* administered, not simply the concentration. The dose is determined by the dosage regimen. The combination of Norden, Gil and Dean neither teaches nor suggests low dose brimonidine, much less administering in a single step a single eyedrop of 0.025% brimonidine, to reduce redness.

To the extent Norden and Gil taught brimonidine alone could reduce redness, which PO does not concede, these references at best taught dosing brimonidine at ~0.2% or more. And Dean's data-less suggestion that low concentration brimonidine *may* vasoconstrict sufficiently to augment brinzolamide's bioavailability (for IOP treatment) would not have been viewed by POSAs as synonymous with the *dose* sufficient to reduce eye redness.

Indeed, whether vasoconstriction occurs at low concentration (or even low dose) misses the point. The *prior art taught that the minimum effective dose to reduce eye redness was about 0.2% brimonidine*, which emanates not from prophetic examples, like Gil or Dean, but from the FDA-approved Alphagan clinical studies. POSAs would have viewed the statistically-analyzed conjunctival blanching (whitening) data from these studies as especially relevant and reliable and understood that, if POSAs wanted to use brimonidine to reduce eye redness, there is

no reason to administer a dose below about 0.2%. The message in the prior art was clear—dose high. Yet, administering in a single step, one drop of 0.025% brimonidine, embodied by Lumify, not only worked but it unexpectedly reduced redness 3-6.5 times greater than the closest prior art, and without side-effects, representing a difference in kind.

II. Claim 1 is Limited to Administering a Single Drop of 0.025% Brimonidine

Petitioners agree that the transitional phrase “consisting of” in the method of claim 1 limits the claimed method to a single step of reducing eye redness but disagree that the single step is limited to administering a single ocular drop. They argue (Reply, 1-2) that because “an ocular drop” modifies “composition” in a prepositional phrase, the claim says nothing about how many drops are administered.¹

However, Petitioners admit (*id.*) that the claim’s references to “‘an ocular drop’ describes the *form* of the ‘composition’ in the claims.” Thus, while PO is not advancing an argument “that *every* subsequent use of ‘a’ or ‘an’ must be interpreted

¹ Contrary to Petitioners’ assertion, PO did not mislead by using ellipses to remove “a composition in the form,” for its POR (at 11) referenced the full claim language when addressing how transitional phrase “consisting of” limits claim.

in the singular sense” as Petitioners suggest (*id.*, 2), no party disputes that the plainly read **subject** of what is administered in the single claimed step is an eyedrop. EX1147, ¶¶54-55; EX2279, 22:13-23:14. The drop embodies the composition, and the prepositional phrase does not alter the plain reading that the method administers an eyedrop. It is the legal consequence/impact of “consisting of” that limits the single step to administering a single drop. *Norian Corp. v. Stryker Corp.*, 432 F.3d 1356, 1359 (Fed. Cir. 2005).²

Petitioners’ argument that “consisting of” modifies “composition” not “an ocular drop” still leads to the same construction. Petitioners admit (Reply, 2), under *Norian*, claim 1 is limited to administering a single composition, which they say is an eyedrop. POSAs would understand, if they are administering a **single** composition formulated as an eyedrop, then they are administering just one drop. Administering two drops would be administering two compositions, albeit of the same makeup.

² *Abbott Lab’ys v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1281 (Fed. Cir. 2003) also applies. *Abbott* concluded “consisting of” limited the members of the group because of the presence of “consisting of,” notwithstanding it was a Markush group. *Id.*

Judge Kirsch understood the legal impact of “consisting of” as PO proposes. He determined “consisting of” limited the claim to “*one single step*—topically administering *an eye drop* to a human to reduce eye redness.” EX2030, 23-24, 42-43 (“the patented method is a *single step* focused on applying *a low dose brimonidine drop*....”) (emphases added). That Judge Kirsch understood “consisting of” to limit the single step to a single drop is unequivocally evidenced by the distinction he drew between claim 1 and Norden, stating “[Norden] ‘patients received two drops [of 0.2% brimonidine] fifteen minutes prior to surgery and five minutes prior to surgery,’ exposing the patient to significantly greater levels than *a single drop* of .025% brimonidine.” *Id.* at 52 (emphasis added).

If PO meant for claim 1 to encompass the administration of more than one ocular drop it certainly knew how to claim that, and the specification would have supported such a claim. *See, e.g.*, Reply, 4, n.6 (reading Example 2 of the ’245 patent as administering 1-2 eye drops of 0.02% brimonidine); EX2279, 25:9-25. Indeed, patent claim 8 recites the transitional phrase “comprising” and reads on administering one or more eyedrops. EX1001, 22:65-67.

Petitioners incorrectly assert (Reply, 2, n.3) PO did not argue the phrase “an eye” following “consisting of” limits the claims to administering brimonidine to one eye, seemingly suggesting that treating two eyes is a single step. As Dr. Noecker testified, doctors treat one eye at a time. EX1047, 16:6-11, 16:22-17:14, 20:2-20:14;

see generally id. at 16:6-21:17. And while doctors/patients may choose to treat one or both eyes, regardless, each eye is a separate treatment.

Petitioners argue (Reply, 3) the specification describes “ocular drop” by how the composition is formulated, not how many drops are administered, pointing to the passage: “The topical compositions include, but are not limited to, ocular drops, ocular ointments, gels and creams.” In this passage, “ocular drops” is plural because the word to which it refers, “compositions,” is plural. The specification, moreover, discloses embodiments administering one or two drops. EX1001, 21:5-47. Claim 1 is simply one embodiment disclosed therein.

Petitioners also argue (Reply, 3) that none of Examples 1, 4, and 5 and Figures 5A-5C uses a single drop of low-dose brimonidine. This is factually incorrect. As Petitioners acknowledge (*id.*, 4, n.6), Example 2 supports a single drop, which alone would suffice, but other examples provide additional support.

Petitioners misleadingly characterize Example 1 as administering “at least three drops of brimonidine,” giving the impression this was a single treatment with multiple drops. But Example 1 tested three different low concentrations of brimonidine against three different commercial redness-relievers 3-4 hours apart. POSAs would have understood, as Dr. Noecker testified, that each of these administrations were different interventions and discrete events. EX1047, 41:5-42:2, 54:12-21 (describing the comparisons as “different experiments” that cannot be

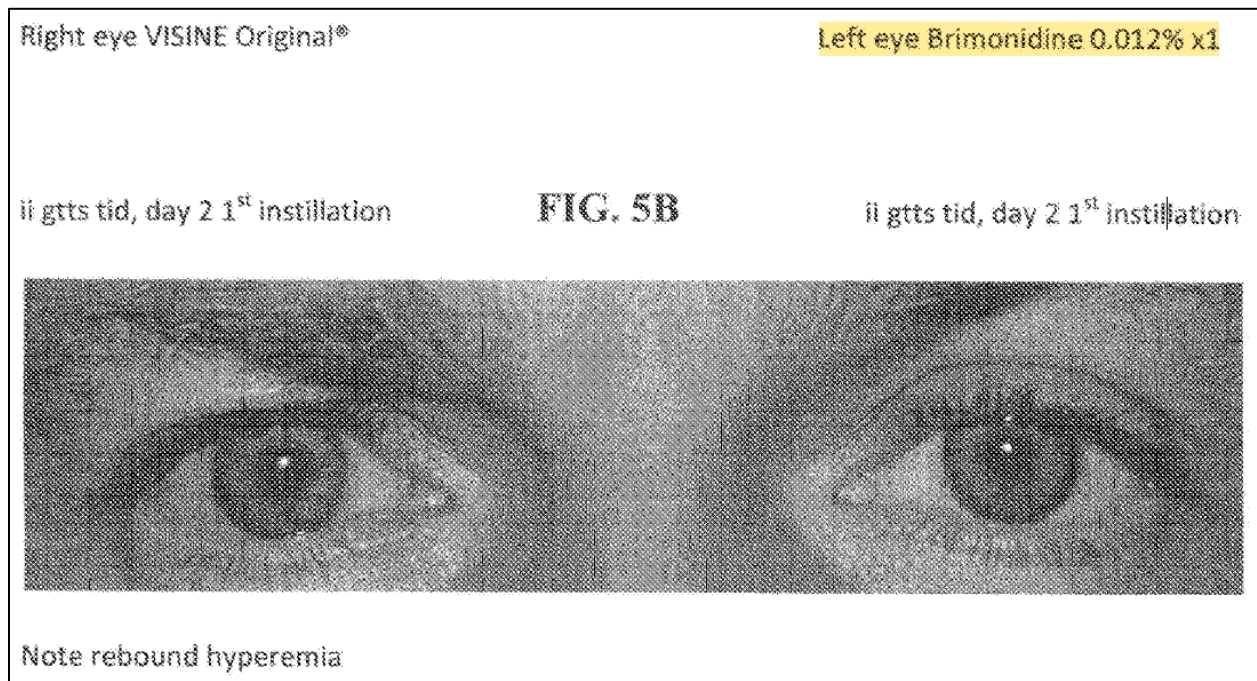
lumped together); *see also* EX1044, 23:9-11 (Example 1 “does not say that one drop was used in this session – in this section, but it’s implied that one drop was used”), 28:22-29:3 (“I would say that this is a single dose delivered every three to four hours and – and not multiple drops.”).

Example 4 compares “reduction in redness score after administration of *a single dose* of brimonidine 0.018%” compared to Visine “after *a single application*.” EX1001, 21:62-22:22 (emphasis added). POSAs would have understood the specification’s reference to “a single dose” and “a single application” to refer to a single drop of each product. *See* EX1044, 32:2-3 (“A single dose and a single – single drop are synonymous, in my estimation.”); EX2279, 28:19-23 (where clinician meant multiple drops, it was explicitly stated). Petitioners’ suggestion (Reply, 4) that a “single dose” may refer to more than one drop is non-sensical, for no POSA would have understood that in this head-to-head comparison more drops of brimonidine were administered than Visine.

Example 5 compares extreme low dose brimonidine to the commercial redness-reliever, Naphcon-A[®]. Petitioners assert (Reply, 3) the example’s statement that “treatment was through *drops* [of brimonidine] twice a day” suggests more than one drop per administration. That is a strained reading. It ignores there are two administrations of brimonidine per day, the net result being (multiple) drops are administered per day. POSAs would have understood, absent a statement to the

contrary, a one-drop versus one-drop comparison was performed, albeit twice daily for weeks. EX2279, 28:5-23.

Petitioners argue (Reply, 3-4) that the experiment in Figures 5A-C used multiple drops, asserting that Figure 5B's annotation "ii gtts tid, day 2 1st instillation" means two drops three times per day. Petitioners did not read the entire experiment and cropped Figure 5B. The experiment sought to prove that low-dose brimonidine could reverse rebound hyperemia. Starting from a baseline visual before instilling medication (EX1001, 3:47-48, Fig. 5a), the experiment describes administering Visine to induce rebound hyperemia (*id.*, 3:49-52), typically occurring after "repeated applications of [prior art] vasoconstrictors." *Id.*, 4:46-49. Figure 5B, reproduced below in full, notes the rebound hyperemia that two drops, tid, of Visine induced. But "full" Figure 5B, when describing the dosing of brimonidine, which Petitioners omitted, indicates that brimonidine was applied only once ("Brimonidine 0.012% ***xI***", emphasis highlighted), consistent with a single drop.



EX1001, Fig. 5B.

Thus, the specification supports administering a single drop of brimonidine in a single step to reduce redness. As PO's interpretation "most naturally aligns with the patent's description of the invention[, it] will be, in the end, the correct construction." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005).

Petitioners argue (Reply, 4-5) the prosecution history does not support PO's construction, stating when PO amended "comprising" to "consisting of", PO said nothing about the number of drops administered. But PO did not need to make such proclamation, for that amendment surrendered claim scope beyond the single step, single drop method now claimed. That is the legal consequence, which Judge Kirsch recognized, in amending to the closed transitional phrase. EX2030, 24-25 (PO

“narrowed the claim to ‘exclude[] any elements, steps, or ingredients not specified in the claim.’”) (citing *Multilayer Stretch Cling Film Holdings, Inc. v. Berry Plastics Corp.*, 831 F.3d 1350, 1358 (Fed. Cir. 2016)).

Petitioners argue (Reply, 5-6) PO’s “single-drop construction” reads claim 1 one way for validity and another for infringement. Although the “Lumify label instructs users to ‘instill 1 drop in the affected eye(s) every 6-8 hours,’” which could result in users administering “up to four drops of Lumify per day,” the Lumify label requires only administering one drop to achieve the desired redness-reduction effect, stating it works in one minute and lasts eight hours. *Id.*; see EX2050, 2. That users may, in a day, decide to administer additional Lumify after the effect wears off is irrelevant. As Dr. Noecker explained, Lumify’s dosing regimen for the redness-reducing effect consists of a single drop. EX1047, 83:5-11; see generally *id.*, 77:2-83:11.

The single-drop dosing regimen of Lumify significantly differs from Gil Example 1’s dosing regimen, which hyper-doses brimonidine preoperatively to load the eyes with an amount of drug (e.g., four drops the day before surgery and then 6-7 drops two hours before surgery to approach ~0.2% brimonidine) to theoretically reach an effective dose. EX1004, 4:54-57. Postoperatively each subject receives an additional 0.03% brimonidine drop every four hours while awake. *Id.*, 4:58-60. Petitioners misleadingly focus (Reply, 5) on the post-surgical dosing, while ignoring

the loading doses, to suggest a discrepancy in Dr. Noecker's testimony. POSAs would have understood that one drop of 0.03% brimonidine, whether before or after surgery, is insufficient to obtain an effective pain-relieving dose. POSAs would have understood that Gil Example 1's multiple doses of low-concentration brimonidine would have been needed to reach an effective dose. *Donnenfeld* ¶¶67; *Noecker* ¶144.

Thus, it is the dosing regimens required to achieve the desired effect that differs between Lumify and Gil Example 1. No inconsistency or discrepancy exists in Dr. Noecker's application of the so-construed claims to the Lumify label or how the dosage regimen of Gil Example 1 significantly differs from claim 1.

Patent Owner requests its construction be adopted.

III. Petitioners Failed to Prove the Challenged Claims Obvious

A. Petitioners Failed to Rebut That the Gold-Standard Alphagan Clinical Studies Demonstrated Brimonidine's Minimum Effective Dose for Redness Reduction was 0.2%

POSAs seeking to develop an improved redness reliever using brimonidine would have considered the clinical studies of the Alphagan products, including the NDA and labels therefor. *POR*, 41-48. Recognizing that these studies collectively demonstrated a dose-related response wherein 0.5% brimonidine caused conjunctival blanching in 50% of patients, while precipitously dropping to 3.5% of patients at 0.2% brimonidine and no longer being reported at 0.15% and 0.1% brimonidine (Alphagan P), POSAs would have understood that the minimum

effective dose for blanching/whitening the conjunctiva and reducing redness was about 0.2%. Noecker ¶¶185, 195. An independent clinical study in the peer-reviewed journal, *Ophthalmology*, confirmed as much, acknowledging the blanching effect of 0.5% and 0.2% brimonidine, while grouping 0.08% brimonidine with the placebo-established floor therefor. EX1029, 5; Noecker ¶200. Absent hindsight, therefore, POSAs looking to optimize brimonidine for redness reduction would not have dosed brimonidine below 0.2% with any expectation of reducing eye redness. *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1306 (Fed. Cir. 2015).

1. Petitioners’ Criticisms of the Alphagan Data Fall Flat

Petitioners represented to the district court “[i]n the decade that followed the commercial release of Alphagan,” which includes the Alphagan P trials, that “brimonidine was among the most well-studied and well-characterized drugs on the market.” EX2279, 24:1-13. Yet, here they argue the Alphagan studies provide “scant data” of “limited information” regarding conjunctival blanching. Reply, 18. Petitioners make this litigation-driven argument notwithstanding their “closest prior art” and *raison-d’etre* for lowering brimonidine’s concentration (Gil Examples 1, 4)

contains *zero* data, as does Dean, which additionally lacks any teaching about reducing eye redness.³

**a. Statistically-Analyzed Conjunctival Blanching Data
Would Have Been Highly Relevant**

POSAs would have understood the Alphagan labels’ reference to “conjunctival blanching” to mean, as the words themselves convey and the Federal Register indisputably supports, whitening of the conjunctiva and reduction in redness. EX1009, 9 (describing action of ocularly-applied vasoconstrictors “as *blanching*, bleaching, and *whitening* of reddened *conjunctiva*”); See Noecker ¶189, corroborated by EX2107, 2 (“whitening of the see-through layer which covers the surface of the eye”). Even the Board in the ’142-IPR (EX1003, 59) understood blanching the conjunctiva meant redness reduction.

That the Alphagan studies’ endpoints pertained to IOP reduction and were not designed to statistically evaluate redness reduction does not detract from their relevancy. Reply, 18-19 (citing EX1003, 59). Indeed, Petitioners’ reliance on the

³ Petitioners’ suggestion that POSAs would ignore the teachings of the Alphagan studies regarding blanching is particularly troubling given their position that “[n]o substantiating data is required” in Gil Example 4 because it “is prior art for all that it discloses.” Reply, 14-15.

Alphagan NDA itself evidences the studies' relevancy to POSAs looking to develop an improved redness-reliever. And, as Dr. Noecker testified in the '142-IPR, data on conjunctival blanching were still collected, and a statistical analysis was indisputably conducted thereon, making them highly relevant to such POSAs. EX1053, 68:17-19; EX1030, 52, 54, 109, 111 (indicating brimonidine 0.2% "p-values" for all adverse events, including conjunctival blanching and footnoting "[b]" beneath the table for Pearson's Chi-square test), 13 (referencing "significantly" greater incidence of conjunctival blanching for brimonidine 0.5% and 0.35% than vehicle).

That conjunctival blanching is listed as "adverse" would not have dissuaded POSAs from considering the statistically-analyzed Alphagan data regarding brimonidine's blanching/whitening effects. Any event affecting the eye would have been reported as "adverse." EX2019, 81:4-83:1, 155:6-22, 161:10-163:5; Noecker, ¶¶185-199. But that does not mean "undesirable" for any purpose. EX2280, 57:9-59:20 (noting that "mild to moderate" blanching would have been "what you would want to be targeting" for redness reduction). Notably, the Alphagan NDA indicates, in assessing conjunctival blanching at 0.5% and 0.35%, that brimonidine was "safe and comfortable," (EX1030, 13), consistent with the Alphagan P monograph (EX2119, 8 of "mild or moderate"). No patient withdrew from the Alphagan studies due to conjunctival blanching. EX1030, 129. Nor is it listed as a serious adverse

event (*id.*, 55), confirming Dr. Noecker’s testimony that conjunctival blanching was not considered a “danger,” contrary to Petitioners’ litigation-driven position. Noecker ¶¶191.

Thus, for POSAs seeking an improved redness reliever, the statistically-analyzed conjunctival blanching data from the Alphagan studies would have been highly relevant. Noecker ¶¶185-199.

b. Alphagan’s Conjunctival Blanching Data Carried an Imprimatur of High-Reliability

As a clinician in the Alphagan studies, Dr. Noecker testified that once observed in those studies, conjunctival blanching would have been monitored and reported if observed in the Alphagan P studies. Noecker ¶¶193-195. The Alphagan NDA confirms that “[a]ny adverse event occurring during the study was *recorded*.” EX1030, 119. The Alphagan P monograph, authored in 2003 and revised post-2008, corroborates the veracity of Dr. Noecker’s uncontested testimony that the Alphagan P investigators knew that 0.5% and 0.35% blanched/whitened the conjunctiva, as also disclosed in the Alphagan NDA (EX1030, 13), and that it would have been monitored in the Alphagan P studies and reported if patients presented with it. Noecker ¶¶194-195.

But none was reported for Alphagan P—not at an occurrence of 1-4% or even at *less than* 1% of subjects. EX1068, 4. The Alphagan P monograph corroborates as

much. EX2119, Table 2, 8-9. POSAs, moreover, would have compared the conjunctival blanching effects across the clinical studies for Alphagan and Alphagan P, for Alphagan P clinicians did so for adverse events. EX1075, 65, § 7.3 (comparing oral dryness/asthenia data between Alphagan and 0.1% brimonidine (Alphagan P) while identifying no limitations on adverse-event data).

Relying on the appealed FWD, Petitioners wrongly argue (Reply, 19) the Alphagan studies do not indicate how/when redness was measured, the degree of blanching needed to be an adverse event, the grading scale used, or the severity of blanching to make it on the label.

As established, all adverse events, including conjunctival blanching, would have been recorded, if present. EX1030, 119; Noecker ¶¶195. The Alphagan NDA describes that baseline evaluations for adverse events were made at the trials' start and each visit thereafter for changes from baseline.⁴ EX1030, 52, 119. Using an FDA-preapproved protocol implemented by expert clinicians trained to make such evaluations (Noecker ¶¶197-198), changes from baseline were “graded for severity (trace, mild, moderate, or severe),” thereby covering the waterfront of each event. EX1030, 119. Importantly, the FDA noted that in “[a]n adequate number of

⁴ POSAs would understand that an *increase* in blanching/whitening from baseline would mean a *decrease* in redness.

subjects, . . . [t]he doses and durations of [brimonidine] exposure were adequate to assess *safety* for the intended use.” EX1075, 63 (emphasis added). Relatedly, the FDA stated that “[t]he submitted safety database appeared adequate and complete” to conclude that Allergan’s “evaluation of potential adverse effects for [brimonidine] is adequate.” *Id.*⁵

Petitioners try to undermine the clinical studies’ reliability seeking more information about protocols. But it remains uncontroverted that the FDA thoroughly considered the adverse events data as sufficiently well-supported to approve the statistically-analyzed conjunctival blanching values reported (including the lack thereof) in the adverse event data on the Alphagan and Alphagan P labels, giving these data an imprimatur of high-reliability. Noecker ¶¶193-199; EX2008, 114:3-13, 124:6-19.

Accordingly, POSAs considering the Alphagan NDA and the labels for the Alphagan products, would have understood that ~0.2% brimonidine was the

⁵ Petitioners suggest (Reply, 20) a lack of clarity between hyperemia and blanching. The Alphagan NDA consistently treats these ocular events as separate, never conflating them, and clarifying that hyperemia pertains only to conjunctival redness. EX1030, 52, 109, 111 n. “d”.

minimum effective dose for redness reduction and amounts below 0.2% did not cause sufficient vasoconstriction to reduce redness. Noecker ¶¶180-199.

B. None of the Challenged Claim is Obvious

1. No Reasonable Expectation of Success Administering in One Step a Single Drop of 0.025% Brimonidine to Reduce Redness

Petitioners assert (Reply, 8) that sufficient motivation exists to modify Norden's and Gil's trauma models in view of Dean's glaucoma treatment when developing a redness-reducing ocular drop because they allege these references teach brimonidine vasoconstricts in the front of the eye and Dean suggests lowering its concentration to reduce side-effects. Petitioners further argue (Reply, 17) that a POSA would readily determine the correct concentration of brimonidine for the intended purpose. On the contrary, absent hindsight, a POSA would not have been so motivated and, even if they were, there would have been no reasonable expectation that lowering the dose to one drop of 0.025% brimonidine would result in sufficient vasoconstriction to reduce eye redness. None of Norden, Gil, or Dean provides such expectation, for the art's blazemarks told a different story: Go high. POR, 39-48.

As a preliminary matter, Petitioners incorrectly argue (Reply, 16) that because an administered dose is measured as a concentration, the number of drops Norden, Gil, and Dean administer is irrelevant. That is nonsensical. Concentration indicates

the amount of the active drug per unit volume. Stamer ¶40. But it is the *amount* of ocularly-delivered drug that matters for efficacy, which depends on the dosing regimen. *Id.*, ¶¶41-42. Administering one drop of Alphagan 0.2% (w/v) provides a specific amount of brimonidine. But a regimen that double-doses sequential drops of 0.2% brimonidine (Norden) administers twice the amount of brimonidine, equivalent to one drop of 0.4%, though each eyedrop’s concentration remains at 0.2%. *Id.*

a. Norden

Petitioners’ Reply (at 12-13) makes three points regarding Norden: (1) his reference to “hyperemia” is vasodilation, (2) he measured “hyperemia” once at five minutes postoperatively, and (3) he controlled for the effects of brimonidine alone. Even assuming these were true, which PO contests in its POR, POSAs were left with the inescapable conclusion that they would have to use a *high* dose of brimonidine, not low, to achieve sufficient vasoconstriction to reduce redness.

Norden administers 0.2% brimonidine 10 minutes apart in two separate instillations, which *Petitioners do not contest* approaches a drug amount close to what one eyedrop of 0.4% would ocularly deliver—16 times higher than one drop of 0.025%. Even if Norden’s reference to “hyperemia” is vasodilative hyperemia, Norden teaches no more than what the statistically-robust Alphagan studies do: $\geq 0.2\%$ brimonidine is the minimum effective dose to reduce eye redness. Petitioners

(Reply, 8) take Dr. Donnenfeld's statement that brimonidine was a strong vasoconstrictor out of context. Being questioned about Norden, Dr. Donnenfeld simply acknowledged that double-dosing of 0.2% brimonidine would strongly vasoconstrict, as the conjunctival blanching data for Alphagan 0.5% and 0.35% already showed. Nothing in Norden suggests lowering the dose.

b. Gil

Nor does Gil provide the motivation to lower the dose and expect it to reduce redness. The steady and consistent messaging in Gil is clear: when ocularly dosing brimonidine to reduce pain or even pain-associated redness, use high amounts of drug. *Petitioners do not dispute* Gil Example 1 describes a dose-loading regimen involving *multiple administrations* of 0.03% brimonidine to achieve a sufficiently *high amount of drug* in the eye to block pain from surgery. Indeed, just focusing on the two hours before surgery, no one disputes Gil proposes 6-7 drops to approach the amount of drug one eyedrop of 0.2% would deliver for pain relief.

Similarly, Gil Examples 4 and 5, which look at the effect of brimonidine on ocular pain (and symptoms of neurogenic inflammation) using the Corneal Nerve Conduction Model, would have informed POSAs to dose brimonidine high, not low. Example 4 proposes a dose-study using brimonidine at concentrations ranging from 0.01%-0.5% to assess pain relief in the presence of an ocular surface sensory challenge such as topical capsaicin, potassium chloride or fine hairs. EX1004, 5:20-

21, 5:31-37. Example 5 performs the same study using Alphagan 0.2% and a standard NaCl stimuli. In these experiments, the brimonidine test formulations are filled into a chamber, about *1 cc (20-30 drops)*, fitted on the ocular surface of the anesthetized rabbit and nerve traffic is recorded in the presence of the stimuli. EX1004, 5:63-6:13; EX2279, 39:23-40:3.

For Example 4's data-less dose-ranging study, as Dr. Gil explained, POSAs would have expected the lower end of the concentration range to be ineffective or have minimal effect and the higher end of the range to have most promising effects. EX2093, 106:15-108:2, 117:14-118:23; EX2009, 107:16-108:13. Here, even at the lowest concentration within the range proposed, the amount of brimonidine administered would be close to what a single eyedrop of *0.2% to 0.3% (0.01% x 20-30 drops)* would ocularly deliver. Noecker ¶¶160-61. And as the brimonidine concentration went up, an even higher dose would be delivered. Similarly, for Example 5, which used 1 cc of Alphagan 0.2%, the amount delivered is equivalent to a dose of *20-30 drops of 0.2% brimonidine*. *Id.*; POR, 32; EX1004, 5:65-66.

At these amounts, and based on this model, which Petitioners' expert admits is incapable of evaluating redness (EX2017, 136:21-137:1), no POSA would have inferred one drop of 0.025% brimonidine would have expectedly reduced redness. This is particularly true in view of the art's blazemarks consistently confirming the need for high amounts of brimonidine ($\geq 0.2\%$). *See* EX1030, 13, 52, 109; EX1067,

4, 9; EX1068, 4 (establishing about 0.2% brimonidine as the minimum effective redness-relieving dose); EX1029, 4-5 (*dose-ranging study* establishing doses below 0.2% brimonidine no better than placebo for whitening the conjunctiva); EX1006, 4-5 (Norden double-dosing 0.2% brimonidine); EX2005, 5 (Alphagan 0.2% blanched/whitened the conjunctiva).

Additionally, as Dr. Gil testified, there would have been no reason to retest doses below the 0.2% minimum effective redness-relieving dose, independently confirmed by EX1029's dose-ranging study, exposing Petitioners' hindsight reconstruction of Gil. EX2016, 153:6-15. Indeed, the Allergan discovery team, led by Dr. Gil and contemporaneously charged with repurposing brimonidine, never considered brimonidine, much less low-dose brimonidine (e.g., single drop of 0.025%), for redness reduction focusing instead on $\alpha 1$ -adrenergic agonists. Gil ¶¶19-24, 40-46; EX2011, Abstract, 1:44-53, 2:27-38.

c. Dean

Dean provides neither the motivation nor the expectation that reducing the dose of brimonidine to a single drop of 0.025% would reduce eye redness. Dean mentions nothing about reducing eye redness, but because Dean notes that brimonidine constricts ocular vessels and reduces the flux of blood through the eye, Petitioners assert (Reply, 9-10, 15-16) POSAs would have inferred it reduces redness at all concentrations. Not so.

As Petitioners' experts acknowledged, POSAs would have read that passage about vasoconstricting scleral vessels as relating to Alphagan 0.2%, discussed at column 1, lines 20-25. EX2014, 794:4-795:13. Further, brimonidine's "primary purpose" in Dean is IOP reduction. Dean merely hypothesizes that brimonidine "should" vasoconstrict to augment brinzolamide's bioavailability. EX1007, 2:60-62. And, in this context, while Dean suggests administering brimonidine-only drops having a concentration from 0.01% to 0.2%, preferably 0.1% to 0.2%, as Dr. Galanis conceded, at least 0.1% brimonidine is required to maintain brimonidine's IOP control. EX2085, 44:14-45:5. Thus, POSAs would have understood multiple brimonidine-only drops were needed at the lower end of Dean's concentration range to serve its intended purpose. *Id.*

Similarly, POSAs would have understood that low doses (e.g., a single drop at the lower concentrations) *might* vasoconstrict enough to increase brinzolamide's bioavailability but not enough to reduce redness. EX1007, 2:57-65; Noecker ¶¶116-117, 152. No data exist in Dean proving amounts less than 0.2% brimonidine would have vasoconstricted sufficiently to reduce redness. Nor, absent such data, would POSAs have made such an inference. *See Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1376 (Fed. Cir. 2011) (such speculation is insufficient to direct POSAs to the invention). And given POSAs were aware that brimonidine's minimum effective dose for relieving eye redness was about 0.2% based on

statistically robust pre-2008 clinical studies, they would have expected that lowering brimonidine's dose to reduce hyperemic side-effects would have eliminated brimonidine's redness reducing effect.

At bottom, POSAs seeking a better redness reliever would not have read Norden, Gil, and Dean, in view of brimonidine's statistically-analyzed clinical conjunctival blanching data, and envisaged modifying these references to administer, in one step, a single eyedrop of 0.025% brimonidine and reasonably expected successful redness reduction therefrom.⁶ The 2008 Fudenberg review article independently corroborates that POSAs were not contemplating viably using brimonidine to whiten/blanch reddened conjunctiva. Noecker ¶¶111-112.⁷

⁶ Petitioners' citation to Hong (Reply, 16-17) is irrelevant. Hong administered a drop of 0.15% brimonidine—a six times higher dose than 0.025%—to prophylactically reduce bleeding, not hyperemia, during strabismus surgery together with other active ingredients. Thus, Hong, when viewed in the context of the prior art as a whole, would provide neither the motivation nor the expectation of success to arrive at the claimed invention.

⁷ Petitioners criticize Fudenberg as glaucoma-centric and failing to consider all uses, as it cites none of Norden, Gil, or Dean. Reply at 7, n.8. They are wrong on

C. Petitioners Misapply Inherent-Obviousness Law for “Ocular Hyperemia Is Reduced”

Petitioners failed to meet the high burden of proving that the alleged inherent limitation *necessarily* flows from combined elements in the art rather than mere “probabilities or possibilities” therefrom. *Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014). The ’245 patent undermines inherency. EX1001, 22:5-10 (68.71% redness-reduction efficiency for low-dose brimonidine).

PO also proffered evidence rebutting the overlapping-ranges argument, including teaching away and unexpected results (POR, 39-57), dissolving “the *prima facie* case [premised on optimization]” and requiring “consider[ation of] all of the evidence anew.” *In re Kumar*, 418 F.3d 1361, 1366, 1368 (Fed. Cir. 2005). The Alphagan studies would have taught a POSA away from dosing below the clinically-established minimum effective dose of 0.2% brimonidine for reducing eye redness. *Allergan*, 796 F.3d at 1306. Yet, one eyedrop of 0.025% brimonidine not only worked but that it reduced redness 3-6.5 times greater than the closest prior art without side-effects, demonstrating an unexpected difference in kind. Noecker

both points. Fudenberg cited Petitioners’ reference Derick 1997 (EX1029), which disclosed brimonidine’s conjunctival blanching effects at 0.5% and 0.2% while grouping a lower concentration as no better than placebo. EX2028, 5.

¶¶223-228; *Allergan*, 796 F.3d at 1307 (differentiating inventions possessing unexpected efficacy/safety results from claims merely reciting “unknown [inherent] properties” of an obvious formulation); *Allergan Sales, LLC v. Sandoz, Inc.*, 717 F. App’x 991, 994 (Fed. Cir. 2017) (holding non-obvious claims reciting additional efficacy limitations “neither suggested nor inherent” in prior art).

IV. Objective Indicia of Non-Obviousness

A. Unexpected Results

Petitioners do not challenge the data submitted to establish the claimed invention’s unexpected results over the prior art. Petitioners argue only that PO did not test against the closest prior art (Reply, 24-25), relying on the prior Board’s holding. But PO appealed that issue, and its POR details the impropriety of that holding, applying *In re Merchant*, 575 F.2d 865 (C.C.P.A. 1978) and *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356 (Fed. Cir. 2017). Petitioners do not contest the applicability of *Merchant* and merely state the FWD considered *Millennium* inapposite.

The prior Board, however, committed essentially the same error the district court did in *Millennium*. It found the closest prior art comparator is what it acknowledged was obvious from the prior art (EX1003 at 63-64, Gil “*suggests* that [0.03% brimonidine] would be effective in reducing eye redness”), not what was known and disclosed in Gil. Requiring PO to test against what was allegedly obvious

would require a comparison of the invention against itself. That is not the law and is what *Millennium* meant when holding that “[u]nexpected results are shown in comparison to what was known, not what was unknown.” *Millennium*, 862 F.3d at 1368.

B. Commercial Success and Industry Praise

Petitioners argue PO presents the “same objective-indicia arguments” from the ’142-IPR. Reply, 24. But as Petitioners’ expert Mr. Masztak admitted, the challenged claims and evidence here are *different* than the ’142-IPR. EX2281, 68:4-70:6, 181:16-185:8. Petitioners’ attack centers on nexus; they do not seriously dispute commercial success or industry praise from unpaid and unaffiliated physicians in the optical care industry.

It remains Petitioners’ burden to rebut PO’s established presumption of nexus, *Crocs, Inc. v. ITC*, 598 F.3d 1294, 1311 (Fed. Cir. 2010), and their only attempt is arguing “PO’s evidence turns on the use of low-concentration brimonidine, which was known in the prior art.” Reply, 26. As set forth above, the prior art did not teach use of a single drop of 0.025% brimonidine to reduce eye redness. PO’s evidence thus has clear, un rebutted nexus with the ’245 patent.

Petitioners’ remaining arguments are afterthoughts. Petitioners first accuse PO of failing to apportion Lumify’s commercial success among its Orange Book-listed patents or the challenged claims. Reply, 25; EX1203, ¶73. There are no such

requirements in the law, and *Nevro* is distinguishable, involving failure to apportion “different features not claimed” of a mechanical system. *Nevro Corp. v. Boston Sci. Neuromodulation Corp.*, IPR2019-01313, Paper 74, at 52 (P.T.A.B. Jan. 19, 2021). Mr. Masztak never reviewed *Nevro*, and testified that cases (like *Nevro*) involving different patents from this case “are not analogous cases to compare an argument in one versus the other.” EX2281, 109:2-118:11.

Mr. Masztak ignored record evidence to conclude that marketing drove Lumify’s success rather than patented features. Citing years-old evidence, Mr. Masztak touts “detailing to eye care professionals” and television advertising spend (EX1203, ¶33) despite Bausch’s John Ferris testifying that “advertising and promotion expenses are *near their lowest* since the product debuted. *This product has no dedicated sales detail.*” EX2230, ¶29. PO has presented strong evidence of nexus, commercial success, and industry praise that weighs against obviousness.

V. Estoppel

There is no estoppel under 37 CFR § 42.73(d)(3). The FWD’s legal holdings and factual findings are being appealed, they can be reversed/modified, and no ’742 patent claim has been finally canceled. *Ex Parte Stuart A Nelson* is inapposite because PO voluntarily took a *final* consent judgment. Appeal 2020-004978, 2020 WL 8186425, at *3, *5 (P.T.A.B. Dec. 31, 2020). Additionally, based on how the

'742 patent claims were construed in the FWD, the claims here are patentably distinct therefrom as well as over the asserted prior art.

VI. Conclusion

Petitioners have failed to prove any challenged claim unpatentable.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this Patent Owner's Response complies with the type-volume limits of 37 C.F.R. § 42.24(b)(1), because it contains 5,586 words, according to the word-processing system used to prepare this Patent Owner's Response, excluding the words in the Table of Contents, Table of Authorities, Table of Abbreviations, Certification Under § 42.24(d), and Certificate of Service, as set forth in 37 C.F.R. § 42.24(a)(1).

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