

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 RESPONSE

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I. Introduction

Patent Owner Eye Therapies, LLC submits this Patent Owner Response to the Petition for *Inter Partes* Review of U.S. Patent No. 11,833,245 (“the ’245 patent”) filed by Dr. Reddy’s Laboratories S.A. and Dr. Reddy’s Laboratories, Inc.

Petitioners advance an oversimplistic, hindsight-riddled obviousness position composed of mainly two points: (1) Norden (EX-1006) and Gil (EX-1004) disclosed comparative studies with brimonidine as the sole variable that would have taught brimonidine alone could reduce eye redness, and (2) using 0.025% brimonidine to reduce redness would have been presumptively obvious from overlapping brimonidine ranges taught in Gil and Dean (EX-1007). Petitioners’ position fails to properly consider the ’245 patented invention as a whole.

Claim 1 is a method of reducing eye redness by ocularly administering in a single step a single drop of 0.025% brimonidine to achieve redness reduction. Assuming *arguendo* POSAs would have divined that Norden and Gil suggested brimonidine alone could reduce redness, they teach multiple steps of administering multiple drops of brimonidine that ocularly dose at amounts near or above 0.2% (Gil) or approaching 0.4% (Norden). Dean is about co-administering two intraocular pressure (IOP) lowering drugs (brimonidine/brinzolamide) to treat glaucoma and mentions nothing about using brimonidine to reduce eye redness. Although Dean mentions brimonidine vasoconstricts, it guides POSAs not to lower brimonidine’s

dose below its ability to control IOP ($\geq 0.1\%$), whether as a single drop or multiple drops.

The single administration of a single drop of 0.025% brimonidine would not have been presumptively obvious from the Gil and Dean ranges. Dr. Daniel Gil—first-named inventor on the Gil patent and an Allergan scientist tasked with repurposing brimonidine—testified his patent focused on alleviating ocular pain and, if anything, high-concentration brimonidine would be needed to do so before impacting any pain-associated redness. EX-2009, 113:6-115:21. Lacking any suggestion of using brimonidine to reduce redness, Dean would have motivated POSAs to keep brimonidine's concentration on the higher end to maintain its IOP-lowering effect.

Here, the overlapping-range obviousness presumption is rebutted. The prior art—multiple human clinical studies with brimonidine (Alphagan studies)—taught away from 0.025% brimonidine to reduce redness. As brimonidine's concentration dropped below 0.2%, the clinical studies evidenced that brimonidine's vasoconstriction ability was insufficient to reduce redness. Additionally, the '245 patented method, embodied by the commercial product Lumify, unexpectedly exhibited up to 600% better redness-reducing efficacy than the closest prior art redness reliever, while advantageously lacking the side-effects that plagued these prior redness relievers for decades. Lumify's excellent efficacy and safety profile

drew doctors' praise, propelling it to the #1 doctor-recommended redness relieving drop and revitalizing a stagnant market to garner significant commercial success.

Only with hindsight would POSAs have considered brimonidine, known to cause ocular redness and allergies, as a potential redness reliever. Indeed, even Dr. Gil, who invested years to repurpose brimonidine, expressed surprise when he learned of Lumify's market-approval. Gil ¶¶ 19-24, 40-42, 46. Consistent therewith, publications reviewing the state-of-the-art just before the '245 patent filing date revealed that no one ever considered using brimonidine to relieve ocular redness.

II. The '245 Patent

The earliest-effective filing date of the '245 patent is August 1, 2008. The patent claims methods for reducing ocular hyperemia (eye redness from vasodilation) using 0.025% brimonidine as the only active ingredient for reducing ocular hyperemia, in an ocular drop including benzalkonium chloride ("BAK") and having a pH between 5.5 to 6.5. Unlike prior art methods for reducing ocular hyperemia, the claimed methods are suitable for long-term, chronic use because they do not cause common side effects, such as rebound hyperemia (eye becoming redder after initial reduction in redness) and tachyphylaxis (tolerance to the drug).

Claims 1 and 8 of the '245 patent are independent claims. They recite the same preamble, "[a] method for reducing eye redness in a human subject having ocular hyperemia," and require administration of brimonidine at a concentration of 0.025%

and actual reduction in ocular hyperemia. Claims 1 and 8 differ in their transitional phrases.

Claim 1 contains the transitional phrase “consisting of” that limits the claimed method to a single step of ocularly administering a single drop of 0.025% brimonidine as the only active ingredient, where the single step is the only step taken to reduce eye redness. *See infra* § VII.B; EX-1001, 22:36-44. Claim 8 uses the open-ended transitional phrase “comprising,” before reciting the step of ocularly administering “brimonidine as the sole redness reducing active ingredient.” EX-1001, 22:65-23:6. All claims require that the ocular drop include BAK at a pH between 5.5 to 6.5. *Id.*

The dependent claims include additional elements, such as, *inter alia*: “wherein the ocular drop induces a low incidence of rebound hyperemia in the eye of the human subject administered the ocular drop” (claims 2-7, 9-14), “wherein the eye redness of said human is not associated with an ocular disease or the result of a surgical procedure on the eye” (claims 4, 7, 11, 14-15, 17, 19-20, 22), “wherein the method retains normal intraocular pressure in the eye of the human subject administered the ocular drop” (claims 5, 7, 12, 14, 17, 19, 22, 24), and “wherein the ocular drop reduces redness in the eye to which the ocular drop was administered to improve the aesthetic appearance of said eye” (claims 6-7, 13-14, 16-17, 19, 21-22, 24, 25-28).

All claims read on the use of Lumify, when used in accordance with its FDA-approved label to reduce eye redness. Noecker ¶¶243-262.

III. The '142-IPR Final Written Decision Is Not Applicable

Petitioners rely on the Final Written Decision (“FWD”) in IPR2022-00142 (“’142-IPR”), arguing that it involved similar issues present here and suggesting incorrectly that those issues need not be revisited. The ’142-IPR is currently on appeal at the Federal Circuit and addressed the patentability of the claims of U.S. Patent No. 8,293,742 (“the ’742 patent”), which, as construed by the prior panel, materially differ in scope from the narrower ’245 patented methods.

The Board in the ’142-IPR construed the preamble of the ’742 patent claims as limiting and requiring brimonidine be administered with the intentional purpose of reducing eye redness but not requiring that redness actually be reduced. EX-1003, 11-12. It construed eye redness to include hemorrhage. *Id.*, 31. It construed the transitional phrase “consisting essentially of” as open to additional steps and drops including drops of active ingredients that may vasoconstrict. *Id.*, 14-16. Lastly, it construed “about 0.025%” to include 0.03%. *Id.*, 29.

The ’245 patented methods differ materially from how the Board construed the ’742 patented invention. Neither party disputes that the ’245 patent claims are limited to methods of reducing eye redness (from vasodilation) and require actually achieving redness reduction. They also specifically require 0.025% brimonidine. In

this context, claim 1 is further limited to a single step of ocularly administering a single drop of 0.025% brimonidine as the sole active ingredient. *See* §VIII.A.2, *infra*. Claim 8 ocularly administers 0.025% brimonidine as the sole redness reducing active ingredient. The claims also require that the ocular drop include BAK.

Because the claims of the '245 patent are materially narrower in scope, and the '142-IPR is on appeal, this Board panel needs to make its own findings and conclusions, independent of the prior Board's decision.

IV. Technical Background

A. Vasodilative Hyperemia Versus Hemorrhage

Red eye is broadly categorized into ocular hyperemia and hemorrhage. Noecker ¶26; Donnenfeld ¶51. Ocular hyperemia refers to simple eye redness caused when vasodilation—an increase in blood vessel diameter—results in an influx of blood that reddens the eye's appearance. Noecker ¶26. It can occur in any visible layer of the eye with vasculature, including the conjunctiva or sclera. Noecker ¶26; Donnenfeld ¶37. Conversely, constricting dilated ocular blood vessels will decongest them, which on the surface can reduce redness and make the eyes appear whiter. This is known as vasoconstriction. Noecker ¶26.

On the other hand, hemorrhage occurs when ocular blood vessels rupture, e.g., during surgery, leaking blood under the conjunctiva. Noecker ¶28; Donnenfeld ¶¶50-52. Subconjunctival hemorrhage occurs when a significant amount of blood

enters the conjunctiva and forms red patches/blotches. Noecker ¶28; Donnenfeld ¶52. Micro-vessel hemorrhage is another type of hemorrhage that occurs when a small amount of red blood cells leaks from ocular surface blood vessels, making the eyes appear pink. Donnenfeld ¶52.

This distinction between ocular hyperemia and hemorrhage matters clinically. Noecker ¶29; Donnenfeld ¶52. Ocular hyperemia can be reduced by sufficiently vasoconstricting visible ocular blood vessels using alpha-adrenergic agonists, which regulate constriction and dilation of blood vessels. Noecker ¶29. In contrast, hemorrhage—whether subconjunctival or micro-vessel—*cannot be reduced* through vasoconstriction after it arises and only dissipates over time. Noecker ¶29.

B. Adrenergic Receptors Regulate Blood Vessel Size

The eye contains two types of alpha-adrenergic receptors relevant here: $\alpha 1$ and $\alpha 2$. Stamer ¶¶26-32. Agents that activate these α -receptors are known as $\alpha 1$ and $\alpha 2$ agonists. *Id.*

Alpha-1 agonists trigger an excitatory response contracting smooth muscles, thereby constricting blood vessels and reducing eye redness—the so-called “ $\alpha 1$ effect.” EX-1024, 3 (“[v]asoconstriction is mediated mainly via $\alpha 1$ -adrenergic receptors”); Stamer ¶¶29-30. “Conjunctival blanching,” another way of referring to redness reduction or whitening a reddened conjunctiva (EX-1009, 9), is simply an $\alpha 1$ effect. EX-2003, 1; EX-1029, 2; EX-2040, 51:17-52:8; Gil ¶25; Stamer ¶¶30, 46.

By contrast, α -2 agonists trigger relaxation of smooth muscles, thereby dilating blood vessels and causing eye redness—an “ α 2 effect.” Stamer ¶¶29, 31, 46; EX-1024, 3. It was known that brimonidine, an α 2 agonist, can “produce vasodilatation via α 2-adrenoceptors on endothelial cells,” located in the front of the eye. EX-1035, 5; Stamer ¶¶31, 75, 90-92; EX-2004, 1.

Alpha-adrenergic receptor agonists fall into three categories: selective α 1, mixed α 1/ α 2, and selective α 2. Noecker ¶34. Whether a particular agonist interacts with an α 1 or α 2 receptor depends on its selectivity for a specific receptor subtype. EX-2003, 1; Stamer ¶50. Brimonidine is a highly selective α -2 agonist, being at least 1000-fold more selective for the α 2 receptors than the α 1 receptors. EX-2005, 5; Stamer ¶46; EX-1035, 2; Gil ¶25. Because of brimonidine’s low affinity for α 1 receptors, the art taught that “brimonidine would be the least likely to produce α 1-adrenoceptor-mediated side effects, such as ... ocular vasoconstriction.” EX-1035, 2. But at high concentrations, brimonidine may activate α 1 receptors and blanch/whiten the conjunctiva. EX-2003, 1; Stamer ¶46; Gil ¶25.

C. Prior Art Redness Relievers

The active ingredients available as ocular redness relievers pre-August 2008, shown below, contained either α 1-selective receptor agonists or mixed α 1/ α 2 agonists, with a predominant α 1 effect. *See* EX-1009, 16; EX-1001: 22-25; Noecker ¶34.

Tradename	α -Agonist API	α -Agonist Type
Naphcon-A [®]	naphazoline 0.025%	Mixed α 1/ α 2 agonist
Ocu-Clear [®]	oxymetazoline 0.025%	Mixed α 1/ α 2 agonist
Visine Original [®]	tetrahydrozoline	Selective α 1 agonist

These eye redness relievers, despite being the standard of care, triggered various side-effects, including rebound hyperemia and tachyphylaxis. EX-1001, 2:37-44; EX-1009, 10; Noecker ¶35. Rebound hyperemia occurs after the vasoconstrictive effects of redness relievers wear off and compensatory vasodilation occurs to flood/engorge the vessels with blood, making the eyes appear redder than before drug instillation. Noecker ¶36; EX-1001, 4:46-51. Tachyphylaxis manifests as a rapid decrease in drug effectiveness after repeated uses. Noecker ¶37. As a result, consumers unwittingly instill more drops more frequently to obtain the same level of whitening, leading to ocular toxicity and chronic swelling/redness even after discontinuation. EX-1001, 4:46-61; Noecker ¶37.

Eye care professionals (“ECPs”) often did not recommend the prior art commercial redness relievers because of their side-effects of rebound hyperemia and tachyphylaxis. Noecker ¶¶38-39; Ferris ¶7. Lumify would solve that problem/need. *Id.*

V. Lumify

Lumify demonstrated excellent redness reducing efficacy, unexpectedly outperforming the closest VISINE product by up to 600%. Noecker ¶¶223-228. It also worked within one minute, reducing redness for up to eight hours, 30% longer than VISINE. *See, e.g.*, EX-2050, 2; Noecker ¶245. FDA concluded that Lumify did not show tachyphylaxis or rebound hyperemia and thus predicted that it would provide a potential advantage to consumers of the over-the-counter (“OTC”) product. EX-2027, 3.

In just three months after Lumify’s 2018-launch, the FDA’s prediction came to fruition. Ferris ¶¶7, 24. Lumify became the #1 ECP recommended redness relieving drop, drawing praise from doctors for its advantageous efficacy and safety profile. Ferris ¶24; EX-2066, 1. It simultaneously disrupted and revitalized a stagnant redness reliever market, while garnering significant commercial success. Ferris ¶26.

VI. POSA

The POSA definitions provided by the parties do not differ much, except in years of experience in the relevant fields of discipline to which the ’245 patent pertains. *See, e.g.*, Noecker ¶¶21-25. Even when applying Petitioners’ POSA definition, the claims of the ’245 patent are patentable.

VII. Claim Construction

A. The Claims Are Limited to Methods for Reducing Eye Redness Requiring Actual Redness Reduction

No party disputes that the preamble “[a] method for reducing eye redness in a human subject having ocular hyperemia” requires that the method be performed with the intentional purpose of reducing eye redness. EX-1003, 11-12. In light of the “wherein the ocular hyperemia is reduced” clause, and reading the claim as a whole, the method states more than a purpose—it requires actual reduction in ocular hyperemia. *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333 (Fed. Cir. 2003); Noecker ¶61.

B. The Transitional Phrase “Consisting of” Limits the Claim to a Single Step of Administering a Single Drop of 0.025% Brimonidine

The transitional 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 administering *a single drop of 0.025% brimonidine as the only active ingredient in a single step*, where *the single step is the only step taken to reduce eye redness*. This interpretation flows from the “consisting of” transitional phrase and aligns with the intrinsic record and Federal Circuit law.

“Consisting of” as a transition term limits and closes off, relative to the invention’s operative environment of the preamble, additional steps or components.

See Norian Corp. v. Stryker Corp., 363 F.3d 1321, 1331 (Fed. Cir. 2004). The body then recites the steps and components used in the method’s environment. Here, the body 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-1001, 22:37-41. All other steps are closed off.

Further, the indefinite article “an” in the phrase “an ocular drop” should be interpreted as a single drop. The Federal Circuit has held that the transitional phrase “consisting of” when used in conjunction with a claim term introduced with the indefinite article (“a” or “an”) limits that term to its singular sense. *Norian Corp. v. Stryker Corp.*, 432 F.3d 1356, 1359 (Fed. Cir. 2005); *see also Abbott Lab’ys v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1281 (Fed. Cir. 2003). Consistent therewith, the claim language refers later to “**the** ocular drop” in the singular form.

This construction is further supported by the intrinsic record. For example, claim 29 (issued claim 1) of the as-filed application originally included the open-ended transition term “comprising”—in a method “comprising topically administering ... an ocular drop.” EX-1010, 4. Because the transition was open ended, the claim embraced both the administration of one or more eye drops and one or more steps to reduce redness. *Norian Corp.*, 432 F.3d at 1359. The Patentee subsequently replaced “comprising” with “consisting of” in response to a rejection, stating that “the transitional phrase ‘consisting of’ ... means that brimonidine is the

sole active ingredient administered in the method for reducing redness of claim 29, and excludes other active ingredients ... from the method.” EX-1010, 288. The Examiner then allowed the claims over the art of record, including Gil, Norden, and Dean, as well as the ’142-IPR FWD.

By replacing “comprising” with “consisting of,” Patentee surrendered claim scope beyond the single step, single drop method now claimed. EX-1010, 185, 189, 288; *see also Norian Corp.*, 432 F.3d at 1359-61 (replacing the transitional phrase “comprising” with “consisting of ... a sodium phosphate” surrendered scope and limited the claim to “a single type of sodium phosphate”).

This construction aligns with the specification’s examples administering a single drop of brimonidine in a single step to reduce redness. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (*en banc*) (construction that “most naturally aligns with the patent’s description of the invention will be, in the end, the correct construction”) (citation omitted). Examples 1, 4, and 5, and Figures 5A-C all use a single drop of low-dose brimonidine to reduce redness better than prior art redness relievers. EX-1001, 20:39-21:3, 21:61-22:22, 22:24-34.

Patent Owner requests its construction be adopted. Noecker ¶¶62-65.

VIII. The Petition Fails to Establish a Reasonable Likelihood that Any Challenged Claim Is Unpatentable

A. Failure to Establish Claim 1 of the '245 Patent Would Have Been Obvious

The Institution Decision (at 25) characterized the dispute between the parties as whether a POSA, in view of the asserted art (Norden, Gil, Dean, Alphagan, and Federal Register), “would have (1) used brimonidine as the sole active agent for reducing eye redness, and (2) used 0.025% brimonidine and reasonably expected it to reduce eye redness.” The Decision also stated (*id.*) that the parties “dispute whether the prior art teaches ‘wherein the ocular hyperemia is reduced’ by administering 0.025% brimonidine.”

Respectfully, the claimed method is not simply directed to the use of 0.025% brimonidine as the sole active agent to reduce eye redness; it is limited to using a *single ocular drop* of 0.025% brimonidine including BAK *administered in a single step*. These limitations further distance the invention from the asserted prior art.

Petitioners’ obviousness analysis is flawed at least for failure to consider each of these limitations, much less the claimed method as a whole. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007); *Jones v. Hardy*, 727 F.2d 1524, 1529 (Fed. Cir. 1984) (“Failure to consider the claimed invention as a whole is an error of law.”).

1. “A Method for Reducing Eye Redness in a Human Subject Having Ocular Hyperemia”

Claim 1 is directed to “[a] method for reducing eye redness in a human subject having ocular hyperemia.” This limiting preamble requires that the claimed single drop of 0.025% brimonidine be administered with the intention of reducing eye redness to patients with ocular hyperemia, i.e., eye redness caused by vasodilation. Noecker ¶¶113-114; *see also* Paper 14 at 13 (preamble was “limiting” in ’142 IPR).

Petitioners assert that Gil and Norden teach using brimonidine to reduce eye redness. Pet., 37-39. Not so. The threshold obviousness inquiry asks what POSAs would have considered pre-August 2008 to develop a better redness reliever. *Unigene Lab’ys, Inc. v. Apotex, Inc.*, 655 F.3d 1352, 1361 (Fed. Cir. 2011) (considering the reason to select and combine prior art to solve the problems in the relevant field and make the invention). Relatedly, the “definition of the relevant artisan provid[es] the perspective that governs the obviousness analysis and of the problem addressed by the [claimed invention].” *Axonics, Inc. v. Medtronic, Inc.*, 73 F.4th 950, 958 (Fed. Cir. 2023). Petitioners define the POSA as an ophthalmologist and pharmaceutical formulator with collectively 6-9 years of “experience developing eye drop formulations *for clinical trial and regulatory approval*.” Pet., 16-17 (emphasis added).

Consistent therewith, Petitioners’ Dr. Galanis admitted that the POSA is “inherently a practical person” who would look at prior art to determine what would reasonably work for purposes of “develop[ing] a *commercially approved [eye]*

redness reliever.” EX-2017, 83:10-84:2. *See Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1385-86 (Fed. Cir. 2018) (obviousness inquiry for pharmaceutical inventions considers the market demands/design needs motivating POSAs to develop a commercially viable therapy). And Petitioners’ Dr. Dana admitted that ocular trauma models have *never* been considered in assessing a redness reliever for regulatory approval:

Q. Are you aware of any study that would have used the ocular setting of LASIK surgery for assessing a redness reliever for an OTC product for FDA approval?

A. No.

EX-2008, 150:19-23. These undisputed facts frame the obviousness inquiry.

Norden and Gil involve *surgical trauma models*, cutting and damaging blood vessels. Noecker ¶¶114-115; Donnenfeld ¶¶48, 64. Neither is directed to the use of brimonidine *in people with ocular hyperemia* that typical eye redness relievers would address. Noecker ¶¶114-115. Norden discloses preventing *bleeding complications* associated with LASIK surgery.¹ EX-1006, 4, 7; Noecker ¶115. Gil Example 1 prophesizes preventing *ocular pain*, not hyperemia, associated with

¹ Section VIII.A.2.a.i, *infra*, explains that POSAs would have understood Norden’s reference to hyperemia as micro-vessel hemorrhage, not vasodilative-hyperemia.

radial keratotomy (“RK”) surgery. EX-1003, 35-36. Gil Example 4 proposes essentially a “*torture*” model *in rabbits* to assess brimonidine’s ability to relieve ocular pain from corneal exposure to stimuli. Donnenfeld ¶¶68-70; Noecker ¶115; EX-1004, 5:18-46. Indeed, both parties’ experts agreed that Gil’s animal pain model can neither be performed in humans nor used for assessing eye redness reduction. Noecker ¶115; EX-2017, 136:16-137:1.

A POSA—who is experienced in developing eyedrops for regulatory approval (Pet., 16-17; EX-1012, ¶12)—would have practically considered the prior art with an eye toward developing and marketing an improved redness reliever. Noecker ¶¶120-129; EX-2017, 83:10-84:2; EX-2008, 150:19-23; Gil ¶¶47-52. Thus, there would have been no reason absent hindsight for a POSA to have “plucked” Norden or Gil from the “sea of prior art” relating to the field of redness relievers to which the ’245 patent invention pertains. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1337 (Fed. Cir. 2016) (finding no motivation to “pluck” two references from “the sea of prior art” and combine them in a way to render the invention obvious); *see* Gil ¶¶41-46. Rather, *pre-August 2008* POSAs would have considered the products typically used to reduce redness in subjects with healthy and intact ocular blood vessels. *See* Noecker ¶120; Gil ¶¶47-48; Williams ¶¶83-85; Karst ¶¶71-87; EX-1012, ¶12 (identifying the POSA as having experience in the use of “topical vasoconstrictors such as naphazoline and tetrahydrozoline”).

Dean, directed to the combined use of brinzolamide with brimonidine to treat certain ocular diseases, including glaucoma due to high IOP, fares no better. Noecker ¶¶116-119; EX-1007, 2:51-54. Both brinzolamide and brimonidine were known IOP lowering drugs. *Id.*, 1:11-26; Noecker ¶116. Because they work via different mechanisms, combining the two drugs “represent[ed] a novel approach to producing potent and long lasting IOP lowering mediations.” EX-1007, 2:51-54; Noecker ¶116. Dean also states that the bioavailability of brinzolamide should increase due to brimonidine’s ability to cause vasoconstriction. EX-1007, 2:57-65.

Dean, however, does not address redness reduction, much less redness reduction in patients with ocular hyperemia. Noecker ¶117. On the contrary, Dean states: “While brimonidine is a relatively safe compound it has been shown to *cause*...ocular hyperemia.” EX-1007, 2:38-41. Dean acknowledges that “[t]he mechanism by which brimonidine causes hyperemia is not well understood” and speculates that it may be dose related. *Id.*, 2:41-48. But Dean never suggests brimonidine could have a beneficial effect on patients with ocular hyperemia. Noecker ¶117.

Nonetheless, Petitioners wrongly argue that Dean teaches brimonidine can act as a vasoconstrictor and suggests brimonidine as a redness reducer. Paper 14 at 30-31. But there is no support for Petitioners’ inference that all vasoconstrictors, including brimonidine, would be redness relievers at all concentrations. Noecker

¶118. The Federal Register is a final monograph under which OTC drug products can be generally recognized as safe, effective, and not misbranded. EX-2098, 1; Noecker ¶118. The monograph stated that “for ophthalmic vasoconstrictor drug products” (listing four acceptable APIs—not brimonidine), the labeling should identify the product as a “redness reliever or a vasoconstrictor (redness reliever).” EX-1009, 7 POSAs, however, would not interpret the monograph to mean that *all* drugs that can vasoconstrict, much less at all concentrations, were known to be useful redness reducers. Noecker ¶118. Many reasons exist why a drug with vasoconstriction potential may fail as a redness reliever—toxicity and side effects being just two. *Id.*

Before Lumify, no OTC redness reliever was a selective $\alpha 2$ -receptor agonist. Noecker ¶119. No basis in the prior art existed to infer that brimonidine—much less a single drop of 0.025% brimonidine via a single step—would have been useful to reduce ocular hyperemia. *Id.* Neither Dean nor the Federal Register provide such teaching. *Id.*

Thus, absent hindsight, a POSA would not have plucked surgical trauma model references like Norden and Gil or glaucoma treatment references like Dean from the sea of prior art when seeking to develop an improved method of reducing ocular hyperemia. Noecker ¶120; *WBIP*, 829 F.3d at 1337. The “state of the art” publications in 2008 confirm this, describing brimonidine’s uses though never

mentioning redness relief and highlighting its allergy-based drawbacks. Noecker ¶122; EX-2028. Even Dr. Gil himself—an industry expert who ran drug repurposing efforts for brimonidine at Allergan—confirmed this. Gil ¶¶19-24, 40-46. Neither he nor Allergan ever considered using brimonidine as a redness reliever, though Allergan invented (and published!) *other* non-brimonidine formulations for ocular redness relief. Gil ¶¶40-47.

2. “Consisting of Topically Administering ... an Ocular Drop Consisting of 0.025% Brimonidine as the Sole Active Ingredient”

The claim 1 method of reducing eye redness consists of a single step—administering a single ocular drop consisting of 0.025% brimonidine as the sole active ingredient. No one disputes the prior art methods (1) are *not directed* to reducing eye redness in a human subject having ocular hyperemia, (2) are *not directed* to administering brimonidine as the sole active ingredient, (3) are *not directed* to administering a single ocular drop of 0.025% brimonidine only, and (4) *each requires* multiple administration steps. Likewise undisputed is that brimonidine was known to cause ocular allergy and redness, limiting its use. EX-2028, 4.

The asserted prior art would not have motivated POSAs to make all these modifications with any reasonable expectation of success. Noecker ¶130.

a. None of Norden, Gil, or Dean teaches or suggests a single step administration of brimonidine as the only active ingredient

The Institution Decision states (at 29) that Petitioners showed Norden, Gil, and/or Dean “suggests using brimonidine as the sole active ingredient to reduce eye redness.” Patent Owner disagrees.

i. Norden

Norden discloses a multi-step method for assessing “the effect of prophylactic brimonidine on *bleeding complications* and flap adherence after [LASIK]” surgery. EX-1006, 4. Petitioners argue a POSA would have been motivated to administer brimonidine alone to reduce redness because the “test” and “control” groups in Norden both received the same set of other active ingredients, and because the brimonidine test group showed less “hyperemia.” Pet., 39-40. A POSA would not have understood Norden’s teachings this way. Donnenfeld ¶¶49-60; Noecker ¶¶131-132; Stamer ¶¶84-89.

Norden distinguished three types of *bleeding complications* in LASIK surgery—subconjunctival hemorrhage, hyperemia, and superior micropannus. EX-1006, 6; Noecker ¶133. A POSA would have understood that Norden’s “hyperemia” is not vasodilative hyperemia, but rather bleeding of a small number of red blood cells into the eye (*i.e.*, micro-vessel hemorrhage). Donnenfeld, ¶¶50-54; EX-2009, 59:20-61:8, 64:11-65:17, 67:13-68:17. The blood-vessel-rupturing impact of LASIK

causes micro-vessel hemorrhage and makes the eye appear pink. Donnenfeld ¶¶50-51.

The Board questioned “why Norden would record and report that amounts of subconjunctival hemorrhage and hyperemia separately, if they were the same.” Paper 14 at 29. They are not the same; while they are both forms of bleeding, they present differently. Unlike the pink appearance from micro-vessel hemorrhages, subconjunctival hemorrhage appears as bright red patches on the white of the eye. Donnenfeld ¶52; *see also* Section IV.A. This is a clinically relevant distinction that Norden recognizes and records separately. Donnenfeld ¶52; Noecker ¶133.

Further, a POSA would have understood that the reduction in bleeding complications observed by Norden in the brimonidine group (EX-1006, 6) was due to brimonidine’s narrowing of the blood vessels in the eye before surgery. Donnenfeld ¶55. Post-operatively, this resulted in less observable blood vessel damage, manifesting either as subconjunctival hemorrhage or micro-vessel hemorrhage (Norden’s “hyperemia”). *Id.*; Noecker ¶134.

Importantly, a POSA would have understood that the observed differences between the “test” and “control” groups in Norden *could not, scientifically*, be due to differences in vessel diameter by the second examination (≥ 12 hours post-surgery). Because brimonidine’s half-life was known to be 4-6 hours (EX-2009, 33:21-34:22), by the second examination (2-3 half-lives later), the brimonidine amount remaining

on the ocular surface (and any vasoconstrictive effects) would be far less than the amount the art taught necessary to reduce redness.² *See infra*, § VIII.A.5.a.ii (Alphagan Trials); Donnenfeld ¶¶53-55; Noecker ¶135; EX-2009, 60:5-19.

Additionally, all patients received the corticosteroid prednisolone—“the single strongest anti-inflammatory drop used in all of ophthalmology”—four times per day for 4 days after surgery. Donnenfeld ¶58; EX-2009, 60:22-25. Prednisolone would have unquestionably resolved any vasodilation in both the “test” and “control” groups thus normalizing vessel diameter between the groups (and resolving any true vasodilative hyperemia) at the time of examination. EX-2009, 61:25-61:8. Nevertheless, “hyperemia” persisted in both groups, confirming that Norden’s “hyperemia” must have been micro-vessel hemorrhage—a bleeding complication that can only dissipate over time. *Id.*; Donnenfeld ¶¶54, 58; Noecker ¶136.

Thus, any difference in redness “appearance” between the two groups could *not* be explained by brimonidine’s vasoconstrictive effects at the time of the second examination. Donnenfeld ¶¶54, 58. That differences were observed is consistent

² This holds true even if the half-life is 6-8 hours as Petitioners allege. EX-2009, 33:21-24.

with Norden’s stated purpose of looking at differences involving **bleeding**, not hyperemia due to vasodilation. Donnenfeld ¶¶48, 57; Noecker ¶¶137-138.

ii. Gil

Gil is directed to a “method for treating ocular pain.” EX-1004, 1:1, 1:11-13. Petitioners rely on Gil Examples 1 and 4—prophetic and dataless (EX-2014, 802:16-22; Gil ¶¶45, 49-50)—to argue that a POSA would have used brimonidine as the only active ingredient to reduce redness. Pet., 39-40. Their argument selectively quotes and ignores Gil’s other teachings, as well as Dr. Gil’s testimony, which undermine Petitioners’ position. Without hindsight, POSAs would have had no reason or motivation to modify Gil’s teachings to arrive at the claimed invention. Noecker ¶139; *Impax Lab’ys Inc. v. Lannett Holdings Inc.*, 893 F.3d 1372, 1379 (Fed. Cir. 2018).

Example 1 describes a clinical study that topically administers **multiple drops of 0.03% brimonidine**—“one drop ... every four hours while awake one day prior to surgery and again every 20 minutes for the two hours just before surgery.” EX-1004, 4:54-57. Assuming 8 hours of sleep, this represents 10 separate administrations of brimonidine (*i.e.*, 10 steps) prior to surgery. Noecker ¶¶139-140; Donnenfeld ¶65. Following surgery, each subject also receives one drop of brimonidine every four hours while awake for 14 days, accounting for an additional 56 administrations/steps. EX-1004, 4:58-60. The method of Example 1 is thus a far cry from the single step

method of claim 1 of the '245 patent. Noecker ¶140; Donnenfeld ¶66. And any efficacy assessed, including the evaluation of “pain intensity, pain relief, subjective global analgesic efficacy” using Example 1 (if it had been performed) would neither have motivated nor provided a reasonable expectation of yielding the single step method of claim 1. Noecker ¶140; EX-1004, 4:46-48, 4:53-63.

Nor does Gil Example 1 teach or suggest using brimonidine as the only active ingredient. Noecker ¶141. Example 1 proposes assessing the pain-relieving effect of brimonidine from RK surgery, a surgical predecessor to LASIK involving cutting and reshaping the cornea. EX-1004, 4:46-48; Donnenfeld ¶64. Petitioners’ experts acknowledge that RK and LASIK surgeries would require co-administering brimonidine with other medicated eyedrops as a necessity. EX-2013, ¶126 (“The patients in Norden and Gil received other drugs as a necessity—the patients were undergoing surgical procedures on their eyes.”). Omitting them would be malpractice. EX-2018, 22:24-23:13; Noecker ¶142.

Accordingly, POSAs would not have understood Gil Example 1 as a “controlled” experiment designed to evaluate brimonidine’s ability alone to prophylactically reduce pain but rather to assess brimonidine’s pain-reduction ability as part of the dosing regimen with other pain-relieving eyedrops. Donnenfeld ¶64; Noecker ¶143. Nor, given Example 1’s context, would POSAs have expected that administering brimonidine alone would have any meaningful pain-reduction effect.

Donnenfeld ¶¶67; Noecker ¶¶143. And the example’s lack of data would have precluded POSAs from assessing any additive pain-relieving effect from brimonidine. *Id.*

Nor would a POSA have gleaned from Example 1, or Gil as a whole, that a single administration of brimonidine alone would have reduced eye redness. Gil ¶¶40-46. Because Example 1 seeks to evaluate pain relief, not redness reduction, as the ’142-IPR Board found (EX-1003, 35-36), the only conclusion that the prophetic example draws is that hyper-dosing 0.03% brimonidine—resulting in a net administration of brimonidine greater than even a single dose of 0.2%—“appears to suggest” that preoperatively administered brimonidine blocks the perception of pain. EX-1004, 5:1-2; Donnenfeld ¶¶67; Noecker ¶¶144. Such “speculative and tentative disclosure of what ‘might’ or ‘may’” happen “does not sufficiently direct or instruct one of skill in th[e] art” to the claimed invention. *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1376 (Fed. Cir. 2011).

Likewise, Gil Example 4 fails to teach or suggest using brimonidine alone in a single step method for reducing human eye redness. Example 4 uses a rabbit model to evaluate the “effect of brimonidine on ocular pain.” EX-1004, 5:20-21; Noecker ¶¶145; Donnenfeld ¶¶68. It describes a surgical procedure involving cutting ocular tissues, including the conjunctiva and episclera, surrounding the rabbit’s eye to expose the ciliary nerve behind the eyeball, and connecting a hook electrode to

measure nerve signals to external corneal stimuli. EX-1004, 5:25-30; Noecker ¶¶145; Donnenfeld ¶¶68-69. Example 4 proposes a broad dose-ranging study of 0.01% to 0.5% brimonidine—a 50-fold difference in endpoints—to determine brimonidine’s ability “to reduce *the* neurogenic response,” *i.e.*, ocular pain from external stimuli. EX-1004, 5:41-45; Noecker ¶¶145; Donnenfeld ¶70.

The Institution Decision states (at 28) that this prophetic example renders the claimed invention obvious because it postulates that “brimonidine, the only active ingredient of the ophthalmic formulation, ‘is effective in reducing such neurogenic responses,’ including redness.” Patent Owner disagrees.

It is undisputed that the Example 4 study cannot be performed on humans, evaluates only pain relief, and is incapable of assessing redness reduction. Noecker ¶¶146-150; EX-2017, 136:21-137:1 (“Q. But you agree that the model itself is not capable of actually making an assessment of whether redness exists or whether it was reduced, correct? A. It measures pain, that’s correct then.”); EX-2009, 76:25-77:21; EX-2002, 96:11-98:9. As such, the mere incantation of the words “is effective in reducing such neurogenic responses,” without any substantiating data, would not have led a POSA to reasonably expect that brimonidine alone, particularly at the low concentrations, would have reduced pain or any downstream effects, including redness, as confirmed by Dr. Gil himself. EX-2009, 113:6-19 (Dr. Gil testifying that Example 4 “does not show any effect on redness”); Gil ¶¶40-46, 49-50; Noecker

¶146; Donnenfeld ¶70. Indeed, as discussed in § VIII.A.2.b below, a POSA would have understood that administering low-concentration brimonidine would have necessitated multiple drops (*i.e.*, **multiple steps**) to achieve an effective dose for relieving any pain-associated redness. Noecker ¶146; EX-2085, 44:14-45:5.

iii. Dean

Dean is singularly focused on co-administering brimonidine and brinzolamide, whether in the same or separate eyedrops, for treating ocular diseases such as glaucoma. EX-1007, 2:21-27; Noecker ¶151. Petitioners rely on a statement in Dean that brimonidine “serves to constrict ocular vessels and thereby reducing the flux of blood through the anterior portion of the eye” (EX-1007, 2:57-60) to argue a POSA would have understood this to mean that brimonidine reduces eye redness. Pet., 41. Not so.

Petitioners improperly equate any amount of vasoconstriction with redness reduction without any supporting evidence. The record evidence supports only that high-concentration brimonidine exerts **sufficient** vasoconstriction to reduce eye redness. *See infra* § VIII.A.5.a.ii; Noecker ¶152. Dean never mentions using brimonidine to reduce eye redness, and it does not teach or suggest, absent hindsight, that the vasoconstriction effects discussed (EX-1007, 2:57-60) are sufficient to reduce eye redness, especially when the concentration of brimonidine is lowered below 0.2%, as discussed in § VIII.A.2.b.ii *infra*. Noecker ¶¶152-155; Stamer ¶79.

Indeed, Dean teaches away from administering brimonidine alone, for its entire inventive concept resides in the combined therapy of these two IOP-lowering drugs to permit lower doses than when administered alone. Noecker ¶152; EX-1007, 1:4-8, 2:51-54.

iv. Context of the Prior Art Matters

The Institution Decision (at 30) stated that the trauma surgical settings of Norden and Gil and the glaucoma treatment context of Dean do not matter, citing *Axonics, Inc. v. Medtronic, Inc.*, 73 F.4th 950, 957 (Fed. Cir. 2023). Patent Owner disagrees.

Here, unlike *Axonics*, where the claims were not limited to a specific context, 73 F.4th at 957, the '245 patent claims ***require a specific context***—ocularly administering a single drop of 0.025% brimonidine as the only active ingredient in a single step for reducing eye redness. Each of Norden, Gil, and Dean requires administration of brimonidine with other active ingredients: Norden and Gil in surgical trauma models and Dean in the treatment of glaucoma. Indeed, POSAs, as defined herein, seeking to develop a better redness reliever would not have looked to Norden, Gil, or Dean, particularly when considering their teachings as a whole together with the pre-August 2008 state-of-the-art publications discussing drawbacks to brimonidine's use generally. Noecker ¶¶111-112, 122; EX-2028, 4;

see Gil ¶¶47-52.³ “It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.” *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965).

b. None of Gil, Dean, or Federal Register teaches administering a single eyedrop of 0.025% brimonidine for reducing vasodilative hyperemia

Petitioners argue that the use of 0.025% brimonidine would have been obvious in view of Gil and Dean. Pet., 45-46. Not so. Neither Gil nor Dean discloses using a single drop of 0.025% brimonidine for reducing ocular hyperemia, as Petitioners’ expert Dr. Laskar candidly concedes. EX-2040, 41:1-43:20, 47:17-48:15. In fact, Gil and Dean teach that a high dose of brimonidine is needed to achieve the efficacy they sought to achieve. Noecker ¶156.

i. Gil

³ This contemporaneous scientific article reviewed brimonidine’s past and potential future clinical applications, never even remotely suggesting using brimonidine to reduce redness and noting instead its drawbacks of ocular intolerance from allergies and hyperemia—anathema to brimonidine’s use as a redness reliever.

Gil teaches the administration of brimonidine to reduce ocular pain, a symptom of neurogenic inflammation. EX-1004, 1:11-19. Gil notes that other neurogenic responses associated with inflammation and pain may include the possible downstream effects of edema, vasodilative-redness, vascular permeability, or pupillary constriction. EX-1004, 1:40-43, 5:39-40; Noecker ¶157.

Example 1 hypothetically proposed evaluating the effects of *repeat-dosing* of 0.03% brimonidine on *ocular pain* from surgery. EX-1004, 4:46-48, 4:54-61, 4:66-5:2. The patients received one drop of 0.03% brimonidine “*every four hours* while awake one day prior to surgery and again *every 20 minutes* for the two hours just before surgery.” EX-1004, 4:54-58 (emphasis added). After surgery, patients were given one drop of 0.03% “every four hours while awake for 14 consecutive days.” EX-1004, 4:58-61. The amount of brimonidine administered pre-operatively (10 drops of 0.03%)—a fraction of the total brimonidine administered—is 12 times greater $[(10 \times 0.03)/0.025]$ than the single drop of 0.025% required by claim 1. Noecker ¶¶157-158; Stamer ¶42. Further, a POSA would have understood that the repeat dosing in Gil is required, given the low concentration of brimonidine so that the amount of brimonidine is high enough to relieve the pain from surgery. Donnenfeld ¶¶63, 65-66; Noecker ¶158.

Prophetic Example 4 proposed a dose-ranging study of 0.01% to 0.5% brimonidine in a rabbit model to evaluate brimonidine’s effect on ocular pain. EX-

1004, 5:20-21, 5:31-32. A POSA would not have expected that all concentrations, particularly the low-concentrations, to reduce pain, let alone reduce any possible downstream effects of pain, like redness. *Donnenfeld* ¶70; *Noecker* ¶159.

Indeed, Dr. Gil testified that a POSA would have expected, as is typical with dose-ranging studies, the lower end of the brimonidine concentration range (e.g., 0.05% and below) to be ineffective and act as a control to assess the higher concentrations expected to have pain-relieving effects (e.g., 0.2% and above). *EX-2009*, 107:16-108:13. Thus, if low concentrations within the range were selected, a POSA would have instilled multiple drops per application, consistent with Example 1, so that the total dose administered would at least approach an effective dose of approximately 0.2%. *Noecker* ¶160.

Example 5—an actual study conducted based on the protocols described in Example 4—confirms as much. Example 5 used *1 cc of 0.2% brimonidine* (Alphagan®) to test its efficacy on decreasing “sensory response” in the rabbit cornea to reduce ocular pain. *EX-1004*, 6:5-7, 6:9-13. A POSA would have understood that 1 cc contains about 20-30 drops of Alphagan, which is a significantly higher dose than a single drop of 0.025% brimonidine. *Noecker* ¶161. Thus, Example 5 confirms that a high dose of brimonidine, whether through a highly concentrated drop or administering multiple drops, is needed to reduce ocular pain, including any sequelae to pain, like redness. *Id.*

Moreover, notwithstanding the broad range disclosed in Example 4, the use of copious amounts of high-concentration brimonidine (0.2%) in Example 5 (EX-1004, 6:5-13), would have conveyed to a POSA that, if a low concentration is selected, multiple drops would have been needed. Noecker ¶¶162; *see* Gil ¶¶25-39; Stamer ¶¶50-74. This is all a POSA could have concluded from an animal model acknowledged by all experts to be incapable of assessing redness and in a patent primarily focused on ocular pain relief. Noecker ¶¶162; EX-2017, 125:9-14, 136:21-137:1; EX-1004, 2:53-55.

ii. Dean

Dean likewise fails to teach or suggest using a single drop of 0.025% brimonidine for reducing eye redness. Noecker ¶¶163.

The Institution Decision states (at 32-33) that Dean teaches brimonidine vasoconstricts when administered first, albeit in sequence with brinzolamide. According to the Board, when administered in such sequential fashion, brimonidine can be formulated at a concentration from 0.01% to 0.2% by weight. *Id.* Because this range overlaps with 0.025% brimonidine, the Board states this “creates a presumption of obviousness.” *Id.* Patent Owner disagrees.

Dean does not teach using brimonidine to reduce redness, much less ocular hyperemia. Noecker ¶¶164; EX-2014, 784:23-25. Dean does not provide any evidence that any of its brimonidine formulations, whether alone or combined with

brinzolamide, cause sufficient vasoconstriction to reduce redness. Noecker ¶164; EX-2014, 784:23-25. As discussed in Section VIII.A.5.a.ii, from clinical trial data available at the time, a POSA would have had no reasonable expectation that reducing the dose of brimonidine below 0.2%, let alone a single drop of 0.025% brimonidine, would have reduced eye redness. Noecker ¶164. When read as a whole, Dean neither teaches nor suggests dosing a single drop of low-concentration brimonidine. *Wesslau*, 353 F.2d at 241; Noecker ¶164.

Specifically, Dean teaches co-administering two known IOP lowering drugs, brimonidine and brinzolamide, to treat glaucoma. EX-1007, 1:11-25. Dean states this “represent[s] *a novel approach* to producing potent and long lasting IOP lowering medications,” which allows lower amounts of the drugs to be dosed “with fewer side-effects....” *Id.*, 2:51-54 (emphasis added). Dean concludes with respect to brimonidine that “lowering the overall dose of brimonidine *while maintaining IOP control* would be advantageous.” EX-1007, 2:48-50 (emphasis added). A POSA would have understood that Dean suggested lowering brimonidine’s dose to lessen its side-effects, but not so low that it would eliminate brimonidine’s primary purpose of exerting an IOP controlling effect. Noecker ¶165.

As Dr. Galanis acknowledged, brimonidine concentrations below 0.1% would not have been expected by POSAs to lower IOP. EX-2085, 44:14-45:5; Noecker ¶166. Relatedly, Dean teaches ocularly applying 1-3 drops of brimonidine 1-4

times/day. EX-1007, 5:20-27. Based on Dean's desire to administer brimonidine at an amount that would maintain IOP control, a POSA would have known that low-concentration brimonidine within the broad range of 0.01% to 0.2% would have required multiple drops. Noecker ¶166. That, of course, would have led the POSA when dosing brimonidine alone to formulate the drop in Dean's preferred range of 0.1% to 0.2%, and even then Dean teaches using multiple drops. EX-2040, 47:17-48:15; Noecker ¶166. Thus, a POSA would not have been motivated from Dean to administer a single drop of 0.025% brimonidine in a single ocular administration.

iii. Federal Register 1988

Though brimonidine was known in 1988, the Federal Register does not mention using it as an ophthalmic vasoconstrictor or redness reliever. It lists only ephedrine, naphazoline, phenylephrine, and tetrahydrozoline as vasoconstrictors for eye redness relief, none of which is an α -2 agonist like brimonidine. EX-1009, 16. Petitioners, however, argue that the concentrations of *non-brimonidine* vasoconstrictors disclosed in Federal Register 1988 would somehow have rendered 0.025% brimonidine for eye redness obvious. The vasoconstrictors in Federal Register 1988 were all α 1 and/or mixed α 1/ α 2 agonists, and their high α 1 effect made them very effective redness relievers. Noecker ¶167; Stamer ¶30. POSAs would not have interpreted the reference to suggest the highly selective α -2 agonist brimonidine, particularly at a single drop of 0.025% in a single step, would have

been expected to reduce vasodilative hyperemia. Noecker ¶¶167; Stamer ¶¶46, 50-72.

3. “Wherein the Ocular Hyperemia Is Reduced” Is Not Inherent

For this element, Petitioners firstly rely on the Board’s finding in the ’142-IPR to argue the prior art taught that ocular hyperemia is reduced by low-dose brimonidine alone. Pet., 54. Next, Petitioners argue that this element “adds nothing to the claimed method” and is inherent in the context of its obviousness position. *Id.* Both points fail.

First, the ’142-IPR FWD does not control. It addressed different (broader) claims with a different factual record and construed the claims to have an appreciably different scope than the ’245 patented invention. The Board there construed the claims as limited to a method of reducing redness but not requiring actual redness reduction. EX-1003, 11. Not so here, for this “wherein” clause mandates actual redness reduction for the claimed method. That Board also construed “about 0.025%” to read on 0.03%. *Id.* at 16. Not so here, for the ’245 patented methods require specifically 0.025% brimonidine.

Contrary to Petitioners’ position, this “wherein” clause adds patentable weight to the claims. *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1376 (Fed. Cir. 2019) (“wherein” clause held limiting where the specification and prosecution

history demonstrated it was “material to patentability and express[ed] the inventive aspect of the invention”). The specification contains statements and examples demonstrating actual redness reduction. EX-1001, 14:43-46, 14:47-48, 14:32-38, Examples 1, 4, and 5. During prosecution, in adding the “wherein” clause to pending claims, the patentee argued “all claims require actual redness reduction.” EX-1010, 189. Like the “wherein” clause in *Allergan*, “wherein the ocular hyperemia is reduced” is limiting. 935 F.3d at 1376.

Actual redness reduction does not inherently flow from the prior art. The Institution Decision (38-39) refers to a statement in the specification that the disclosed invention achieves vasoconstriction and to testimony from Dr. Galanis that practicing the claimed method will inherently achieve redness reduction. The question is not whether redness reduction is an inherent property of the claimed method, but whether it is a property that necessarily and unavoidably flows from practicing the combination of Norden, Gil, and Dean. *Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014). It does not.

Focusing on 0.025%, because none of Petitioners’ references disclose this concentration, Petitioners rely on “overlapping ranges” to argue that 0.025% would be presumptively obvious from ranges of 0.01% to 0.5% (Gil) and 0.01% to 0.2% (Dean). In this context, therefore, the question is not whether 0.025% brimonidine will always reduce redness, but whether the disclosed ranges always and

unavoidably result in redness reduction. *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003) (inherency requires the property necessarily and inevitably be present in the prior art). They do not.

At 0.2% brimonidine, for example, the Alphagan studies demonstrated that only 3.5% of patients experienced redness reduction, and at 0.15% and 0.1% brimonidine, none did, though those concentrations *did* cause redness. Noecker ¶¶168-170; Stamer ¶¶46-49; *see infra* § VIII.A.5.a.ii. That some concentrations within these ranges may reduce redness is insufficient for inherency. *Par Pharm.*, 773 F.3d at 1195.

Even if redness reduction were inherent from Petitioners' reference combination, a showing of nonobvious based on unexpected results (*see infra* § VIII.B) nullifies Petitioners' inherency-premised obviousness argument. *Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. DE C.V.*, 865 F.3d 1348, 1354-55 (Fed. Cir. 2017).

4. Nonobviousness of Benzalkonium Chloride in a Redness-Reducing Eyedrop with a pH of 5.5-6.5

The art taught away from using BAK in an ophthalmic redness reliever, as it was known to be toxic and poorly-tolerated. Williams ¶¶59-65; Noecker ¶171; EX-2040, 39:19-40:9. The Federal Circuit has acknowledged "BAK was known to

cause ... *hyperemia* ... and to exacerbate other eye disorders”—making it particularly unsuitable for use in a redness-relieving product. *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015) (emphasis added). Williams ¶¶64-65.

Dr. Laskar suggests that the POSA would have copied the formulation approach in Alphagan (0.2%). EX-1013, Laskar, ¶¶ 35-36. But he overlooks that this product was discontinued in 2002, and by 2008, the only commercially available brimonidine eye drops contained *Purite* (a gentle preservative), not BAK. Williams ¶¶54-58, 62-63. Dr. Laskar fails to explain why a POSA would have favored an old, discontinued approach over a newer, preferred approach. Williams ¶¶56-58, 67-69.

Moreover, physiological pH (i.e., ~7.4 for the newer brimonidine products) is “desirable” to avoid ocular side effects like irritation, burning, stinging, and—crucially—redness. Noecker ¶¶172-174; Williams ¶¶69-82. Particularly for a redness-relieving product, a POSA would have avoided both the claimed pH and BAK, as they were known to *cause* eye redness, contravening the invention’s purpose. Williams ¶¶69-82.

5. No Reasonable Expectation of Success Administering a Single Drop of 0.025% Brimonidine to Reduce Ocular Hyperemia

As discussed above, a POSA would not have been motivated, absent hindsight, to administer in a single step a single drop of 0.025% brimonidine as the

sole active agent to reduce eye redness caused by vasodilation. Nor would there have been any reasonable expectation of success. Noecker ¶175; Stamer ¶¶50-83, 94-95.

Petitioners argue the “overlapping ranges” from Gil and Dean would have made it presumptively obvious to administer 0.025% brimonidine for reducing eye redness. Pet., 45-46. On the contrary, the prior art as a whole taught away from administering a single drop of 0.025% brimonidine, and the invention enjoys significant objective indicia of nonobviousness, thereby rebutting any alleged presumption of obviousness. Noecker ¶176; *Allergan*, 796 F.3d at 1305-06.

a. Prior Art Taught Away from a Single Administration of a Single Eyedrop of 0.025% Brimonidine

A reference can teach away if it would have led a POSA “in a direction divergent from the path that was taken by the applicant,” *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009), or “if it suggests that the line of development ... is unlikely to be productive of the result sought by the applicant,” *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999).

i. Gil and Norden

Assuming that Gil and Norden taught brimonidine could reduce ocular hyperemia (they do not), the amount reportedly used was an order of magnitude higher than the single 0.025% of claim 1. For example, as explained in

§ VIII.A.2.b.i, the amount of drug administered in Gil's Example 1 is equivalent to a single drop of about 0.2% brimonidine (6-7 drops x 0.03%), counting only the doses for the two-hour period prior to surgery. Noecker ¶178; Donnenfeld ¶¶65, 67; EX-2009, 33:21-34:22. Norden teaches a dose of approximately 0.4% (2 drops x 0.2%) to prevent bleeding complications from LASIK surgery. EX-1006, 5; Noecker ¶178.

Pre-August 2008 POSAs would have had no reasonable expectation that lowering the dose administered in the multi-step studies of Norden and Gil to a single application of a single drop of 0.025% brimonidine would have reduced eye redness. Noecker ¶179; Donnenfeld ¶¶60, 71; Gil ¶¶25-39; Stamer ¶¶50-83, 94-95. The prior art as a whole, including the human clinical studies reported for the Alphagan products and in Derick 1997, coupled with brimonidine's pharmacology, directed POSAs to significantly higher concentrations to obtain sufficient vasoconstriction to actually reduce redness. Noecker ¶179; *DePuy Spine*, 567 F.3d at 1327; Stamer ¶¶50-83.

ii. Alphagan Trials

The Board requested further record development of whether conjunctival blanching means reducing ocular hyperemia. Paper 14, 35. The Board also preliminarily indicated that POSAs would not have interpreted the lack of reported blanching in the Alphagan P studies (0.15% and 0.1%) as "evidence that low doses

of brimonidine did not cause vasoconstriction” because blanching determination was subjective. *Id.*, 37. As the following sections discuss, the prior art and the ’245 patent confirm that conjunctival blanching is redness reduction. And the Alphagan studies reliably substantiate that pre-August 2008 POSAs would not have expected low-dose brimonidine to cause vasoconstriction sufficient to reduce redness. Noecker ¶ 180.

(a) Conjunctival Blanching Means Redness Reduction

Petitioners proffer “evidence-free” expert opinion testimony that conjunctival blanching is “not synonymous with vasoconstriction,” and it is a dangerous adverse event causing “significant whitening of the eye, which can lead to damage of vascular endothelial cells caused by lack of blood flow.” Pet., 49-50. Such unsubstantiated opinions are entitled to little or no weight. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 294 (Fed. Cir. 1985).

Ironically, Petitioners’ own prior art reference teaches that conjunctival blanching is any redness reduction in the eye. Noecker ¶¶187-192. Specifically, Federal Register 1988, which is the FDA’s monograph for OTC ophthalmic drug products, states that “redness is a symptom of irritation which can be relieved by a vasoconstrictor,” and 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-1009, 9 (emphases added). A POSA would have understood this statement to describe blanching as the method by which a redness reliever whitens the conjunctiva, assuming sufficient vasoconstriction. Noecker ¶189. Consistent therewith, the ’245 patent uses “whitening” as another way of describing redness reduction. EX-1001, 6:64 (“visibly effective whitening”), 14:23-38 (“more effective scleral whitening), Example 1 (“whitening brightening effects” with brimonidine). Noecker ¶190.

Nowhere does the FDA’s monograph state that conjunctival blanching is such “significant” whitening to the point it causes ocular damage. Conjunctival blanching is simply “an α_1 effect” (EX-2003, 1), which is the same effect exerted by the α_1 -agonist tetrahydrozoline discussed in the Federal Register (EX-1009, 9, 10). Noecker ¶191.

In fact, the product monographs for *both* Alphagan and Alphagan P note that “[c]onjunctival blanching was observed primarily at the 0.35% and 0.5% concentrations, and was *generally mild or moderate in nature*,” corroborating the evidence from the Federal Register and the ’245 patent that conjunctival blanching was not dangerous. EX-2119, 12 (emphasis added); Noecker ¶191; EX-2107, 2 (“whitening of the see-through layer which covers the surface of the eye”); Gil ¶25. Indeed, had it been so dangerous, the FDA would have pulled Alphagan from the

market, as Dr. Noecker, who was a clinical investigator in the Alphagan trials, testified. Noecker ¶191.

Additionally, in the '142-IPR, Slayback and its experts relied on Scruggs 2000 (EX-2005, 5) to equate blanching with whitening as motivation to use brimonidine to reduce redness. EX-2023, Laskar, ¶ 93; EX-2022, Sher, ¶ 99; EX-2021, 20. The Institution Decision (at 36) dismissed this admission, stating that “[b]oth the prior art and the petition in the '142 IPR relate to skin blanching on the cheek, not conjunctival blanching.” Respectfully, Scruggs unequivocally teaches that “*conjunctival blanching* has been reported as an infrequent local effect of brimonidine.” EX-2005, 5 (emphasis added). Dr. Laskar in fact admitted that Scruggs is not limited to skin blanching but also teaches brimonidine “‘blanch[es],’ *i.e.*[,] whiten[s],” the conjunctiva. EX-2040, 49:17-52:8, 53:20-54:13; EX-2023, Laskar, ¶ 93; Noecker ¶192.

**(b) Once Observed in the Alphagan Studies,
Conjunctival Blanching Would Have
Been Monitored and Reported if
Observed in the Alphagan P Studies**

Once an ocular surface event is observed for a drug in a clinical trial, it will be recorded and monitored going forward, even in future trials of the drug at different concentrations. Noecker ¶193; EX-2008, 116:13-117:15. Federal regulations *require* observing and reporting the frequency of potential adverse effects of FDA-

approved drugs like Alphagan. *See* 21 C.F.R. § 201.57(a)(11)(i); Karst ¶¶64-68, 88-94.

Because conjunctival blanching was observed at concentrations of 0.5% and 0.35% (EX-2119, 12), the clinical investigators monitored and reported that Alphagan 0.2% caused conjunctival blanching in 3.8% of patients. EX-2108, 9 (Table 2), 12; Noecker ¶194.

The product monograph for the Alphagan P trials similarly notes that conjunctival blanching was observed at concentrations of 0.5% and 0.35%, indicating to POSAs that the investigators would have been monitoring patients for conjunctival blanching. *Id.*, 12; Noecker ¶195. But none was reported. EX-2119, Table 2, 8-9 (reporting adverse events “[o]ccurring at $\geq 1\%$ with ALPHAGAN P”); *see also* EX-1068, 4 (not mentioning conjunctival blanching for adverse events reported in less than 1% of patients). From the lack of reporting of conjunctival blanching for Alphagan P, POSAs would have understood that 0.15% brimonidine did not sufficiently vasoconstrict to reduce eye redness. Noecker ¶195. These data would have also confirmed for POSAs that the minimum effective dose of brimonidine for reducing ocular hyperemia would have corresponded approximately to 0.2%. Noecker ¶195.

Thus, these product monographs corroborate that the subjective determination of conjunctival blanching in the Alphagan studies would have had no impact on

whether conjunctival blanching would have been reported. Noecker ¶195; Donnenfeld ¶44. If it were observed in the Alphagan P studies, it would have been reported. Noecker ¶195; Donnenfeld ¶44.

Nor does the “subjective” determination of conjunctival blanching lessen the data’s reliability for POSAs. Donnenfeld ¶¶44-45; Noecker ¶196. Dr. Noecker was a clinical investigator in Alphagan studies and provides testimony supporting the robustness of the studies and the reliability of the data they generated. Noecker ¶196.

The conjunctival blanching data in the Alphagan labels and the NDA were collected from robust randomized, double-masked, and bilateral clinical studies designed for FDA approval—the “gold standard” for reliability in clinical trials. Noecker ¶197; Donnenfeld ¶¶42, 46; EX-1075, 63 (the Alphagan Medical Review described the study as “a well-controlled, randomized, clinical trial”). These studies had a well-established protocol clinical investigators were required to follow to minimize subjectivity and variability between the investigators. Noecker ¶197; Donnenfeld ¶¶43-45. Before the study began, the clinical investigators would have met to develop protocols, including which adverse events to record and how to record them to ensure consistency and reliability. Noecker ¶197; Donnenfeld ¶42; EX-1075, 63 (“The methods and ophthalmologic tests used and their frequency were adequate to effectively monitor the subject population.”).

As the Alphagan NDA indicates, the study protocol for monitoring and recording adverse events, including conjunctival blanching, included an initial visit to determine a baseline, and subsequent evaluations for changes from baseline were measured using a scale, which states: “Adverse Events[:] Number and Percentage of Subjects with *at Least One Severity Grade Increased from Baseline* at One or More Follow-up Visits” and lists “Conjunctival Blanching” as one of the adverse events observed. EX-1030, 52 (emphasis added); Noecker ¶198; Donnenfeld ¶44. Importantly, “[a]ny adverse event occurring during the study *was recorded*” and “graded for severity (*trace, mild, moderate, or severe*).” *Id.*, 119 (emphases added); Donnenfeld ¶44; EX-1030, 119. Additionally, grading of the adverse events was made and recorded by highly experienced ophthalmologists who would have been well familiar with all the study’s protocols, thereby minimizing variability and ensuring reliability of the collected data among the clinicians. Noecker ¶198; Donnenfeld ¶44; EX-1075, 63 (“The applicant’s evaluation of potential adverse effects for this pharmacological class of drug is adequate.”).

An independent auditor would have monitored and checked the collected data, and then a statistician would have performed statistical analysis of the data before submitting it to the FDA. Noecker ¶199; Donnenfeld ¶¶43-46. The FDA reviewed all the data, including the safety data, and approved the information included in the package insert. Noecker ¶199; Donnenfeld ¶¶43-46; EX-1075, 38 (“All trials were

conducted under the review of approved Institutional Review Board committees.”). Thus, the adverse events data identified on Allergan FDA-approved labels are highly reliable data, collected from well-controlled robust human clinical trials. Noecker ¶199; Donnenfeld ¶46; EX-2008, 108:20-122:11, 124:6-19.

(c) Data from Alphagan Clinical Trials

At 0.5% brimonidine, Alphagan reported conjunctival blanching at a rate of 50%. Noecker ¶200; EX-1030, 13 (Study S342-108-8042); EX-1067, 4. But when the concentration dropped to 0.2%, conjunctival blanching precipitously dropped to about 3.5% of patients. Noecker ¶200; EX-1067, 4, 9; EX-1068, 4; EX-1030, 13, 52, 109. And when brimonidine’s concentration was lowered further to 0.15% and 0.1% in the Alphagan P studies, conjunctival blanching was no longer observed. Noecker ¶200; EX-1068, 1, 4. These data demonstrated brimonidine’s dose-dependent effects on conjunctival blanching and would have conveyed to a POSA that a minimum effective dose of brimonidine for reducing eye redness was approximately 0.2%. Noecker ¶¶200-203; *see also* EX-1029, 4-5 (concluding a “dose response relation” for brimonidine’s ability to blanch the conjunctiva).

B. Objective Indicia of Nonobviousness

Evidence of objective indicia “can be the most probative evidence of nonobviousness in the record” and can also enable “the court to avert the trap of hindsight.” *Millennium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir.

2017) (quoting *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013)).

1. Unexpected Superior Results of the Claimed Invention

As previously discussed, the claims of the '245 patent meaningfully differ from the claims of the '742 patent involved in the '142-IPR, imparting even greater alignment between the closest prior art comparator, Visine L.R., and the claimed methods for unexpected results. The '245 patented methods of reducing eye redness specifically require that it be reduced through the single administration of a single drop of only 0.025% brimonidine. EX-1001, 22:36-24:37.

Below, Patent Owner presented evidence comparing the '245 patented method (embodied by Lumify's FDA-approved use) to Visine L.R. to demonstrate Lumify's unexpectedly superior redness reducing efficacy and safety profile. *See infra* § VIII.B.1.c. Visine L.R., a representative prior art redness reliever, compares well with the '245 patented method. Noecker ¶¶214-222. Visine L.R. is approved to reduce eye redness where, in a single step, it is administered as a single eyedrop containing only the vasoconstrictor oxymetazoline at a concentration of 0.025% and achieves redness reduction. *Id.*

The Board disagreed that Visine is the closest prior art, adopting instead the holding in the '142-IPR that Gil constitutes the closest prior art because Gil allegedly “suggests” 0.03% brimonidine would reduce eye redness. EX-1003, 62-64. Patent

Owner respectfully disagrees. The closest prior art comparator must embody two principles: (1) it must be closest to the claimed invention (reducing eye redness), *In re Merchant*, 575 F.2d 865, 868-69 (CCPA 1978); and (2) the comparative embodiment must have been disclosed or prepared in the art, **not** what is asserted as obvious therefrom, *Millennium Pharms.*, 862 F.3d at 1368.

a. Law Governing the Closest Prior Art

In *Merchant*, the court addressed what constituted the closest prior art for unexpected results. 575 F.2d at 869. The appellant in *Merchant* claimed a process for removing hydrogen fluoride (HF) contaminants from gaseous hydrogen chloride (HCl) using a dry technique. *Id.* at 866. The appellant presented evidence of the unexpected superiority of the claimed process compared to a prior art process **also** directed to removing HF from HCl gas (“Lowdermilk’s process”), although it utilized a wet technique. *Id.* at 867. The Board found that instead of the Lowdermilk process, the closest prior art was a process for removing HF contaminants from air using a dry technique (“Pring’s process”). *Id.* at 868.

The court disagreed, finding that Lowdermilk’s process, not Pring’s, was closest because, like the invention, it removed HF from HCl gas, whereas Pring disclosed a different method—removing HF from air. *Id.* at 868-69. Additionally, although Lowdermilk’s process lacked the dry technique, the court held that did not “diminish its position as the closest prior art.” *Id.*

Similarly, in *Millennium*, the district court refused to consider unexpected results because the patent owner did not compare its invention against a specific compound (glycerol bortezomib ester) that was only generally suggested in the prior art. 862 F.3d at 1368. But the Federal Circuit rejected that compound as the closest prior art: it “was not specifically disclosed, prepared, or tested in the” prior art. *Id.* It did not matter that the prior art “‘generically’ encompassed” the compound. *Id.* The patent owner “was not required to create the [compound], when the product had not been created in the prior art,” for “[u]nexpected results are shown in comparison to what was known, not what was unknown,” *Id.*

b. Gil Is Not the Closest Prior Art

To declare Gil the closest prior art, the ’142-IPR Board found Gil disclosed 0.03% brimonidine (EX-1004, Example 1) and then, citing Gil Example 4 (*id.*, 5:38-45), concluded that Gil “**suggests** that [0.03% brimonidine] would be effective in reducing eye redness.” EX-1003, 63-64 (emphasis added). That conclusion would, contrary to law, require comparing the invention against what the Board held was obvious.

The ’142-IPR Board already acknowledged when it found no anticipation by Gil that the administration of 0.03% brimonidine in Gil’s Example 1 was not for the purpose of relieving redness but instead for treating pain. *Id.*, 35-36. The limiting preamble of the ’245 patent, moreover, is firstly “[a] method for reducing eye

redness”—a significant claim limitation defining the invention’s *raison d’etre* for administering a single drop of only 0.025% brimonidine in a single step and distinguishing the invention from art for novelty purposes. *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003).

Consistent with *Merchant*, therefore, the closest prior art to the ***claimed invention*** for comparative testing must at least be a method of reducing redness. *Phillips*, 415 F.3d at 1312 (a “bedrock principle” of patent law is that claims define the invention entitling the patentee to the right to exclude). Indeed, recognizing that a court should “bear[] in mind the relative importance of particular limitations,” *Merchant* sanctioned the unexpected-results comparison to a method directed to the same end as the claimed invention, while rejecting as closest a prior art method directed to a different method from that claimed. 575 F.2d at 868-69. Because Gil’s Example 1 postulates administering 0.03% brimonidine for ***reducing pain*** and not for reducing eye redness (EX-1003, 35-36), it is not “closest” to the invention.

Regarding Visine L.R., the ’142-IPR Board stated that it does “not contain brimonidine” and “[t]he only similarity” to the invention is redness reduction. EX-1003, 63. But like Pring’s disclosure of a “dry” process in *Merchant*, the mere fact that Gil proposes using 0.03% brimonidine does not make it the closest prior art. *See* 575 F.2d at 869. POSAs reading Gil’s Example 1 would have understood that it is about treating pain, not redness reduction, just like the “dry” process in

Pring taught removing contaminants from air, not the claimed removal from HCl gas.

Even though Visine L.R. lacks brimonidine, like in *Merchant*, that does not “diminish its position as the closest prior art.” *Id.* Indeed, Visine contains far more claim elements of significance in common with the claimed invention than Gil’s Example 1. *Id.* (considering the number of claim limitations the reference has in common with the invention and their importance in determining the closest prior art).

Significantly, the Visine is for reducing redness; Gil’s Example 1 is not. Like the invention, Visine is administered as a single drop in a single step. Not so for Gil’s Example 1; it administers multiple drops of brimonidine as part of its dosing regimen. Like the invention, Visine ocularly doses the same concentration (0.025%) of a vasoconstrictor in a single drop application. Gil’s Example 1 administers 0.03% brimonidine 6-7 times just before surgery to achieve a significantly higher dose in the eye compared to the invention. Like the invention, Visine achieves redness reduction. Gil’s Example 1 says nothing about redness reduction and merely “appears to suggest” that brimonidine “blocks the perception of pain.” EX-1004, 5:1-2.

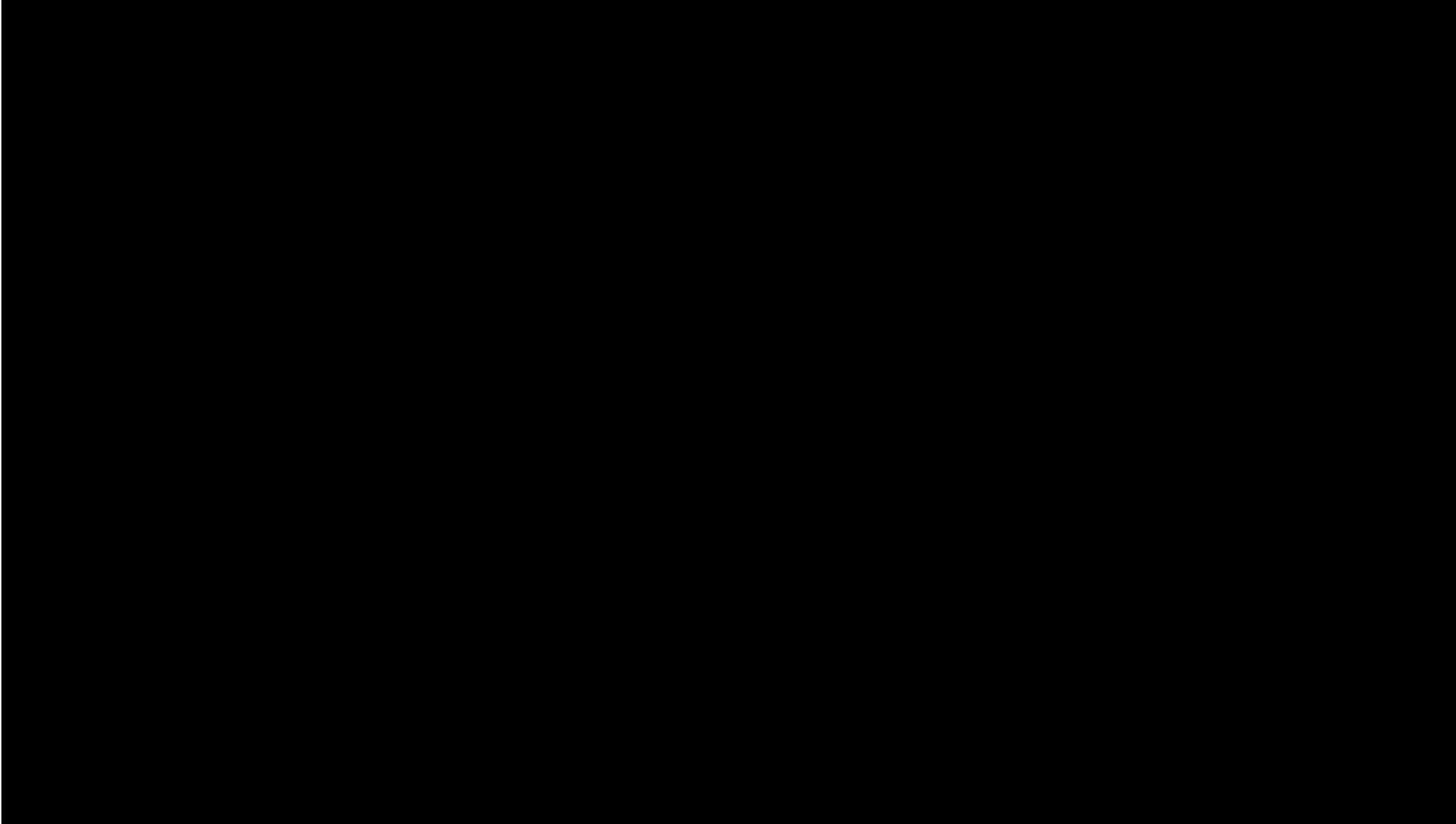
The ’142-IPR Board, moreover, required a comparison to a method it held was obvious from the combination of Gil’s Examples 1 and 4. EX-1003, 63. But just

as the patentee in *Millennium* was not required to create and compare against an allegedly obvious compound, nor is Patent Owner obligated to create a method that Gil did not disclose, prepare, or test and compare it to the invention. *See* 862 F.3d at 1368.

Indeed, to make that comparison, Patent Owner would need to disassemble Gil's Example 1, already found neither to be directed to reducing redness nor to patients having redness, take it outside of the RK setting, which necessarily requires co-administering the repeatedly-dosed brimonidine with other drugs, and then test a single eyedrop (not 6-7 drops) of only 0.03% brimonidine against Lumify in humans with eye redness. That is a study Gil never did, and it violates the *Millenium* requirement to compare to what the closest art *actually* disclosed, not reconstructed modifications alleged to be obvious. *Id.*

c. Lumify's Combined Unexpected Superior Redness Reduction and Safety Profile

A head-to-head Phase II clinical trial compared the eye redness reduction of Lumify (single drop of 0.025% brimonidine only) against the prior art standard of care Visine L.R. (single drop of 0.025% oxymetazoline only). The table below shows Lumify reduced redness about 3 to 6.5 times better than Visine. Noecker ¶¶223-228.



Lumify's superior redness reduction was unexpected. Noecker ¶¶223-224. The art taught that stimulating $\alpha 1$ receptors would sufficiently vasoconstrict ocular blood vessels to effectively reduce redness. EX-2003, 4, Table 3; EX-1009, 14. Indeed, adrenergic vasoconstriction was known to be predominantly mediated by $\alpha 1$ receptor activation. EX-1051, 1-3 ($\alpha 1$ -adrenoreceptor activation is "quantitatively much more important in peripheral vasoconstriction than" $\alpha 2$ -adrenoreceptor activation). The pre-August 2008 redness relievers were either $\alpha 1$ or mixed $\alpha 1/\alpha 2$ agonists. *See supra* §IV.C. Visine's oxymetazoline, a mixed $\alpha 1/\alpha 2$ agonist, had a 200-fold greater affinity for $\alpha 1$ over $\alpha 2$ than brimonidine and would have expectedly outperformed Lumify. Noecker ¶¶223-224; EX-2026, Fig. 2a; EX-1035, 2 (because of its low affinity for $\alpha 1$ -adrenoreceptors, "brimonidine would be the least likely to produce $\alpha 1$ -adrenoceptor-mediated side effects, such as ... ocular vasoconstriction").

Moreover, human clinical trials showed that as the concentration of brimonidine drops, its vasoconstriction ability decreased and was insufficient to produce eye redness reduction at low concentrations. EX-1030, 13, 52, 109; EX-1067, 4, 9; and EX-1068, 2 (at 0.5%, brimonidine blanched/whitened the conjunctiva at a rate of 50%, dropping to 3.5% at 0.2% brimonidine, and was no longer observed when brimonidine's concentration was lowered to 0.15% and 0.1%); EX-1029, 4-5 (concluding a "dose response relation" for brimonidine's ability to blanch the conjunctiva); Noecker ¶¶185-186.

Yet, the data show a single administration of a single drop of Lumify unexpectedly reduced redness far more effectively than a single drop of the same concentration of oxymetazoline, in spite of oxymetazoline's overwhelming greater affinity for the predominant vasoconstricting $\alpha 1$ -receptor. Noecker ¶¶225-228. So markedly outperforming the industry-leading redness reliever constitutes an unexpected difference in kind rather than a trivial difference in degree. *Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1274 (Fed. Cir. 2018) (finding enhanced bioavailability of the claimed invention more than a trivial difference in degree).

The FDA independently recognized that Lumify surprisingly did not show tachyphylaxis or rebound hyperemia in clinical trials, a distinctly meaningful “real-world” advantage over the commercial products and important for OTC products susceptible to noncompliant misuse. Noecker ¶¶235-236; EX-2027, 3; EX-2006, 394:1-395:25; *see Allergan*, 796 F.3d at 1307 (finding a difference in kind for unexpected results demonstrating a difference between an effective and safe drug versus one with significant side effects that led to patient noncompliance). Lumify's unexpectedly superior redness-reliever efficacy with essentially no side effects is a nonobvious difference in kind. Noecker ¶237; *see also In re May*, 574 F.2d 1082, 1092-93 (CCPA 1978) (finding nonobvious a method-of-use invention with uniquely desirable combination of potent efficacy (analgesia comparable to morphine) and a beneficial safety profile (non-addictiveness)).

2. Lumify’s Commercial Success Demonstrates Nonobviousness

Lumify’s unexpected clinical effectiveness and beneficial safety profile rapidly disrupted the stagnant, decades-old eye-redness-reducing market. Before Lumify’s 2018 launch, less than 10% of EPCs recommended redness relievers to their patients. Ferris ¶7. Within three months of Lumify’s launch, it was the #1 doctor-recommended redness-relieving drop—and still is today. No competitor comes close. Ferris ¶24. Indeed, Lumify has disrupted the redness reliever marketplace, taking share from competitors and solely driving the growth of the entire marketplace since launch. Jarosz ¶91; Ferris ¶26. The marketplace has grown by more than █████ since Lumify’s debut, but non-Lumify redness relievers have grown by only █████. Jarosz ¶91; Ferris ¶26. This performance suggests that Lumify filled a gap in the marketplace that other eye redness relievers had not adequately met. Jarosz ¶101; Ferris ¶26. That Lumify has enjoyed such commercial success, despite its premium pricing compared to other, long-existing redness relievers, is particularly instructive. *See PPC Broadband, Inc. v. Iancu*, 739 F. App’x 615, 626 (Fed. Cir. 2018) (“[m]aintaining market share with a price premium is also meaningful” in assessing commercial success).

Commercial success is important objective evidence of nonobviousness because the economic and reputational rewards of a later invention would surely

have motivated its earlier development if it were obvious to do so. *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). Discovered in 1978 (EX-2011), high-concentration brimonidine was known to blanch/whiten reddened conjunctiva at least by 1996. EX-1067, 4. The Board’s alleged closest prior art, Gil, was provisionally filed in 2000 by Allergan, a sophisticated ophthalmic drug company with deep expertise in “repurposing” drugs. Yet not until the ’245 patent’s August 2008 filing did the solution to the decades-long quest for a clinically-effective redness reliever without side effects arrive. This longstanding lag speaks volumes to the invention’s nonobviousness given the substantial rewards flowing from Lumify’s ultimate development. *Leo Pharm.*, 726 F.3d at 1359.

Moreover, [REDACTED]

[REDACTED] Jarosz ¶¶66, 85; Ferris ¶22. It is a top-ten product for the company with over [REDACTED] in net revenue in 2023, and [REDACTED]

[REDACTED] Ferris ¶¶21-22. [REDACTED]

[REDACTED]

[REDACTED] Ferris ¶29. Such success is groundbreaking and attributable to the patented invention. Jarosz ¶¶107, 115; Ferris ¶29.

3. Lumify's Significant Industry Praise Is Further Evidence of Nonobviousness

Industry praise provides probative evidence of nonobviousness meriting substantial weight where, as here, a nexus exists between the praise and the claimed invention. *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1346-47 (Fed. Cir. 2013).

Lumify's success speaks for itself: it is the #1 eye doctor-recommended redness-relieving drop, receiving multiple awards and recognitions since launch. Jarosz ¶¶125-27; Ferris ¶6. Both doctors and consumers have praised Lumify, effectively becoming the new standard of care and changing the trajectory of the entire redness-reliever category. Jarosz ¶¶125-27; Ferris ¶¶6-7; Noecker ¶¶238-242.

Lumify's success directly ties to the claimed invention: redness reduction generated by using a single drop of only 0.025% brimonidine. Lumify's clear and consistent messaging focuses on its approved redness-relieving indication using this specific concentration. Jarosz ¶137; Ferris ¶¶11-13. And market research substantiates that its success is both directly and indirectly tied to the invention of the '245 patent. Ferris ¶¶14-20.

Indeed, Lumify's surprisingly superior redness-relieving efficacy without the side effects of rebound or tachyphylaxis benefitted consumers and drew praise from industry, including recent features in *The Wall Street Journal* and *Good Morning*

America. See Jarosz ¶¶125-27; Ferris ¶6. Even Dr. Reddy’s North America Generics CEO publicly commented on being “pleased to license” the ANDA for its copy of Lumify, calling it an “important OTC ophthalmic product for the U.S. market.” EX-2160, 1.

4. Solid Nexus Between the Objective Evidence of Nonobviousness and the Invention as a Whole

Nexus between objective indicia of nonobviousness and the patented invention is presumed if the commercially successful product “is the invention disclosed and claimed in the patent.” *Crocs, Inc. v. ITC*, 598 F.3d 1294, 1310-11 (Fed. Cir. 2010). It is undisputed that the ’245 patent claims read on using Lumify in accordance with its FDA-approved label to reduce eye redness. Noecker ¶¶243-262. Petitioners have the burden to rebut that presumption, *Crocs*, 598 F.3d at 1311, but have not and cannot.

Petitioners argue the ’142-IPR Board held that “low-dose brimonidine” was known in the prior art, and thus “Lumify’s success was not the result of the novel features of the claim.” EX-1003, 66. It is the ’245 patented redness-reducing method as a whole that makes it novel, not simply low-dose brimonidine. *Id.*, 35-36. Moreover, as discussed *supra*, Gil’s Example 1 does not administer low-dose brimonidine but an amount more akin to 0.2% brimonidine. Nonetheless, the nexus for objective indicia can be tied to the invention as a whole. *WBIP, LLC v. Kohler*

Co., 829 F.3d 1317, 1330-31 (Fed. Cir. 2016). And where, as here, an invention constitutes a novel combination of interdependent elements, separate alleged teachings of individual claimed elements in the art do not negate nexus. *Chemours Co. FC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1378 (Fed. Cir. 2021) (“Concluding otherwise would mean that nexus could never exist where the claimed invention is a unique combination of known elements from the prior art.”). Lumify’s redness-relieving success is tied to the novel ’245 patented methods as a whole, providing solid nexus to the strong objective evidence of nonobviousness.

Relying on the ’142 FWD, Petitioners argue Lumify’s success was not “due to the claimed invention alone,” but “also due” to “Bausch’s sales and marketing campaigns.” EX-1003, 67. The law does not require the patented invention be solely responsible for objective indicia for that evidence to be given weight. *Cont’l Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1273 (Fed. Cir. 1991). A commercial success challenger “must make a convincing case that those market [activities] indeed were the likely cause of the success.” *Crocs*, 598 F.3d at 1311.

Petitioners have not proven that marketing “likely” caused Lumify’s commercial success. Lumify’s unique, patented features have enabled Bausch to

[REDACTED]

[REDACTED]. Ferris ¶29; Jarosz ¶140. This indicates Lumify’s performance is driving sales and user satisfaction, not simply “marketing.” Ferris

¶29. Marketing is a part of almost every innovative drug launch; if carrying out an industry-typical marketing campaign prevented a finding of nexus, commercial success would never be considered. While marketing might make a consumer try a product once, it can neither cultivate repeat users nor rectify a bad experience. ■■■■■

Lumify's success is due to the '245 patented redness-reducing method as a whole. Ferris ¶¶14-20. And Lumify is marketed to this method (Ferris ¶¶8, 29), giving the objective indicia of nonobviousness a clear nexus with the invention.

C. Patentability of Claim 8 and the Challenged Dependent Claims

Claim 8 stands patentable because, as explained above, the prior art taught away from lowering the dose to 0.025% brimonidine, and the objective indicia of nonobviousness pertaining to Lumify apply equally to claim 8. Noecker ¶205.

Regarding the challenged dependent claims, Petitioners argue (Pet., 57-61) unpatentability due to inherency, without proof of such, or that the invention would have been expected to work regardless of the reason for redness. Patent Owner disagrees and provides additional reasons beyond what it argued above for claim 1.

The claims reciting that redness is not associated with surgery or an ocular disease represent a different target population than Norden/Gil (surgery) and Dean (ocular disease), which art POSAs would not have considered absent hindsight in developing an OTC redness reliever lacking the side effects plaguing the state-of-

the-art products. Noecker ¶206. The claims requiring maintenance of normal IOP are patentable because Dean counsels against lowering brimonidine below an effective IOP-lowering dose, and dropping so low would have been expected to reduce vasoconstriction below the minimum effective amount to reduce redness. Noecker ¶208. The claims reciting a low incidence of rebound embody nonobvious unexpected benefits permitting long-term use of the claimed invention, which was not possible with prior commercial redness relievers. Noecker ¶207.

D. SCOTUS’s Recent Decision Renders IPRs Unconstitutional

Petitioners’ invocation of these post-grant proceedings is an unconstitutional encroachment of Patent Owner’s property rights. *SEC v. Jarkesy*, 144 S. Ct. 2117 (2024). Petitioners’ argument that the PTAB should render the challenged claims unpatentable in view of the Board’s Final Written Decision in the ’142-IPR is likewise unconstitutional. *Id.*

IX. 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)(2), because it contains 13,652 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, 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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