

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

EYE THERAPIES, LLC,
Patent Owner

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

Title: VASOCONSTRICTION COMPOSITIONS AND METHODS OF USE

Inter Partes Review No. IPR2024-00467

PETITIONERS' REPLY

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The claimed method of the '245 patent would have been obvious in view of crystal-clear disclosures in the prior art: Norden teaches 0.2% brimonidine reduces hyperemia; Gil teaches low-concentration brimonidine to reduce redness; and Dean instructs lowering concentration to reduce side effects. These references teach brimonidine as the sole redness-reducing active ingredient. Patent Owner ("PO") largely ignores these express disclosures, stripping the POSA of the ability to make reasonable, common-sense inferences therefrom. Further, PO's evidence of non-obviousness is unpersuasive.

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

The Board should reject PO's argument that the transitional phrase "consisting of" limits claim 1 to administering "a single drop of 0.025%" brimonidine because it finds no support in the plain language of the claims, the specification, or the prosecution history.¹ Beginning with the claim, PO argues "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....'" Paper-25, 12. PO misleadingly uses an ellipsis to omit the full claim

¹ PO's argument applies *only* to claim 1. Claim 8 recites a method "***comprising*** topically administering ... brimonidine" and thus is not so limited.

language, which is “topically administering to an eye *a composition in the form of* an ocular drop.” EX-1001, 22:37-39.² The reference to “an ocular drop” appears in the prepositional phrase modifying the noun “composition,” saying nothing about how many drops are “topically administered.” Put another way, “an ocular drop” describes the form of the “composition” in the claims, not the number of drops administered. Under *Norian*, on which PO relies heavily, claim 1 is properly limited to administration of a single *composition* (which happens to be in the form of an ocular drop). *Norian Corp. v. Stryker Corp.*, 432 F.3d 1356, 1359 (Fed. Cir. 2005). *Norian* does not stand for the broader principle advanced by PO that *every* subsequent use of “a” or “an” must be interpreted in the singular sense.^{3, 4}

² Emphases added unless otherwise noted.

³ Tellingly, PO does not argue the phrase “an eye” (appearing before both “a composition” and “an ocular drop”) limits the claims to administering brimonidine to one eye.

⁴ PO’s reliance on *Abbott* is likewise misplaced because *Abbott* addressed the use of indefinite articles in conjunction with a Markush group not at issue here. *See Abbott Lab’ys v. Baxter Pharm. Prods., Inc.*, 334 F.3d 1274, 1280 (Fed. Cir. 2003).

Unlike *Norian*, the specification undermines PO's construction. In every instance in the specification, the phrase "ocular drop" describes how the composition "is formulated," not how many drops are administered. EX-1001, 6:20-21, 6:27-28, 7:29-30, 9:51-52, 9:59-60, 10:25-26, 10:34-35; *see also* 17:16-17 ("The topical compositions include, but are not limited to, ocular drops, ocular ointments, gels and creams[.]"). PO points to Examples 1, 4, and 5 and Figures 5A-5C, but none of those examples involve administration of 0.025% brimonidine as claimed. Paper-25, 13; EX-1047, 68:3-69:3. PO is also wrong that those examples "all use a single drop of low-dose brimonidine." Paper-25, 13. In Example 1, the same eye of one patient received at least *three* drops of brimonidine over a 12-hour period that evaluated, among other things, rebound hyperemia. EX-1147, ¶14; EX-1001, 20:40-67.⁵ Example 5 discloses "treatment ... through *drops* [of brimonidine] twice a day"—suggesting more than one drop per administration. EX-1147, ¶17; EX-1001, 22:29-30. Most significantly, Figures 5A-5C reveal multiple drops were used. *Id.*, 20:8-26, Figs. 5A-5C. Figure 5B is annotated "ii gtts tid, day 2 1st instillation":

⁵ PO's expert Dr. Noecker refused to concede this undeniable fact, asserting the multiple administrations were "different interventions" or "discrete events." EX-1047, 41:5-18.

ii gtts tid, day 2 1st instillation

FIG. 5B

ii gtts tid, day 2 1st instillation

This annotation means two drops (“ii gtts”) administered three times per day (“tid”). EX-1147, ¶18; EX-1044, 37:1-8, 38:21-39:2.⁶ Likewise, Figure 5C is annotated “ii gtts,” meaning two drops. EX-1147, ¶18; EX-1044, 40:13-21. Finally, Example 4 is silent on the number of drops, referring only to “a single dose of brimonidine,” saying nothing about how many drops in that dose. EX-1147, ¶16.

The prosecution history similarly does not support PO’s argument. When PO made that amendment replacing the phrase “compromising” with “consisting of”, PO said nothing about the number of drops administered:

Moreover, the claim phrase ‘consisting of’ has been introduced in [claim 1]. By consisting of, it is meant that brimonidine is *the sole active ingredient* administered in the method, though inactive ingredients/excipients (such as benzalkonium chloride as recited in the claim) would not be excluded; however, it is clear that other active ingredients (such as steroids, anesthetics, carbonic anhydrase inhibitors, or NSAIDs, for example) would be excluded.

⁶ Example 2, ignored by PO, discloses “[b]rimonidine 0.02% applied topically *[i]-ii gtts per eye.*” EX-1001, 21:32; EX-1147, ¶15.

EX-1010, 189. Nowhere in its explanation did PO refer to a specific number of drops. EX-1147, ¶21.

PO's use of the single-drop construction to avoid prior art cannot be reconciled with PO's assertion that the claims "read on using Lumify in accordance with its FDA-approved label to reduce eye redness." Paper-25, 61. According to PO, "[t]he Lumify label instructs users to 'instill 1 drop in the affected eye(s) every 6-8 hours.'" EX-2223, ¶248. That is, users administer up to four drops of Lumify per day. Yet Dr. Noecker asserts the label does *not* instruct four administrations/steps of Lumify. EX-1047, 77:2-83:11. On the other hand, PO asserts Gil's Example 1—which discloses "each subject receives one drop of [0.03% brimonidine] in the operated eye every four hours while awake," which Dr. Noecker confirmed would be four drops per day (*id.*, 71:17-72:21)—is a "far cry from the single step method of claim 1." Paper-25, 24-25; *see also* EX-2223, ¶140 (asserting Gil's post-surgery dosing amounts to "an additional 56 administrations/steps."). Dr. Noecker could not explain the discrepancy. EX-1047, 83:5-84:16 (testifying Gil's Example 1 is a "preordained regimen" to treat pain but users following Lumify's label "can instill one drop at a time and to expect that this drop is going to do its thing for about six to eight hours"). PO's unprincipled positions on what constitutes a single drop versus multiple drops further highlights the problematic nature of PO's

construction. *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995) (“Claims may not be construed one way in order to obtain their allowance and in a different way against accused infringers.”).

II. ALL CHALLENGED CLAIMS ARE OBVIOUS

PO advances four arguments in its response.⁷ First, PO challenges whether a POSA would have been motivated to combine the teachings of Gil, Norden, and Dean, accusing Petitioners of “pluck[ing]” those references from a “sea of prior art.” Paper-25, 17. Second, PO dissects each reference individually, without ever addressing the express teaching in them—namely, brimonidine was a known vasoconstrictor in blood vessels in the front of the eye and eyecare professionals

⁷ PO did not address whether claim 1 and its dependent claims are obvious under the plain-and-ordinary understanding that the claims are not limited to a single drop. Thus, PO is precluded from doing so in sur-reply. *Samsung Elecs. Co., Ltd. v. Promos Techs. Inc.*, IPR2017-01413, Paper 33 at 20 (P.T.A.B. Oct. 22, 2018) (“A sur-reply ... is not an opportunity for [PO] to raise a new [claim construction] argument that should have been asserted earlier.”). Under either construction, however, the claims should be found unpatentable.

were *already* using brimonidine for this purpose at the time of the invention.⁸ EX-1014, ¶121; EX-1006, 4; EX-1131, 1. Third, PO repeats the same argument the Board rejected in the '742 IPR that partial data in the Alphagan labels about the *adverse event* referred to as “conjunctival blanching” taught away from 0.025% brimonidine to reduce redness. Finally, PO briefly addresses three limitations—efficacy, BAK, and pH—arguing they confer patentability. PO’s arguments lack merit.

A. A POSA Would Be Motivated to Combine Norden, Gil, and Dean

PO disputes whether a POSA would have turned to the teachings of Norden, Gil, and Dean when developing a redness-reducing ocular drop. Paper-25, 14-20, 29-30. In doing so, PO ignores that all three references expressly direct the POSA to brimonidine’s redness-reducing mechanism of action: vasoconstriction of blood vessels in the front of the eye. EX-1006, 4 (referring to brimonidine as a “strong

⁸ PO argues Fudenberg does not explicitly mention redness relief as one of the uses of brimonidine. Paper-25, 19-20; EX-2223, ¶111. Fudenberg is an article by glaucoma doctors about brimonidine’s “role in glaucoma management.” EX-2028, Abstract. Fudenberg does not claim to list all uses of brimonidine and fails to cite Norden, Dean, and Gil. Paper-2, 37-39; EX-1014, ¶121.

vasoconstrictor” used to “help prevent bleeding-related problems in the [front] segment”); EX-1004, 5:38-40 (“[b]rimonidine is effective in reducing ... neurogenic responses,” including “redness”); EX-1007, 2:33-36 (“brimonidine causes vasoconstriction in scleral vessels”). Indeed, PO’s expert Dr. Donnenfeld agreed:

Q. Okay. And you would agree that as of 2002, brimonidine, this alpha-2 agonist, was known to be a strong vasoconstrictor?

A. Yes.

EX-2009, 80:24-81:1. PO agrees that a POSA developing a redness-relieving drop would look to vasoconstrictors. EX-1009, 7 (“the term ‘eye redness reliever’ is a complete and accurate description of the principal action of an OTC ophthalmic vasoconstrictor ingredient, which is used to relieve redness in the eye”); Paper-25, 9, 17 (“POSAs would have considered the products typically used to reduce redness in subjects with healthy and intact ocular blood vessels”). Norden, Gil, and Dean describe brimonidine having that very effect, including at low concentrations, and Dean specifically instructs to lower the concentration to reduce side effects. No more motivation is required. *Intel Corp. v. PACT XPP Schweiz AG*, 61 F.4th 1373, 1380 (Fed. Cir. 2023) (“That [prior art references] address the same problem and that [one reference’s teaching] was a known way to address that problem is precisely the reason that there’s a motivation to combine under *KSR* and our precedent.”).

PO argues Norden and Gil are irrelevant because they administer brimonidine in connection with “surgical trauma models.” Paper-25, 15-16. The *cause* of redness in Norden and Gil is not the point. Norden and Gil teach the mechanism of action of brimonidine—vasoconstriction—and its effectiveness in reducing redness caused by different stimuli. EX-1006, 4; EX-1004, 5:31-45. Similarly, like Norden, the specification reinforces that the claimed method can be used in connection with LASIK and other surgeries. *See, e.g.*, EX-1001, 7:42-44, 10:36-38; 21:5-47 (Example 2). Indeed, claim 1 is silent as to the cause of the ocular hyperemia and necessarily includes redness that *is* “the result of a surgical procedure on the eye” because dependent claim 4 purports to exclude that cause with a negative limitation. *Alcon Rsch., Ltd. v. Apotex, Inc.*, 687 F.3d 1362, 1367 (Fed. Cir. 2012) (“It is axiomatic that a dependent claim cannot be broader than the claim from which it depends.”).

PO argues “Dean ... does not address redness reduction, much less redness reduction in patients with ocular hyperemia.” Paper-25, 18. Dean teaches using brimonidine as a *vasoconstrictor*—“to constrict ocular vessels and thereby reducing the flux of blood through the anterior portion of the eye,” which a POSA would understand to refer to the visible blood vessels in the eye. EX-1007, 2:55-65. Thus,

the POSA would have appreciated from Dean that brimonidine reduces redness as a result of its vasoconstrictive properties.

Finally, PO incorrectly frames the necessary motivation of a POSA in terms of “assessing a redness reliever for regulatory approval.” Paper-25, 15-16 (citing *Endo Pharms. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374 (Fed. Cir. 2018)). The Federal Circuit, however, has made clear “[t]here is *no requirement* in patent law that the [POSA] be motivated to develop the claimed invention based on a rationale that forms the basis for FDA approval.” *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291-92 (Fed. Cir. 2013). The motivation-to-combine analysis “is not limited to what already has or could gain FDA approval.” *Bayer Pharma AG v. Watson Lab’ys, Inc.*, 874 F.3d 1316, 1326 (Fed. Cir. 2017). For those reasons, PO’s reliance on *Endo* is misplaced. In *Endo*, the parties disputed whether reasonable expectation of success should be viewed from the perspective of a POSA adjusting an injection regimen for an individual patient or patient population. *Endo*, 894 F.3d at 1385-86. Based on the specific facts of that case, the Federal Circuit determined the latter was proper. *Id.* The court did not hold the POSA’s motivation to develop a therapeutic must stem from data sufficient for FDA approval.

B. PO's Criticisms of Norden, Gil, and Dean Fail

The Board previously found that “Norden’s disclosure, coupled with Gil’s teaching that low-dose brimonidine ‘is effective in reducing such neurogenic response’ like ‘redness,’ and in view of Federal Register’s disclosure that ocular vasoconstrictors are eye-redness-reducers and Dean’s disclosure that topical brimonidine is an ocular vasoconstrictor, is sufficient motivation for a POSA to pursue low-dose brimonidine in a method to reduce eye redness with a reasonable expectation of success.” EX-1003, 56. PO should be estopped from relitigating this finding. *Infra* §IV. At a minimum, the Board should reject PO’s criticisms of Norden, Gil, and Dean, which once again miss the forest for the trees.

1. Norden

PO first argues that Norden’s repeated references to “hyperemia” do not actually mean “hyperemia,” but something called “micro-vessel hemorrhage.” Paper-25, 21-23; EX-2009, 84:16-21. There is no evidence to support this other than litigation-inspired testimony from PO’s experts. EX-2224, ¶¶50-51. Indeed, one of PO’s experts had not even heard of “micro-vessel hemorrhage” before Dr.

Donnenfeld told him about it.⁹ EX-1047, 95:17-96:4. All Dr. Sonnenfeld can point to is a single publication, Doshi, published 15 years after the priority date, that does not even mention “micro-vessel hemorrhage.” EX-1147, ¶¶36-37. To the contrary, the literature took Norden’s conclusion at face value, and ophthalmologists discussed Norden’s findings as relevant to redness, separate from hemorrhage. EX-1147, ¶38; EX-1144, 97 (citing Norden and stating “use of brimonidine prior to [LASIK] ... demonstrated that brimonidine was effective at reducing subconjunctival hemorrhage *and ocular redness*”); EX-2101; EX-1062, 1; EX-1063, 4; EX-1131, 1.

To support its forced reading of Norden, PO assumes hyperemia was measured at the patients’ second examination (the day after surgery). Paper-25, 22-23. But PO’s expert Dr. Noecker initially read Norden differently: “Norden 2002 measured redness only once, five minutes after the LASIK surgery.” EX-1129,

⁹ In his prior declaration, Dr. Noecker opined “hyperemia is a type of redness arising in *intact* blood vessels due to the *vasodilation* of ocular blood vessels.” EX-1129, ¶168. Dr. Noecker attributed his differing definitions to different POSAs—one specializing in LASIK and one specializing in glaucoma—which is not how the concept of a POSA works in patent law. EX-1047, 96:5-103:10.

¶170; *compare with* EX-1047, 106:17-109:8. Although Norden does not specify which measurements were recorded during each observation, a POSA would have understood brimonidine’s vasoconstrictive effects could only be observed immediately after surgery, in line with Dr. Noecker’s initial assessment, because of brimonidine’s half-life. EX-1147, ¶¶39-41. For the same reason, PO’s argument that the corticosteroid prednisolone would have “resolved any vasodilation in both the ‘test’ and ‘control’ groups” (Paper-25, 23) also fails. EX-1147, ¶42.

Although PO argues “[n]o one disputes the prior art methods ... are not directed to administering brimonidine as the sole active ingredient,” PO does not address Norden in Section VIII.A.2.b of the POR. Paper-25, 30-36. Nor can PO reasonably dispute Norden’s data shows a statistically significant reduction in hyperemia in eyes receiving brimonidine compared to those that did not. EX-1006, 6-7. The only difference between these groups was administration of brimonidine, demonstrating brimonidine alone caused the reduction in hyperemia. *Id.*; EX-1147, ¶43.

2. Gil

PO disputes whether Gil’s disclosure that brimonidine “is effective in reducing such neurogenic responses,” including “redness,” would teach a POSA that brimonidine is in fact effective in reducing redness. PO again “turns a blind eye to

the rest of the disclosure [in Gil] and what that would have suggested to a [POSA].” EX-1003, 57.

Beyond relying on the flawed single-drop claim construction, PO argues Gil does not teach using brimonidine as the sole active ingredient to reduce redness, focusing exclusively on Gil’s pain-related disclosures. Paper-25, 24-28. The Board already rejected these arguments in connection with the ’742 IPR. *See* EX-1003, 57. Gil’s disclosures are not limited to treatment of pain, and Gil’s Example 4 measures neurogenic response as a proxy for redness. EX-1147, ¶¶45-49. Specifically, Example 4 describes a study evaluating “[o]cular responses characteristic of neurogenic inflammation, including redness ... are also observed in rabbits following external stimuli.” EX-1004, 5:38-41. The “stimuli” are described as an “ocular surface sensory challenge such as topical capsaicin, potassium chloride or fine hairs.” *Id.*, 5:35-37. Dr. Gil explained this study involved “a range of doses of brimonidine ... tested [when] the ocular surface is challenged with these different topical stimuli.” EX-1031, 109:21-113:20.

PO also argues “Example 4 fails to teach or suggest using brimonidine alone in a single step method for reducing human eye redness.” Paper-25, 26. PO argues Example 4 does not include “substantiating data” and thus would not have led the POSA to expect brimonidine would reduce redness. *Id.*, 27. No “substantiating

data” is required, however, because Example 4 is prior art for all that it discloses. *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, 377 F. App’x 978, 982-83 (Fed. Cir. 2010) (“For purposes of § 103, a prior art reference need not itself be enabled but is prior art for all that it discloses.”). Further, under PO’s single-drop claim construction, Example 4 does *not* require administration of multiple drops. Thus, the POSA would have reasonably inferred that a single drop of low-concentration brimonidine would be effective in reducing redness. EX-1147, ¶49.

3. Dean

PO similarly takes an overly narrow view of Dean, arguing Dean relates only to using brimonidine with brinzolamide to treat glaucoma. PO presents no evidence why the POSA would have believed brimonidine’s vasoconstrictive activity described in Dean somehow depended on the presence of brinzolamide or would be relevant only to glaucoma treatment.

PO argues Dean “fails to teach or suggest using a single drop of 0.025% brimonidine for reducing eye redness,” disagreeing with the Board’s Institution Decision concluding the opposite. Paper-25, 28, 33. The concentration range disclosed in Dean—0.01% to 0.2%, encompassing the claimed 0.025%—does not require multiple drops, but includes both single-drop and multiple-drop administrations. *See* EX-1007, 15:20-27 (“for topical presentation **1-3 drops** ...

would be delivered ... 1-4 times a day *according to the routine discretion of a skilled clinician*”). Further, the POSA would have understood this disclosure to represent the range of concentrations Dean expected brimonidine to work *as a vasoconstrictor*, which is brimonidine’s primary purpose in Dean. EX-2085, 44:14-45:5; EX-1147, ¶¶50-53.

4. PO’s Arguments Regarding Number of Drops Administered Are Misplaced

PO argues the number of brimonidine drops administered in Norden, Gil, and Dean would impact the POSA’s conclusions about brimonidine’s redness-reducing action. PO misses the mark because, as the prior art demonstrates, the POSA would not focus on the number of drops but rather the *concentration* of brimonidine in those drops. Notably, all of the prior art refers to brimonidine formulations by concentration. Unlike oral drugs, the dose of an ocular drop is not measured in the absolute amount of drug administered, but the concentration applied to the eye. A POSA would have understood the concentration in the drop is the critical factor, partially in light of the variability in the size of each drop from an eye drop bottle. EX-1147, ¶¶54-59; EX-1069, Abstract ; EX-1070, Abstract.

PO also ignores Hong, which explicitly discloses administration of a single drop of brimonidine to reduce redness in strabismus surgery patients. Hong administered a single drop of 0.15% brimonidine to induce vasoconstriction,

resulting in reduced subconjunctival hemorrhage—a direct result of narrowing the blood vessels before the surgery. EX-1064, 1-2; EX-1147, ¶60.

C. The Alphagan Blanching Reports Do Not Undermine the POSA’s Reasonable Expectation of Success

Ignoring the express disclosure of overlapping concentration ranges in the prior art, PO argues the “prior art taught away from a single administration of a single eyedrop of 0.025% brimonidine.” Paper-25, 39-40. But PO cannot avoid the undisputed testimony that a POSA would readily determine the appropriate concentration of brimonidine for the intended purpose. EX-2225, ¶38; EX-1045, 24:13-25:7 (“They take a drug and they expose humans to different doses and look at both the therapeutic effects and the off-target effects. So that’s pretty standard in drug development.”); EX-2016, 142:10-12 (Dr. Gil admitting the “dose finding process” is a “routine part of pharmacology”). The POSA would have easily determined the proper concentration, size, and number of drops that would reduce redness while minimizing side effects, as the POSA is motivated to find the minimum effective dose (as well as the minimum effective concentration). *E.I. Dupont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (“[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.”) (cleaned up).

PO relies heavily on limited information reported in the Alphagan labels, which include no data regarding the claimed concentration of 0.025% brimonidine. Paper-25, 43-46; *see Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 963-64 (Fed. Cir. 2014) (explaining “silence does not imply teaching away”). A POSA would have given little weight to such scant data, and PO’s willingness to draw firm conclusions from one-sentence descriptions of undefined adverse events across different clinical trials evaluating different products highlights the disparate treatment PO affords to the express teachings in Norden, Gil, and Dean.

PO points to the Alphagan labels, specifically the “blanching”¹⁰ listed as an adverse reaction. Paper-25, 46-47. PO’s argument pulls individual data points (rates of “blanching”) from three separate clinical trials (Alphagan 0.5%, 0.2%, and 0.15%) and contends this would allow a POSA to draw definitive conclusions regarding the dose needed for an effect that was not an endpoint in any of those studies. As the Board previously concluded, however, the Alphagan studies “did not

¹⁰ PO does not appear to dispute that “blanching” is listed in the adverse reaction sections because it is *undesirable*. *See* EX-2228, ¶88 (“FDA’s prescription drug labeling regulations require that Section 6 of the Prescribing Information contain certain information on adverse reactions—*i.e.*, ‘*an undesirable effect....*’”).

provide information about how redness was measured, what degree of blanching was needed to be listed as an ‘adverse event,’ or when blanching was observed,” and did not rise to the level of teaching away. EX-1003, 59.

These trials were not designed to evaluate redness reduction. EX-1147, ¶¶63-65. And there is no evidence in the record to substantiate PO’s arguments about what protocols the trials may have used,¹¹ including whether a specific definition of “blanching” was used, what grading scale (if any) was used, when in the study (and how many times) blanching was observed in each patient, what severity of blanching was necessary to be reported on the label,¹² etc. EX-1147, ¶67; EX-1014, ¶¶131-33; EX-1053, 53:12-55:20. PO points to the Alphagan 0.2% NDA, which states “[a]ny

¹¹ Dr. Donnenfeld *speculates* about what may have been done in the Alphagan trials, but he does not actually know, and PO has cited no documentation evidencing what was actually done. EX-1044, 44:2-45:21, 48:10-49:7.

¹² PO’s reliance on Alphagan monographs published in 2022 (EX-2108, EX-2119) should be ignored because these documents could not have influenced the POSA in 2008. *Acorda Therapeutics, Inc. v. Roxane Labs, Inc.*, 903 F.3d 1310, 1320 n.7 (Fed. Cir. 2018) (unavailable data “could not have informed the legally relevant [POSA]”).

adverse event occurring during the study was recorded” and “graded for severity (trace, mild, moderate, or severe).” Paper-25, 47. But that NDA does not indicate the level of severity required for the adverse event to be included on the label or provide objective definitions of the stated gradations. EX-1147, ¶¶68-69. Further, it is unclear whether any alleged grading scale for hyperemia was separate from that for blanching and how/whether they related to one another, e.g., whether a reduction in hyperemia would be recorded as the adverse event of “blanching.” *Id.*

Thus, the Alphagan labels would have been unpersuasive to the POSA who would have been motivated to find the minimum effective concentration of brimonidine and would have done so as a matter of routine optimization.

D. “Wherein the Ocular Hyperemia Is Reduced” Is Inherent

This Board already found Norden and Gil teach that administration of low-concentration brimonidine reduces ocular hyperemia (i.e., redness). EX-1003, 54-56. In addition, this limitation merely recites the inherent result of administering low-concentration brimonidine.

PO argues the “wherein the ocular hyperemia is reduced” clause “adds patentable weight to the claims,” relying on *Allergan Sales, LLC v. Sandoz, Inc.*, 935 F.3d 1370, 1376 (Fed. Cir. 2019). Paper-25, 36-37. *Allergan* does not discuss inherency; rather, it simply addresses whether a “wherein” clause was limiting as a

matter of claim construction. *Allergan*, 935 F.3d at 1376. A claim element is not automatically saved from inherency by virtue of being a “limiting” claim element. *Persion Pharms. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1190 (Fed. Cir. 2019) (“[I]nherency may supply a missing claim **limitation** in an obviousness analysis.”).

PO argues “[t]he 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,” citing *Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014). Paper-25 at 37. But PO’s reliance on *Par* is misplaced. In *Par*, the Board found insufficient evidence that the alleged inherent property resulted from the obvious combination. *See Ex Parte Takamiya*, Appeal 2016-001471, 2017 WL 1091179, at *5 (P.T.A.B. Mar. 20, 2017). Where the specification “admit[s] ... that the [invention] that would have been obvious in light of the prior art *has the claimed properties*,” however, the Board has found the property inherent. *Id.* Here, the specification admits the obvious invention (administration of 0.025% brimonidine) inherently has the claimed property of reducing ocular hyperemia. EX-1001, 20:40-22:34; *Alcon Rsch., Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012).

PO cites to *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003) for the proposition that “the question is not whether 0.025% brimonidine will always reduce redness, but whether the disclosed ranges always and unavoidably result in redness reduction.” Paper-25, 37-38. But *Schering* says no such thing. Rather, the question is whether the obvious method of using 0.025% brimonidine to reduce eye redness would inherently result in redness reduction. *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (“[A]n obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the [results].”). The record shows administration of 0.025% brimonidine reduces redness, making this element inherent.

E. Use of BAK in an Eyedrop at a pH of 5.5-6.5

PO argues the prior art taught away from formulating eyedrops with BAK at a pH of 5.5-6.5. Paper-25, 38-39. Although the prior art includes *alternatives* to BAK and the claimed pH range, the “mere disclosure of more than one alternative does not constitute a teaching away.” *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

As all experts agree, BAK was a well-known preservative in 2008 and is still commonly used today. EX-1013, ¶¶52-57; EX-2042, 5 (Dr. Noecker admitting BAK is the “most common antimicrobial preservative” and is “highly efficacious

against numerous microbes.”). PO cannot point to any evidence in the record suggesting a formulator could not use BAK in redness-reliever drops. EX-1072, 21:14-22:2. PO’s position that a POSA would be discouraged from using BAK in 2008 is belied by real-world evidence that the FDA continues to approve numerous eye drops containing BAK. EX-1013, ¶¶58-60. Similarly, PO’s assertion that BAK was known to cause redness is belied by PO’s expert. EX-1048, 55:13-56:3. (admitting that the redness on warning labels is not caused by the inclusion of BAK).

PO’s arguments regarding the claimed pH range similarly fail. PO claims the POSA would consider the pH of only Alphagan P and not the original Alphagan formulation. Paper-25, 39. But there is no evidence to support that a POSA would ignore the original Alphagan product when formulating brimonidine. Indeed, a POSA would understand the benefit of using the Alphagan pH when targeting brimonidine to the surface of the eye. EX-1013, ¶¶38-42. As such, the POSA would recognize brimonidine was successfully formulated at a pH of 5.5-6.5, and there is no evidence suggesting this pH range would not work. EX-1013, ¶¶38-51; EX-1072, 39:12-42:9.

Nowhere does PO suggest the addition of BAK or the claimed pH range produced unpredictable results. Rather, the claimed invention simply combines known elements according to their known function to achieve predictable results.

F. Claim 8 and Dependent Claims

PO's cursory arguments regarding claim 8 and the dependent claims fail to rebut the prima facie case of obviousness presented in the Petition. See Paper-25, 63-64. Additionally, PO fails to explain why the "comprising" claims (claim 8 and its dependent claims), which are undisputedly not limited to single-drop administration, would not be obvious over the prior art in view of PO's emphasis on its (incorrect) "single drop" claim construction.

III. OBJECTIVE INDICIA DO NOT OVERCOME OBVIOUSNESS

PO repeats the same objective-indicia arguments already considered and rejected by this Board. See Paper-25, 48-63; EX-1003, 62-68. PO provides no reason why the Board should conclude differently here.

A. Gil Is the Closest Prior Art

PO argues Gil is not the closest prior art, relying on *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). Paper-25, 50-54. Neither case supports PO's argument. PO argues, "the closest prior art to the ***claimed invention*** for comparative testing must at least be a method of reducing redness." Paper-25, 52 (emphasis in original). As explained, and as the Board found previously, Gil *is* a method of reducing redness. Paper-2, 28-30, 38-39; EX-1003, 63 ("Gil discloses the use of low-dose 0.03% brimonidine and that low-dose brimonidine is effective in reducing ocular responses

characteristic of neurogenic inflammation, such as redness.”). PO’s argument narrowly focuses on Gil’s Example 1 and ignores Example 4, which teaches a range of 0.01 % to 0.5% brimonidine is “effective in reducing ... neurogenic responses,” including “redness.” EX-1004, 5:38-45. PO repeats the *Millennium* argument this Board already rejected because “*Millennium* ... is inapposite.” EX-1003, 63-64.

B. Lack of Nexus

Presenting essentially the same arguments from the ’742 IPR, PO again fails to establish a nexus between the claims and PO’s alleged secondary considerations. PO argues “the claims of the ’245 patent meaningfully differ from the claims of the ’742 patent” (Paper-25, 49), yet PO’s evidence of commercial success is essentially the same evidence PO presented in connection with the ’742 patent. *See* Paper-25, 60-63; EX-1162, ¶¶23-31, 62-72; *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1377-78 (Fed. Cir. 2019). PO fails to apportion any of Lumify’s alleged success to the ’245 patent (as opposed to the ’742 patent). EX-1162, ¶¶67-73; *Nevro Corp. v. Boston Sci. Neuromodulation Corp.*, IPR2019-01313, Paper 74, at 42 (P.T.A.B. Jan. 19, 2021).

PO argues Lumify’s alleged commercial success and “significant industry praise” are directly related to “redness reduction generated by using a single drop of only 0.025% brimonidine.” Paper-25, 60. As was the case in the ’742 IPR, all of

PO's evidence turns on the use of low-concentration brimonidine, which was known in the prior art. *Id.*, 60; EX-1003, 66; *see also Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006) (“[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent.”).

C. PO's Evidence of Objective Indicia Is Unpersuasive

PO's evidence of unexpected results, commercial success, and praise is unpersuasive and fails to overcome the strong case of obviousness.

PO's evidence of unexpected results fails to compare the claims to the closest prior art (Gil) and shows only a difference in degree, not in kind. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). The POSA would have expected low concentrations of brimonidine to reduce redness, and the data on which PO relies (comparing Lumify to Visine) shows nothing more than incremental improvement over the prior art. EX-1147, ¶¶74. It cannot upend the strong evidence of obviousness.

Further, PO's evidence of commercial success was largely driven by a marketing campaign on which PO spent considerable resources. EX-1162, ¶¶32-66. And PO's evidence of industry praise consists largely of self-serving, non-scientific publications. *Id.*, ¶¶35-47.

IV. ESTOPPEL

PO is estopped from taking positions contrary to this Board’s findings in the ’742 IPR. Under 37 CFR § 42.73(d)(3), PO is “precluded from taking action inconsistent with [an] adverse judgment.” As part of the determination in the ’742 IPR, this Board made factual determinations related to the prior art, most of which overlap with issues raised here. PO’s positions are nothing more than an attempt to relitigate issues the Board already decided in the ’742 IPR. *See Ex Parte Stuart A. Nelson*, Appeal 2020-004978, 2020 WL 8186425, at *5 (P.T.A.B. Dec. 31, 2020) (“[G]iven an adverse judgment in an *inter partes* review applying [prior art references] to claims 1 and 3, estoppel may prevent Appellant from re-arguing in reexamination whether [the prior art references] render claims 1 and 3 obvious as making such arguments (i.e., ‘taking action’) is inconsistent with the adverse judgment.”). Section 42.73(d)(3) ensures efficient use of the Board’s resources and should prevent PO from being able to relitigate the findings of the prior FWD.

V. CONCLUSION

For at least these reasons, all challenged claims would have been obvious.

IPR2024-00467
U.S. Patent No. 11,833,245

Date: February 25, 2024

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this Petition for *Inter Partes* Review complies with the type-volume limits of 37 C.F.R. § 42.24(c) because it contains 5,594 words according to the word-processing system used to prepare this Reply, excluding the words in the Table of Contents, Table of Authorities, List of Exhibits, Certification Under §42.24(d), and Certificate of Service, as set forth in 37 C.F.R. § 42.24(c).

Date: February 25, 2025

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CERTIFICATE OF SERVICE

I, Linnea P. Cipriano, certify that I caused to be served a true and correct copy of the foregoing **PETITIONERS' REPLY** by email, as follows:

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February 25, 2025

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