

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SLAYBACK PHARMA LLC,
Petitioner,

v.

EYE THERAPIES, LLC,
Patent Owner.

IPR2022-00142
Patent 8,293,742 B2

Before JOHN G. NEW, TINA E. HULSE, and
ROBERT A. POLLOCK, *Administrative Patent Judges*.

NEW, *Administrative Patent Judge*.

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314, 37 C.F.R. § 42.4

I. INTRODUCTION

Slayback Pharma, LLC (“Petitioner”) has filed a Petition requesting *inter partes* review of claims 1–6 of U.S. Patent No. 8,293,742 B2 (Ex. 1001, “the ’742 patent”). Paper 2 (“Pet.”). Eye Therapies, LLC. (“Patent Owner”) filed a Preliminary Response to the Petition. Paper 7 (“Prelim. Resp.”). With our authorization filed a Reply to Patent Owner’s Preliminary Response and Patent Owner filed a Sur-Reply. Papers 10, 12.

Under 35 U.S.C. § 314, the Board “may not authorize an *inter partes* review to be instituted unless ... the information presented in the petition ... and any response ... shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” Upon consideration of the Petition and Preliminary Response, and the evidence of record, we determine that the evidence presented demonstrates a reasonable likelihood that Petitioner would prevail in establishing the unpatentability of at least one of the challenged claims of the ’742 patent. Accordingly, we institute *inter partes* review of claims 1–6 of the ’742 patent.

II. BACKGROUND

A. *Real Parties in Interest*

Petitioner identifies itself and Slayback Pharma India LLP as the real parties-in-interest. Pet. 65. Patent Owner identifies itself and Bausch & Lomb, Inc. and Bausch & Lomb Ireland Limited as the real parties-in-interest. Paper 4, 2.

B. Related Matters

Petitioner states that the '742 patent has been asserted in pending civil action *Bausch & Lomb Inc. et al. v. Slayback Pharma LLC et al.*, 3:21-cv-16766 (D.N.J.). Ex. 2006. Pet. 65. Patent Owner adds that the '742 patent has also been asserted in *Bausch & Lomb, Inc, et al. v. Harrow Health, Inc. et al.*, 3:21-cv-19252 (D.N.J.). Paper 4, 2.

Petitioner also filed a petition for *inter partes* review of U.S. Patent No. 9,259,425 in IPR2022-00146.

C. The Asserted Grounds of Unpatentability

Petitioner contends that claims 1–6 of the '742 patent are unpatentable, based upon the following grounds:

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–2	102	Gil ¹
1–2	102	Walters ²

¹ Gil et al. (US 6,294,553 B1, September 25, 2001) (“Gil”). Ex. 1004.

² T.R. Walters et al., *A Pilot Study of the Efficacy and Safety of AGN 190342-LF 0.02% and 0.08% in Patients with Elevated Intraocular Pressure*, 32(4) ASSOC. RES. VISION AND OPHTHALMOL. 988 (1991) (“Walters”). Ex. 1005.

Claim(s) Challenged	35 U.S.C. §	Reference(s)/Basis
1–6	103	Gil, Norden ³ , Dean ⁴ , Alphagan ⁵ , and Federal Register ⁶

Petitioner also relies upon the Declarations of Dr. Neal A. Sher (the “Sher Declaration,” Ex. 1002) and Dr. Paul A. Laskar (the “Laskar Declaration,” Ex. 1003).

D. The '742 Patent

The '742 patent is directed to compositions and methods for preferential vasoconstriction of smaller blood vessels relative to larger blood vessels. Ex. 1001 Abstr., col. 2, ll. 47–48. The compositions are administered to patients with ocular conditions, resulting in the reduction eye redness. *Id.* at col. 12, ll. 14–59.

In one embodiment, a selective α -2 adrenergic receptor agonist is administered to reduce vasoconstriction at a concentration below about 0.05% weight by volume. Ex. 1001, col. 5, ll. 19–26. The α -2adrenergic receptor agonist preferably has a binding affinity 100-fold to 500-fold or greater for α -2adrenergic receptors than α -1 adrenergic receptors. *Id.* at col.

³ R.A. Norden, *Effect of Prophylactic Brimonidine on Bleeding Complications and Flap Adherence after Laser in Situ Keratomileusis*. 18(4) J. Refractive Surg. 468–471 (2002) (“Norden”). Ex. 1006.

⁴ Dean et al. (US 6,242,442 B1, June 5, 2001) (“Dean”). Ex. 1007.

⁵ ALPHAGAN® (*brimonidine tartrate ophthalmic solution*) 0.2%. Physicians’ Desk Reference, 52th ed., Medical Economics Company, Inc., 487 (1998) (“Alphagan”). Ex. 1008.

⁶ 53 Fed. Reg. 7076–7093 (Mar. 4, 1988) (“Federal Register”). Ex. 1009.

5, ll. 20–25, 46–48. The preferred α -2adrenergic receptor agonist is brimonidine. *Id.* at col. 5, ll. 52–55; cols. 5–6, ll. 65–4.

E. Illustrative Claim

Independent claim 1 of the '742 patent is representative of the challenged claims and recites:

A method for reducing eye redness consisting essentially of administering brimonidine to a patient having an ocular condition, wherein brimonidine is present at a concentration between about 0.001% weight by volume and about 0.05% weight by volume.

Ex. 1001, col. 22, ll. 17–22.

E. Prosecution History of the '742 Patent

The '742 patent issued from U.S. Application 12/460,941 (the “'941 Application”) filed on July 27, 2009 and claims the priority benefit of provisional Application Ser. No. 61/207,481, which was filed on February 12, 2009; provisional Application Ser. No. 61/203,120, filed on December 18, 2008; provisional Application Ser. No. 61/192,777, filed on September 22, 2008; and provisional Application Ser. No. 61/137,714 filed on August 1, 2008. Ex. 1001, code (60).

The claims of the '742 patent, including claims 1–6, were allowed on October 23, 2012. *Id.*, code (45).

III. Analysis

A. Claim Construction

The Board applies the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. § 282(b). *See* 37

C.F.R. § 100(b) (2020). Under that standard, claim terms “are generally given their ordinary and customary meaning” as understood by a person of ordinary skill in the art at the time of the invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc). “In determining the meaning of the disputed claim limitation, we look principally to the intrinsic evidence of record, examining the claim language itself, the written description, and the prosecution history, if in evidence.” *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 469 F.3d 1005, 1014 (Fed. Cir. 2006) (citing *Phillips*, 415 F.3d at 1312–17). Extrinsic evidence is “less significant than the intrinsic record in determining ‘the legally operative meaning of claim language.’” *Phillips*, 415 F.3d at 1317 (quoting *C.R. Bard, Inc. v. U.S. Surgical Corp.*, 388 F.3d 858, 862 (Fed. Cir. 2004)).

Petitioner proposes construction of two terms: “about 0.025%” and “ocular condition.” Pet. 26–31. Patent Owner disputes Petitioner’s arguments regarding the first term. Prelim. Resp. 29–36. Patent Owner does not take a position regarding the latter term. Prelim. Resp. 36.

1. “about 0.025%”

Petitioner urges us to construe the claim term “about 0.025%” as including 0.03%. Pet. 26–27. According to Petitioner, the language of the claims, the Specification of the ’742 patent, and the prosecution history provide no explicit disclosures as to whether “about 0.025%” includes or excludes “0.03%.” Pet. 27 (citing Ex. 1003 ¶ 63). Consequently, argues Petitioner, whether “about 0.025%” includes 0.03%, “must be interpreted in its technologic and stylistic context” and depends upon “the criticality of the [numerical limitation] to the invention.” *Id.* at 27–28 (quoting *Cohesive*

Techs. v. Water Corp., 543 F.3d 1351, 1368 (Fed. Cir. 2008). Moreover, “[t]he relevant inquiry ‘is the purpose of the limitation in the claimed invention.’” *Id.* at 34 (quoting *Cohesive*, 543 F.3d at 1368).

Petitioner points to six disclosures of the ’742 patent that support its contention that “about 0.025%” includes “0.03%.” First, Petitioner points to the Abstract of the ’742 patent, which states that its invention is directed to “low concentrations” of brimonidine, which the Specification defines as “concentrations from between about 0.0001% to about 0.05%; more preferably, from about 0.001% to about 0.025%; even more preferably, from about 0.01% to about 0.025%; and even more preferably, from about 0.01% to about 0.02% weight by volume.” *Id.* at 28 (quoting Ex. 1001 col. 3, ll. 61–65, and citing Ex. 1003 ¶ 65).

Second, argues Petitioner, the Specification identifies concentration ranges that from 0.010% and 0.015% to about 0.05% brimonidine as “preferred” embodiments. Pet. 29 (citing Ex. 1001, col. 12, ll. 60–63, col. 14, ll. 14–16; Ex. 1003 ¶ 66). Petitioner also notes that the Specification identifies brimonidine as a “selective α -2 agonist” and that in a “preferred embodiment” the concentration of the “the selective α -2 adrenergic receptor agonist” is in a range up to “about 0.035%.” *Id.* (quoting Ex. 1001, col. 5, ll. 52–54, col. 9, ll. 14–16, and citing Ex. 1003 ¶ 67).

Third, Petitioner points to Figure 4E of the Specification, which depicts the left eye of a patient “after being treated with a composition of the present invention comprising brimonidine at 0.033%.” Pet. 30 (quoting Ex. 1001, col. 3, ll. 30–33, Fig. 4E). Petitioner notes that the Specification states that the application of 0.033% brimonidine did not result in rebound

hyperemia, an asserted problem in the prior art. *Id.* (citing Ex. 1001, col. 20, ll. 17–19, Ex. 1003 ¶ 69).

Fourth, and relatedly, Petitioner asserts that brimonidine is “a known selective alpha 2 agonist [] associated with significant rebound hyperemia (primary or delayed onset vasodilation) in its current concentration range for treating glaucoma of about 0.1% to 0.2%.” Pet. 30 (citing Ex. 1001, col. 2, ll. 2–8; Ex. 1003 ¶ 70). Petitioner argues that a person of ordinary skill in the art would understand that, compared to the recited prior art range of “about 0.1% to 0.2%,” a concentration of “0.03%” accomplishes a reduction in brimonidine concentration that “is the purpose of the *limitation* in the claimed invention.” *Id.* (quoting *Cohesive*, 543 F.3d at 1368).

Fifth, Petitioner argues that the Specification does not disclose that keeping the brimonidine concentration below 0.03% is critical, and notes that Figure 2 shows that a concentration of 0.03% is included in the range where net vasoconstriction benefits” are the highest. Pet. 30 (citing Ex. 1001, Fig. 2; Ex. 1003 ¶ 71).

Sixth, Petitioner asserts that, from the perspective of a pharmaceutical formulator, “about 0.025%” includes 0.03% because, as the upper limit of a range, “about 0.025%,” rounded to two decimal points, is “0.03%”. Pet. 31 (citing Ex. 1003 ¶ 72). Petitioner contends that a skilled artisan would expect, in the context of the ’742 patent, that it would be difficult to distinguish between the clinical effect of 0.025% and 0.03% brimonidine. *Id.*

Patent Owner argues that the Specification of the ’742 patent separately discloses concentrations of “about 0.025%” and “about 0.03%” within the broader concentration range of less than 0.05% brimonidine.

Prelim. Resp. 30. Patent Owner notes that, in two successive paragraphs, the Specification discloses using in related applications “about 0.001% to about 0.025%” brimonidine and “about 0.001% to about 0.03%” brimonidine. *Id.* (quoting Ex. 1001, col. 8, ll. 46–55, 56–63, also citing Ex. 1001, Ex. 3 (describing the use of a composition containing 0.03% brimonidine)). According to Patent Owner, a person of ordinary skill in the art would understand that, because the concentrations are separately described, “about 0.025%” is not the same as “about 0.03%.” *Id.*

Furthermore, argues Patent Owner, the Specification discloses that brimonidine at a concentration of 0.025% reduces redness without significant rebound hyperemia (that is, the development of redness in an eye after a temporary occurrence of whitening). Prelim Resp. 31 (citing Ex. 1001, cols. 13–14, ll. 65–5, col. 14, ll. 23–31, col. 9, ll. 20–24). Patent Owner asserts that the ’742 Specification thus effectively draws a further distinction between “about 0.025%” and 0.03% brimonidine by noting that rebound hyperemia begins to increase at a concentration of brimonidine around 0.03%. *Id.* (citing Ex. 1001, col. 19, ll. 52–54).

“When ‘about’ is used as part of a numeric range, the use of the word “‘about’” avoids a strict numerical boundary to the specified parameter.” *Cohesive*, 543 F.3d at 1368 (internal quotations omitted). When “about” is used to define the limit of a numerical range, the extension beyond the stated number depends on what “a person having ordinary skill in the art ... would reasonably consider ‘about ...’ to encompass.” *Monsanto Tech. LLC v. E.I. DuPont de Nemours & Co.*, 878 F.3d 1336, 1342 (Fed. Cir. 2018). Furthermore, when determining how far beyond the claimed range the term “about” extends the claim, “[w]e must focus ... on the criticality of the

[numerical limitation] to the invention.” *Ortho–McNeil Pharm., Inc. v. Caraco Pharm. Labs., Ltd.*, 476 F.3d 1321, 1327 (Fed. Cir. 2007).

“Extrinsic evidence of meaning and usage in the art may be helpful in determining the criticality of the parameter.” *Id.* at 1326 (quoting *Pall Corp. v. Micron Separations, Inc.*, 66, F.3d 1211, 1217 (Fed. Cir. 1995)).

At this stage of the proceeding, and on this record, we find Petitioner’s reasoning that the claim term “about 0.025%” includes 0.03% to be more persuasive. As Petitioner points out, the Specification discloses a number of embodiments with concentration ranges of brimonidine that include both values. Furthermore, Patent Owner has not persuasively pointed to any disclosures of the ’742 patent that expressly support the criticality of 0.025% brimonidine as the upper end of the concentration range. Indeed, the passage pointed to in this respect by Patent Owner states:

FIG. 6 depicts a graphical representation of a finding of the present invention that an increased rebound hyperemia begins at around 0.03% for brimonidine. It thus demonstrates that the net effectiveness of brimonidine as a decongestant is greatest between about 0.01% and about 0.03%; preferably, between about 0.012% and about 0.02%.

Ex. 1001, col. 19, ll. 52–57. This passage does not expressly or implicitly disclose the criticality of “about 0.025%” as the upper limit of the effective range of brimonidine concentration.

Figure 6 of the '742 patent is reproduced below:

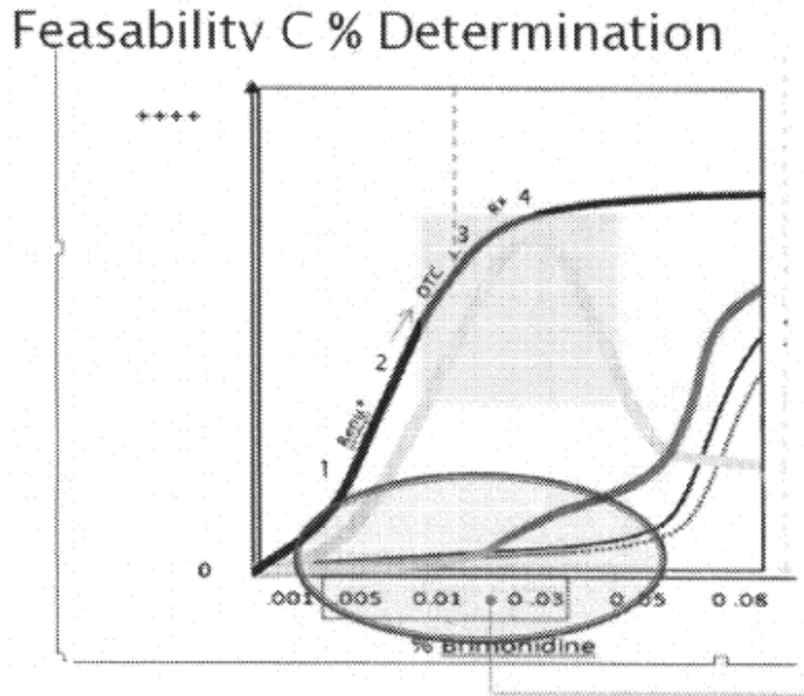


Figure 6 of the “742 patent depicts a graph entitled “Feasability C% Determination.”

Despite being labeled “Feasability C% Determination,” Figure 6 has no legend explaining what the various line plots represent or what the oval is highlighting. Patent Owner relies on the teaching that Figure 6 demonstrates that increased rebound hyperemia “begins at around 0.03% for brimonidine.” Prelim. Resp. 26. But it is unclear which illustrated function of Figure 6 supports that assertion, and the Specifications of those patent applications do not explain, either.

As further evidence that “about 0.025%” does not exclude 0.03% brimonidine, Figure 4E of the references cited by Patent Owner illustrates that, four hours after a third application of a concentration of 0.033% brimonidine, there is no indication of rebound hyperemia. *See, e.g.,* Ex.

2021, Fig. 4e, ¶ 186. This therefore suggests that increased hyperemia may not necessarily occur until the brimonidine concentration exceeds 0.03%.

Finally, absent expert testimony to the contrary, we credit the testimony of Dr. Laskar who opines that a person of ordinary skill in the art would understand that “about 0.025%” includes 0.03% because of rounding and because it would be difficult to distinguish between the clinical effect of “about 0.025%” and 0.03%. Ex. 1003 ¶ 70.

Because Petitioner has persuasively argued that a person of ordinary skill in the art would not recognize any criticality of the five-thousandths weight percentile difference between 0.025% and 0.03% from the teachings of the ’742 Specification, for the purposes of this Decision, we construe the claim term “about 0.025%” as including “0.03%.”

2. “ocular condition”

Petitioner argues that the ’742 patent defines “ocular condition” broadly and without limitation. Pet. 31 (citing Ex. 1001, col. 12, ll. 14–49). Petitioner therefore urges us to construe “ocular condition” as including, without limitation eye redness, glaucoma (including open-angle glaucoma); elevated intraocular pressure, also known as ocular hypertension, postoperative reduction of subconjunctival hemorrhage and hyperemia after refractive surgery such as LASIK and radial keratotomy, subconjunctival hemorrhage and hyperemia prophylaxis prior to refractive surgery such as LASIK and radial keratotomy, and redness in the eye following LASIK or radial keratotomy. *Id.* (citing Ex. 1001, col. 12, ll. 14–49; Ex. 1002 ¶ 47).

Patent Owner makes no argument with respect to construction of this claim term, other than to note that the phrase would be understood by a skilled artisan to have its ordinary meaning consistent with the Specification.

Given the capacious disclosures of the Specification of the '742 patent in this respect, we find Petitioner's proposed construction to be reasonable. *See* Ex. 1001, col. 12, ll. 14–52. We consequently construe, for the purposes of this Decision, the claim term “ocular condition” as including, without limitation, “eye redness, glaucoma (including open-angle glaucoma); elevated intraocular pressure, also known as ocular hypertension, postoperative reduction of subconjunctival hemorrhage and hyperemia after refractive surgery such as LASIK and radial keratotomy, subconjunctival hemorrhage and hyperemia prophylaxis prior to refractive surgery such as LASIK and radial keratotomy, and redness in the eye following LASIK or radial keratotomy.”

3. Additional claim construction

Reviewing the present record, the panel the panel concludes that no other claim term needs express construction for the purposes of this Decision. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (per curiam) (claim terms need to be construed “only to the extent necessary to resolve the controversy” (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

B. A Person of Ordinary Skill in the Art

Petitioner contends that a person of ordinary skill in the art would have been a composite person (or team) that included a medical doctor and a pharmaceutical formulator. Pet. 15 (citing Ex. 1002 ¶ 26; Ex. 1003 ¶ 29). Petitioner asserts that the medical doctor would have been an ophthalmologist with at least three to four years of experience in LASIK surgery, clinical trials, and U.S. FDA regulation of eye products, and had experience in the use of topical brimonidine, apraclonidine; and topical vasoconstrictors such as naphazoline and tetrahydrozoline. *Id.* (citing Ex. 1002 ¶ 26). Petitioner contends that the pharmaceutical formulator would have had a doctoral degree in pharmaceuticals, or a related degree, and at least three to five years of experience developing eye drop formulations for clinical trial and regulatory approval. *Id.* (citing Ex. 1003 ¶ 29).

Patent Owner does not contest this definition in its Preliminary Response, stating it does not take a position at this time regarding the qualifications of the person of ordinary skill in the art. Prelim. Resp. 29. Patent Owner further notes that Petitioner's characterization of a person of ordinary skill in the art goes beyond that of ordinary skill. *Id.*

We find Petitioner's proposed characterization to be reasonable and consequently adopt Petitioner's definition for the purposes of this Decision.

C. Ground I: Alleged Anticipation of Claims 1–2 by Gil

1. Overview of Gil (Ex. 1004)

Gil was published September 25, 2001, and issued from US Appl. Ser. No. 09/783,160 filed on February 14, 2001. Ex. 1004, code 21, 22. Gil

claims the priority benefit of provisional application Ser. No. 60/182,609, filed on February 15, 2000. *Id.* at code 60.

Gil is directed to:

A method for alleviating ocular surface pain in a mammalian eye comprising administering to a mammalian eye having ocular surface pain an amount of brimonidine effective to alleviate the ocular surface pain.

Id., claim 1.

Gil teaches that an effective dose of brimonidine to provide ocular pain relief is between 0.01% and 0.5%. Ex. 1004, col. 3, ll. 46–49. Gil further teaches that brimonidine relieves pain associated with corneal injuries, and that ocular responses characteristic of neurogenic inflammation, include redness and pupillary constriction. *Id.* at col. 2, ll. 52–54, col. 5, ll. 38–39.

2. Anticipation of Claims 1–2 by Gil: Petitioner’s Contentions

a. Claim 1

Petitioner argues that the disclosures of Gil anticipate each of the limitations of claims 1–2. Pet. 32–36.

i. **[1.P] A method for reducing eye redness**

Petitioner argues that Example 1 of Gil discloses administration of 0.03% brimonidine is inherently a method “for reducing eye redness.” Pet. 34 (citing Ex. 1002 ¶ 55 (“Whether intended or not, the administration of 0.03% brimonidine to the radial keratotomy patients in Example 1 of [Gil] is a method for reducing eye redness”)).

ii. [1.1] “consisting essentially of administering brimonidine”

Petitioner contends that Example 1 of Gil compares administration “brimonidine and placebo”: brimonidine is the only drug identified. Pet. 34 (citing Ex.1004, col. 4, ll. 46–47; Ex. 1002 ¶ 57). Petitioner also notes that Example 1 of Gil also discloses that “brimonidine is administered as a 0.03% ophthalmic solution” and that the “preferred vehicle” of Gil “is purified water.” *Id.* at 35 (citing Ex. 1004, col. 4, ll. 52–53, col. 4, ll. 4–5; Ex. 1003 ¶ 77). Petitioner asserts that, in the context of a vasoconstrictor eye drop this indicates “consisting essentially of brimonidine.” *Id.*

iii. [1.2] “to a patient having an ocular condition”

Petitioner contends that a person of ordinary skill in the art would have understood “ocular condition” to include, without limitation, postoperative reduction of subconjunctival hemorrhage and hyperemia after LASIK and radial keratotomy, subconjunctival hemorrhage and hyperemia prophylaxis prior to LASIK and radial keratotomy, and redness in the eye following LASIK or radial keratotomy. Pet. 35 (citing Ex. 1001, col. 12, ll. 14–49; Ex. 1002 ¶ 58). Petitioner argues that administration of brimonidine in Example 1 of Gil to refractive surgery patients discloses this limitation. *Id.* (citing Ex. 1004, Ex. 1, Ex. 1002 ¶ 59).

iv. **[1.3] “wherein brimonidine is present at a concentration between about 0.001% weight by volume and about 0.05% weight by volume”**

Petitioner asserts that concentrations disclosed by Gil are weight per unit volume. Pet. 35 (citing Ex. 1004, col. 3, ll. 48; Ex. 1003 ¶¶ 78–79). Petitioner contends that a skilled artisan would have understood the 0.03% solution in Example 1 of Gil as “weight by volume.” *Id.* at 36 (citing Ex. 1003 ¶¶ 78–79). Petitioner further argues that, given brimonidine’s solubility, it would have been routine to formulate a brimonidine solution anywhere in the range from 0.001% to 0.05%. *Id.* (citing Ex. 1033, Tables I, II; Ex. 1003 ¶¶ 102–103).

b. Claim 2

Claim 2 depends from claim 1, and Petitioner incorporates the arguments made with respect to claim 1 by reference into claim 2. Pet. 36

i. **[2.1] “wherein brimonidine is present at a concentration between about 0.001% to about 0.025% weight by volume”**

Petitioner argues that “between about 0.001% to about 0.025% weight by volume,” includes “0.03%,” as taught by Example 1 of Gil. Pet. 36 (citing Ex. 1004, col. 4, ll. 48–52; Ex. 1003 ¶ 73; *see also* Section III.A.1 *supra*).

3. Patent Owner’s Preliminary Response

Patent Owner responds that Gil is directed to the use of brimonidine to treat ocular pain. Prelim. Resp. (citing, e.g., Ex. 1004, Title, Abstr.). With

respect to Petitioner’s contention that Gil inherently discloses eye redness reduction, Patent Owner argues that, to establish inherent anticipation, the Petitioner must prove that all of the elements of claims 1 and 2 necessarily and inevitably flow from the elements explicitly disclosed by Example 1. *Id.* at 37 (citing *Endo Pharm. Sols., Inc. v. Custopharm Inc.*, 894 F.3d 1374, 1381 (Fed. Cir. 2018); *Galderma Labs., L.P. v. Teva Pharms. USA, Inc.*, 799 F. App’x 838, 845 (Fed. Cir. 2020)). Petitioner asserts that, because Example 1 is silent as to redness reduction, or even whether the subjects had redness in the first place, the Petitioner’s argument rests entirely on mere “probabilities or possibilities,” which cannot establish anticipation. *Id.* (citing Ex. 1004, cols. 4–5, ll. 66–2; also citing *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011) (citing *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)).

Patent Owner argues further that, because there is no basis in Example 1 to conclude that the patients undergoing unilateral radial keratotomy had eye redness, the Petitioner relies on a reference describing a different study, with different patients undergoing LASIK. Prelim. Resp. 39 (citing Pet. 33–34 (citing Ex. 1025⁷)). However, argues Patent Owner, a 2013 study on patients with different ocular maladies cannot inform one of anything regarding the condition of the entirely different patient population in Example 1 of Gil. *Id.*

⁷ T.A. Pasquali, *Dilute Brimonidine to Improve Patient Comfort and Subconjunctival Hemorrhage After LASIK*, 29(7) J. REFRACT. SURG. 469–75 (2013) (Ex. 1025).

Patent Owner also argues that Example 1 of Gil administered brimonidine at a concentration of 0.03%, whereas Claim 2 recites a concentration of “about 0.025%” brimonidine at its upper limit, which does not include 0.03%. Prelim Resp. 39.

3. Analysis

We find that Petitioner has established a reasonable likelihood of prevailing at trial, and that Patent Owner’s arguments are insufficient to overcome that likelihood.

As an initial matter, we have already explained why we construe, for the purposes of this Decision, the claim term “about 0.025%” includes 0.03%. *See* Section III.A.1. *supra*. Patent Owner’s argument that Gil does not teach “about 0.025%” is therefore not persuasive for purposes of this Decision.

A claim is unpatentable under 35 U.S.C. § 102 only when “every element and limitation of the claim was previously described in a single prior art reference, either expressly or inherently, so as to place a person of ordinary skill in possession of the invention.” *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1082 (Fed. Cir. 2008). With respect to Petitioner’s argument that Gil inherently discloses the preamble limitation reciting a “method for reducing eye redness,” we agree that, although Gil teaches that “[o]cular responses characteristic of neurogenic inflammation, including redness and pupillary constriction, are also observed in rabbits following external stimuli,” Example 1 of Gil does not expressly teach that administration of 0.03% brimonidine reduces redness in the subject patients. *See* Ex. 1004, col. 5, ll. 38–40.

Nevertheless, we do not agree with Patent Owner that Gil teaches only the reduction of ocular pain *via* administration of brimonidine in the claimed concentrations. Gil discloses that a person of skill in the art would understand that inflammation of the eye is accompanied by both redness and pain, and expressly discloses that its invention is directed to “the topical application of brimonidine for treating ocular pain and *neurogenic inflammation*.” *Id.* at col. 1, ll. 11–13. Gil also discloses that “neuropeptides enhance inflammatory reactions in the injured tissue, *contributing to vasodilation, edema, and increased vascular permeability*, this phenomenon is called ‘neurogenic inflammation.’” *Id.* at col. 1, ll. 40–43. We find that a skilled artisan would understand that “neurogenic inflammation,” and particularly “vasodilation, edema, and increased vascular permeability” are proximal causes of eye redness. *See id.* at col. 5, ll. 38–40.

Furthermore, and as Petitioner argues, the ’742 Specification also expressly teaches that administration of doses of brimonidine of 0.02–0.033% resulted in redness reduction. *See* Ex. 1001, cols. 19–20, ll. 65–25. Although Gil is generally silent with respect to redness reduction, using pain as an indicator of neurogenic inflammation, the ’742 Specification demonstrates that application of 0.03% brimonidine would also necessarily reduce redness when administered to patients with an ocular condition. *See also* Ex. 1025. We therefore conclude that Petitioner has established a reasonable likelihood of success in prevailing at trial with respect to at least one claim upon Ground 1.

4. Summary

Having determined that Petitioner has established a reasonable likelihood of success in establishing at trial that claim 1 is unpatentable under 35 U.S.C. § 102 as anticipated by Gil (Ground I of the Petition), we consequently institute trial on claims 1–6 for all of the Grounds set forth in the Petition. *See SAS Institute, Inc. v. Iancu*, 138 S.Ct. 1348, 1354–55 (2018) (holding that, when *inter partes* review is instituted, the Board shall issue a final written decision with respect to the patentability of any patent claim challenged by the petitioner). We add below our comments on the remaining grounds for guidance to the parties.

D. Ground II: Alleged Anticipation by Walters

1. Overview of Walters (Ex. 1005)

Walters is a presentation abstract published in the Annual Meeting Abstract Issue of Investigative Ophthalmology & Visual Science, and was publicly available at least on March 28, 1991. *See* Ex. 1005, 1. Walters is therefore prior art to the '742 patent.

Walters discloses administering 0.02% of a compound designated “AGN 190342-LF” to patients with open-angle glaucoma or ocular hypertension. Ex. 1005. Walters does not identify “AGN 190342-LF” as brimonidine. Petitioner cites a number of exhibits that identify AGN 190342-LF as

brimonidine. *See* Pet. 37–39 (citing Ex. 1015⁸; Ex. 1034⁹; Ex. 1029¹⁰; Ex. 1030¹¹; Ex. 1028¹²; Ex. 1031¹³; Ex. 1035¹⁴).

2. Anticipation of Claims 1–2 by Walters: Petitioner’s contentions

Petitioner argues that the disclosures of Walters anticipate each of the limitations of claims 1 and 2. Pet. 40–43.

⁸ P. B. M. W. M. Timmermans, *Structure-Activity Relationships in Clonidine-Like Imidazolidines and Related Compounds*, 3(1) Prog. Pharmacol. 21–60 (1980) (“Timmermans”) (Ex. 1015).

⁹ C. Du-Shieng et al., *Corneal and Conjunctival/Scleral Penetration of p-aminoclonidine, AGN 190342, and Clonidine in Rabbit Eyes*, 9(11) CURRENT EYE RES. 1051–059 (1990) (“Du-Shieng”) (Ex. 1034).

¹⁰ R. David et al., *Brimonidine in the Prevention of Intraocular Pressure Elevation Following Argon Laser Trabeculoplasty*, 111 ARCH. OPHTHALMOL. 1387–390 (1993) (“David”) (Ex. 1029).

¹¹ Huang et al. (US 2005/0244463 A1, November 3, 2005) (“Huang”) (Ex. 1030).

¹² J. Burke et al., *Adrenergic and Imidazoline Receptor-Mediated Responses to UK-14,304-18 (Brimonidine) in Rabbits and Monkeys: A Species Difference*, 763 ANNALS N.Y. ACAD. SCIS. 78–95 (1995) (“Burke”) (Ex. 1028).

¹³ Michael Weintraub, M.D., *letter to Dr. Adelbert L. Stagg, Ph.D.*, dated “September (illegible), 199(illegible)” (“Stagg letter”) (Ex. 1031).

¹⁴ J. Burke et al., *Preclinical Evaluation of Brimonidine*, 41 (Supp. 1) SURVEY OF OPHTHALMOL. S9-S18 (1996) (“Burke 2”) (Ex. 1035).

a. Claim 1

i. [1.P] “A method for reducing eye redness”

Petitioner argues that Walters discloses this limitation because 0.02% brimonidine falls within the range in claim 1 of the '742 patent, and because the '742 patent admits that administration of 0.02% brimonidine is a method “for reducing eye redness.” Pet. 40 (citing *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1352, 1367 (Fed. Cir. 2012) (holding that an effective concentration recited in an independent claim must include concentration range recited in dependent claim)). Petitioner notes that Figures 4C and 4D of the '742 patent illustrate administration of 0.02% brimonidine as a method of the “present invention.” *Id.* (citing Ex. 1001, col. 3, ll. 20–29); Ex. 1002 ¶ 71).

Petitioner further asserts that the 0.02% “AGN 190342-LF” (i.e. brimonidine) disclosed by Walters falls within the “about 0.015% to about 0.02%” range disclosed as “even more” preferred by the '742 patent. Pet. 41 (citing Ex. 1001, col. 14, ll. 14–18; Ex. 1003 ¶ 89). Petitioner contends that, because of its activity as a vasoconstrictor, the administration of 0.02% brimonidine disclosed by Walters reduced redness by causing vasoconstriction of the red vasculature in the eyes of the patients in Walters 1991. *Id.* (citing Ex. 1002 ¶ 71). Petitioner points to the Declaration of its Declarant, Dr. Sher, who opines that the administration of 0.02% brimonidine in Walters is inherently a method “for reducing eye redness.” *Id.* (citing Ex. 1002 ¶ 72).

ii. [1.1] “consisting essentially of administering brimonidine”

Petitioner argues that Walters discloses comparing brimonidine “0.08, 0.02% and vehicle,” with no mention of any other drug. Pet. 41-42 (quoting Ex. 1005, 4, and citing Ex. 1002 ¶ 74).

iii. [1.2] “to a patient having an ocular condition”

Petitioner contends that the patients in Walters had an ocular condition as defined in the '742 patent, i.e., “open-angle glaucoma or ocular hypertension.” Pet.42 (citing Ex.1002 ¶ 74; *see* Ex. 1005, 4).

iv. [1.3] “wherein brimonidine is present at a concentration between about 0.001% weight by volume and about 0.05% weight by volume”

Petitioner argues that Walter discloses this limitation because a person of ordinary skill in the art would have understood that “AGN 190342-LF” is brimonidine and that the brimonidine concentration percentages disclosed by Walters are “weight by volume,” because that is the standard understanding when no units are given. Pet. 42 (citing Ex. 1003 ¶¶ 84, 85). Petitioner also contends that it would have been routine for a skilled artisan to formulate a brimonidine solution anywhere in the range between 0.001% and 0.05%, including 0.02%. *Id.* at 43 (citing Ex. 1003 ¶¶ 102–103).

b. Claim 2

Claim 2 depends from claim 1 and adds the following limitation:

- i. **[2.1] “wherein brimonidine is present at a concentration between about 0.001% to about 0.025% weight by volume”**

Petitioner repeats its arguments with respect to limitation [1.3] *supra*, contending that it would have been routine for a person of ordinary skill in the art to formulate a brimonidine solution anywhere in the range between 0.001% and 0.05%, including 0.02%. Pet. 44 (citing Ex. 1003 ¶¶ 102–103

3. Patent Owner’s Preliminary Response

Patent Owner argues that Walters discloses a study in which administration of the test compound resulted in a reduction of intraocular pressure (“IOP”) and is silent with respect to “redness” or the “reduction of redness.” Prelim Resp. 40 (citing Ex. 1005, 4). Patent Owner argues that Petitioner has failed to provide sufficient proof that practicing the protocol described in Walters would have necessarily and inevitably resulted in the claimed invention. *Id.* (citing, e.g., *Sandoz Inc. v. EKR Therapeutics, LLC*, IPR2015-00008, Paper No. 20 at 7 (P.T.A.B. April 24, 2015) (denying institution for lack of data to support inherency theory)).

Patent Owner argues that, even assuming that some patients may have had eye redness, it is not known whether those patients only received the 0.08% brimonidine solution or the placebo instead of the 0.02% brimonidine solution. Prelim Resp. 41. Patent Owner notes that one cannot determine if, for example, patients included in the study took any commercially available eye whiteners, because hyperemia is a common side-effect of glaucoma medication, and thus would not have had eye redness. *Id.* (citing Ex. 2011, 1; Ex. 1001, col 8, ll. 24–37, Example 1).

According to Patent Owner, because there are no disclosures in Walters proving redness reduction, no information on the individual patient's ocular condition, no information on which dose each patient received, and no inclusion/exclusion criteria, a multitude of inferences are required to be drawn. Prelim. Resp. 41. Patent Owner asserts that the Petitioner cannot therefore satisfy its burden of proving inherent anticipation. *Id.* (citing *Kingston Tech. Co., Inc. v. SPEX Techs., Inc.*, 798 F. App'x 629, 634 (Fed. Cir. 2020)).

4. Analysis

We find that Petitioner has failed to establish a reasonable likelihood of prevailing at trial, and that Patent Owner's arguments with respect to Ground 2 are persuasive. To show anticipation of a claim, "each claim element must be disclosed, either expressly or inherently, in a single prior art reference, and the claimed arrangement or combination of those elements must also be disclosed, either expressly or inherently, in that same prior art reference." *Therasense, Inc. v. Becton, Dickinson and Co.*, 593 F.3d 1325, 1332–33 (Fed. Cir. 2010). An anticipation analysis also "accommodates situations where the common knowledge of technologists is not recorded in the reference; i.e., where technical facts are known to those in the field of the invention." *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1269 (Fed. Cir. 1991). Furthermore, a reference may anticipate inherently if a claim limitation that is not expressly disclosed "is necessarily present, or inherent, in the single anticipating reference." *Verizon Servs. Corp. v. Cox Fibernet Va., Inc.*, 602 F.3d 1325, 1337 (Fed. Cir. 2010).

Independent claim 1 of the '742 patent recites “1. A method for reducing eye redness consisting essentially of administering brimonidine to a patient having an ocular condition....” Ex. 1001, col. 22, ll. 17–19. Walters discloses:

In this randomized, double-masked, pilot study, we evaluated the efficacy and safety of bilateral, twice-daily administration of AGN 190342-LF [brimonidine] 0.08%, 0.02% or vehicle in 13 patients with open-angle glaucoma or ocular hypertension. Overall mean reductions in IOP were 6.0 mm Hg (23.9%), 3.4 mm Hg (13.8%), and 2.0 mm Hg (7.2%) for the 0.08%, 0.02%, and vehicle groups, respectively, following three days of treatment.... The results of this pilot study indicate that AGN 190342-LF has potential in the treatment of elevated intraocular pressure.

Ex. 1005, 4. Although Walters discloses administration of dosages of brimonidine that are within the ranges claimed in the '742 patent to patients with ocular conditions (open-angle glaucoma or ocular hypertension), Walters is entirely silent with respect to the reduction of redness in the eyes of these patients. Nor, we find, would a person of ordinary skill in the art understand, from the disclosures of Walters, that patients with open-angle glaucoma or ocular hypertension would necessarily also experience reduction of redness after application of brimonidine. Consequently, and at this stage of the proceeding, we agree with Patent Owner that the disclosures of Walter do not inherently anticipate challenged claims 1 and 2 of the '742 patent.

5. Summary

Because we find, at this stage of the proceeding, that Walters does not anticipate, either expressly or inherently, the claims of the '742 patent, we

conclude that Petitioner has not established a reasonable likelihood of prevailing at trial.

E. Ground III: Alleged Obviousness of Claims 1–6 over Gil in view of Norden, Dean, Alphagan, and Federal Register: Petitioner's Contentions

1. Overview of Norden (Ex. 1006)

Norden is an article published in the July/August 2002 issue of the peer-reviewed Journal of Refractive Surgery, and is prior art to the '742 patent. Ex. 1006, 4. Norden teaches that brimonidine is an α -2 adrenergic agonist, and that α -2 adrenergic agonist drugs are considered strong vasoconstrictors. *Id.* Norden describes a study in which patients were administered one drop of brimonidine 15 minutes before LASIK surgery and a second drop 5 minutes before surgery. *Id.* at 5. The drops were only administered to one eye, selected arbitrarily. *Id.* LASIK surgery was subsequently performed and the amount of subconjunctival hemorrhage, hyperemia, bleeding from the micropannus, and flap slippage/wrinkling were recorded. *Id.* at 5.

Norden teaches that:

Subconjunctival hemorrhage was observed in 22 of 61 eyes (36.1 %). Three of 22 eyes (13.6%) received the prophylactic brimonidine; 19 eyes with subconjunctival hemorrhage (86.3%) did not receive brimonidine (Chi-square $P < .0001$).

Id. at 5, *see also* Table 1. Norden also teaches that:

Hyperemia developed in all but three of 61 eyes (95.1 %) (Fisher's exact $P = .2393$). The three eyes without hyperemia were in the brimonidine group. The amount of hyperemia, however, was notably lower in eyes treated prophylactically with brimonidine (Fisher's exact $P < .0001$). Eighty-four percent of

treated eyes had grade 1 or no hyperemia, as compared with just 10% of the untreated eyes.

Id. Norden also teaches that “[b]leeding from the superior micropannus occurred in four of 61 eyes (6.6%). Three of these eyes did not receive brimonidine (Fisher's exact $P=.3385$).” *Id.*, *see also* Table 2.

Norden concludes that:

These data demonstrate that brimonidine administered before LASIK can significantly reduce subconjunctival hemorrhage as well as the amount of hyperemia. By preventing bleeding, the surgeon can help prevent incomplete ablation. Bleeding can also increase postoperative patient anxiety, as LASIK is sometimes perceived as a cosmetic procedure and patients prefer to look normal after surgery.

....

This study suggests that brimonidine minimizes subconjunctival hemorrhage without inducing flap slippage. Given the findings of this prospective trial, the efficacy of prophylactic brimonidine for reducing LASIK-related bleeding and flap complications deserves further study in more eyes.

Ex. 1006, 7.

2. Overview of Dean (US 6,242,442 B1) (Ex. 1007)

Dean issued on June 5, 2001 and claims priority to PCT/US99/28987, filed on December 7, 1000. Ex. 1007, codes 21, 86). Dean is directed to “[m]ethods and compositions for treating ocular conditions which find their etiology in compromised ocular blood flow with brinzolamide and brimonidine.” *Id.*, Abstr.

Specifically, Dean teaches that:

Brimonidine is a potent and relatively selective α_2 agonist which has been shown to effectively lower IOP in rabbits, monkeys and man. Upon topical ocular administration brimonidine causes vasoconstriction in scleral vessels. However, brimonidine does not appear to be a vasoconstrictor in vessels in the back of the eye.

Ex. 1007, col. 2 ll. 33–42. Dean also teaches brimonidine administration at concentrations of 0.01%–0.2% by weight. *Id.* at col. 5, ll. 33–35.

3. Overview of Alphagan (Ex. 1008)

Alphagan is an entry in the Physician’s Desk Reference, vol. 52, published in 1998. Alphagan teaches that “Alphagan 0.2%” is a brimonidine tartrate ophthalmic solution that is a relatively selective alpha-1 adrenergic agonist. Ex. 1008, 3. Alphagan teaches that Alphagan 0.2% “is indicated for lowering intraocular pressure in patients with open-angle glaucoma or ocular hypertension.” *Id.* Alphagan also teaches that Alphagan 0.2% may be adjusted to pH 6.3–6.5. *Id.*

4. Federal Register (Ex. 1009)

Federal Register is an entry in the Federal Register, Vol. 53, No. 43 published on March 4, 1988. Ex. 1009, 1. Federal Register teaches publication of a final rule establishing conditions for branding of over-the-counter ophthalmic drug products. *Id.* Federal Register states that vasoconstrictors can be identified as “redness reliever” or labeled with “eye redness reliever.” *Id.* at 7. Federal Register identifies several vasoconstrictors, including 2-imidazoline derivatives, naphazoline

hydrochloride (0.01 to 0.03%) and tetrahydrozoline hydrochloride (0.01 to 0.05%). *Id.* at 14.

5. Obviousness of Claims 1–6 over Gil, Norden, Dean, Alphagan and Federal Register: Petitioner’s Contentions

Petitioner argues that claims 1–6 are obvious over the disclosures of Gil in view of Norden, Dean, Alphagan, and Federal Register. Pet. 50.

Petitioner first turns to claim 3.

a. Claim 3

i. **[3.P] “A method for reducing eye redness consisting essentially of”**

[3.1] “topically administering to a patient having an ocular condition a composition

Petitioner repeats its argument with respect to Ground 1 that Example 1 of Gil discloses a method of reducing eye redness consisting essentially of topically administering a composition to a patient having an ocular condition a composition. Pet. 50 (citing Ex. 1002 ¶ 142). Specifically, argues Petitioner, Gil teaches in Example 1 that the method of reducing eye redness is the topical administration of 0.03% brimonidine drops into the eyes of patients undergoing radial keratotomy surgery, and no other drugs, compositions or steps are identified for reducing eye redness. *Id.*

Petitioner next argues that Norden also teaches “a method of reducing eye redness consisting of topically administering to a patient having an ocular condition a composition,” because Norden discloses anecdotal reports that some refractive surgeons now administer topical brimonidine to prophylactically reduce subconjunctival hemorrhage and improve the post-

operative appearance, and no other drugs, compositions or steps are identified in the anecdotal reports. Pet. 51 (citing Ex. 1006, 468; Ex. 1002 ¶ 142).

ii. [3.2] “to a patient having an ocular condition”

Petitioner contends that Gil and Norden 2002 both disclose administration “to a patient with an ocular condition” because they both disclose refractive surgery patients where the “ocular condition” is preoperative prophylaxis and/or the post-operative treatment of the subconjunctival hemorrhage and hyperemia caused by refractive surgery. Pet. 51 (citing Ex. 1002 ¶ 145).

iii. [3.3] “a composition consisting essentially of brimonidine”

Petitioner argues that Example 1 of Gil teaches this limitation because the study medication is a 0.03% brimonidine ophthalmic solution, no other active ingredient is listed, and the “preferred vehicle” is purified water. Pet. 52 (citing Ex. 1002 ¶ 146). Furthermore, Petitioner contends, in Example 4 of Gil, brimonidine is the only active ingredient of the ophthalmic formulation, and that brimonidine is effective in reducing neurogenic responses, such as redness. *Id.* (citing Ex. 1002 ¶ 147).

Petitioner asserts that Norden also teaches a composition consisting essentially of brimonidine because anecdotal reports of refractive surgeons administering brimonidine before LASIK surgery state that brimonidine helps to prevent bleeding-related problems in the anterior segment. *Id.* (citing Ex. 1002 ¶ 148).

According to Petitioner, a person of ordinary skill in the art would have been motivated to use only a single active ingredient in the method of treatment so as to avoid possible negative side effects from a second drug and possible negative drug interactions. Pet. 52 (citing Ex. 1002 ¶ 149). Petitioner also contends that a person of skill in the art would have had a reasonable expectation that brimonidine could be successfully used as a vasoconstrictor in topical eye drops to reduce redness, because: (1) 2-imidazoline derivatives had been in commercial use for decades as vasoconstrictor compounds in redness reducing topical eye drops; (2) brimonidine was a 2-imidazoline derivative and was known to be a potent vasoconstrictor; (3) brimonidine was known to exert its vasoconstrictor activity on the front but not the back portion of the eye; (4) brimonidine was approved by the U.S. FDA for use in a topical eye drop for over ten years; (5) brimonidine was considered to be safe, well tolerated and with a low rate of allergic response; and (6) it had been reported that brimonidine drops dripping from the eye caused “blanching,” i.e. whitening, of the skin on the cheeks. *Id.* at 53.

iv. [3.4] “into ocular tissue”

Petitioner argues that Example 1 of Gil teaches that, subsequent to surgery, “each subject receives one drop of the study medication in the operated eye.” Pet. 54 (quoting Ex. 1004, col. 4, ll. 58–59). Petitioner asserts that a person of ordinary skill in the art would have understood this to mean topical administration to the eye. *Id.* (citing Ex. 1002 ¶ 152).

Petitioner argues that Norden teaches that there were “many anecdotal reports that the use of topical brimonidine before laser *in situ*

keratomileusis (LASIK) can help prevent bleeding–related problems in the anterior segment.” Pet. 54 (Ex. 1006, 468). Petitioner notes that, in the clinical study of Norden, “ophthalmic technicians applied the brimonidine drops.” *Id.* (citing Ex. 1006, 469). Petitioner contends that a skilled artisan would have understood this to mean topical administration to the surface of the eye. *Id.* (citing Ex. 1002 ¶ 152).

Petitioner also contends that Federal Register shows that, when used as vasoconstrictor compounds to reduce eye redness, 2-imidazoline compounds, naphazoline and tetrahydrozoline, are applied topically to the eye. Pet. 54 (citing Ex. 1009, 14; Ex. 1003 ¶ 96). Petitioner further argues that a person of ordinary skill in the art would have understood that topical administration to the surface of the eye is a way to minimize systemic side effects by applying a relatively small amount of brimonidine directly to the part of the body where the brimonidine is needed. *Id.* at 55 (citing Ex. 1002 ¶ 152).

v. [3.5] “wherein pH of said composition is between about 5.5 and about 6.5”

Petitioner next argues that Alphagan expressly teaches that brimonidine eye drops with a pH of 6.3 to 6.5. Pet. 55 (citing Ex. 1008, 3; Ex. 1003 ¶ 98).

Petitioner argues further that the pKa of brimonidine was known in the art to be about 7.78. Pet. 55 (citing Ex. 1003 ¶ 99; Ex. 1033¹⁵, col. 13, l. 59). Petitioner argues that a formulator of ordinary skill would have understood that a pH below the pKa would help maintain brimonidine at the

¹⁵ Olejnik et al. (US 6,562,873 B2, May 13, 2003) (“Olejnik”). Ex. 1033.

eye surface for a longer time, which would be a useful property in a topical vasoconstrictor eye drop. *Id.* (citing Ex. 1003 ¶ 99). Petitioner also notes that Olejnik teaches that the solubility of brimonidine tartrate is relatively high at pH 5.55, lower at pH 6.14, and much lower at pH 6.57. *Id.* (citing Ex. 1033, Table II; also Ex. 1003 ¶ 100). Petitioner therefore contends that a person of skill in the art would have understood from Olejnik that, because pH can change over time in storage, brimonidine tartrate solution in the range of pH 5.55 to 6.14. *Id.* (citing Ex. 1003 ¶ 100).

vi. [3.6] “wherein said brimonidine concentration is between about 0.001% and about 0.025% weight by volume”

Petitioner next argues that, as argued in Section III.A.1 *supra*, the limitation reciting “between about 0.001% and about 0.025% weight by volume,” includes “0.03%.” Pet. 56. Petitioner contends that there is a presumption of obviousness when the claimed concentration range overlaps a range disclosed in the prior art. Pet. 57 (citing, e.g., *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955)). Petitioner further notes that Example 4 of Gil teaches a range of “0.01% to 0.5%” brimonidine. *Id.* (citing Ex. 1002 ¶ 156, 157). Petitioner also notes that Example 1 of Gil teaches 0.03% brimonidine in the context of refractive surgery. *Id.* at 58 (citing Ex. 1002 ¶ 157).

Petitioner next argues that dose ranging is routine and a person of ordinary skill in the art would have been motivated to find an effective concentration while minimizing side effects. Pet. 58 (citing Ex. 1002 ¶ 158; Ex. 1003 ¶ 104). Petitioner contends that Dean teaches that 0.2% brimonidine is associated with hyperemia in some patients. *Id.* (citing Ex. 1007, col. 2, ll. 38–41; Ex. 1002 ¶ 158). Patent Owner also contends that the

cited prior art teaches that brimonidine at 0.08%, 0.2% and 0.5% was reported to “significantly” reduce intraocular pressure, an unwanted side effect in a redness reducing eye drop. *Id.* (citing EX-1002, Sher, ¶158; see Ex. 1004, 4).

b. Claim 1

Petitioner repeats its argument *supra* that claim 1 is anticipated by Gil. Pet. 60. Petitioner also argues that Claim 1 is obvious because claim 3 is encompassed by claim 1. *Id.* at 60. Petitioner notes that claim 1 is broader than claim 3, with a broader concentration range, that the composition in claim 1 does not have to be “topically administered” “into ocular tissue,” that there is no pH limitation in claim 1, and that the composition in claim 1 does not have to be formulated as an ocular drop. *Id.*

c. Claim 2

Petitioner repeats its argument *supra* that claim 2 is anticipated by Gil. Pet. 61. Petitioner argues further that Claim 2 is obvious because claim 2 is broader than claim 3. *Id.* at 60. Petitioner asserts that the composition in claim 2 does not have to be “topically administered” “into ocular tissue,” there is no pH limitation in claim 2, and the composition in claim 2 does not have to be formulated as an ocular drop. *Id.*

d. Claim 4

Claim 4 depends from claim 3 and recites, in relevant part “wherein said composition is topically administered within about 24 hours after a Lasik surgery on said patient.” Ex. 1001, col. 22, ll. 33–35.

Petitioner argues that a person of ordinary skill in the art would have been motivated to topically administer the composition within about 24 hours after a LASIK surgery for several reasons. First, argues Petitioner, both LASIK and radial keratotomy are refractive surgeries that cause the eye to appear red for a period of time after surgery. Pet. 61. Petitioner points to Norden’s statement that “patients prefer to look normal after surgery.” *Id.* (citing (Ex. 1006, 7; Ex. 1002, ¶ 170).

Second, Petitioner argues, Norden (EX-1006, p. 468) teaches that “some refractive surgeons now administer [brimonidine] prophylactically to reduce subconjunctival hemorrhage and improve the post-operative appearance.” *Id.* (quoting Ex. 1006, 7: Ex. 1002 ¶ 170).

The third argument advanced by Petitioner is that dose ranging is routine and a skilled artisan would have been motivated to find an effective concentration while minimizing side effects. Pet. 61 (citing Ex. 1002 ¶ 158; Ex. 1003 ¶ 104). Petitioner argues that it was known that 0.2% brimonidine was associated with hyperemia in some patients. *Id.* (citing Ex. 1007, col. 2, ll. 38–41; Ex. 1002 ¶ 158). Petitioner also contends that brimonidine at 0.08%, 0.2%, and 0.5% was reported to “significantly” reduce intraocular pressure, an unwanted side effect in a redness reducing eye drop. *Id.* (citing Ex. 1002 ¶ 158).

e. Claims 5 and 6

Claims 5 and 6 both depend from claims 1 and 3, respectively, and recite “wherein said ocular condition is chronic red eye.” Ex. 1001, col. 22, ll. 36–39.

Petitioner notes that the Specification of the ’742 patent does not identify what is meant by “chronic red eye,” but contends that a person of ordinary skill in the art would have understood “chronic red eye” as including eye redness caused by seasonal allergies. Pet. 62 (citing Ex. 1002 ¶ 175). According to Petitioner, eye redness due to seasonal allergies is a relatively benign ocular condition, and because of its vasoconstrictor properties, a skilled artisan would expect brimonidine to reduce eye redness in a person with this condition. *Id.* (citing Ex. 1002 ¶ 175). Petitioner therefore asserts that a person of ordinary skill in the art would have been motivated to use brimonidine to reduce eye redness in an ocular condition that was chronic red eye, and would have done so with a reasonable expectation of success. *Id.* (citing Ex. 1002 ¶176).

6. Patent Owner’s Preliminary Response

Patent Owner responds that Petitioner’s arguments are driven by impermissible hindsight analysis. Prelim. Resp. 45. Patent Owner contends that, even assuming, *arguendo*, the skilled artisans possessed the backgrounds of Petitioner’s proposed definition of a person of ordinary skill in the art, Petitioner has failed to show that such a person attempting to develop a method for reducing redness of the eye would have looked to brimonidine—a prescription glaucoma drug, with known side-effects

including redness. *Id.* at 45–46 (citing Ex. 2012¹⁶, 9) (listing “ocular hyperemia” as the second most common side effect of brimonidine).

Patent Owner contends that, although brimonidine was first approved in 1996, it was approved for lowering IOP in patients with open-angle glaucoma or ocular hypertension. Prelim. Resp. 46 (citing Pet., 19-20; Ex. 2012, 7). According to Patent Owner, as of the time of invention, no brimonidine product had been approved by the FDA for the reduction of redness; and, brimonidine products were known to elicit hyperemia. *Id.* Indeed, argues Patent Owner, a skilled artisan would have been motivated to pursue other active ingredients due to the serious adverse events associated with the use of Alphagan® and Alphagan® P (the only FDA-approved brimonidine products), including fatigue, fainting, drowsiness, hyperemia, and significant allergic reactions. *Id.* (citing Ex. 2012, 3–4, 8–10; Ex. 2014¹⁷, 2, 4). Patent Owner contends that active ingredient with this adverse event profile would have disincentivized and deterred a person of skill in the art from using brimonidine to reduce eye redness, particularly when other options existed and had already been commercialized. *Id.*

Patent Owner therefore contends that Petitioner’s arguments with respect to Ground 3, which are focused on using brimonidine at a new, unapproved dose to reduce eye redness, “smack[s] of pure hindsight, particularly where there were other products, including over-the-counter redness relievers, from which to choose.” Prelim. Resp. 46–47.

¹⁶ NDA 20-490/S-007 et al., *Alphagan® (brimonidine tartrate ophthalmic solution) 0.5%*, 3–7 (2001) (“Alphagan 2”). Ex. 2012.

¹⁷ NDA 21-262/S-018, *Alphagan® P (brimonidine tartrate ophthalmic solution) 0.1% and 0.15%*, 3–7 (2005) (“Alphagan P”). Ex. 2014.

Patent Owner argues further that a person of ordinary skill in the art would not have been motivated to pursue brimonidine because it had not previously been approved as an active ingredient in an over-the-counter product, and had only been approved for glaucoma. Prelim. Resp. 47. According to Patent Owner, Alphagan® and Alphagan® P, the only FDA-approved brimonidine products, were prescription products. *Id.* at 47–48 (citing Ex. 2012, 5, 10; Ex. 2014, 5). Patent Owner asserts that a skilled artisan would have recognized that there were numerous over-the-counter drops for reducing redness of the eye, and that seeking to market an over-the-counter product with an active ingredient that had only been approved for prescription use would present significant regulatory hurdles. *Id.* at 48.

Finally, Patent Owner argues that Petitioner relies on Allergan, ignoring the later-developed Alphagan P product, which, Patent Owner asserts, undermines Petitioner’s analysis. Prelim. Resp. 49-50. Alphagan, a 0.2% brimonidine tartrate ophthalmic solution, was replaced by Alphagan P, a 0.15% brimonidine tartrate ophthalmic solution, in 2002. *Id.* (citing Ex. 2018¹⁸). According to Patent Owner, Allergan P showed comparable efficacy with fewer adverse events. *Id.* (citing Ex. 2018¹⁹).

¹⁸ Janice M. Soreth, M.D. Director, Division of Anti-Infective and Ophthalmology Products, HFD-520, Dept. of Health and Human Services, *letter to Allergan Inc.*, 2 pp. (undated) (“Soreth letter”). Ex. 2019.

¹⁹ Healio Press Release, *Allergan to focus on Alphagan-P, discontinue Alphagan*, July 08, 2002, available at: <https://www.healio.com/news/ophthalmology/20120331/allergan-to-focus-on-alphagan-p-discontinue-alphagan> (last visited May 4, 2022) (“Allergan P Press Release”). Ex. 2018.

Furthermore, Patent Owner asserts that, whereas administration of Alphagan 0.5% resulted in conjunctival blanching in 40.9% of subjects (EX-1029 at 3), administration of Alphagan® 0.2% resulted in conjunctival blanching in just 6.8% of subjects. Prelim. Resp. 50 (citing Ex. 1031, 52). Furthermore, Patent Owner contends, there were no reported incidents of conjunctival blanching in either of the Alphagan P products (0.15% and 0.1% brimonidine). *Id.* (citing Ex. 2014, 4). Notably, Patent Owner points out, in the Alphagan® P label, blanching was not reported, but hyperemia (redness) was reported as one of the most common side effects, occurring in approximately 10-20% of subjects. *Id.* (citing Ex. 2014, 4).

Therefore, argues Patent Owner, and in light of this clinical data, a person of ordinary skill in the art would have had neither a motivation nor a reasonable expectation of success in achieving a method of reducing redness of the eye consistently essentially of administering brimonidine at a concentration between about 0.001% and about 0.05%. Prelim. Resp. 50. Patent Owner asserts that these data suggest that it was the higher concentrations of brimonidine in Alphagan® (0.5%, 0.2%) that resulted in blanching and that lower concentrations of brimonidine did not have such an effect. *Id.* (citing, e.g., *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009)).

7. Analysis

We find that Petitioner has established a reasonable likelihood of prevailing at trial upon Ground 3. We have explained our reasoning as to why we conclude that Gil likely anticipates claims 1 and 2 of the '742 patent. *See* Section III.C.3. Claims 1 and 2 are therefore also likely obvious

over Gil. *See In re McDaniel*, 293 F.3d 1379, 1385 (Fed. Cir. 2002) (holding that it is well settled that anticipation is the epitome of obviousness).

With respect to the remaining claims 3–6, we agree with Petitioner that the combined cited references likely teach or suggest the remaining limitations, for the reasons argued by Petitioner. Specifically, and most importantly, Norden teaches topical application of 0.02% brimonidine tartrate (Allergan) prophylactically in patients undergoing LASIK surgery. Ex. 1006, 4. Norden teaches that such application significantly reduces postoperative subconjunctival and superior micropannus hemorrhage, which a person of ordinary skill in the art would both understand to contribute to eye redness. *Id.* at 6. Similarly, Norden teaches that topical application of 0.2% brimonidine tartrate also significantly reduces the severity of postoperative hyperemia. *Id.* Norden concludes that:

This study suggests that brimonidine minimizes subconjunctival hemorrhage without inducing flap slippage. Given the findings of this prospective trial, the efficacy of prophylactic brimonidine for reducing LASIK-related bleeding and flap complications deserves further study in more eyes. Other vasoconstrictors, such as naphazoline (Vasocon-A), may also produce similar results and should be studied for this application.

Id. at 7. Although the concentration of brimonidine tartrate taught by Norden (0.2%) is higher than the concentration range recited in the challenged claims, at this stage of the proceeding, we credit the testimony of Petitioner’s experts stating that dose ranging studies would have been routine for a person of ordinary skill in the art. Ex. 1002 ¶¶ 125–128; Ex. 1003 ¶ 103; *see also In re Boesch*, 617 F.2d 272, 276 (C.C.P.A. 1980) (holding that “discovery of an optimum value of a result effective variable ...

is ordinarily within the skill of the art”); *see also In re Ethicon, Inc.*, 844 F.3d 1344, 1351 (Fed. Cir. 2017) (holding that “[t]he normal desire of artisans to improve upon what is already generally known can provide the motivation to optimize variables such as the percentage of a known [ingredient] for use in a known” product)). Furthermore, the Gil’s teaching of employing 0.03% brimonidine for the relief of neurogenic inflammation of the eye subsequent to radial keratotomy would also point the skilled artisan towards the claimed range.

Additionally, Alphagan teaches that the pH of 0.2% brimonidine tartrate can be adjusted to 6.3–6.5.

With respect to claim 4, Norden teaches preoperative application of brimonidine prior to Lasik surgery, and not within 24 hours after LASIK surgery. Ex. 1006, 4. However, Gil expressly teaches postoperative application of 0.03% brimonidine pre- *and* postoperatively to patients who had undergone radial keratotomy (a precursor surgical procedure to LASIK) for the alleviation of neurogenic inflammation. *See* Ex. 1004, Example 1.

With respect to claims 5 and 6, we find the question to be somewhat closer. None of the cited references expressly teach “chronic red eye” (which is not expressly defined in the ’742 Specification). Nevertheless, Gil expressly teaches application of brimonidine for neurogenic inflammation. Ex. 1004, col. 1, ll. 39–43, Example 4. The parties may wish to develop these arguments further at trial.

On this record, we do not find Patent Owner’s allegation that Petitioner’s arguments impermissibly rely upon hindsight analysis to be persuasive. *See* Prelim. Resp. 45–49. Patent Owner’s argument that brimonidine was known in the art to cause hyperemia is correct, up to a

point, but Patent Owner ignores the express teachings of Norden and Gil, which expressly teach, respectively, that application of brimonidine *decreases* redness caused by subconjunctival hemorrhage and neurogenic inflammation in eye surgery patients. *See* Ex. 1004, Example 1, 4; Ex. 1006, 6, 7. We find that these teachings would likely have motivated a skilled artisan to apply brimonidine topically to patients with an ocular condition to decrease eye redness, and with a reasonable expectation of success.

Furthermore:

Any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper.

In re McLaughlin, 443 F.2d 1392, 1395 (C.C.P.A. 1971). Patent Owner has not pointed to any knowledge that could have been gleaned only from the Specification of the '742 patent and not from the prior art. Therefore, in view of the record as presently developed at this stage of the proceeding, we are not persuaded that Petitioner impermissibly relied upon hindsight analysis.

Additionally, we fail to see the relevance of Patent Owner's argument concerning Allergan and Allergan P. *See* Prelim. Resp. 49–50. As we interpret the teachings of Exhibits 1031 and 2014, higher concentrations of brimonidine tartrate solution cause increased instances of blanching (i.e., whitening) of the sclera of the eye. If brimonidine, like other 2-imidazoline derivatives, was known to be a vasoconstrictor and “redness reducer,” increased redness reduction (whitening) of the eye with increasing

concentration of applied brimonidine would scarcely be surprising. *See* Ex. 1009, 14.

In summary, we conclude that Petitioner has established a reasonable likelihood of prevailing at trial upon Ground 3.

8. Summary

We conclude that Petitioner has established a reasonable likelihood of success at trial with respect to Ground 3, and find that Patent Owner’s arguments to the contrary are insufficiently persuasive, at this stage of the proceedings, to overcome Petitioner’s contentions.

IV. DISCRETIONARY DENIAL

A. Discretionary Denial Under 35 U.S.C. § 314(a)

Patent Owner urges us to exercise our discretion under 35 U.S.C. § 314(a) and deny institution under the Board’s precedential decision in *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 (PTAB Mar. 20, 2020) (precedential) (“*Fintiv*”). Prelim. Resp. 4–13. For the reasons discussed below, we decline to exercise discretion under 35 U.S.C. § 314(a) to deny institution of *inter partes* review.

In our precedential decision in *NHK Spring Co. v. Intri-Plex Techs., Inc.*, IPR2018-00752, Paper 8 at 19–20 (PTAB Sept. 12, 2018) (precedential), the Board held that, in the event there exists a parallel district court proceeding, in which the Petitioner asserted the same prior art and arguments, then instituting *inter partes* review “would not be consistent with ‘an objective of the AIA . . . to provide an effective and efficient alternative to district court litigation.’” *NHK* at 20 (quoting *General Plastic Ind. Co.*,

Ltd. v. Canon Kabushiki Kaisha, IPR2016-01357, Paper 19 at 16–17 (PTAB Sept. 6, 2017).

Our subsequent precedential decision in *Apple v. Fintiv*, IPR2020-00019, Paper 11 (P.T.A.B. Mar. 20, 2020) held that, as with other non-dispositive factors considered for institution under 35 U.S.C. § 314(a), an early trial date should be weighed as part of a “balanced assessment of all relevant circumstances of the case, including the merits.” *Fintiv*, 5 (citing the Consolidated Trial Practice Guide, November 2019 (“TPG”) at 58; *also citing Abbott Vascular, Inc. v. FlexStent, LLC*, IPR2019-00882, Paper 11 at 31 (PTAB Oct. 7, 2019) (declining to adopt a bright-line rule that an early trial date alone requires denial in every case)).

In *Fintiv*, the Board set forth six factors relating to whether efficiency, fairness, and the merits support the exercise of authority to deny institution in view of an earlier trial date in the parallel proceeding:

1. whether the court granted a stay or evidence exists that one may be granted if a proceeding is instituted;
2. proximity of the court’s trial date to the Board’s projected statutory deadline for a final written decision;
3. investment in the parallel proceeding by the court and the parties;
4. overlap between issues raised in the petition and in the parallel proceeding;
5. whether the petitioner and the defendant in the parallel proceeding are the same party; and
6. other circumstances that impact the Board’s exercise of discretion, including the merits.

Fintiv at 5–6.

1. *Fintiv* factor 2

If the district court’s trial date is before the projected deadline for the final written decision, the Board has generally weighed this fact in favor of exercising discretion. *See Fintiv*, Paper 11 at 9.

The parties agree that the trial date in the district court proceeding is projected to begin no earlier than the Fall of 2023, which is at least four months after the deadline to enter the Final Written Decision in this proceeding. Prelim. Resp. 6; Reply 1.

We consequently find this factor weighs against exercise of our discretion to deny institution. Indeed, we find that proceeding with this *inter partes* review may actually assist the district court, as it may benefit from our decision should the case proceed to trial. Furthermore, we find that, in view of this factor, the remaining *Fintiv* factors do not sufficiently weigh towards denial.

2. Summary

We have considered the specific facts and circumstances of this case and we find the balance of factors weighs against exercise of our discretion to deny institution.

We consequently decline to exercise our discretion under 35 U.S.C. § 314(a) to deny institution of *inter partes* review

B. Discretionary Denial of Institution under 35 U.S.C. § 325(d)

Patent Owner next argues that we should exercise our discretion to deny institution of trial under 35 U.S.C. §325(d). Prelim. Resp. 18. Under § 325(d), we have discretion to deny a petition that presents the same or substantially the same prior art or arguments as previously presented to the Office. *See* 35 U.S.C. § 325(d). In evaluating whether the factual predicate under § 325(d) is met, we consider a number of non-exclusive factors, as set forth in our decision in *Becton, Dickinson and Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential) (“the *Becton Dickinson* factors”):

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
- (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson, IPR2017-01586, Paper 8 at 17–18.

In performing an analysis under § 325(d), “the Board uses the following two-part framework: (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.... If, after review of [*Becton, Dickinson*] factors (a), (b), and (d), it is determined that the same or substantially the same art or arguments previously were presented to the Office, then factors (c), (e), and (f) relate to whether the petitioner has demonstrated a material error by the Office.” *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential). Consequently, we first turn to an analysis of Becton-Dickinson factors (a), (b), and (d) to determine whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office.

1. Becton Dickinson factors (a), (b), and (d)

Becton Dickinson factors (a) and (b) require us to determine, respectively: (a) “the similarities and material differences between the asserted art and the prior art involved during examination;” (b) “the cumulative nature of the asserted art and the prior art evaluated during examination,” and (d) “the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the

prior art or Patent Owner distinguishes the prior art.” *Becton, Dickinson*, IPR2017-01586, Paper 8 at 17.

a. Ground 1

With respect to Ground 1, Patent Owner argues that, although Gil was not before the Examiner, Dean, Lee (Ex. 2009²⁰), Cantor (Ex. 2007²¹), and Gluchowski (Ex. 2010²²) were considered by the Examiner and collectively provide the same substantive teachings as Gil. Prelim. Resp. 24.

During prosecution, the Examiner acknowledged that Dean does not teach the administration of brimonidine after LASIK surgery, and relied on Lee as teaching administration of one drop of 0.2% Alphagan to assert that a person of ordinary skill in the art “would expect with a reasonable degree of success that the conditions as set forth by Dean would also be useful post-Lasik surgery.” Prelim. Resp. 24 (citing Ex. 1024, 98).

Patent Owner next points to Gluchowski, which was considered by the Examiner and discloses a method for reducing or maintaining intraocular pressure involving the administration of an effective amount of a (2-imidazolin-2-ylammino) quinoxaline derivative—a drug class that includes brimonidine. Prelim. Resp. 25 (citing Ex. 2010, col. 1, ll. 9–16, col. 4, ll.

²⁰ J.H. Lee et al., *Efficacy of Brimonidine Tartrate 0.2% Ophthalmic Solution in Reducing Halos after Laser in situ Keratomileusis*, 34 J. CATARACT REFRACT. SURG. 963–67 (2008) (“Lee”). Ex. 2009.

²¹ L.B. Cantor, *Brimonidine in the treatment of glaucoma and Ocular Hypertension*, :2(4) Therapeutics Clin. Risk Mgmt. 337–46 (2007) (“Cantor”). (Ex. 2007).

²² Gluchowski (US 5,021,416, June 4, 1991) (“Gluchowski”). Ex. 2010.

11–15, 34–37; also citing Ex. 1001 col. 4, ll. 7–11; Ex. 1004, col. 3, ll. 25–39). Patent Owner asserts that Cantor also teaches disclosing the administration of 0.1% and 0.15% brimonidine to rabbits. *Id.* (citing Ex. 2007, 6). Patent Owner asserts that Dean, Lee, Cantor, and Gluchowski were all considered by the Examiner. *Id.*

Petitioner replies that a single reference cannot be cumulative of four references, “collectively.” Reply 3 (citing *Semiconductor Energy Laboratory Co. Ltd., v. Samsung Electronics Co., Ltd.*, 204 F.3d 1368, 1374 (Fed. Cir. 2000)). Furthermore, argues Petitioner, none of the references cited by Patent Owner, teaches administration of 0.03% brimonidine to reduce ocular inflammation caused by refractive surgery, or the use of brimonidine to reduce eye redness caused by inflammation, as taught by Gil and as relied upon by Petitioner. *Id.* (citing Pet. 45–46).

We agree with Petitioner. Dean teaches the combined use of brimonidine and brinzolamide for the treatment of “ocular conditions which find their etiology in compromised ocular blood flow.” Ex. 1007, Abstr. Dean is silent with respect to the treatment of either inflammation or eye redness. Cantor and Gluchowski are directed to the administration of brimonidine as a method of reducing IOP. *See* Ex. 2007, 1; Ex. 2010, Abstr. Lee teaches postsurgical administration of brimonidine as a means of reducing visual “halos” resulting from LASIK surgery. Ex. 2009, 4.

We consequently find that Gil was not considered by the Examiner, and the references that were considered do not teach the use of brimonidine for the treatment of eye neurogenic inflammation or redness, as taught by Gil and relied upon by Petitioner. We consequently conclude that neither Gil nor any reference teaching substantially the same material was

considered by the Examiner. And because Gil is the sole anticipatory reference of Ground 1, we therefore conclude the *Advanced Bionics* analysis of Ground 1 at this stage of the analysis.

b. Ground 2

Patent Owner implicitly acknowledges that Walters was not considered by the Examiner, but argues that the disclosures of Dean are substantively the same as the relevant disclosure of Walters. Prelim. Resp. 26. Patent Owner asserts that, as taught by Dean, open-angle glaucoma is an ocular disease that has its etiology in compromised blood flow and that brimonidine has been administered to patients with ocular hypertension. *Id.* (citing Ex. 1007, col. 3, ll. 35–44, col. 1, ll. 19–25).

Petitioner replies that, whereas Walters teaches the use of brimonidine alone to treat IOP, Dean teaches using the combination of brimonidine and brinzolamide in such treatments, and that this was the basis for the Examiner’s initial rejection of the claims. Reply 4 (citing Ex. 1024, 144). Petitioner asserts that it was the amendment of the claims to include the transition term “consisting essentially of” that overcame the Examiner’s rejection, limiting the claims to reciting administration of a single active agent. *Id.*

We agree with Petitioner that Walters was not considered by the Examiner during prosecution, and that Dean is not substantially the same as Walters because Dean expressly teaches administration of a combination of brimonidine and brinzolamide, rather than brimonidine alone, for reducing IOP. And because Walters is the sole anticipatory reference of Ground 2,

we therefore conclude the *Advanced Bionics* analysis of Ground 2 at this stage of the analysis.

c. Ground 3

Patent Owner implicitly acknowledges that Norden was not considered by the Examiner during Examination of the '742 patent, but argues that the combination of Dean and Lee includes substantively the same disclosure as Norden. Prelim. Resp. 21.

We disagree. Dean teaches the use of a combination of brimonidine and brinzolamide in the treatment of ocular conditions which find their etiology in compromised ocular blood flow, such as intraocular hypertension and open angle glaucoma. Ex. 1007, Abstr., col. 1, ll. 11–18. Lee teaches postsurgical administration of brimonidine as a means of reducing visual “halos” resulting from LASIK surgery. Ex. 2009, 4. Neither Dean nor Lee teaches the use of about 0.025% brimonidine for the treatment of eye redness in patients having an ocular condition and, consequently, cannot be considered to be “substantially the same” as Norden.

Moreover, Norden and Gil are the only references forming the basis of Ground 3 that teach the administration of brimonidine for the reduction of eye redness. Alphagan teaches that 0.2% brimonidine is indicated for the treatment of open angle glaucoma and intraocular hypertension. Ex. 1008, 3. Federal Register teaches that a number of over-the-counter compositions, including 2-imidazoline derivatives, such as naphazoline hydrochloride (0.01 to 0.03%) and tetrahydrozoline hydrochloride (0.01 to 0.05%) can be labeled as “eye redness reliever[s].” Ex. 1009 at 7. Federal Register, however, is entirely silent with respect to brimonidine.

In short, we find that Gil and Norden are the only references that are relied upon by Petitioner's Ground 3 as teaching administration of brimonidine for the reduction of eye redness reduction in individuals with an ocular condition. Furthermore, we find that neither Gil nor Norden, nor any other references cited by Patent Owner as disclosing substantially the same information, were considered by the Examiner during prosecution of the '742 patent. We therefore conclude, with respect to Ground 3, that: (1) there are substantial material differences between the asserted art and the prior art involved during examination, *viz.*, the lack of any teaching of the use of brimonidine in the reduction of eye redness in a patient with an ocular condition (*Becton Dickinson* factor (a)); (2) the cumulative nature of the asserted art and the prior art evaluated during examination did not include administration of brimonidine in the reduction of eye redness in a patient with an ocular condition (*Becton Dickinson* factor (b)); and (3) there was no significant overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art with respect to the administration of brimonidine in the reduction of eye redness in a patient with an ocular condition (*Becton Dickinson* factor (d.)). We consequently conclude our *Advanced Bionics* analysis of Ground 3 at this point.

d. Summary

Because we conclude, for all of Grounds 1–3, according to *Becton Dickinson* factors (a), (b), and (d), the same or substantially the same art or arguments were not previously presented, under the *Advanced Bionics* framework, we decline to exercise our discretion to deny institution of *inter partes* review under 35 U.S.C. § 325(d)

V. CONCLUSION

For the foregoing reasons, we conclude that the information presented in the Petition establishes a reasonable likelihood that Petitioner would prevail in showing that claims 1–6 of the '742 patent are unpatentable. Accordingly, we institute *inter partes* review of all claims on all grounds raised in the Petition.

Our determination in this Decision is not a final determination on the patentability of any challenged claims and, thus, leaves undecided any factual issues necessary to determine whether sufficient evidence supports Petitioner's contentions by a preponderance of the evidence in the final written decision. *See TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1068 (Fed. Cir. 2016) (noting that “there is a significant difference between a petitioner's burden to establish a ‘reasonable likelihood of success’ at institution, and actually proving invalidity by a preponderance of the evidence at trial”) (quoting 35 U.S.C. § 314(a) and comparing § 316(e)).

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–6 of U.S. Patent No. 8,293,742 B2 is instituted with respect to the ground set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial, which will commence on the entry date of this decision.

IPR2022-00142
Patent 8,293,742 B2

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