UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FLATWING PHARMACEUTICALS, LLC and
MYLAN PHARMACEUTICALS INC.,
Petitioners,

v.

ANACOR PHARMACEUTICALS, INC.,
Patent Owner.

Case No. IPR2018-00169[1]
U.S. Patent No. 9,566,289

PATENT OWNER'S NOTICE OF APPEAL

[1] Case No. IPR2018-01359 has been joined with this proceeding.

Notice is hereby given, pursuant to 37 C.F.R. § 90.2(a), that Patent Owner Anacor Pharmaceuticals, Inc. ("Anacor") appeals to the United States Court of Appeals for the Federal Circuit from the Final Written Decision (Paper 35) entered on June 5, 2019, as it relates to the claims of U.S. Patent No. 9,566,289 ("the '289 patent") and any finding or determination supporting or relating to that decision. A copy of the Final Written Decision is attached hereto as Exhibit A.

In accordance with 37 C.F.R. § 90.2(a)(3)(ii), Anacor indicates that the issues on appeal include, but are not limited to, the Board's determinations that claims 1 and 2 are unpatentable as obvious over WO 95/33754 ("Austin") and US 2002/0165121 ("Brehove"); that claims 4–7, 10, and 11 are unpatentable as obvious over Austin, Brehove, and U.S. Patent No. 6,224,887 ("Samour"); and that claims 3, 8, 9, and 12–15 are unpatentable as obvious over Austin, Brehove, Samour, and the *Handbook of Pharmaceutical Excipients* (3d ed. 2000).

Pursuant to 37 C.F.R. § 90.2(a), with this submission: (1) a copy of this Notice of Appeal is being filed electronically with the Patent Trial and Appeal Board in accordance with 37 C.F.R. § 42.6(b); (2) a paper copy of this Notice of Appeal, an electronic copy of this Notice of Appeal via the CM/ECF, and the docketing fee of $500 are being filed simultaneously with the United States Court of Appeals for the Federal Circuit; (3) this Notice of Appeal is being filed by hand with the United States Patent and Trademark Office as provided in 37 C.F.R.

§ 104.2; and (4) a copy of this Notice of Appeal is being served on Petitioners FlatWing Pharmaceuticals, LLC and Mylan Pharmaceuticals Inc.

Date: August 6, 2019

Respectfully submitted,

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CERTIFICATE OF FILING

The undersigned hereby certifies that on August 6, 2019, the foregoing was electronically filed through PTAB E2E and, pursuant, to 37 C.F.R. § 104.2 is being filed by hand delivery with the Director of the United States Patent and Trademark Office at the following address:

Director of the United States Patent and Trademark Office
Office of the General Counsel
Madison Building East, 10B20
600 Dulany Street
Alexandria, VA 22314

The undersigned also hereby certifies that on August 6, 2019, a true and correct paper copy of the foregoing, a true and correct electronic copy of the foregoing, and the docketing fee of $500 are being filed by hand, CM/ECF, and Pay.gov, respectively, with the United States Court of Appeals for the Federal Circuit.

/Anthony H. Sheh/
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CERTIFICATE OF SERVICE (37 C.F.R. § 42.6(e))

The undersigned hereby certifies that a true and correct copy of the foregoing was served on August 6, 2019, by delivering a copy via electronic mail on the following counsel of record for Petitioners:

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Paper No. 35
Entered: June 5, 2019

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FLATWING PHARMACEUTICALS, LLC and
MYLAN PHARMACEUTICALS INC.,
Petitioners,

v.

ANACOR PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2018-00169[1]
Patent 9,566,289 B2

Before GRACE KARAFFA OBERMANN, TINA E. HULSE, and JACQUELINE T. HARLOW, *Administrative Patent Judges*.

HULSE, *Administrative Patent Judge*.

FINAL WRITTEN DECISION
35 U.S.C. § 318(a) and 37 C.F.R. § 42.73

[1] Case No. IPR2018-01359 has been joined with this proceeding.

I. INTRODUCTION

FlatWing Pharmaceuticals, LLC ("FlatWing") filed a Petition requesting an *inter partes* review of claims 1–15 of U.S. Patent No. 9,566,289 B2 (Ex. 1001, "the '289 patent"). Paper 1 ("Pet."). Anacor Pharmaceuticals, Inc. ("Patent Owner") did not file a Preliminary Response to the Petition. On June 8, 2018, we instituted an *inter partes* review of claims 1–15 of the '289 patent. Paper 9 ("Dec. Inst."), 16. On October 11, 2018, we granted Mylan Pharmaceuticals, Inc.'s (collectively with FlatWing, "Petitioners") Motion for Joinder (IPR2018-01359, Paper 3), and joined Case IPR2018-01359 with this proceeding. Paper 16.

Patent Owner filed a Response to the Petition. Paper 13 ("PO Resp."). Petitioners filed a Reply. Paper 19 ("Pet. Reply"). With our authorization, Patent Owner filed a Surreply. Paper 24 ("PO Surreply").

The parties also filed Motions to Exclude certain evidence. Paper 23 (Patent Owner's Motion); Paper 27 (Petitioners' Motion). The parties filed responsive papers to those motions. Paper 30 (Petitioners' Opposition to Patent Owner's Motion); Paper 33 (Patent Owner's Amended Reply to Petitioners' Opposition); Paper 29 (Patent Owner's Opposition to Petitioners' Motion); Paper 31 (Petitioners' Reply to Patent Owner's Opposition).

An oral hearing was held on March 1, 2019, a transcript of which has been entered in the record. Paper 34 ("Tr.").

We have authority under 35 U.S.C. § 6. This Final Written Decision is issued pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73.

For the reasons that follow, we determine Petitioners have shown by a preponderance of the evidence that claims 1–15 of the ’289 patent are unpatentable as obvious.

A. Related Proceedings

Petitioners filed three other petitions for *inter partes* review of related patents: U.S. Patent No. 9,549,938 (IPR2018-00168), U.S. Patent No. 9,566,290 (IPR2018-00170), and U.S. Patent No. 9,572,823 (IPR2018-00171). Paper 4, 2.

A fourth proceeding, Case IPR2015-01776, was filed by a different petitioner and is an *inter partes* review of U.S. Patent No. 7,582,621 (“the ’621 patent”), which, according to Patent Owner, “asserts substantially the same claim of priority as U.S. Patent No. 9,566,289.” *Id.* The Board there determined each of the claims of the ’621 patent was unpatentable over the prior art. *Coalition for Affordable Drugs X LLC v. Anacor Pharms., Inc.*, Case IPR2015-01776, slip op. at 42 (PTAB Feb. 23, 2017) (Paper 70). The Federal Circuit affirmed the Board’s final written decision as to claim 6 of the ’621 patent (the only claim on appeal) in *Anacor Pharmaceuticals, Inc. v. Iancu*, 889 F.3d 1372, 1385 (Fed. Cir. 2018).

The parties also identify U.S. Patent Application Nos. 15/355,393 and 15/355,813 as administrative matters that may be affected by this proceeding. Pet. x; Paper 4, 2.

B. The ’289 Patent

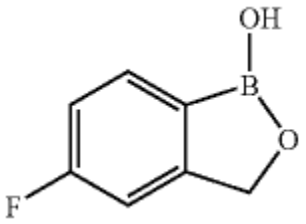
The ’289 patent relates to boron-containing compounds useful for the topical treatment of onychomycosis and/or cutaneous fungal infections. Ex. 1001, Abstract. The claimed invention is directed to compounds that are active against fungi and have physiochemical properties that facilitate penetration of the nail plate. *Id.* According to the Specification, current

treatment for ungual and/or periungual infections generally falls into three categories: systemic administration of medicine; surgical removal of the nail or hoof followed by topical treatment of the exposed tissue; or topical application of medicine with bandages to keep the medication in place on the nail or hoof. *Id.* at 1:47–53.

Each of those approaches has major drawbacks. *Id.* at 1:53–54. Systemic administration of medicine typically requires long-term, high-dose therapy, which can have significant adverse effects on, for example, the liver and testosterone levels, which further negatively affects patient compliance. *Id.* at 1:58–2:8. Surgical treatment is painful and undesirable cosmetically (or not realistic for animals such as horses). *Id.* at 2:10–16. And topical dosage forms cannot keep the drug in contact with the infected area for therapeutically effective periods of time and, because of the composition of the nail, topical therapy for fungal infections have generally been ineffective. *Id.* at 2:17–41. Accordingly, the Specification states that "there is a need in the art for compounds which can effectively penetrate the nail. There is also need in the art for compounds which can effectively treat ungual and/or periungual infections." *Id.* at 2:66–3:2.

Dermatophytes are the most common cause of onychomycosis. *Id.* at 131:29–31. Onychomycosis caused by a dermatophyte is called *Tinea unguium*. *Id.* at 131:31–32. The most frequently isolated dermatophyte in *Tinea unguium* is *Trichophyton rubrum* (*T. rubrum*) followed by *Trichophyton mentagrophytes* (*T. mentagrophytes*). *Id.* at 131:32–33.

The ’289 patent claims a pharmaceutical formulation comprising 1,3-dihydro-5-fluoro-l-hydroxy-2, 1-benzoxaborole, which is referred to as compound 1 (*see id.* at 137:52–61) or compound C10 (*see id.* at 180:21) in the Specification, and has the chemical structure shown below.



C. Illustrative Claim

Petitioners challenge claims 1–15 of the ’289 patent, of which claims 1, 4, and 12 are independent claims. As explained further below, Patent Owner concedes that claims 1–9 and 11 are unpatentable, and contests only claims 10 and 12–15. Of the remaining claims, claim 12 is illustrative and is reproduced below:

> 12. A pharmaceutical formulation, comprising:
>
> about 5% w/w 1,3-dihydro-5-fluoro-l-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof;
>
> propylene glycol;
>
> ethanol; and
>
> ethylene diamine tetraacetic acid (EDTA) or a pharmaceutically acceptable salt thereof.

Ex. 1001, 324:12–19.

Claim 10 depends from claim 4 and further requires a 5% w/w concentration of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole (referred to by the parties as “tavaborole” (Dec. Inst. 7)). *Id.* at

324:3–6. Claim 13 depends from claim 12 and claim 15 depends from claim 14, and further requires that the formulation be suitable for the treatment of onychomycosis due to *T. rubrum* or *T. mentagrophytes* by topical application. *Id.* at 324:20–33. Claim 14 depends from claim 12 and further recites that a specific concentration range of EDTA. *Id.* at 324:25–28.

D. The Instituted Grounds of Unpatentability

We instituted trial on the following grounds:

References	**Basis**	**Claims challenged**
Austin[2] and Brehove[3]	§ 103	1 and 2
Austin, Brehove, and Samour[4]	§ 103	4–7, 10, and 11
Austin, Brehove, Samour, and the Excipients Handbook[5]	§ 103	3, 8, 9, and 12–15
Austin and Freeman[6]	§ 103	1 and 2
Austin, Freeman, and Samour	§ 103	4–7, 10, and 11

[2] Austin et al., WO 95/33754, published Dec. 14, 1995 ("Austin," Ex. 1007).
[3] Brehove, US 2002/0165121 A1, published Nov. 7, 2002 ("Brehove," Ex. 1008).
[4] Samour et al., US 6,224,887 B1, issued May 1, 2001 ("Samour," Ex. 1010).
[5] PJ Weller, *Handbook of Pharmaceutical Excipients* 191–94 (Arthur H. Kibbe, ed., 3d ed. 2000) ("Excipients Handbook," Ex. 1011)
[6] Freeman et al., WO 03/009689 A1, published Feb. 6, 2003 ("Freeman," Ex. 1009).

References	Basis	Claims challenged
Austin, Freeman, Samour, and the Excipients Handbook	§ 103	3, 8, 9, and 12–15

Dec. Inst. 16.

E. Procedural History of Related Cases

We previously found unpatentable all claims of related U.S. Patent Nos. 7,582,621 B2 ("the '621 patent") and 7,767,657 B2 ("the '657 patent") in three prior *inter partes* review proceedings over the same or similar prior art raised in this proceeding. *Coalition for Affordable Drugs X LLC v. Anacor Pharms., Inc.*, Case IPR2015-01776 (PTAB Feb. 23, 2017) (Paper No. 70) (finding claims of the '621 patent unpatentable as obvious over the combinations of (1) Austin and Brehove and (2) Austin and Freeman) ("-1776 IPR"); *Coalition for Affordable Drugs X LLC v. Anacor Pharms., Inc.*, Case IPR2015-01780 (PTAB Feb. 23, 2017) (Paper No. 70) (finding claims of the '657 patent unpatentable as obvious over various combinations of references, including (1) Austin and Brehove and (2) Austin, Brehove, and Samour) ("-1780 IPR"); *Coalition for Affordable Drugs X LLC v. Anacor Pharms., Inc.*, Case IPR2015-01785 (PTAB Feb. 23, 2017) (Paper No. 70) (finding claims of the '657 patent unpatentable as obvious over various combinations of references, including (1) Austin and Freeman and (2) Austin, Freeman, and Samour) ("-1785 IPR").

In the Final Written Decision of the -1776 IPR, we found the combination of Austin and Brehove teaches each limitation of independent claims 1, 11, and 12 of the '621 patent. In particular, we found Brehove teaches a method of treating onychomycosis by topically administering to a toenail a therapeutic amount of a pharmaceutical composition. Ex. 1014, 15.

We also found Austin teaches that tavaborole is effective against *Candida albicans*. *Id.* We found a person of ordinary skill in the art would have selected tavaborole from among the numerous compounds disclosed by Austin because Austin describes tavaborole as a preferred fungicide and as having the lowest Minimum Inhibitory Concentration[7] ("MIC") against several pathogens, including *C. albicans*. *Id.* at 15–16. We also found that a person of ordinary skill in the art would have had a reason to combine Austin and Brehove in light of the structural similarities and the similar fungicidal activity against *C. albicans*. *Id.* at 21. Moreover, although factors such as lipophilicity, keratin binding, and potency of the compound may influence transungual drug delivery, we were persuaded that low molecular weight is the most important factor in predicting whether a molecule will penetrate the nail plate, and that the remaining factors described by Patent Owner's declarant, Dr. Lane, are of less importance, "particularly with a low molecular weight and low MIC molecule such as tavaborole." *Id.* at 23–24. Accordingly, we determined that a person of ordinary skill in the art would have had a reasonable expectation that tavaborole administered topically would penetrate the nail. *Id.* at 24.

The Final Written Decisions in the -1780 IPR and -1785 IPR were similar to that of the -1776 IPR. The challenged claims of the '657 patent, at issue in the -1780 IPR and -1785 IPR, recite a pharmaceutical formulation comprising tavaborole that is for topical administration to an animal suffering from an infection. *See, e.g.*, Ex. 1015, 323:2–8 (claim 1). As in the -1776 IPR, we found in the -1780 IPR that a person of ordinary skill in

[7] The Minimum Inhibitory Concentration is the lowest concentration at which a drug inhibits the growth of a pathogen.

the art would have had a reason to use Austin's tavaborole in Brehove's pharmaceutical composition for topical treatment of nail infections such as onychomycosis. Ex. 1017, 28.

Patent Owner did not appeal the Final Written Decisions in the -1780 IPR or the -1785 IPR. Patent Owner only appealed the Final Written Decision as to claim 6 of the '621 patent in the -1776 IPR,[8] and the Federal Circuit affirmed our determination of unpatentability over the combination of Austin and Brehove.[9] *Anacor Pharms.*, 889 F.3d at 1385.

Given those prior decisions, Patent Owner states that it "acknowledges the Board's rulings in these prior cases, as well [as] the affirmance of the Board's final written decision in IPR2015-01776 . . . , and does not challenge here limitations that were found to have been obvious in those proceedings." PO Resp. 6. Patent Owner contends, however, that claims 10 and 12–15 of the '289 patent in this proceeding recite a specific formulation of tavaborole that was not at issue in the prior proceedings. *Id.*

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[8] Claim 6 of the '621 patent depends from claims 1 and 4, all of which recite:

> 1. A method of treating an infection in an animal, said method comprising administering to the animal a therapeutically effective amount of 1,3-dihydro-5-fluoro-l-hydroxy-2,1-benzoxaborole, or a pharmaceutically acceptable salt thereof, sufficient to treat said infection.
> 4. The method of claim 1, wherein said infection is onychomycosis.
> 6. The method of claim 4, wherein said onychomycosis is tinea unguium.

Anacor Pharms., 889 F.3d at 1375.

[9] The Federal Circuit did not address the unpatentability of claim 6 over the combination of Austin and Freeman because it affirmed our conclusion that claim 6 was obvious over the combination of Austin and Brehove. *Id.* at 1376 n.2.

Specifically, Patent Owner contends that tavaborole at a 5% w/w concentration was not considered by the Board or the Federal Circuit and is not obvious over the cited prior art. *Id.* at 6–7. For those claims that do not recite the 5% w/w concentration limitation, counsel for Patent Owner concedes that they are unpatentable. Tr. 33:11–18.[10]

Accordingly, we focus this Decision primarily on Petitioners' challenges to claims 10 and 12–15 of the '289 patent.

II. ANALYSIS

A. Person of Ordinary Skill in the Art

Petitioners assert that a person of ordinary skill in the art at the time of the invention would have had either a Master's degree or Ph.D. in chemistry, pharmacology, or biochemistry, and at least two years of experience with the research, development, or production of pharmaceuticals. Pet. 18 (citing Ex. 1005 ¶¶ 19–21; Ex. 1003 ¶ 22). Patent Owner does not address the level of ordinary skill in the art in its Patent Owner Response.

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[10] We appreciate the candor of Patent Owner's counsel during oral argument:

> JUDGE HULSE: [D]o you concede that the other claims [that do not recite the 5% w/w limitation] are invalid per our prior decisions and the Federal Circuit decision?
>
> MR. MAURER: Correct. We're not challenging the petition on those claims as a result of the prior determinations that were made.
>
> JUDGE HULSE: You're not challenging it; but do you concede that they are unpatentable?
>
> MR MAURER: Right. We're not defending those other claims. Yes; we concede that they are unpatentable.

Tr. 33:11–18.

Absent opposition from Patent Owner, we accept and adopt Petitioners' description of the level of ordinary skill in the art because it is consistent with the level of skill reflected in the asserted prior art references. In that regard, the prior art itself is sufficient to demonstrate the level of skill in the art at the time of the invention. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required "where the prior art itself reflects an appropriate level and a need for testimony is not shown" (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp*., 755 F.2d 158, 163 (Fed. Cir. 1985))).

B. Claim Construction

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 42.100(b) (2017);[11] *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016) (affirming applicability of broadest reasonable construction standard to *inter partes* review proceedings). Under that standard, and absent any special definitions, we generally give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms

[11] A recent amendment to this rule does not apply here, because the Petition was filed before November 13, 2018. *See* "Changes to the Claim Construction Standard for Interpreting Claims in Trial Proceedings Before the Patent Trial and Appeal Board," 83 Fed. Reg. 51,340 (Oct. 11, 2018) (to be codified at 37 C.F.R. pt. 42).

must be set forth in the specification with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

In our Decision on Institution, we construed the term "1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole," which is recited in each of the claims, as equivalent to the compound referred to in Austin as "5-fluoro-1,3 dihydro-1-hydroxy-2,1-benzoxaborole" and referred to by the parties as "tavaborole." Dec. Inst. 7. Neither party contests that construction. *See generally* PO Resp.; Reply. Accordingly, we adopt the construction and, for convenience, refer to the claimed compound as "tavaborole" in this Decision.

C. Obviousness of Claims 1–9 and 11 over Austin, Brehove, Samour, and the Excipients Handbook

Petitioners assert that claims 1 and 2 of the '289 patent are unpatentable as obvious over the combination of Austin and Brehove. Pet. 31–40. Petitioners further rely on Samour to assert that claims 4–7 and 11 are unpatentable as obvious. *Id.* at 41–46. And Petitioners further rely on the Excipients Handbook to assert that claims 3, 8, and 9 are unpatentable as obvious. *Id.* at 46–48.

1. Austin (Ex. 1007)

Austin relates to the use of oxaboroles as industrial biocides, and especially as fungicides for the protection of plastic materials. Ex. 1007, 1 (Abstract).[12] The Abstract further states that "[p]referred compounds are 5- and 6-fluoro or bromo-1,3-dihydro-1-hydroxy-2,1-benzoxaborole including O-esters thereof." *Id.* Austin notes that it has been found that compounds

[12] Unless stated otherwise, the cited page numbers in this Decision refer to the page numbers provided by the parties pursuant to 37 C.F.R. § 42.63(d)(2).

containing an oxaborole ring are "particularly effective against micro-organisms such as bacteria, algae, yeasts and particularly fungi, especially fungi which cause degradation of plastics materials." *Id.* at 3:35–38.

Along with a number of different preferred oxaboroles, Austin discloses tavaborole as Example 64, as well as the results of a study showing tavaborole has effective antifungal activity against five different fungi: *Aspergillus niger* (AN), *Candida albicans* (CA), *Aureobasidium pullulans* (AP), *Gliocladium roseum* (GR), and *Penicillium pinophylum* (PP). *Id.* at 39 (Table 9). Of the preferred compounds tested (i.e., Examples 64, 68, and 70), tavaborole had the lowest Minimum Inhibitory Concentration ("MIC") value of five parts per million for *Candida albicans*. *Id.*; Ex. 1003 ¶ 36.

According to Austin, "[t]he concentration of the oxaborole in the biocide composition is preferably up to a level at which the biocide composition is stable under the conditions of storage or transportation and is preferably from 1 to 50%, especially from 5 to 30% and more especially from 10 to 20% by weight relative to the total weight of the biocide composition." Ex. 1007, 9:5–9.

2. Brehove (Ex. 1008)

Brehove relates to the topical treatment of nail infections such as onychomycosis caused by bacteria, fungi, and other pathogens. Ex. 1008 ¶ 3. Brehove explains that onychomycosis is a nail disease typically caused by *Candida albicans*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, or *Epidermpophyton floccusum*. *Id.* ¶ 5. Brehove states that *Candida albicans* is the most common pathogen causing onychomycosis. *Id.* ¶ 18. Brehove teaches that to be effective for onychomycosis, the topical treatment should exhibit a powerful potency for pathogens, be permeable through the nail barrier, and be safe for patient use. *Id.* ¶ 6. According to

Brehove, "[t]here exists a need in the art for a topical application that combines these traits in high degree." *Id.*

Brehove states that the "safety and non-toxicity of organo-boron compounds has been questioned." *Id.* ¶ 13. On the one hand, Brehove describes one reference that states that boron compounds are "very toxic," while on the other hand, Brehove describes references that found the toxicity of a certain boron-containing compound to be "very low" and another industrial fungicide compound called Biobor® JF to cause only "mild irritation." *Id.* ¶¶ 14–15.

Biobor® JF contains a combination of 2,2'-(1-methyltrimethylene dioxy) bis-(4-methyl-1, 3, 2-dioxaborinane) (referred to by Brehove as "S1") and 2,2'-oxybis (4, 4, 6-trimethyl-1, 3, 2-dioxaborinane) (referred to by Brehove as "S2"). *Id.* ¶¶ 15, 30. Brehove describes the results of in vitro testing of the antifungal activity of S1 and S2 against *Candida albicans*. *Id.* ¶¶ 30–33. Brehove also describes successful examples of in vivo testing of S1 and S2 on various patients with onychomycosis of the toenails. *Id.* ¶¶ 34–38 (Examples 16–20).

According to Brehove, the active dioxaborinane ingredient is preferably at least about 0.1 wt % of the composition. *Id.* ¶ 28. "Most preferably, dioxaborinane ingredient constitutes between about 0.1 wt % and 25 wt % of the composition." *Id.*

3. Samour (Ex. 1010)

Samour relates to a nail lacquer formulation effective for treating or preventing fungal infections, such as onychomycosis. Ex. 1010, Abstract. Samour states that onychomycosis is frequently caused by dermatophytes,

but can also be caused by molds and *Candida*. *Id.* at 1:22–24.[13] Samour states "[t]here is no particular limitation on the antifungal agents used in the composition of this invention; any of the agents known to be effective for this purpose may be used." *Id.* at 11:39–41. Samour also states that typically, "the amount of active [antifungal] agent is generally about 1 to 50%, preferably about 2 to 35%, more preferably, from about 2 to 30%, especially preferably from about 5 to 20%, by weight of the composition." *Id.* at 12:23–26. Samour's Examples 6–8 provide examples of lacquer formulations containing 5% w/w active antifungal ingredient econazole with propylene glycol and ethanol. *Id.* at 21:41–24:8. Samour's Example 9 taught the effect of changing the concentration of econazole "for a single dose application," testing the efficacy of 1%, 2%, 5%, 10%, and 20% w/w econazole. *Id.* at 24:24–25:15.

4. The Excipients Handbook (Ex. 1011)

The Excipients Handbook is an excerpt from the *Handbook of Pharmaceutical Excipients* relating to edetic acid, which is also known as EDTA. Ex. 1011, 1, 3. The Excipients Handbook states that EDTA is used in pharmaceutical formulations as chelating agents. *Id.* at 3. That is, EDTA forms "water-soluble complexes (chelates) with alkaline earth and heavy metal ions." *Id.*

5. Analysis

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the

[13] We cite the column and line numbers of the Samour patent rather than the page numbers provided by the parties.

invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. "[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." *Id.* Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014).

Patent Owner does not challenge Petitioners' assertions and concedes that claims 1–9 and 11 are unpatentable in light of the prior proceedings. PO Resp. 6; Tr. 33:11–18. Having considered the arguments and evidence presented in the Petition, and, in light of Patent Owner's concession of unpatentability, we find that each limitation of those claims is taught by the cited combinations of prior art and that a person of ordinary skill in the art would have had a reason to combine the cited references to achieve the claimed invention with a reasonable expectation of success for the reasons stated in the Petition, as supported by the cited evidence. *See* Pet. 31–48, 51–61; Ex. 1005 ¶¶ 101–155, 160–184; *see also Anacor Pharms.*, 889 F.3d at 1382–85 (affirming the Board's finding that a person of ordinary skill in the art would have had a reason to combine Austin and Brehove to achieve

the claimed invention with a reasonable expectation of success). We further note that Patent Owner has not asserted any objective indicia of nonobviousness of the claimed invention. *See Graham*, 383 U.S. at 17–18.

Accordingly, having considered the arguments and evidence presented at trial, we determine that Petitioners have established by a preponderance of the evidence that claims 1–9 and 11 are unpatentable as obvious over the cited prior art.

D. Obviousness of Claims 10 and 12–15 over Austin, Brehove, and Samour

Petitioners assert that claim 10 is unpatentable as obvious over the combination of Austin, Brehove, and Samour (Pet. 43–44) and that claims 12–15 are unpatentable as obvious over the combination of Austin, Brehove, Samour, and the Excipients Handbook (*id.* at 48–50). We incorporate our findings above with respect to the teachings of those references.

Claim 10 of the '289 patent depends from independent claim 4, and claims 13–15 depend from independent claim 12. Ex. 1001, 324:3–6, 12–33. Each claim requires a pharmaceutical composition comprising 5% w/w of tavaborole.[14] *Id.* Patent Owner contests Petitioners' challenge only with respect to the 5% w/w concentration of tavaborole limitation. PO Resp. 6. Accordingly, the parties agree that claims 10 and 12–15, which all include the 5% w/w limitation, rise and fall together. Tr. 8:23–9:10; 33:7–10. Patent Owner also concedes that the Excipients Handbook reference is not relevant to its arguments with respect to the 5% w/w limitation. *Id.* at

[14] Claims 12–15 further recite a pharmaceutical formulation comprising propylene glycol, ethanol, and EDTA that is suitable for treating onychomycosis due to *T. rubrum* or *T. mentagrophytes*. Ex. 1001, 324:12–33. These limitations also appear in claims 1–9 and 11, found unpatentable above over the same prior art references. *See id.* at 323:2–324:2, 324:7–11.

40:20–25. We, therefore, focus our analysis—as the parties do—on the limitation requiring 5% w/w of tavaborole.

Austin teaches a preferred concentration of tavaborole of "especially from 5 to 30% . . . by weight relative to the total weight of the biocide composition." Ex. 1007, 9:5–9. Brehove teaches that its active organoboron compound "[m]ost preferably . . . constitutes between about 0.1 wt % and 25 wt % of the composition." Ex. 1008 ¶ 28. And Samour teaches a topically applied pharmaceutical composition with 5% w/w active antifungal ingredient, econazole. Ex. 1010, 22:20–24:23. Thus, because the use of 5% by weight of an antifungal agent falls within the ranges disclosed in Austin and Brehove, and Samour specifically teaches the use of that amount, we find that the combination of Austin, Brehove, and Samour teaches the topical application of a composition having 5% w/w of tavaborole to treat onychomycosis.

Petitioners assert that a person of ordinary skill in the art would have had a reason to use 5% by weight of tavaborole in a pharmaceutical composition to treat onychomycosis. Pet. 43–44. We are persuaded that a preponderance of the evidence supports Petitioner's assertion. As explained above, the use of 5% by weight of an antifungal agent is within the range of preferred concentrations of tavaborole taught by Austin as a fungicide and of organoboron as taught by Brehove to treat onychomycosis. Ex. 1007, 9:5–9; Ex. 1008 ¶ 28; Ex. 1005 ¶ 165. Moreover, Samour specifically teaches topically applying a pharmaceutical composition with 5% w/w active antifungal ingredient to treat onychomycosis. Ex. 1010, 22:20–24:23. Petitioners' declarant, Dr. Narasimha Murthy, testifies that "[f]ormulating pharmaceutical compositions involves nothing more than routine experimentation based on well-known protocols." Ex. 1005 ¶ 142. Dr.

Murthy also notes that the ’289 patent states that formulating pharmaceutical compositions was well known in the art. *Id.* (citing Ex. 1001, 162:50–60 (“Those skilled in the art will recognize various synthetic methodologies that may be employed to prepare non-toxic pharmaceutical formulations incorporating the compounds described herein.”)).

Petitioners further assert that a person of ordinary skill in the art would have had a reasonable expectation of success using 5% by weight of tavaborole to treat onychomycosis. Pet. 44–46. According to Petitioners’ declarant, a person of ordinary skill in the art would have had a reasonable expectation of success in light of Samour’s successful use of 5% by weight of econazole, which has a molecular weight that is twice that of tavaborole. Ex. 1005 ¶¶ 143–144; Ex. 1026, 1 (disclosing molecular weight of econazole is 381.68 Daltons); Ex. 1027, 1 (disclosing molecular weight of tavaborole is 151.93 Daltons). We find the evidence of record supports Petitioners’ assertion that a person of ordinary skill in the art would have reasonably expected that a 5% by weight concentration of the smaller tavaborole would more effectively penetrate the nail plate than Samour’s econazole. Ex. 1005 ¶¶ 143–144; *see also* Ex. 1020, 9 (“As expected, molecular size has an inverse relationship with penetration into the nail plate. The larger the molecular size, the harder it is for molecules to diffuse through the keratin network and [the] lower the drug permeation.”). We also note that conclusive proof of efficacy is not required to show obviousness. *See Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) (“Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success.”).

Patent Owner does not dispute that the combination of Austin, Brehove, and Samour teaches concentration ranges that overlap with the

claimed 5% w/w tavaborole limitation. The Federal Circuit has held that "where 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." *E.I. DuPont de Nemours & Co. v. Synvina CV*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (quoting *In re Aller*, 220 F.2d 454, 456 (CCPA 1955)). In *E.I. Dupont*, the Federal Circuit—in an appeal from an *inter partes* review—held that an overlap of ranges of a claimed composition with the ranges disclosed in the prior art "creates a presumption of obviousness." *Id.* (citing *Galderma Labs, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737–38 (Fed. Cir. 2013)). The patentee can rebut that presumption if the modification of the parameter "produce[s] a new and unexpected result which is different in kind and not merely in degree from the results of the prior art." *Id.* (quoting *Aller*, 220 F.2d at 456). Alternatively, a patentee may rebut the presumption of obviousness by showing the prior art taught away from the claimed range or that the change to a parameter was not recognized as "result-effective." *Id.* In sum,

> "where there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence" of teaching away, unexpected results or criticality, or other pertinent objective indicia indicating that the overlapping range would not have been obvious in light of that prior art.[15]

Id. at 1008 (quoting *Galderma*, 737 F.3d at 738).

[15] To be clear, it is the burden of production that shifts to Patent Owner, and not the burden of persuasion, which always lies with Petitioners. The Federal Circuit has expressly approved this burden-shifting framework in the context of overlapping range cases in *inter partes* reviews. *Id.* at 1006–08.

As explained above, we find the combination of Austin, Brehove, and Samour teaches the use of 5% by weight of tavaborole in light of the overlapping concentration ranges of antifungal agent taught in those references. There is, therefore, a rebuttable presumption that the claims are obvious unless Patent Owner can come forward with evidence that the use of 5% by weight of tavaborole would not have been obvious.[16] *Id.*

To satisfy its burden of production, Patent Owner makes three arguments in response to Petitioners' assertions. First, Patent Owner argues that the cited art teaches away from the use of 5% by weight of tavaborole. Second, Patent Owner argues that a person of ordinary skill in the art would not have arrived at the claimed invention by simple substitution or routine experimentation. Third, Patent Owner argues a person of ordinary skill in the art would have used more than 5% by weight of tavaborole to treat onychomycosis in light of the state of the art concerning transungual drug delivery and boron chemistry. We address each argument in turn.

1. Whether the Prior Art Teaches Away from the Use of 5% by Weight of Tavaborole

A reference may "teach away" when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir.

[16] Patent Owner asserts that Petitioners improperly "pivot[ed]" in their Reply to a theory based on overlapping ranges to respond to Patent Owner's evidence of teaching away raised in its Patent Owner Response. PO Surreply 12–13. We disagree. Petitioners relied on the disclosure of overlapping ranges in Austin and Brehove in the Petition with respect to the 5% w/w limitation. Pet. 44–45 (citing Ex. 1007 (Austin), 9:5–9 and Ex. 1008 (Brehove) ¶ 28).

1994). Moreover, a "reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *Id.*

Patent Owner asserts that Petitioners rely primarily on Samour for the 5% by weight of tavaborole limitation, and that Samour's examples teach away from using that amount. PO Resp. 29–36. Examples 6–8 of Samour each teach the use of 5% by weight of econazole in an antifungal lacquer formulation. Ex. 1010, 21:40–23:66. According to Patent Owner, however, econazole is very different than tavaborole, as it is not a boron-containing compound and, therefore, does not have the unique chemistry and reactivity that such compounds possess. PO Resp. 30 (citing Ex. 2013 ¶¶ 27–29, 60, 69). As a boron-containing compound, Patent Owner asserts that tavaborole has a higher keratin-binding affinity[17] than econazole and a person of ordinary skill in the art would have used a higher concentration of tavaborole to compensate for the higher affinity binding. *Id.* at 30–31 (citing Ex. 2013 ¶ 60; Ex. 2014 ¶ 79).

Patent Owner further criticizes Petitioners' reliance on Examples 6–8 because none of those examples addresses the question of what drug concentration to use in the formulation. *Id.* at 31–32. Example 6 tests absorption of 5% by weight of econazole when using different polymer

[17] The main chemical constituent in human nails is the polypeptide keratin, which has electron-rich functional groups. Ex. 2013 ¶¶ 44–48. According to Patent Owner's expert, Dr. Paul J. Reider, boron-containing compounds like tavaborole have a high keratin-binding affinity because of boron's electron-deficient nature. *Id.* ¶¶ 61–64. Dr. Reider opines that a person of ordinary skill in the art would, therefore, have expected tavaborole to bind keratin and become entrapped within the keratin network of the nail rather than treat the underlying infection. *Id.* ¶¶ 65–68.

lacquers. Ex. 1010, 21:41–22:18. Example 7 tests different concentrations of enhancer in a series of lacquer formulations containing 5% by weight of econazole. *Id.* at 22:20–23:50. And Example 8 tests the effect of various excipients in formulations containing 5% by weight of econazole. *Id.* at 23:53–24:22. Patent Owner argues that none of the examples guides a person of ordinary skill in the art to use 5% w/w and only uses 5% econazole to compare the various samples within each test. PO Resp. 31–32; Ex. 2014 ¶ 72.

Patent Owner asserts that Example 9, which Petitioners do not address, is the relevant example in Samour. PO Resp. 33–36. Example 9 teaches the effect of changing the concentration of antifungal agent on the ability of the formulation to deliver the drug to the nail. Ex. 1010, 24:24–25:15. Example 9 tests three different drug concentrations: 5% w/w, 10% w/w and 20% w/w econazole. Ex. 1010, 24:33. According to Patent Owner and its declarant, Dr. Majella E. Lane, Example 9 demonstrates that the total amount of penetration for the 5% w/w formulation is "30% worse than the 10% w/w formulation and 17% worse than the 20% w/w formulation." PO Resp. 33; Ex. 2014 ¶¶ 73–74. Example 9 also tests formulations of 1% w/w, 2% w/w, 5% w/w, and 10% w/w econazole and found the 10% w/w formulation had the highest total penetration of the four concentrations tested and over two times that of the 5% w/w formulation. Ex. 1010, 24:62–25:16. Accordingly, Dr. Lane opines that based on Example 9, when read in the context of the entire reference, a person of ordinary skill in the art would have used more than 5% w/w of an antifungal agent. Ex. 2014 ¶ 75.

Patent Owner further asserts that the broad ranges relied upon in Austin and Brehove would not have led a person of ordinary skill in the art

to the use of 5% by weight of tavaborole. PO Resp. 37–38. According to Patent Owner, the references "clearly prefer concentrations greater than 5% w/w," as the preferred range of Austin is "10 to 20% by weight" and of Brehove is "between about 0.1 wt. % and 25 wt. %." *Id.* at 37.

We are not persuaded. Although we agree that Samour's Example 9 teaches that 10% w/w of econazole has greater drug penetration than 5% w/w of econazole for a single dose study, the law is clear that "just because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes." *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) (citing *Gurley*, 27 F.3d at 553). Samour does not teach that 5% w/w of econazole should not be used or would not work to treat onychomycosis. Nor does Samour criticize or otherwise discourage the use of 5% w/w of antifungal agent. On the contrary, Samour expressly claims a drug composition with a concentration range that includes 5% w/w of an antifungal agent. Ex. 1010, 32:26–28 (claiming a composition comprising "from about 1 to about 10% by weight of (a) antifungal agent").

Nor are we persuaded that the ranges taught by Austin and Brehove are overly broad such that they do not teach the use of 5% w/w of tavaborole. The prior art does not, as Patent Owner asserts, "teach[] ranges 'so broad as to encompass a very large number of possible distinct compositions.'" PO Surreply 13 (quoting *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1306 (Fed. Cir. 2011)). In *Genetics Institute*, the prior art encompassed 68,000 possible variants and there was no motivation to optimize for some value within that range. *Id.* In contrast, here, the disclosed concentration ranges are not as broad and include a motivation to optimize the concentration of drug to treat

onychomycosis. Moreover, Austin expressly states that the concentration of the antifungal agent is "especially from 5 to 30%" by weight. Ex. 1007, 9:5–8. That Austin may also teach that the concentration is "more especially from 10 to 20% by weight" (*Id.* at 9:8) does not detract from Austin's teaching of an "especially" preferred overlapping range that includes 5% by weight of an antifungal agent. *See Mouttet*, 686 F.3d at 334.

Patent Owner also argues that a person of ordinary skill in the art, knowing the unique chemistry of boron-containing compounds, would have used a higher concentration of tavaborole than the 5% by weight of econazole that Samour teaches because econazole is not a boron-containing compound and given tavaborole's keratin-binding affinity. PO Resp. 30–31; PO Surreply 4. Patent Owner's declarant, Dr. Reider, also testifies that boron-containing compounds are "inherently susceptible to hydrolysis or oxidation to boric acid." Ex. 2013 ¶ 40 (citing Ex. 2016, 9); *see* PO Surreply 15–16.

Having considered the arguments and evidence presented during trial, however, we are not persuaded by Patent Owner's arguments. Although tavaborole may have different chemistry and reactivity than econazole because it is a boron-containing compound, we credit the testimony of Dr. Murthy, which is supported by objective proof and persuasively explains that, because tavaborole is half the size of econazole, a person of ordinary skill in the art would have had a reasonable expectation of success using 5% by weight of tavaborole. *See* Ex. 1005 ¶¶ 144–146 (including citations to evidence therein). This is consistent with our finding in the Final Written Decision of the -1776 IPR, where we stated:

> Although other factors such as lipophilicity, keratin binding, and potency of the compound may influence transungual drug

> delivery, we are persuaded by the well-supported testimony of Dr. Murthy that low molecular weight is the most important factor in predicting whether a molecule will penetrate the nail plate, and that the remaining factors described by Patent Owner's declarant, Dr. Lane, are of less importance, particularly with a low molecular weight and low MIC molecule such as tavaborole.

Ex. 1014, 23–24.

As for Dr. Reider's concerns regarding the susceptibility of boronic acids and borate esters to hydrolysis or oxidation (Ex. 2013 ¶ 40), we note that the reference he cites for support states that that process is "slow." Ex. 2016, 9 ("[T]he ultimate fate of all boronic acids in air and aqueous media is their *slow oxidation* into boric acid.") (emphasis added). When asked about this during cross-examination, Dr. Reider testified that he did not consider the kinetics of the reaction and the rate at which such compounds might decay in forming his opinions. Ex. 1045, 84:14–85:5. Petitioners' declarant, Dr. Kahl, further explains that the degradation of boronic acids and esters is usually extremely slow and would take much longer than the treatment period for tavaborole to penetrate the nail.[18] Ex. 1047 ¶¶ 3–5. On balance, therefore, we find Dr. Kahl's testimony more persuasive than Dr. Reider's, because the objective evidence on point supports Dr. Kahl's position, and Dr. Reider's cross-examination testimony reveals a significant weakness in his concern that a person of ordinary skill

[18] Patent Owner criticizes Dr. Kahl's testimony as conclusory and unsupported and therefore deserving zero weight. PO Surreply 19–20. Generally speaking, opinion testimony that does not disclose underlying facts or data is "entitled to little or no weight." *See* 37 C.F.R. § 42.65(a). Here, however, Dr. Kahl's testimony is supported by evidence cited by Patent Owner's declarant. *See* Ex. 2013 ¶ 40 (citing Ex. 2016, 9). In light of this, we decline to discount Dr. Reider's testimony for failure to cite supporting evidence in his declaration.

in the art would be dissuaded from using tavaborole in view of its susceptibility to hydrolysis or oxidation.

Having considered the arguments and evidence presented at trial, we are not persuaded that the prior art would have suggested to a person of ordinary skill that "the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *Gurley*, 27 F.3d at 553. Stated differently, we find that a preponderance of the evidence supports Petitioners' assertion that a person of ordinary skill in the art, considering Austin, Brehove, and Samour as a whole, would not have been discouraged from using 5% by weight of tavaborole to treat onychomycosis, as recited in the challenged claims. *See id.*

2. Whether the Use of 5% by Weight of Tavaborole Was a Matter of Simple Substitution or Routine Experimentation

Petitioners assert "formulating pharmaceutical compositions, and the amount of active ingredient therein, was well known in the art of topical pharmaceuticals and involves nothing more than routine experimentation based on well-known protocols." Pet. 45 (citing Ex. 1005 ¶ 142). In response, Patent Owner contends that because there was very little data or experience regarding the formulation of boron-containing compounds for pharmaceutical applications, it could not have been a matter of routine experimentation. PO Resp. 39. Rather, Patent Owner asserts that a person of ordinary skill in the art would have found the formulation of boron-containing compounds unpredictable because boron is "promiscuous" and interacts with known pharmaceutical excipients. PO Resp. 39–40.

We are not persuaded by Patent Owner's argument. The parties agree that, generally speaking, according to Fick's law, the rate of diffusion through the nail plate of any given compound is "proportional to the

compound's concentration gradient across the nail plate." Ex. 2014 ¶ 77 (Dr. Lane); Pet. Reply 19 ("Patent Owner agrees that concentration is a result effective variable, arguing that a [person of ordinary skill in the art] would have known that increasing this percentage would increase penetration."); Tr. 22:11–17 (Patent Owner's counsel stating "[it] is true that a person of skill in the arts understands that the higher the concentration, the more drug that you're going to get across the nail plate"). Thus, it is undisputed that a person of ordinary skill in the art would have understood concentration to be a result-effective variable, such that increasing the concentration of a drug would increase the drug's penetration across the nail plate. *In re Applied Materials*, 692 F.3d 1289, 1297 (Fed. Cir. 2012) ("A recognition in the prior art that a property is affected by the variable is sufficient to find the variable result-effective."). We, therefore, find that using 5% by weight of tavaborole would have been a matter of "discover[ing] an optimum value of a result effective variable in a known process." *See In re Boesch*, 617 F.2d 272, 276 (CCPA 1980).

There is no persuasive evidence in the record that indicates that determining the optimum concentration of tavaborole would have been outside the abilities of a person of ordinary skill in the art in 2005. Rather, as Petitioner's declarant notes, the '289 patent admits that methods for determining an antifungal's MIC and keratin-binding properties were known in the prior art. Ex. 1005 ¶ 30 (citing Ex. 1001, 189:18–190:50). Similarly, the '289 patent admits methods for determining the efficacy of nail penetration by antifungal compounds were known in the prior art. *Id.* ¶ 32 (citing Ex. 1001, 133:64–134:11, 192:48–197:7).

As the Federal Circuit has held, "[o]nly if the 'results of optimizing a variable' are 'unexpectedly good' can a patent be obtained for the claimed

critical range." *In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997). Patent Owner has admitted, however, that it does not assert unexpected results in this proceeding:

> JUDGE HULSE: Do you agree though that there is no evidence that there's anything special about 5 percent in the record?
>
> MR. MAURER: We're not relying on unexpected results with the 5 percent; yes, I agree with that.

Tr. 32:11–14.

Regarding the unpredictability of boron's "promiscuous" nature, Patent Owner has already conceded that claim 11—which recites a formulation of tavaborole suitable for the treatment of onychomycosis—is unpatentable as obvious over Austin, Brehove, and Samour. In other words, Patent Owner concedes that a person of ordinary skill in the art would have had a reason to combine Austin's tavaborole with Brehove and Samour's methods of treating onychomycosis with a reasonable expectation of success. *See supra*. If there is a reasonable expectation of success in using a "promiscuous" boron-containing compound like tavaborole to treat onychomycosis, we are not persuaded that a person of ordinary skill in the art would not have been able to optimize the concentration of that same compound because of the unpredictability of boron's "promiscuous" nature. This is particularly true where, as explained above, the methods for doing so were known in the art. *See* Ex. 1005 ¶¶ 30, 32.

Patent Owner also argues that using boron-containing compounds in a pharmaceutical formulation could not have been routine or predictable in 2005 given that Velcade was the only FDA-approved boron-containing drug product in 2005. PO Resp. 38–39. Patent Owner and its declarant, Dr.

Reider, rely on "[t]he story of VELCADE®" as demonstrating that boron-containing compounds have substantial stability issues that would have warned a person of ordinary skill in the art that "formulating a boron-containing compound like tavaborole would be a significant and unpredictable technical challenge." Ex. 2013 ¶ 74; PO Resp. 38–39 (citing *Millennium Pharm., Inc. v. Sandoz, Inc.*, 862 F.3d 1356, 1361 (Fed. Cir. 2017)).

We do not find Patent Owner's reliance on Velcade and the *Millennium* case to be compelling. It is true the Federal Circuit has stated that "FDA approval may be relevant to the obviousness inquiry." *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291 (Fed. Cir. 2013). For example, the failure of others to obtain FDA approval may be considered as objective evidence of nonobviousness. *See Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004). And the potential for FDA approval may be considered in determining whether one of ordinary skill in the art would have been motivated to develop a drug product and whether there was skepticism regarding the efficacy of that product. *Allergan*, 726 F.3d at 1291–92.

That Velcade was the only FDA-approved boron-containing drug on the market in 2005, however, is not dispositive of the issue of obviousness in this proceeding. As explained above, the combination of Austin, Brehove, and Samour renders claim 4 of the '289 patent unpatentable as obvious because it suggests the use of tavaborole to treat onychomycosis with a reasonable expectation of success. *See supra*. This is consistent with our decisions in the prior proceedings. *See* Ex. 1014, 14–37; *Anacor Pharms.*, 889 F.3d at 1385 (affirming decision in the -1776 IPR). If there is a reasonable expectation of success in using tavaborole to treat

onychomycosis, we are not persuaded, for all the reasons stated above, that Velcade's status as the only FDA-approved boron-containing drug on the market necessarily implies that optimizing a 5% tavaborole formulation could not have been routine.

Nor are we persuaded that the Federal Circuit's decision in *Millennium* requires us to find differently. The asserted claim in *Millennium* recited a new compound produced as a result of lyophilizing (i.e., freeze drying) bortezomib (a boronic acid) with D-mannitol. 826 F.3d at 1361. The Federal Circuit repeatedly emphasized that the "new compound" was not obvious over the prior art. That is, the prior art did not teach or suggest that lyophilization of bortezomib in the presence of mannitol "would produce a chemical reaction and form a *new chemical compound*, or provide a reason to make this specific *new chemical compound*, or that this *new compound* would solve the previously intractable problems of bortezomib formulation." *Id.* at 1364 (emphasis added). Here, claims 10 and 12–15 of the '289 patent do not recite a new chemical compound. Rather, claims 10 and 12–15 recite the use of a specific concentration of a known compound, whose use has already been found obvious (via claim 4). *Millennium* is therefore readily distinguishable from the facts of this case.

In sum, taking the arguments and evidence presented at trial as a whole, we find the following:

(1) There is no dispute that the prior art teaches a range of concentrations of antifungal agents, within which is the use of 5% w/w of tavaborole, as recited in claims 10 and 12–15. Ex. 1007 (Austin), 9:5–9; Ex. 1008 (Brehove) ¶ 28; Ex. 1010 (Samour), 22:20–24:23.

(2) The concentration of tavaborole is a result-effective variable, as the higher the concentration, the greater the penetration of the drug. Ex. 2014 ¶ 77; Pet. Reply 19; Tr. 22:11–17.

(3) Methods for determining an antifungal's MIC, keratin-binding properties, and efficacy of nail penetration were routine and known in the art. Ex. 1005 ¶¶ 30, 32; Ex. 1001, 189:18–190:50, 133:64–134:11, 192:48–197:7.

(4) Patent Owner admits it does not rely on unexpected results from using 5% w/w of tavaborole. Tr. 32:11–14.

(5) The prior art does not teach away from the use of 5% w/w of tavaborole.[19] *See supra*.

Given these findings, we determine that the preponderance of the evidence supports Petitioners' assertion that it would have been obvious for a person of ordinary skill in the art to discover the use of 5% w/w of tavaborole through routine optimization and experimentation, particularly in

[19] We also note that our findings here are consistent with those in the Final Written Decision of the -1780 IPR—which Patent Owner did not appeal—where we found the use of 10% w/w of tavaborole to treat onychomycosis to be unpatentable as obvious over Austin, Brehove, and Samour for many of the same reasons stated in this Decision. *See* Ex. 1017, 42–44 (finding claim 7 of the '657 patent unpatentable as obvious).

light of the fact that the concentration of tavaborole is a result-effective variable. *See In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997) ("[I]t is not inventive to discover the optimum or workable ranges by routine experimentation.") (quotations omitted).

3. Whether the State of the Art Would Have Led to the Use of More Than 5% by Weight of Tavaborole

Patent Owner argues that a person of ordinary skill in the art would have used the highest possible concentration of tavaborole to generate maximum flux through the nail plate, particularly given the known challenges of transungual drug delivery. PO Resp. 42–43; PO Surreply 9. According to Patent Owner, Samour would have led a person of ordinary skill in the art to use concentrations much higher than 5% w/w, particularly given Samour's teaching of drug concentrations as high as 20% w/w. PO Resp. 43; PO Surreply 10; Ex. 1010, 15:54–60; Ex. 2014 ¶¶ 73–75. Once again, Patent Owner argues that a person of ordinary skill in the art would have used more than 5% by weight of tavaborole to compensate for the high keratin binding affinity that would have been predicted in light of tavaborole's boron-containing chemical structure. PO Resp. 44–47. Patent Owner again criticizes as overly simplistic Petitioners' assertion that a person of ordinary skill would have expected tavaborole to more effectively penetrate the nail relative to the compounds of Brehove and Samour because it has a lower molecular weight. *Id.* at 44.

Petitioners disagree with Patent Owner, stating the purpose of selecting pharmaceutical doses is not to deliver the largest possible dose. Pet. Reply 17. Rather, Dr. Murthy explains that a person of ordinary skill in the art would have considered safety, side effects, stability, and cost. Ex. 1048 ¶¶ 15–16 (citing Ex. 1049, 1). Thus, according to Dr. Murthy, a

person of ordinary skill in the art would have "at a minimum, tested an active ingredient concentration of 5% by weight as part of a routine dose ranging study," which is a routine part of drug development and is well understood by those skilled in the art. *Id.* ¶¶ 17–18. Petitioners and Dr. Murthy cite the dose-ranging studies for Kerydin as typical studies conducted as part of the regulatory approval process.[20] *Id.* ¶ 19; Ex. 1040, 67–70.

On balance, we find Petitioners have the better position. We find persuasive the testimony that a person of ordinary skill in the art would not necessarily have used the largest dose possible to treat onychomycosis. Ex. 1048 ¶¶ 15–16 (citing Ex. 1049, 1). As explained above, we are persuaded that a person of ordinary skill in the art would have optimized the dosage of tavaborole through routine experimentation known in the art to achieve the 5% w/w limitation. Patent Owner's arguments that a person of ordinary skill in the art would not have considered the experimentation routine in light of the unique characteristics of boron-containing compounds and its high keratin binding affinity have been considered above and found not to be persuasive.

Accordingly, having considered the arguments and evidence presented at trial, we determine Petitioners have shown by a preponderance of the evidence that claim 10 of the '289 patent is unpatentable as obvious over

[20] Patent Owner criticizes Petitioners' reference to the Kerydin dose-ranging studies because it describes studies conducted after the '289 patent's priority date. PO Surreply 21. We do not rely on the Kerydin dose-ranging studies for purposes of this Decision, but we are persuaded that methods for performing dose-ranging studies (like that conducted in Example 9 of Samour) were known in the art by 2005. *See, e.g.*, Ex. 1010, 24:24–25:16.

Austin, Brehove, and Samour, and claims 12–15 are unpatentable as obvious over Austin, Brehove, Samour, and the Excipients Handbook.

E. Obviousness of Claims 1–15 over Combinations Including Austin and Freeman

Petitioners assert claims 1 and 2 of the '289 patent are unpatentable as obvious over Austin and Freeman, claims 4–7, 10, and 11 are unpatentable over Austin, Freeman, and Samour, and claims 3, 8, 9, and 12–15 are unpatentable over Austin, Freeman, Samour, and the Excipients Handbook. Pet. 51–61. The arguments are largely the same, but replace Brehove with Freeman. For the reasons discussed above, however, we have already determined that claims 1–15 are unpatentable as obvious over the combinations of Austin, Brehove, and other cited references. In light of that determination, we need not address whether the same claims are also unpatentable as obvious over similar combinations that rely on Freeman instead of Brehove.

III. MOTIONS TO EXCLUDE

The party moving to exclude evidence bears the burden of proving that it is entitled to the relief requested—namely, that the material sought to be excluded is inadmissible under the Federal Rules of Evidence ("FRE"). *See* 37 C.F.R. §§ 42.20(c), 42.62(a).

A. Patent Owner's Motion to Exclude (Paper 23)

Patent Owner moves to exclude Exhibit 1048, the Reply Declaration of Dr. Murthy, because Patent Owner contends the declaration exceeded the proper scope of reply evidence. According to our rules, "[a] reply may only respond to arguments raised in the patent owner's response." 37 C.F.R. § 42.23(b).

Patent Owner argues that in the reply, Petitioners and Dr. Murthy "pivoted away from relying on Samour in favor of emphasizing overlapping ranges disclosed in the remaining references and arguing that a person of ordinary skill in the art . . . would have arrived at 5% w/w through 'routine' dose-ranging studies." Paper 23, 3. As such, Patent Owner seeks to exclude the entirety of Exhibit 1048.

In response, Petitioners note that it would be improper to exclude Dr. Murthy's Reply Declaration in its entirety because Patent Owner did not timely object to the declaration in its entirety. Paper 30, 1–2. Moreover, Petitioners assert that Dr. Murthy's testimony is proper rebuttal testimony and does not raise a new issue. *Id.* at 3–4. Specifically, Petitioners assert that Dr. Murthy's testimony properly responded to Patent Owner's arguments narrowing the issue to the 5% w/w limitation. *Id.* at 5–7.

Our Rules require that "a reply may only respond to arguments raised in the corresponding opposition or patent owner response." *See* 37 C.F.R. § 42.23(b). This reasoning applies equally to reply declarations, submitted to support a party's reply brief. *See Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) (affirming exclusion of reply brief and supporting declaration). Thus, our Trial Practice Guide provides that "a reply that raises a new issue or belatedly presents evidence will not be considered. . . . The Board will not attempt to sort proper from improper portions of a reply." Office Patent Trial Practice Guide, 77 Fed. Reg. 48,756, 48,767 (Aug. 14, 2012). On the other hand, "the introduction of new evidence in the course of the trial is to be expected in *inter partes* review trial proceedings." *Genzyme Therapeutic Prod. Ltd. P'ship v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1366 (Fed. Cir. 2016). That new

evidence, however, must be responsive to an argument raised by the opposing party in its opposition brief.

We agree with Petitioners that Dr. Murthy's Reply Declaration is proper rebuttal testimony that addresses the arguments raised in the Petitioner and Patent Owner's Response. The Petition asserts that "[i]t would have been obvious to a POSITA to include tavaborole as an active ingredient in the pharmaceutical composition at a concentration of 5% as this value is within the range of preferred concentrations of active ingredient disclosed by both *Austin* and *Brehove*." Pet. 48. The Petitioner further asserts that "*Samour* specifically teaches a topically applied pharmaceutical composition with 5% w/w active antifungal ingredient." *Id.* Dr. Murthy also addressed the 5% w/w limitation in his opening declaration. Ex. 1005 ¶¶ 156–159, 164–165, 193–194. He also testified that "[f]ormulating pharmaceutical compositions involves nothing more than routine experimentation based on well-known protocols." *Id.* ¶ 142. In his reply declaration, he then properly responded to Patent Owner's arguments in its Patent Owner Response regarding the 5% w/w limitation by asserting that routine experimentation would have included dose-ranging studies. Ex. 1048 ¶¶ 2–5, 10–11.

Moreover, we authorized Patent Owner to file a Surreply in response to Petitioners' Reply. As such, Patent Owner was given an opportunity to respond to Dr. Murthy's testimony, which it did. PO Surreply 21–23. Thus, Patent Owner was provided notice of the arguments and evidence and was provided an opportunity to meaningfully respond. *See Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1080 (Fed. Cir. 2015).

Patent Owner argues that the ability to file a surreply does not cure Petitioners' violation of 37 C.F.R. § 42.23(b) because it was not permitted to

file additional evidence beyond the cross-examination testimony of Petitioners' reply declarants. Paper 33, 2–3 (citing *In re NuVasive, Inc.*, 841 F.3d 966, 973 (Fed. Cir. 2016)). Despite Patent Owner's assertion to the contrary, *In re NuVasive* supports our conclusion. In *In re NuVasive*, in IPR2013–00507 (referred to as "IPR507"), the Federal Circuit found the patent owner had sufficient notice where the petition cited the prior art text that addressed the figure that the Board ultimately relied on. *Id.* at 972. Similarly, here, Petitioners provided Patent Owner express notice in the Petition that it was relying on the concentration ranges taught by Austin and Brehove in addition to the 5% w/w concentration taught by Samour. *See* Pet. 45.

We are, therefore, not persuaded that Dr. Murthy's Reply Declaration is beyond the scope of proper reply evidence. Accordingly, Patent Owner's Motion to Exclude is *denied*.

B. Petitioners' Motion to Exclude (Paper 27)

Petitioners filed a motion to exclude various exhibits as improper expert testimony under FRE 702 and 703, improper direct testimony without an affidavit under 37 C.F.R. § 42.53, hearsay under FRE 801 and 802, and lacking adequate foundation and authentication under FRE 901. Paper 27. Even if we consider the objected-to evidence, however, we determine the challenged claims of the '289 patent are unpatentable as obvious. Thus, rather than exclude the objected-to evidence, we find the better course of action is to maintain a complete record of the evidence to facilitate public access and appellate review.

Accordingly, we *dismiss* Petitioners' Motion to Exclude *as moot*.

IV. CONCLUSION

For the foregoing reasons, we conclude that Petitioners have established by a preponderance of the evidence that claims 1–15 of the '289 patent are unpatentable as obvious over the cited prior art.

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that claims 1–15 of the ’289 patent are held unpatentable as obvious;

FURTHER ORDERED that Patent Owner’s Motion to Exclude is *denied*;

FURTHER ORDERED that Petitioners’ Motion to Exclude is *dismissed as moot*; and

FURTHER ORDERED that, because this is a Final Written Decision, the parties to the proceeding seeking judicial review of the decision must comply with the notice and service requirement of 37 C.F.R. § 90.2.

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