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Paper 80
Entered: June 6, 2018

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ACRUX DDS PTY LTD., ACRUX LIMITED, and ARGENTUM PHARMACEUTICALS LLC,
Petitioner,

v.

KAKEN PHARMACEUTICAL CO., LTD. and VALEANT PHARMACEUTICALS INTERNATIONAL, INC.,
Patent Owner.

Case IPR2017-00190[1]
Patent 7,214,506 B2

Before ERICA A. FRANKLIN, SUSAN L. C. MITCHELL, and ROBERT A. POLLOCK *Administrative Patent Judges.*

MITCHELL, *Administrative Patent Judge*.

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

[1] Case IPR2017-01429 has been joined with the instant proceeding.

I. INTRODUCTION

This is a final written decision in an *inter partes* review of claims 1 and 2 of U.S. Patent No. 7,214,506 B2 (Ex. 1001, "the '506 patent") entered pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons set forth below, we determine that Petitioner has shown, by a preponderance of the evidence, that claims 1 and 2 of the '506 patent are unpatentable under 35 U.S.C. § 103(a). *See* 35 U.S.C. § 316(e).

A. Procedural History

Petitioner Acrux DDS Pty Ltd. and Acrux Limited (collectively, "Petitioner")[2] filed a Petition (Paper 1, "Pet.") requesting an *inter partes* review of claims 1 and 2 (the "challenged claims") of the '506 patent. *See* 35 U.S.C. §§ 311–319. Petitioner relied upon Declarations of Kenneth A. Walters, Ph.D. and Jeff Karr. Exs. 1005, 1044, respectively; *see* Pet. 6–61. Patent Owner Kaken Pharmaceutical Co., Ltd. and Valeant Pharmaceuticals International, Inc. (collectively, "Patent Owner") filed a Preliminary Response. Paper 8 ("Prelim. Resp."). Patent Owner relied upon a Declaration of Yoshiyuki Tatsumi, PhD. Exs. 2003 (English translation).

Pursuant to 35 U.S.C. § 314(a), on May 1, 2017, we instituted an *inter partes* review of challenged claims 1 and 2 to determine if the claims are unpatentable under 35 U.S.C. § 103(a) as obvious over the combinations of Ogura with JP '639, '367 Patent, or Hay, or the Kaken Abstracts with JP '639, '367 Patent, or Hay. Paper 12, 5 ("Dec.").

[2] Argentum Pharmaceuticals LLC is also a petitioner in this case by virtue of joinder with IPR2017-01429.

On May 12, 2017, Argentum Pharmaceuticals LLC ("Argentum") filed a petition asserting the same grounds as the Petition in this case. *See Argentum Pharm. LLC v. Kaken Pharma. Co., Ltd.*, IPR2017-1429, Paper 2, 4. On the same day, Argentum filed a motion to join the instant case. *Id*. at Paper 3, 2. On November 13, 2017, we instituted trial in IPR2017-1429 on the same grounds as in this *inter partes* review and granted Argentum's motion to join. *See id*. at Paper 10, 7; Paper 11, 5.

Patent Owner filed its Patent Owner Response (Paper 27, "PO Resp."), along with Declarations of Dr. Tatsumi, Ph.D. (Exs. 2025), Boni E. Elewski, M.D. (Ex. 2027), and Vincent A. Thomas, CPA, CVA, CFF, ABV (Exhibit 2028) to support its positions. Petitioner filed a Reply (Paper 37, "Reply") to the Patent Owner Response along with Declarations of Dr. Walters (Ex. 1509), Jeffrey M. Weinberg, M.D. (Ex. 1510), and John C. Staines, Jr. (Exhibit 1511).

Petitioner and Patent Owner each filed several motions to seal various papers and exhibits. *See* Papers 25, 36, 50, 59, 62, 72, 77. These motions are decided in a separate order. Patent Owner filed a Motion to Strike (Paper 46), which we authorized (*see* Paper 43), and also filed a Motion to Exclude certain exhibits and portions of Dr. Walter's declarations (Paper 58). Petitioner also filed a Motion to Exclude portions of Mr. Thomas's declaration and associated exhibits. (Paper 51 (public version)). These motions are decided in a separate order.

An oral hearing was held on January 26, 2018. A transcript of the hearing is included in the record. Paper 78 ("Tr.").

B. Related Proceedings

Patent Owner indicated that there is a reissue application pending for the '506 patent. Paper 7. We ordered the examination of Reissue Application No.

15/405,171 involving the ’506 patent stayed pending the termination or completion of this *inter partes* review. *See* Paper 31.

C. The ’506 Patent (Ex. 1001)

The ’506 patent involves a method for accurately evaluating an effect of an antimicrobial agent and a therapeutic agent for onychomycosis that can be obtained using this method. *See* Ex. 1001, Abst., 2:55–62. The ’506 patent states that an object of the invention “is to provide a therapeutic agent for onychomycosis which exhibits the effect on tinea unguium by topical application and which is capable of curing tinea unguium [by a] shorter period than that of the marketed oral preparation due to good permeability, good retention capacity and conservation of high activity in nail plate as well as the potent antifungal activity thereof” and “to provide the effective therapeutic agent for onychomycosis exhibiting no side effect even if therapeutically effective amounts of it are administered sufficiently.” *Id*. at 3:40–51. The ’506 patent lists KP-103 as one of the most preferred antimicrobial agents that can be used to cure “disease such as mycosis completely, and prevent[] a relapse.” *Id*. at 9:10–13, 30–31. KP-103 is also known as efinaconazole. PO Resp. 6; Reply 1.

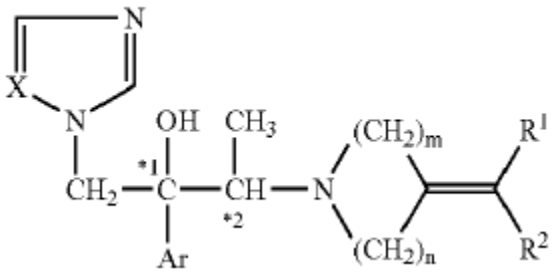
In describing the disease to be cured, the ’506 patent describes onychomycosis as a superficial mycosis caused by invading and proliferating in the nail of a human by *Trichophyton rubrum* or *Trichophyton mentagrophytes*, and in rare cases, *Microsporum*, *Epidermophyton*, *Candida*, *Aspergillus*, or *Fusarium*. *Id*. at 9:32–39. The ’506 patent includes tinea unguium caused by the *Trichophyton* species in the definition of onychomycosis, the symptoms of which include

"opacity, tylosis, destruction and deformation of [the] nail plate." *Id*. at 2:21–25, 9:40–43.[3]

The '506 patent describes the term "nail" as including "nail plate, nail bed, nail matrix, further side nail wall, posterial nail wall, eponychium and hyponychium which make up a tissue around thereof." *Id*. at 4:65–67.

D. Challenged Claims

Claim 1 is independent and claim 2 depends from claim 1. Those claims recite as follows.

> 1. A method for treating a subject having onychomycosis wherein the method comprises topically administering to a nail of said subject having onychomycosis a therapeutically effective amount of an antifungal compound represented by the following formula:
>
> (II)
>
> 
>
> wherein, Ar is a non-substituted phenyl group or a phenyl group substituted with 1 to 3 substituents selected from a halogen atom and trifluoromethyl group,
>
> R^1 and R^2 are the same or different and are hydrogen atom, C_{1-6} alkyl group, a non-substituted aryl group, an aryl group substituted with 1 to 3 substituents selected from a halogen atom, trifluoromethyl group, nitro group and C_{1-16} alkyl group, C_{2-8} alkenyl group, C_{2-6} alkynyl group, or C_{7-12} araklyl group,

[3] According to Petitioner's expert, Dr. Walters, "[O]nychomycosis, also referred to as *tinea unguium*, is a fungal infection of the nail usually caused by a group of keratinophilic fungi known as dermatophytes." Ex. 1005 ¶ 41.

m is 2 or 3,

n is 1 or 2,

X is nitrogen atom or CH, and

*1 and *2 mean an asymmetric carbon atom.

2. The method of claim 1, in which the compound represented by the formula (II) is (2R, 3R)-2-(2,4-difluorophenyl)-3-(4-methylen piperidine-1-yl)-1-(1H-1,2,4-triazole-1-yl)butane-2-ol.

Ex. 1001, 17:33–18:32.

The compound of claim 2, also known as KP-103 or efinaconazole, is the active ingredient in Patent Owner's Julia® product, "an azole antifungal indicated for the topical treatment of onychomycosis of the toenails due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*." Ex. 1043; Pet. 62; PO Resp. 6.

E. Grounds of Unpatentability

We instituted the instant trial based on the following grounds of unpatentability. Dec. 5.

References	Basis	Claims Challenged
JP '639[4] and Ogura[5]	§ 103(a)	1 and 2
'367 Patent[6] and Ogura	§ 103(a)	1 and 2
Hay[7] and Ogura	§ 103(a)	1 and 2
JP '639 and Kaken Abstracts[8]	§ 103(a)	1 and 2
'367 Patent and Kaken Abstracts	§ 103(a)	1 and 2
Hay and Kaken Abstracts	§ 103(a)	1 and 2

II. ANALYSIS

A. Claim Interpretation

In an *inter partes* review, claim terms in an unexpired patent are given their broadest reasonable construction in light of the specification of the patent in which

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[4] Yoichi Ohta and Yukari Tsutsumi, Japanese Pat. App. Pub. No. 10-226639, pub. Aug. 25, 1998 (Ex. 1011, "JP '639"). Petitioner asserts that JP '639 is prior art under 35 U.S.C. § 102(b) because the '506 patent is not entitled to the priority date of the priority document JP 11/214369. Pet. 14–22. Although Patent Owner disagrees, its states that "Petitioner's challenge to the claimed priority application is moot" because Patent Owner has shown reduction to practice before the date of the only intervening prior art, Ogura. PO Resp. 31–32.

[5] Hironobu Ogura et al., *Synthesis and Antifungal Activities of (2R,3R)-2-Aryl-1-azolyl-3-(substituted amino)-2-butanol Derivatives as Topical Antifungal Agents*, 47 CHEM. PHARM. BULL. 1417–25 (1999) (Ex. 1012, "Ogura"). Patent Owner is disputing whether Ogura is prior art based on a prior reduction to practice of the invention. *See infra* Section II.D.1.

[6] Teresa J. DeVincentis et al., U.S. Patent No. 5,391,367, issued Feb. 21, 1995 (Ex. 1013, "'367 patent").

[7] R.J. Hay, R.M. Mackie, and Y.M. Clayton, "*Tioconazole nail solution—an open study of its efficacy in onychomycosis*," 10 CLIN. AND EXPERIMENTAL DERMATOLOGY 111–15 (1985) (Ex. 1014, "Hay").

[8] H. Ogura et al., "*KP-103, a Novel Topical Antifungal Triazole: Structure-Activity Relationships of Azolylamine Derivatives*," ABSTRACTS OF THE 36TH ICAAC F78 (1996); Y. Tatsumi et al., "*In Vitro Activity of KP-103, a Novel Topical Antifungal Triazole*," ABSTRACTS OF THE 36TH ICAAC F79 (1996); Y. Tatsumi et al., "*Therapeutic Efficacy of KP-103, a Novel Topical Antifungal Triazole, on Experimental Superficial Mycosis*," ABSTRACTS OF THE 36TH ICAAC F80 (Ex. 1015, collectively, "Kaken Abstracts").

they appear. 37 C.F.R. § 42.100(b); *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2144–46 (2016). Under this standard, we interpret claim terms using "the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). "Under a broadest reasonable interpretation, words of the claim must be given their plain meaning, unless such meaning is inconsistent with the specification and prosecution history." *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1062 (Fed. Cir. 2016). Only terms in controversy must be construed and only to the extent necessary to resolve the controversy. *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999).

In our Decision on Institution, we discussed the terms "onychomycosis," "nail," and "therapeutically effective amount" as used in the challenged claims of the '506 patent. *See* Dec. 6–9. Specifically, we stated that:

> On the record before us, we find that when read in light of the Specification of the '506 patent, the broadest reasonable construction of the claim term "nail" includes "nail plate, nail, bed, nail matrix, further side nail wall, posterial nail wall, eponychium and hyponychium which make up the tissue around thereof," that includes skin structures. The fact that the '506 patent does not use the term "skin structures" is not dispositive as the Specification of the '506 patent clearly identifies skin structures surrounding the nail plate, matrix, and bed, as part of the "nail."
>
> Patent Owner further asserts that "even assuming that eponychium and hyponychium qualify as 'skin structures,' Petitioner's argument still fails because it provides no support for any construction of the term 'onychomycosis' as including infections of *just* the eponychium and/or hyponychium." Prelim. Resp. 22. This argument lacks merit on the record before us because the challenged claims require treating onychomycosis by "topically administering to a *nail* of

> said subject having onychomycosis a therapeutically effective amount of an antifungal compound . . . ." Ex. 1001, 17:33–18:2. As just discussed, "nail" includes many structures and is not limited to the nail plate, matrix, or bed, or the surrounding structures, but includes all of them. Also, "onychomycosis" is defined in the '506 as a kind of superficial mycosis, "which is caused by invading and proliferating in the *nail* of human or an animal." *Id*. at 9:32–35 (emphasis added).

Dec. 8.

We also noted in our Decision that "[a]lthough the Specification of the '506 patent does not expressly define 'therapeutically effective amount' as it does for 'nail' and 'onychomycosis,' Petitioner does provide citations to references where it alleges a 'therapeutically effective amount' is taught." Dec. 9 (citing Pet. 22–23, 28–29, 30–31, 34, 35–36, 38–39, 41, 45, 47, 49, 51, 53–54).

Patent Owner asserts that because the claims require *treating onychomycosis* by topically administering *to a nail a therapeutically effective amount* of the claimed compound, the claim term "nail" must be read in tandem with the requirements to "treat onychomycosis" by administering a "therapeutically effective amount" of a compound. PO Resp. 27–28. When the claim requirements are read "in tandem," Patent Owner asserts that "[t]he claims therefore require applying the compound to nail in an amount effective to treat onychomycosis *at least in the nail plate and nail bed* where the infection resides." PO Resp. 27–28. Patent Owner also states that "[n]otably, treatment of the eponychium and hyponychium alone would not constitute a treatment for onychomycosis, but rather for paronychia (i.e., an infection of the skin around the nail)." *Id*. at 29–30 (citing Ex. 2007, 3; Ex. 2048, 2628; Ex. 2027 ¶¶ 81–85; *see also* Ex. 1001, 1:47–50, 1:63–67, 3:40–48, 8:10–28, 9:23–26, 11:33–41, 16:58–64; Ex. 2010, 422 (focus on nail plate)).

Patent Owner concludes that "[t]reatment of onychomycosis thus requires treating the infection at least where it primarily resides in the keratinized nail plate and underlying nail bed. Treatment may *also* include eliminating infection in the skin structures surrounding the keratinous nail plate, but those skin structures cannot be singled out for treatment in isolation." PO Resp. 30–31 (citing Ex. 1001, 3:40–48 (stating effective "therapeutic agent for onychomycosis" must have "good permeability, good retention capacity and conservation of high activity in nail plate as well as the potent antifungal activity" after penetrating the plate); Ex. 1005 ¶¶ 76–77 (stating Dr. Walters admits that identifying a "therapeutically effective amount" according to the challenged claims "requires actual testing in an animal model of nail infection"); Ex. 2021, 352).

Petitioner responds that Patent Owner ignores the express definitions of "onychomycosis" and "nail" that are set forth in the '506 patent. Reply 2, 16–17. Specifically, Petitioner asserts that Patent Owner's definition of onychomycosis that excludes onychomycosis of skin structures of the nail, such as white superficial onychomycosis ("WSO" or "SWO"), is contrary to articles authored by Patent Owner's declarant, Dr. Elewski, explaining that onychomycosis usually begins in the hyponychium or nail fold, i.e. skin structures. *Id*. at 2, 16 (citing Ex. 1508, 81:14–82:8 (discussing Ex. 2010); 88:15–90:18 (discussing Ex. 1500), 91:5–92:16 (discussing Ex. 1501)). Petitioner also points to Dr. Elewski's testimony in which she "admitted that 'onychomycosis' as used in the claims is broader and includes SWO, for which 'treatment is fairly simple, . . . you can put any topical antifungal on it.'" Reply 16 (quoting Ex. 1508, 158:8–159:8).

We agree with Petitioner that Patent Owner's definition of "onychomycosis" is not the broadest reasonable construction of the term. Patent Owner applies its narrow definition of onychomycosis in order to restrict the definition of "nail" as

used in the challenged claims to require treatment of "at least the nail plate and nail bed where the infection resides." *See* PO Resp. 27–28. Petitioner is correct that the definitions that are expressly set forth in the '506 patent do not support Patent Owner's view.

The '506 patent states that "[o]nychomycosis means a kind of the above-mentioned superficial mycosis, in the other word a disease which is caused by invading and proliferating in the nail of human or an animal." Ex. 1001, 9:32–35. In discussing what is meant by "mycosis," the Specification of the '506 patent sets forth the following.

> Mycosis means a disease which is caused by invading and proliferating in the tissue of human or animal. Usually mycosis is broadly divided into *superficial mycosis* and deep mycosis. A seat of the disease lie in the *skin or visible mucosa in case of the former*, in viscus, central nervous system, subcutaneous tissue, muscle, born or articulation in case of the latter.

Id. at 5:20–26 (emphases added).

Based on these definitions in the Specification of the '506 patent, the express definition of onychomycosis includes superficial mycosis, which in turn is expressly defined as a disease that lies in the *skin or visible mucosa*. Therefore, the express definition of onychomycosis set forth in the '506 patent includes infections of skin contrary to Patent Owner's interpretation of this term to require infection of the nail plate and nail bed. *See* Ex. 1510 ¶ 46 (stating "in the late 1990s a POSA would have understood the '506 patent claim term, 'treating a subject having onychomycosis' (Ex. 1001, 17:33–18:32), to include any and all types and subtypes of onychomycosis, as broadly defined at col. 9, lines 32–29 of the '506 patent."); Ex. 1005 ¶¶ 48 (onychomycosis includes superficial mycosis), 61; Ex. 1509 ¶ 9 (noting "Dr. Elewski bases her analysis on an interpretation of [onychomycosis] that requires that the nail plate and the nail bed both be infected

'in the deeper structures of the nail' and excluding onychomycosis of the skin structures that are part of the nail (as 'nail is defined in the '506 patent), as well as superficial white onychomycosis, which is an infection on the top surface of the nail plate").

This express definition of onychomycosis also is consistent with the express definition of "nail" as provided in the Specification of the '506 patent. As we noted in our Decision on Institution, the term "nail" is expressly defined in the Specification of the '506 patent as including "nail plate, nail bed, nail matrix, further side nail wall, posterial nail wall, eponychium and hyponychium which make up a tissue around thereof." Ex. 1001, 4:65–67; *see* Dec. 3, 7. Therefore, nail includes the tissue or skin around the nail plate, nail bed, and nail matrix.

Patent Owner's reliance on a statement in the Specification of the '506 patent concerning features of an effective therapeutic agent for onychomycosis as including "good permeability, good retention capacity and conservation of high activity in nail plate as well as the potent antifungal activity" does not convince us that onychomycosis as used in the claims of the '506 patent should be limited to treating infections that involve the nail plate or nail bed. *See* PO Resp. 30–31 (quoting Ex. 1001, 3:40–48). The particular passage of the Specification upon which Patent Owner relies specifically discusses "a therapeutic agent for onychomycosis which exhibits the *effect on tinea unguium* by topical application and which is capable of curing tinea unguium [within a] shorter period than that of the marketed oral preparation . . . ." Ex. 1001, 3:41–45 (emphasis added). This passage in the Specification of the '506 patent is discussing specifically the treatment of tinea unguium, which is included in the definition of onychomycosis, but is not co-extensive with it. *See id*. at 9:40–44 (discussing tinea unguium is included as "a disease which is susceptible to treat with a therapeutic agents for

onychomycosis of the present invention"); *see also id.* at 5:30–31 (stating that [t]inea may be conventionally employed a[s] a synonym with dermatophytosis"). As discussed above, the '506 patent expressly contemplates a broader definition of onychomycosis to include superficial mycosis or diseases of the skin or visible mucosa.

Also, contrary to Patent Owner's assertions that onychomycosis must involve infection in the nail plate and nail bed, Dr. Elewski also testified that white superficial onychomycosis is a form of onychomycosis that "superficially infect[s] the top of the nail plate, so treatment is fairly simple, you can scrape it off and that would cure it or you can put any topical antifungal on it." Ex. 1508, 158:7–159:2; *see also id*. at 82:9–18 (confirming white superficial onychomycosis that infect the surface of the nail plate is a form of onychomycosis); Ex. 1510 ¶ 28 (Dr. Weinberg agreeing that "successful treatment of superficial white onychomycosis is relatively simple with topical antifungals and the same was true in the late 1990s"). Dr. Elewski also confirmed that she agreed with a statement that she made in an article authored in 1998 that distal subungual onychomycosis is the most common form of onychomycosis characterized by invasion of the nail bed and underside of the nail plate beginning in the hyponychium. Ex. 1508, 79:1–80:5 (discussing Ex. 2010). Dr. Elewski admitted that the hyponychium is skin. *Id*. at 80:13–81:13; *see also id*. 81:14–82:8 (reviewing article's discussion of proximal subungual onychomycosis that begins in the proximal nail fold, i.e. skin, through the cuticle area).

Therefore, we conclude that on this record, "nail" includes "nail plate, nail bed, nail matrix, further side nail wall, posterial nail wall, eponychium and hyponychium which make up a tissue around thereof." We also conclude on this record that "onychomycosis" is not limited to infections of the nail plate and nail

bed, but includes superficial mycosis that involves disease of the skin or visible mucosa.

B. Principles of Law

A patent claim is unpatentable under 35 U.S.C. § 103(a)[9] 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 invention was made to a person having ordinary skill in the art to which said 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 ordinary skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In that regard, an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. 398, 418 (2007); *see In re Translogic Tech., Inc.*, 504 F.3d 1249, 1259 (Fed. Cir. 2007). In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a person having ordinary skill:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is

[9] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) ("AIA"), amended 35 U.S.C. §§ 102 and 103. Because the challenged claims of the '506 patent have an effective filing date before the effective date of the applicable AIA amendments, throughout this Final Written Decision we refer to the pre-AIA versions of 35 U.S.C. §§ 102 and 103.

> likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. "*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'" *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles.

C. Level of Ordinary Skill

In its Preliminary Response, Patent Owner disagreed with Petitioner about the breadth of the level of ordinary skill in the art stating that the proper field of art for the challenged claims should be treatment of fungal infections of the nail alone, because there "is little if any overlap between treatments indicated for fungal infections of the nail and treatments for infections of the skin." Prelim. Resp. 23. Petitioner states that the level of skill in the art at the time of the invention is a person who "would have had familiarity with the biology and pathology of common fungal agents that infect the nail and skin, and a familiarity with antifungal agents and their clinical use." Pet. 21. Petitioner also states such a person would have had "(i) a bachelor's or master's degree in medicinal chemistry, biochemistry, pharmacology, and/or biology, and at least 3-5 years of experience working with topical antifungal agents, or (ii) a M.D., Pharm.D., or Ph.D. in medicinal chemistry, biochemistry, pharmacology, and/or biology and at least 1 year of experience working with topical antifungal agents." *Id*.

In our Decision on Institution, we applied Petitioner's stated level of skill set forth above "that encompasses the field of treatment of fungal infections of nails and skin." Dec. 11. In making this determination, we stated:

> We are mindful that the level of ordinary skill in the art is reflected by the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995). The art asserted against the claims in the Petition shows the overlap between treatment of fungal infections of skin and nails. *See* Ex. 1011 (testing antifungal agent on skin and hoof wall); Ex. 101 (describing use of KP-103 on skin). Also, the '506 patent defines nail in such a way as to include the skin structures surrounding the nail plate, matrix, and bed. *See supra* Section II.A.

Id.

In its Patent Owner Response, Patent Owner does not dispute our stated level of skill in the art, but relies on our statement of the relevant field involving treatment of fungal infections of nails and skin to assert that it requires skill in the treatment of both nail and skin, not just skin alone. *See* PO Resp. 24–26. Patent Owner's relies on its definition of "nail" and "onychomycosis" to include only treatment of the nail plate and nail bed to assert that the relevant field excludes experience or knowledge of disorders of the skin such as tinea pedis or tinea corporis alone. *Id*. at 25.

Patent Owner concludes the following:

> There is no basis to extrapolate between treatments indicated for fungal infections of the nail and treatments for infections of the skin. And the art was replete with effective treatments in skin or hair that simply provided no guidance for predictably treating onychomycosis in nail.
>
> A person of ordinary skill in the art would therefore recognize the specialized nature of treating onychomycosis and need to have a specific background in nail and its pathologies beyond just having knowledge of dermatophytosis in skin more generally.

Id. at 25–26 (citations omitted).

As set forth in our claim interpretation analysis above, however, we do not agree that the claim terms "onychomycosis" and "nail" are so limited. *See supra* Section II.A. As we discussed, Dr. Elewski, Patent Owner's declarant, admitted

that onychomycosis includes infections of the skin, such as the hyponychium or the proximal nail fold, in addition to the nail plate and nail bed. *Id*. Because we have determined that the term "nail" includes side nail wall, posterial nail wall, eponychium and hyponychium, which make up a tissue around the nail, and is not limited to only the nail plate, nail bed, and nail matrix, and that the term "onychomycosis" is not limited to the treatment of infections of only the nail plate and nail bed, but includes superficial mycosis that involves disease of the skin or visible mucosa, *see id*., we do not agree with Patent Owner that the relevant field of art is limited to fungal infections of the nail plate or nail bed. We apply Petitioner's stated description of the level of ordinary skill in the art here as we did in our Decision on Institution, wherein that description encompasses the field of treatment of fungal infections of nails and skin, which may be met by knowledge of fungal infections of the skin.

D. Obviousness over the Ogura with each of JP '639, the '367 patent, or Hay

Petitioner presents three challenges to claims 1 and 2 of the '506 patent based on Ogura with each of JP '639, the '367 patent, or Hay. As support, Petitioner provides detailed explanations as to how each claim limitation is met by the references and rationales for combining the references as well as detailed claim charts and the declarations of Dr. Walters (Exs. 1005, 1509), Jeffrey M. Weinberg, M.D. (Ex. 1510), and John C. Staines, Jr. (Exhibit 1511). Pet. 21–40; *see generally* Reply.

Patent Owner asserts that Petitioner fails to explain why one of ordinary skill in the art would have combined the teachings of the asserted references to arrive at the claimed invention and has failed to show a reasonable expectation of success in

making such a combination. PO Resp. 32–33. Patent Owner also presents evidence of secondary considerations. *Id*. at 34.

As an initial matter, however, Patent Owner challenges Ogura as prior art. We address this issue first as it resolves the challenges based on Ogura because we conclude that Patent Owner has shown prior reduction to practice of the invention.

1. *Ogura as Prior Art*

Patent Owner asserts that any challenge to the claims based on Ogura should be denied because the invention was reduced to practice before Ogura was allegedly published. PO Resp. 41–43. Patent Owner relies on a May 1999 Report (Ex. 2004) to establish its claim of prior reduction to practice. *Id*. at 41. This May 1999 Report discusses KP-103 or efinaconazole, the compound specifically claimed in claim 2, and encompassed by claim 1 of the '506 patent. Ex. 1043; Pet. 62; PO Resp. 6.

Regarding the May 1999 Report, Patent Owner asserts the following.

> Kaken's contemporaneous May 1999 Report uses a "guinea pig onychomycosis model and treatment efficacy of KP-103" for *in vivo* testing of efinaconazole. Ex. 2004, 1. It explains that "[w]hen KP-103 was applied 20 times, the number of fungi in the nail significantly declined, and complete curing was confirmed in the nails of 3 of 10 feet." *Id*. By comparison, similar applications of the known antifungal agents lanocoazole or terbinafine did not significantly reduce fungal colonies. *Id*.
>
> Accordingly, the May 1999 Report discloses results from a method of treating a subject (guinea pig) for onychomycosis by topically administering to the nail a therapeutically effective amount of efinaconazole. Thus, the inventors had performed a method by May 1999 that met all limitations of claims 1 and 2. The May 1999 Report also recognizes that the method worked for its intended purpose: "[f]rom these results, it is suggested that KP-103 is effective against onychomycosis in local [i.e., topical] administration." *Id*. The inventors therefore reduced to practice an embodiment of claims 1 and

> 2 of the '506 patent prior to the alleged "October 1999" date of Ogura relied upon by Petitioner.

Id. at 41–42 (citations omitted); *see* Ex. 2003 (Dr. Tatsumi's Declaration).

Petitioner responds that Patent Owner's sole reliance on the testimony of Dr. Tatsumi, an inventor, to establish when the May 1999 Report was created and the veracity of the content of the report is inappropriate. Reply 25–27. Petitioner asserts the following:

> PO provided no testimony from any non-inventor witness corroborating that the experiments were actually performed. No instrument read-outs, photographs, emails, purchase orders, analytical reports or any other objective evidence that the experiments were actually performed on the dates alleged were produced.
>
> Further, PO's arguments are highly suspect. Senda, the alleged author, is still employed by PO, but his testimony is conspicuously absent. In addition, PO filed a patent application related to methods of using efinaconazole two months after the alleged date of the Activity Report (Ex. 1002), but that application contains no mention of using efinaconazole for onychomycosis, as Dr. Tatsumi admitted. Ex. 1506, 70:17–72:9.
>
> Without independent corroboration, the Activity Report, at best, is akin to a notebook supported solely by inventor testimony.

Id. at 26–27.

Petitioner also asserts that even if the May 1999 Report was corroborated, it fails to meet all of the claim elements of the challenged claims. *Id*. at 27–28. Specifically, Petitioner states that "Dr. Tatsumi admitted that the Activity Report does not disclose amounts or weights of the compounds used, or state the chemical name for KP-103." Reply 27 (citing Ex. 1506, 53:14–19, 55:7–10, 55:20–22, 56:9–13.

Petitioner overstates what is required to establish prior reduction to practice. The discussion in *Medichem, S.A. v. Rolabo, S.L.*, a case cited by Petitioner, of

what is required to establish a prior reduction to practice by the United States Court of Appeals for the Federal Circuit ("Federal Circuit") is instructive. 437 F.3d 1157 (Fed. Cir. 2006). The Federal Circuit sets forth the following three criteria for Patent Owner to establish an actual reduction to practice: (1) construction of an embodiment or performance of a method that met all the limitations of the claim; (2) a determination that the invention would work for its intended purpose; and (3) sufficient evidence to corroborate inventor testimony regarding these events. *Id*. at 1169; *see also In re NTP, Inc.*, 654 F.3d 1279, 1291 (Fed. Cir. 2011) ("Sufficiency of corroboration is determined by using a 'rule of reason' analysis, under which all pertinent evidence is examined when determining the credibility of an inventor's testimony.") (quoting *Medichem*, 437 F.3d at 1170). The Federal Circuit provides the following further clarity on what is required to be corroborated.

> For purposes of conceptual clarity, as well as clarity of language, it should be noted that no similar condition of "corroboration" is imposed on an inventor's notebook, or indeed on any documentary or physical evidence, as a condition for its serving as evidence of reduction to practice. Of course, the credibility (and therefore the corroborative value) of an inventor's notebook may vary. Nevertheless, a notebook, unlike the oral testimony of an inventor, may be weighed, for whatever it is worth, in the final determination of reduction to practice. However, in a case involving reduction to practice, an unwitnessed notebook is insufficient on its own to support a claim of reduction to practice. Once properly admitted into evidence, documentary and physical evidence is assigned probative value and collectively weighed to determine whether reduction to practice has been achieved. This is what is meant by the maxim that documentary and physical evidence to not require "corroboration."

Medichem, 437 F.3d 1157, 1169–70 (citations omitted).

It is clear from the above discussion that the May 1999 Activity Report, written by a non-inventor, Dr. Senda, who is employed by Patent Owner, does not

need "corroboration" as inventor testimony alone would require. *See* Ex. 2004 (showing Dr. Senda, as author, signed using his seal); Ex. 2025 ¶ 16 (stating Dr. Senda prepared the May 1999 Activity Report and the Report bears Dr. Senda's seal). Although Petitioner has not preserved a hearsay objection to the May 1999 Activity Report or questioned its authenticity in its argument,[10] we note that Dr. Tatsumi testifies that these types of reports are produced in the normal course of business by Patent Owner to report on research group activities from the previous month, Ex. 2003 ¶ 6; Ex. 2025 ¶ 15, and that Dr. Tatsumi received and reviewed the May 1999 Report, Ex. 2025 ¶ 16; *see also* Ex. 1506, 41:9–12 (testifying that Dr. Tatsumi stored such Activity Reports in his personal records). We also find that the May 1999 Activity Report includes work from the April 1999 to May 1999 time period and reflects work with which Dr. Tatsumi was directly involved. Ex. 2003 ¶ 6; Ex. 2025 ¶ 16; *see also* Ex. 2004 (indicating Dr. Tatsumi is a one of the "Responsible parties").

We disagree with Petitioner that the report is akin to an unwitnessed notebook; the report is not authored by Dr. Tatsumi, but by Dr. Senda, a non-inventor. Dr. Tatsumi's inventor testimony regarding the prior reduction to practice is corroborated by the May 1999 Activity Report.

Dr. Tatsumi testified as follows about the content and the import of such content of the May 1999 Activity Report.

> The Report describes the use of Kaken's guinea pig model to test topical administration of KP-103 to treat onychomycosis. Guinea pigs were infected with a fungal solution of *T. mentagrophytes* SM-110, and

[10] Petitioner did assert in its Objections to Evidence Submitted with Patent Owner's Response that Exhibit 2004 was inadmissible as incomplete, hearsay, and lacking authentication. *See* Paper 28, 3. Petitioner did not preserve such objections in its Motion to Exclude. *See* Paper 51; 37 C.F.R. § 42.64(c) (stating a motion to exclude evidence must be filed to preserve any objection).

> the infection by this species of fungus in toenails was confirmed. Ex. 2002, 1. Test compounds included KP-103, lanoconazole, terbinafine, and control. We tested two treatment frequencies, 15 days and 20 days. Animals were euthanized, and the nails were excised and evaluated for the presence of fungus.
>
> The Report indicates that topical application of KP-103, administered 20 times, was therapeutically effective and significantly reduced the average number of fungi in the nails compared to base control (1.82 ± 0.91 versus 3.23 ± 0.74 respectively, $p < 0.05$). Ex. 2002, Table. Furthermore, KP-103 increased the number of fungus-negative toe nails, thus completely curing the nails of three out of ten toenails. Ex. 2002, Table. Significant fungus reduction efficacy was not confirmed with 20 topical applications of lanoconazole or terbinafine. Ex. 2002, Table.
>
> Based on the results of this experiment, we "conjectured that because KP-103 [has] low affinity with keratin, it exhibited good penetration in the nail plate and demonstrated excellent efficacy." Ex. 2002, 1. In addition, based on the results of this experiment, we knew that topical (or "local") administration of KP103 was effective against onychomycosis. That is, that KP-103 would be suitable for the purpose of topically treating onychomycosis. This was in contrast to existing topical treatments, which did not exhibit efficacy.
>
> Thus, as of May 28, 1999, we concluded that we had invented a method of treating a subject having onychomycosis by topically administering a therapeutically effective amount of KP-103 to the nail of the subject. Ex. 2002, 2.

Ex. 2003 ¶¶ 9–12; *see* Ex. 2025 ¶¶ 17–21.

We find that the May 1999 Activity Report and the testimony of Dr. Tatsumi concerning the Report and the work reflected in the report establish prior reduction to practice of the inventions of the challenged claims before the publication date of the Ogura reference. We credit Dr. Tatsumi's testimony concerning the May 1999 Activity Report as it reasonably explains the import of the content of the Report. As Dr. Tatsumi testified, the Report discusses the topical application of KP-103 or efinaconazole, a compound encompassed in challenged claim 1 and specifically

claimed in challenged claim 2, administered 20 times, was therapeutically effective and significantly reduced the average number of fungi in the nails of the guinea pig subjects. *See* Ex. 2003 ¶¶ 9–10; 2025 ¶¶ 18–19. The report also shows that KP-103 completely cured the fungal infection in 3 out of ten toenails. Ex. 2003 ¶ 10; Ex. 2025 ¶ 19. Dr. Tatsumi concludes based on these results reflected in the May 1999 Activity Report that topical or local administration of KP-103 or efinaconazole was effective against onychomycosis and suitable for topically treating onychomycosis. Ex. 2003 ¶¶ 11–12; Ex. 2025 ¶¶ 20–21. Therefore, Patent Owner has shown performance of a method that met all the limitations of the challenged claims requiring topically administering to a nail of said subject having onychomycosis a therapeutically effective amount of an antifungal compound, KP-103. Moreover, as discussed below, because Petitioner establishes adequately that the KP-103 of the May 1999 Report is efinaconazole, the compound set forth in claim 2, it has also established that the invention would work for its intended purpose.

Petitioner's attack on what the May 1999 Activity Report shows concerning reduction to practice is unpersuasive. Petitioner argues that the May 1999 Activity Report is deficient to show prior reduction to practice because it does not disclose amounts or weights of the compounds used or state the chemical name for KP-103. *See* Reply 27. Such alleged deficiencies are irrelevant, however, because Petitioner has not shown that the challenged claims require a particular level of efficacy necessitating Patent Owner to establish with particularity the amounts or weights of the compounds used in the experiments. It is sufficient for the report to reflect that "[w]hen KP-103 was applied 20 times, the number of fungi in the nail significantly declined, and complete curing was confirmed in the nails of 3 of 10 feet." Ex. 2004, 1 (English Translation); *see also* Ex. 1506, 53:14–19; (testifying

that 1% solution of KP-103 was used); 55:7–13 (same). Dr. Tatsumi confirmed that this meant that KP-103 was effective against onychomycosis in local administration. Ex. 2003 ¶ 11; *see* Ex. 1506, 65:5–66:5 (clarifying that the term "suggested" in the statement "it is suggested that KP-103 is effective against onychomycosis" in the May 1999 Activity Report means "would be able to expect, and it is conceivable it will happen without any mistake").

By the same token, the failure to list the specific chemical formula of KP-103 does not persuade us that Patent Owner has failed to show prior invention. As is clear from the '506 patent itself, KP-103 is defined as the specific formula in challenged claim 2. *See* Ex. 1001, 9:15–17. Identifying KP-103 as the compound that is effective against onychomycosis in local administration in the May 1999 Activity Report is enough. *See* Ex. 2004, 1.

Thus, for the foregoing reasons, we conclude that Patent Owner has established persuasively that Ogura is not prior art. The unavailability of Ogura as prior art undermines Petitioner's obviousness ground, which relies on Ogura as disclosing the antifungal activities of KP-103 or efinaconazole, a compound that falls within the scope of the challenged claims. *See* Pet. 24–30. Petitioner's additional references do not cure this deficiency. Accordingly, because we find that Ogura is not prior art to the '506 patent, we determine that Petitioner has not shown by a preponderance of the evidence that claims 1 and 2 are unpatentable over Ogura in combination with either JP '639, the '367 patent, or Hay.

E. Obviousness over Kaken Abstracts with JP '639, the '367 patent, or Hay

Petitioner presents three challenges to claims 1 and 2 of the '506 patent based on the Kaken Abstracts with either JP '639, the '367 patent, or Hay. As support, Petitioner provides detailed explanations as to how each claim limitation is met by the references and rationales for combining the references as well as

detailed claim charts and supporting Declarations of Dr. Walters (Ex. 1005, 1509), Jeff Karr (Ex. 1044), Jeffrey M. Weinberg, M.D. (Ex. 1510), and John C. Staines, Jr. (Ex. 1511). Pet. 40–55, *see generally* Reply.

Patent Owner asserts that Petitioner fails to show the unpatentability of the challenged claims because the Kaken Abstracts "offer no guidance on the therapeutic efficacy of efinaconazole when applied topically to nail." PO Resp. 35. Also, the additional art used in the combinations with the Kaken Abstracts disclose nail penetrance of compounds unrelated to the claimed compound, and one of ordinary skill in the art would have no reason to apply the claimed compounds to nail with a reasonable expectation of success in treating onychomycosis. *Id*. 47–59. Patent Owner supports its positions with the Declaration of Dr. Elewski. *See* Ex. 2027. Patent Owner also offers evidence of secondary considerations that it asserts supports the nonobviousness of the invention. PO Resp. 60–64. Patent Owner supports its assertions concerning secondary considerations with the Declaration of Mr. Thomas (Ex. 2028).

We have reviewed the complete record before us, including the parties' explanations and supporting evidence presented during this trial. We determine that given the evidence on this record, in light of the breadth of the definitions of "nail" and "onychomycosis" as used in the challenged claims, Petitioner has shown by a preponderance of the evidence that claims 1 and 2 of the '506 patent are obvious over the combination of the Kaken Abstracts with each of JP 639, the '367 patent, and Hay.

1. *Kaken Abstracts (Ex. 1015)*

The Kaken Abstracts are three abstracts involving KP-103 or efinaconazole deemed "a novel topical antifungal triazole." Ex. 1015, 113. In the first abstract F78, Kaken concluded that "the cyclic amine having methylene group at the 3

position is necessary for a broad antifungal spectrum and a potent activity. KP-103 which has a (2R,3R)-absolute configuration and a 4-methylenepiperidine moiety, showed the most potent activity and significantly lower MIC values than clotrimazole (CTZ)." *Id*.

In the second abstract F79, Kaken compared activity of KP-103 with that of clotrimazole, neticonazole, lanoconazole, and butenafine against pathogenic fungi. *Id*. Kaken concluded in the F79 abstract that

> KP-103 was the most active against *C. albicans* and *M. furfur* among the tested drugs. Its activity against *Trichophyton* spp. was almost equal to that of CTZ and NCZ, but was weaker than that of LCZ and BTF.
>
> Anti-*T. mentagrophytes* activities of the reference drugs were reduced by the addition of human serum and horny materials as reported, while that of KP-103 was not affected. Furthermore, Anti-*T. mentagrop[h]ytes* activity of KP-103 on the stripped human horny later was equal to that of LCZ and BTF. These results reflected *in vivo* efficacies.
>
> In summary, KP-103 has a broad antifungal spectrum and could keep a high activity in the horny layer where fungi reside.

Id.

In the third abstract, Kaken examined the therapeutic efficacy of KP-103 on dermatomycosis models in guinea pigs as compared with that of neticonazole, lanoconazole, butenafine, and clotrimazole. Kaken concluded:

> The efficacy of KP-103 on dermatophytosis models was superior to that of NCZ and almost equal to that of LCZ and BTF. KP-103 was effective on skin candidiasis, while the other drugs were not. To clarify the duration of retention time of the drug in skin after topical application, the prophylactic effect of KP-103 on dermatophytosis model was examined. KP-103 exerted prophylactic effect with 90% cure rate at application of 48h before infection.

> In summary, the excellent efficacy of KP-103 on dermatophytosis and skin candidiasis may be attributed to its high activity and long time retention in the horny layer.

Id.

2. *JP '639 (Ex. 1011)*

JP '639 describes a film forming antifungal agent composition that has "excellent releasability of the antifungal agent and high penetrability to the keratinous layers and is effective in treatment of trichophytosis, especially, tinea unguium." Ex. 1011, Abst. Specifically, JP '639 states that

> the inventors of the present invention found that, by using a film forming compound having a tertiary amine and adjusting the pH value of the composition to a pH range wherein the film forming compound can be dissolved or partially dissolved, it is possible to obtain unexpectedly good film formability and, thus, obtain a film forming antifungal agent composition, which has no stickiness after drying without being attached to a contact object, is excellent in adhesiveness to nails and, further, has high penetrability of the antifungal agent to keratin compared with the case wherein the pH value is not adjusted to the above described pH range.

Id. ¶ 23.

JP '639 teaches that the antifungal agent preferably is amorolfine hydrochloride because it has an extremely high water solubility in an acidic region and is thus compatible with the pH-dependency of the film forming compound. *Id*. ¶ 18. JP '639 describes testing the penetrability to keratin of the antifungal agent in its film on the skin removed from the back of an 8-week-old male hairless mouse, *see id*. ¶ 37, and testing the penetrability to nails using the hoof wall of a pig foot, *see id*. ¶ 50. In evaluating its film, JP '639 concludes that "it is possible to effectively treat trichophytosis, especially, tinea unguium." *Id*. ¶ 73.

3. *The ’367 Patent (Ex. 1013)*

The ’367 patent teaches a topical solution for fungal infections of the nails, or onychomycosis. Ex. 1013, 1:5–6. The ’367 patent states “[o]nychomycosis, also called ringworm of nails, or tinea unguium, is a fungus infection of the nails causing thickening, roughness and splitting usually caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*.” *Id*. at 1:9–12.

The topical solution as described in the ’367 patent comprises an effective amount of the antifungal tioconazole, water, an alcohol, and a gel-forming agent, so that when the topical solution is applied to the nails of a human infected with onychomycosis, it creates a reservoir from which tioconazole continuously penetrates the nail. *Id*. at 1:44–52. The ’367 patent concludes that “[i]t has now been found by in vitro microbiological tests that a topical tioconazole formulation is effective in the treatment of onychomycosis.” *Id*. at 2:27–29.

4. *Hay (Ex. 1014)*

Hay involves an open study of the efficacy of a 28% tioconazole nail solution as the sole treatment for onychomycosis caused by *Trichophyton rubrum*, *Hendersonula toruloidea*, and *Acremonium*. Ex. 1014, 111–12. Hay describes the compound as a solution which can be applied to infected nails daily. *Id*. at 112. Hay concludes that “[i]n some patients it is possible to obtain clinical and mycological cures in onychomycosis using topical therapy alone. This is of potential value to patients because the use of prolonged administration of systemically active drugs is thus avoided.” *Id*. at 115.

5. *Analysis*

Petitioner asserts that each of JP ’639, the ’367 patent, and Hay teaches the claim limitation of “a method for treating a subject having onychomycosis wherein the method comprises topically administering to a nail of said subject having

onychomycosis a therapeutically effective amount of an antifungal compound." Pet. 22–23, 30–31, 35–36, 41, 47, 51.

Petitioner points to the following passage in JP '639 as teaching this claim limitation.

> the film forming antifungal agent composition of the present invention comprises a film forming compound having a tertiary amine, an antifungal agent and water and the pH value of the composition falls in a pH range wherein said film forming compound can be dissolved or partially dissolved. As a result, it is possible to form a film, which has no stickiness when applied to nails, is excellent in adhesiveness and, further, has high releasability of the antifungal agent and excellent penetrability to keratin and the nails. Therefore, it is possible to effectively treat trichophytosis, especially, tinea unguium.

Pet. 45 (quoting Ex. 1011 ¶ 73); *see* Pet. 22–23 (citing Ex. 1011, Abst., Table 1, Fig. 5, ¶¶ 8–9, 34, 37–41, 56–57); Ex. 1005 ¶¶ 88–90.

Petitioner points to similar teachings in the '367 Patent to show the method claim limitation set forth above. Petitioner points to where the '367 patent teaches a topical solution of tioconazole that may be formulated into a composition additionally comprising water, an alcohol, and a gel-forming agent for topical application to the "nails of a human infected with onychomycosis creating a reservoir from which tioconazole continuously penetrates the nails." Pet. 30–31, 47, 49; Ex. 1005 ¶¶ 106–108. Petitioner asserts that the formula was found effective in *in vitro* microbiological tests. Pet. 31 (citing Ex. 1013, 2:27–29).

Petitioner states that Hay is a clinical study for the use of a topical nail solution containing tioconazole to treat onychomycosis in which six patients "achieved complete clinical remission and were free of infection" at a 3-month follow-up after completion of the therapy. Pet. 35–36; Ex. 1014, 1, Summary; Ex. 1005 ¶ 116.

Although Petitioner asserts that each of these references, JP '639, the '367 Patent, and Hay teach topical treatment of a nail to treat onychomycosis, Petitioner admits that none of the references teaches the use of a claimed antifungal compound. Pet. 41, 47, 51. Petitioner asserts that the Kaken Abstracts teach this claim feature by disclosing the antifungal activities of KP-103. Pet. 41–43, 47, 51–52.

Petitioner states that one of ordinary skill in the art would have had reason to improve the compositions and topical application methods of JP '639, the '367 Patent, and Hay by using the best antifungal agent for such topical therapy. *See* Pet. 43–44 (citing Ex. 1005 ¶ 131),[11] 48 (citing Ex. 1005 ¶ 138), 52 (citing Ex. 1005 ¶¶ 144–148). Petitioner asserts that one of ordinary skill in the art would have looked to KP-103 as disclosed in the Kaken Abstracts as the best antifungal agent. Petitioner states:

> The Kaken Abstracts demonstrated that KP-103 has potent antifungal activities in inhibiting the growth of *T. mentagrophytes* as demonstrated by *in vitro* studies, and is also effective in inhibiting the growth of *T. mentagrophytes*, one of the major causes of onychomycosis in humans (Ex. 1001, at 9:36-37), in *in vivo* dermatomycosis models. (Ex. 1015, at 4; Ex. 1005, at ¶¶132-133.) A person of ordinary skill in the art would have recognized that *T. mentagrophytes* is one of the major causes of onychomycosis in humans and been motivated to use KP-103 to treat a subject having onychomycosis of the nail with a reasonable expectation of success. (*Id.*

[11] Petitioner asserts a more specific rationale for combining the teachings of the JP '639 with the Kaken Abstracts because JP '639 taught azole antifungal agents and KP-103 is such an azole compound as taught by the Kaken Abstracts. Pet. 43 (citing Ex. 1015, 4). Specifically, Petitioner asserts that a "person of ordinary skill in the art would have been motivated to improve the compositions and topical application method of JP '639 using potent azole antifungal compounds that are effective against the microorganisms that cause onychomycosis and that are not inactivated by keratin." Pet. 43–44.

> at ¶132.) This is so because KP-103 was known to have potent antifungal activity against *T. mentagrophytes* and, as disclosed in the Kaken Abstracts, to not be inhibited by keratin, the major structural component of nails (because its activity was not affected by the addition of horny materials to the testing medium). (*Id*.)

Pet. 44–45, 48–49, 52–53.

Petitioner specifically noted the broad definition of "nail" in the '506 patent strengthened the reason to combine the teachings of the Kaken Abstracts with each of JP '639, the '367 Patent, or Hay. Petitioner states:

> Notably, the '506 patent defines "nail" broadly to include the skin structures surrounding the nail, including the eponychium and hyponychium. (Ex. 1001 at 4:65-67). The Kaken Abstracts demonstrate that KP-103 is therapeutically effective in treating *T. mentagrophytes* infections of the skin *in vivo*. *See, e.g.*, Ex. 1015, at 4, F80. Therefore, a person of ordinary skill in the art would have been motivated to apply KP-103 to treat *T. mentagrophytes* infections of the nail as nail is broadly defined in the '506 patent.

Pet. 44 n.10; *see* Pet. 48 n.11; Pet. 53 n.12.

Patent Owner responds that one of ordinary skill in the art would not have had a reason to use efinaconazole or KP-103 to treat onychomycosis because, with a relatively high molecular weight and low keratin affinity, one of ordinary skill in the art at the time of the invention would have understood that these two properties would hinder therapeutic efficacy in nails for which efinaconazole had not been tested. PO Resp. 32, 38–40; *see* PO Resp. 56–59. Patent Owner asserts that none of JP '639, the '367 Patent, nor Hay provides any reason to use efinaconazole, "as they only evaluate nail penetrance for unrelated compounds and, do not establish efficacy even for the tested agents in treating onychomycosis." PO Resp. 33, 47–56.

Patent Owner asserts that one of ordinary skill in the art would have had no reasonable expectation of success that efinaconazole's effectiveness in treating

fungal infections of the skin would translate to a similar efficacy in treating onychomycosis. PO Resp. 33, 35–37. Patent Owner supports this view by pointing to the long gap in time between when efinaconazole's efficacy in skin models was disclosed and when the inventors developed a model to test efficacy in nail and tested efinaconazole in that model to identify its efficacy in treating onychomycosis. *Id*. at 34.

Patent Owner concludes:

> Petitioner has done nothing more than identify old references evaluating efinaconazole's efficacy *in vitro* or in skin and pointed to other references evaluating structurally unrelated agents that allegedly penetrated nail. Given the numerous other antifungals available in the art, the well-documented uncertainty in predicting effective nail treatments, and the repeated failures with those other agents, Petitioner's conclusions represent a classic example of impermissible hindsight bias using the '506 patent itself as a roadmap.

Id.; *see also* PO Resp. 40 ("Dr. Walter's previous work confirms that permeability to the keratinized horny layers of skin provided no real guidance, as the nail plate's 'permeability properties have been *inferred without foundation* from the behavior of other horny tissues'" (quoting Ex. 2020, 28)); *id.* (citing Ex. 2021, 352; Ex. 2048, 2628).

Additionally, Patent Owner outlines the success of Jublia® to support its position that claims 1 and 2 are patentable. PO Resp. 60–64. Specifically, Patent Owner asserts that there is a nexus between the commercial success of Jublia® because it uses efinaconazole to topically treat onychomycosis as set forth in challenged claim 2. PO. Resp. 60. According to Patent Owner, as the first successful topical monotherapy treatment approved for onychomycosis that does not require an inconvenient nail management system, Jublia®'s surprising efficacy "translated directly into success in the market." *Id*. at 63. Patent Owner assert that the alleged success of Jublia® is not simply due to advertising. *Id*. at 64.

Patent Owner asserts the following details concerning Julia®'s commercial success.

> Julia® saw over two million prescriptions in just its first two years on the market and sales revenue of more than $1 billion, accounting for 60% of total market revenue in the first full year the product was on sale. In fact, Julia® almost singlehandedly shifted the market for onychomycosis treatment from oral to topical therapy.
>
> The immediate and dramatic increase in prescriptions and sales for topical treatments of onychomycosis after the release of Julia® also highlights the long felt, unmet need for an effective topical anti-fungal treatment.

Id. at 63 (citing Ex. 2028 ¶¶ 9–11, 22–23).

In view of the teachings of the Kaken Abstracts, we agree with Petitioner on this record that the Kaken Abstracts point to KP-103 as being known to have potent antifungal activity against *T. mentagrophytes*, one of the major causes of onychomycosis. Pet. 41, 44 (citing Ex. 1001, 9:36–37; Ex. 1015, 4). The Kaken Abstracts also teach that KP-103 is not affected by keratin, the major structural component of nails, because its activity was not affected by the addition of horny materials to the testing medium. *See* Pet 44–45 (citing Ex. 1005 ¶ 132). Additionally, Petitioner's declarant Dr. Walters testifies

> It is my opinion that a person of ordinary skill in the art would have recognized that *T. mentagrophytes* is one of the major causes of a onychomycosis in humans and been motivated to use KP-103 to treat a subject having onychomycosis of the nail with a reasonable expectation of success. This is so because KP-103 was known to have a potent antifungal activity against *T. mentagrophytes* and, as disclosed in the Kaken Abstracts, to not be inhibited by keratin, the major structural component of nails (because its activity was not affected by the addition of horny materials to the testing medium). (Ex. 1015, at 4.)
>
> Notably, the '506 patent defines "nail" broadly to include the skin structures surrounding the nail, including the eponychium and hyponychium. (Ex. 1001, at 4:65–67). The Kaken Abstracts

> demonstrate that KP-103 is therapeutically effective in treating *T. mentagrophytes* infections of the skin *in vivo*. *See, e.g.*, Kaken Abstracts, Ex. 1015, at 4, Abstract F80. Therefore, a person of ordinary skill in the art would have been motivated to apply KP-103 to treat *T. mentagrophytes* infections of the nail as nail is broadly defined in the '506 patent.

Ex. 1005 ¶¶ 132–33; Pet. 44–45.

Patent Owner's argument to the contrary is not persuasive. Patent Owner asserts that the Kaken Abstracts only report *in vitro* work and testing on animal skin, and "offer no guidance on the therapeutic efficacy of efinaconazole when applied topically to nail." PO Resp. 35. Patent Owner relies on the testimony of Dr. Elewski to support this position. Dr. Elewski, however, makes her evaluation of what the Kaken Abstracts teach one of ordinary skill in the art through the lens of an overly narrow view of onychomycosis and nail. *See* Ex. 1510 ¶ 27 (Dr. Weinberg stating "[t]hroughout her declaration, Dr. Elewski bases her analysis on an interpretation of this term as requiring that the nail plate and the nail bed both be infected 'in the deeper structures of the nail' and excluding both onychomycosis of the skin structures that make up the nail (as expressly defined in the '506 patent) as well as white superficial onychomycosis (a superficial infection of the nail plate).

Dr. Elewski describes onychomycosis as follows.

> Onychomycosis is a fungal infection of the nail unit, more commonly found in toenails than fingernails, affecting about 10% of the U.S. population. The most common causes are the dermatophytes *Trichophyton rubrum* and *Trichophyton mentagrophytes*, and sometimes *Epidermophyton floccosum*; these dermatophyte infections are also referred to as tinea unguium. The defining feature of onychomycosis is the *location of the infection*. The fungal infection resides *in the nail bed and/or nail plate*, and can also reside in the nail matrix.

Ex. 2027 ¶ 30 (citations and Figure omitted).

In addressing the broader definition of "nail" as expressly set forth in the '506 patent, Dr. Elewski uses this overly narrow definition of onychomycosis to restrict the parts of the nail that are "treating a subject having onychomycosis" according to the challenged claims of the'506 patent to the nail plate and nail bed. *See* Ex. 2027 ¶ 83. Dr. Elewksi states that the "reference to 'nail' in the claim simply refers to the area receiving the applied drug, but the treatment must still exhibit efficacy against onychomycosis. That in turn requires treating the infection where it primarily resides—in the nail plate and nail bed." *Id*. (citing Ex. 2007, 3; Ex. 2048, 2628); *see* Ex. 1510 ¶ 29 (Dr. Weinberg opining that Dr. Elewski's meaning of "nail unit" is much narrower than the express definition in the '506 patent and the art-recognized meaning of the term).

Applying this definition of onychomycosis requiring infection of the nail bed and/or nail plate, Dr. Elewski testifies that because the Kaken Abstracts test efinaconazole *in vitro* in a guinea pig model of skin infection, the "Kaken abstracts offer no insight on the therapeutic efficacy of efinaconazole when applied topically to nail in patients with onychomycosis." Ex. 2027 ¶ 89. Dr. Elewski dismisses the evidence in Kaken Abstract F78 of the effectiveness of KP-103 against *T. mentagrophytes*, one of the major causes of onychomycosis, because "[n]otably, *T. mentagrophytes* infection is also often found in skin infections. The use of these strains indicates to me that the abstract assessed efinaconazole's broad spectrum of activity rather than providing any guidance on efficacy in onychomycosis specifically." Ex. 2027 ¶ 90. Such testimony shows that Dr. Elewski is applying too narrow of a construction of onychomycosis as an infection of the nail plate and nail bed, but not any associated skin structures.

Dr. Elewski's conclusion concerning the Kaken Abstracts confirms application of an erroneous interpretation of onychomycosis and nail as used in the claims of the '506 patent. Dr. Elewski concludes as follows.

> In summary, the Kaken Abstracts compared efinaconazole to lanoconazole and butenafine against *T. mentagrophytes* in the "stripped human horny layer" (i.e., skin) because the data is intended to show a progression of research on the *skin* efficacy of efinaconazole, starting *in vitro* and working towards a guinea pig model of skin infection, not work demonstrating any clear evidence of topical efficacy in nail. Extrapolation from the skin data to efficacy in treating onychomycosis is not supported scientifically . . . The art clearly recognized the difficulty assuming data showing effects in skin would translate to efficacy in nail.

Ex. 2027 ¶ 94.

In contrast, Drs. Walters and Weinberg apply the broadest reasonable construction of "nail" and "onychomycosis" as used in the challenged claims of the '506 patent. In applying the broadest reasonable interpretation of these claim terms, Dr. Walters and Dr. Weinberg show how Dr. Elewski misconstrues the teachings of the Kaken Abstracts using her narrower construction. *See* Reply 11–18; Ex. 1509 ¶¶ 46–71; Ex. 1510 ¶¶ 39–45. Dr. Walters cites to statements in the Kaken Abstracts showing efficacy of KP-103 or efinaconazole against the same fungal strains that Dr. Elewski readily acknowledges cause onychomycosis, *T. rubrum and T. mentagrophytes*. *See* Ex. 1509 ¶¶ 46–48; Ex. 1005 ¶¶ 126–128, 129, 132 (stating "KP-103 was known to have potent antifungal activity against *T. mentagrophytes* and, as disclosed in the Kaken Abstracts, to not be inhibited by keratin, the major structural component of nails" (because its activity was not affected by the addition of horny materials to the testing medium) (citing Ex. 1015, 4)). Dr. Walters concludes:

> Thus, it strains credulity for Dr. Elewski to argue that a POSA would not have been motivated to treat onychomycosis using the subject

> antifungal agent upon reading a reference that lists onychomycosis treatments in the introduction section, and provides data demonstrating potent, broad-spectrum antifungal activity against the microorganisms known to cause onychomycosis, unique low adsorption to keratin and high release from keratin. Based on everything that was known by 1999, a POSA would have been motivated to use KP-103, a potent, broad-spectrum antifungal compound that is not affected by keratin, to improve topical formulations for treating onychomycosis with a reasonable expectation of success.

Ex. 1509 ¶ 48.

Dr. Weinberg agrees with Dr. Walters. Dr. Weinberg testifies that

> a POSA would have recognized that the Kaken Abstracts demonstrated good antifungal activity against the organisms that were known to be responsible for 90% of onychomycosis. Moreover, as defined in the '506 patent, the nail includes skin structure and onychomycosis was known to initiate with invasion of those skin structure—notably the hyponychium and eponychium—by the infectious fungi. This topical treatment of onychomycosis involves treating infection of the skin.
>
> The efficacy of KP-103 against the same fungal strains that cause onychomycosis was tested in the Kaken Abstracts.

Ex. 1510 ¶¶ 39–40 (citations omitted).

On this record, we agree with and credit Dr. Walters' and Dr. Weinberg's testimony. Again, what is fatal to Patent Owner's argument, on the record before us, is the breadth of the definition of "nail" and "onychomycosis" in the '506 patent to include skin structures and superficial onychomycosis in which the disease lies in the skin or visible mucosa, respectively. The Kaken Abstracts show that KP-103 is effective *in vitro* and *in vivo*, at least with respect to skin, in treating fungal infection. *See* Exs. 1015, 2036–2038.

a. Rationale to Combine and Reasonable Expectation of Success

In addressing the merits of the combinations of the Kaken Abstracts with JP '639, the '367 patent, or Hay, we agree with Petitioner that Patent Owner appears

to view the references in isolation and does not examine what the references would teach one of ordinary skill in the art as a whole. *See KSR*, 550 U.S. at 418 (stating an obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ"); *see* Reply, 1, 7–11. We also agree that Patent Owner applies too stringent a test for a reasonable expectation of success in combining the teachings of the asserted references. *See* Reply 7–9.

Petitioner relies on JP '639 for the statement of the problem to be solved by the combination of the teaching of the nail lacquer references and the Kaken Abstracts, namely, the difficulty of treating tinea unguium because of the lack of ability of antifungal agents to penetrate the keratinuous layers of the nail. Pet. 43. Relying on testimony by Dr. Walters, Petitioner states that "[a] person of ordinary skill in the art would have been motivated to improve the compositions and topical application method of JP'639 using potent azole antifungal compounds that are effective against the microorganisms that cause onychomycosis and that are not inactivated by keratin." Pet. 43–44; Ex. 1005 ¶ 131. Dr. Walters makes similar statements with regard to the '367 patent and Hay, for instance, relying on Hay's statement that "cures of onychomycosis are possible after topical therapy" and may result from topical therapy alone. *See* Pet. 48 (stating "a person of ordinary skill in the art would have been motivated to treat onychomycosis with topical therapy, and would have been motivated to find the best antifungal agent for such topical therapy"); Ex. 1005 ¶ 138; Pet. 52 (same regarding combination with Hay); Ex. 1005 ¶ 145.

Instead of addressing what the combination of references would teach or suggest to one of ordinary skill in the art, Patent Owner responds that JP '639, the

’367 patent, and Hay tested compounds other than KP-103 or efinaconazole in nail. PO Resp. 47; *see* Ex. 1509 ¶¶ 29–45; Ex. 1510 ¶¶ 31–36. Patent Owner states that “[n]ot only were the other tested compounds structurally unrelated to efinaconazole, but they were evaluated, at best, for their ability to penetrate the nail, so they lacked proven efficacy.” PO Resp. 47. Patent Owner concludes that because

> the art suggested efinaconazole would not work in nail, while the other antifungal agents mentioned in the cited secondary references likewise were never tested for efficacy . . . Petitioner fails to explain how or where the prior art disclosed or even suggested a “therapeutically effective amount” of efinaconazole for the topical treatment of onychomycosis given the lack of testing for efinaconazole or even any of the secondary agents.

Id. at 47–48.

We have explained above that Patent Owner’s contention that the art suggested that efinaconazole would not work in nail relies upon an improperly narrow interpretation of the claim terms “nail” and “onychomycosis.” *See supra* Section II.E.5. Thus, Patent Owner’s arguments hinge on a requirement that is not in the challenged claims, treatment of onychomycosis in the nail plate or nail bed. As discussed in our claim interpretation section, the broadest reasonable interpretations of nail and onychomycosis include skin structures and treatment of those skin structures. *See supra* Section II.A. Because of the breadth of the challenged claims, many of Patent Owner’s arguments are misdirected because Patent Owner is presenting arguments that do not address the breadth of the challenged claims.

For instance, Patent Owner’s assertions that the high molecular weight and low keratin affinity would have discouraged one of ordinary skill in the art from using efinaconazole to treat onychomycosis as defined as infection in the nail plate

or nail bed is not persuasive when the claims encompass treating onychomycosis in skin. *See* PO Resp. 32–33. This breadth of the challenged claims is also supported by testimony from Dr. Elewski. As Petitioner points out, Dr. Elewski testified that white superficial onychomycosis is a form of onychomycosis "that is only superficially infecting the top of the nail plate, so treatment is fairly simple, you can scrape it off and that would cure it or *you can put any topical antifungal on it*." Ex. 1508, 158:7–159:2 (emphasis added). Dr. Elewski confirmed that the challenged claims requiring a method of treating onychomycosis might encompass such white superficial onychomycosis. *Id*. at 159:3–8.

Also, Patent Owner's point that one of ordinary skill in the art would have had no reasonable expectation of success that efinaconazole's effectiveness in treating fungal infections of the skin would translate to a similar efficacy in treating onychomycosis is not well taken because onychomycosis, as defined in the '506 patent, includes infection in skin. PO Resp. 33. Requiring one of ordinary skill in the art to make such a leap is unnecessary in light of the breadth of the claims.

Patent Owner's assertions concerning the lack of efficacy of the treatments taught in JP '639, the '367 patent, and Hay is also inadequately supported. PO Resp. 47–59. Dr. Walters points to where JP '639 states that by using its topical formulation to deliver an antifungal agent, "it is possible to effectively treat trichophytosis, especially, tinea ungium." Ex. 1509 ¶ 39 (citing Ex. 1011 ¶ 73). Dr. Walters and Dr. Weinberg point to similar statements in the '367 patent and Hay. *See* Ex. 1509 ¶ 33 (noting the '367 patent states that the topical formulation is effective in the treatment of onychomycosis), ¶ 39 (noting Hay teaches that in some patients it is possible to "obtain clinical and mycological cures in onychomycosis using topical therapy alone"); Ex. 1510 ¶ 32 (addressing the '367

patent), ¶ 35–36 (addressing Hay). We credit the testimony of Drs. Walters and Weinberg and find that each of JP ’639, the ’367 patent, and Hay teaches an effective compound.

As Dr. Walters notes, the question is not whether one of ordinary skill in the art would have been led to use efinaconazole because of the particular compound(s) taught by JP ’639, the ’367 patent, and Hay, but whether one of ordinary skill in the art would have been motivated by the disclosures of JP ’639, the ’367 patent, or Hay in combination with the Kaken Abstracts, as a whole, to improve the topical formulations and methods of JP ’639, the ’367 patent, or Hay by using efinaconazole, “a highly potent antifungal compound with broad spectrum activity that is not inactivated by keratin and has high retention in the horny layer, in the topical formulation and method” of JP ’639, the ’367 patent, or Hay. Ex. 1509 ¶¶ 31, 35, 45; *see* Ex. 1510 ¶¶ 33, 36. Both Drs. Walters and Weinberg answer this question in the affirmative and on this record, we agree.

On the record before us, we credit Dr. Walters’ and Dr. Weignberg’s testimony and find that Petitioner has shown sufficient rationale for one of ordinary skill in the art to combine the teachings of the Kaken Abstracts with the teachings of each of JP ’639, the ’367 patent, or Hay with a reasonable expectation of success.

b. Secondary Considerations

The fourth *Graham* factor that we consider in determining whether the challenged claims would have been obvious over the asserted combination is objective evidence of nonobviousness presented by the Patent Owner. As set forth above, Patent Owner offers evidence of the unexpected results, commercial success, industry praise, and long-felt, but unmet need for its product, Jublia®, to establish that the claims would not have been obvious. *See supra* Section II.5.

"For objective evidence of secondary considerations to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention." *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) (quotation and emphasis omitted). In evaluating the import of Patent Owner's secondary considerations evidence on whether the challenged claims would have been obvious, we apply a presumption of nexus between the secondary considerations and the challenged claims when the Patent Owner "shows that the asserted objective evidence is tied to a specific product and that product 'is the invention disclosed and claimed in the patent.'" *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1329 (Fed. Cir. 2016) (citation omitted). That presumption, however, is rebuttable. *Id.*

(1) presumption of nexus and scope of challenged claims

Here, we determine that Patent Owner is entitled to a presumption of a nexus between secondary considerations relating to Jublia® and the subject matter of the challenged claims because Patent Owner has shown that the secondary considerations are tied to a specific product, Jublia®, that is covered by challenged claims 1 and 2. *See* PO Resp. 60; Ex. 1043, 1. We find, however, that Petitioner has rebutted the presumption of nexus as discussed below.

(2) reasonably commensurate with the scope of the claims

The Federal Circuit has stated that "there is no nexus unless the evidence presented is 'reasonably commensurate with the scope of the claims.'" *ClassCo, Inc. v. Apple, Inc.*, 838 F.3d 1214, 1220 (Fed. Cir. 2016) (citations omitted). Here, Patent Owner presents evidence from Dr. Elewski to establish the nexus between the secondary considerations evidence involving Jublia® and the challenged claims. *Id*. at 60–64. Dr. Elewski testifies:

> Clinical experience with Jublia® demonstrates the surprisingly superior efficacy of treating onychomycosis by applying efinaconazole topically to a nail of a patient, thereby embodying the elements claimed in the '506 patent. I understand that secondary considerations relevant to a patent assessment include evidence of surprising results and long-felt but unresolved need in the art. In the late 1990s, doctors seeking to treat onychomycosis had a long expressed the desire for a topical treatment of onychomycosis. As a practicing dermatologist at the time, I likewise recognized this long-felt need.

Ex. 2027 ¶ 132.[12] Dr. Elewski also testified that Jublia® received industry praise. *See id*. ¶¶ 135–137.

In evaluating the secondary considerations evidence of surprising results, long-felt need, industry praise, and commercial success, all considerations resulting from Jublia®, however, Dr. Elewski applies definitions of nail and onychomycosis that we have found are too narrow as they are limited to infection of nail plate and nail bed. *See supra* Section II.A; Ex. 2027 ¶¶ 132–141. For instance, in evaluating the evidence of the long-felt need, Dr. Elewski distinguishes between treating skin versus nail fungal infections stating that "[i]n 1998, for example, I concluded that although '[t]opical agents [were] in wide use for treating localized dermatophytic infections,' unfortunately 'these topical drugs are generally ineffective against fungal infections of the nails due to their inability to penetrate the entire nail unit and eradicate the infection.'" Ex. 2027 ¶ 133; *see also* Ex. 1510 ¶ 67 (stating Dr. Elewski's opinions narrowly focus on penetration of a drug compound through the nail plate while ignoring the broad definitions of nail as including skin structure and onychomycosis").[13]

[12] Mr. Thomas provided testimony concerning the commercial success of Jublia® and long-felt need. *See* Ex. 2028 ¶¶ 9–11 (summary of opinions).
[13] Mr. Thomas testifies concerning the causal link of Jublia®'s success to the challenged claims of the '506 patent. *See* Ex. 2028 ¶¶ 23–30. Mr. Thomas,

Jublia® is indicated as a "topical solution, 10% is an azole antifungal indicated for the topical treatment of onychomycosis of the toenail(s) due to *Trichophyton rubrum* and *Trichophyton mentagrophytes*." Ex. 1043, 1. Therefore, the product at issue for all asserted secondary considerations, Jublia®, is directed to treatment of specific fungal infections in toenails, and not to a "nail" or to treat "onychomycosis," as those terms are broadly defined and claimed in the '506 patent. *See* Ex. 1509 ¶ 38 (stating Dr. Elewski conceded that the claims of the '506 patent cover methods for treating both fingernails and toenails, onychomycosis caused by any microorganism, and that the term "onychomycosis" in the claims includes white superficial onychomycosis) (citing Ex. 1508, 156:16–159:2).

Dr. Tatsumi testified that efinaconazole or KP-103, the active ingredient in Jublia®, was originally studied for its effect on tinea pedis, a disorder of the skin, as described in the Kaken Abstracts, but ultimately such research was "put aside" by Patent Owner. *See* Ex. 2003 ¶¶ 10–12. Dr. Tatsumi testified:

> The Kaken Abstracts explained that KP-103 was a novel antifungal that had been developed for topical treatment of tinea pedis and that KP-103 showed broad spectrum antifungal activity and positive cure rates against that fungal infection. The progression of *in vitro* experiments in the Kaken Abstracts from MIC activity testing, to testing in stripped horny layer, and then on guinea pig skin illustrates our research focus on tinea pedis and the direction of that work.
>
> Kaken began phase I clinical trials related to using KP-103 to treat tinea pedis in November 1996. Following the conclusion of the phase I trial in November 1997, the company decided to stop any

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however, appears to apply the same inappropriately narrow constructions of nail and onychomycosis as Dr. Elewski. *See, e.g.*, Ex. 2028 ¶ 24 (stating "I understand that, prior to the '506 patent, KP-103 (a.k.a. efinaconazole) was a known antifungal, *but only for its use in treating skin conditions—not toenail fungus*) (emphasis added).

> additional clinical trials or research on KP-103 and the project was subsequently put aside.
>
> To my knowledge, the clinical significance of KP-103 for treating onychomycosis had not yet been recognized by Kaken or by anyone at the ICAAC meeting, nor had I heard of anyone else suggesting at that time to use KP-103 for the indication. Once the KP-103 project was put aside, we were permitted to publish the data from our 1992-1993 research evaluating KP-103's efficacy in tinea pedis.

Id. ¶¶ 10–12.

The evidence of secondary considerations relating to Julia® that is used to treat specific infections of toenails has a nexus to only part of the claimed methods because the definitions of "nail" and "onychomycosis" as used in the claims is broader to encompass treatment of the skin or visible mucosa. *See supra* Section II.A. Dr. Tatsumi's testimony concerning the ultimate abandonment of the study of the use of Julia's active ingredient to treat skin diseases such as tinea pedis supports the conclusion that any secondary considerations concerning Julia inform our patentability analysis for only part of the scope of the claimed methods. As our analysis of the obviousness inquiry "centers on whether 'the claimed invention *as a whole*" would have been obvious," Patent Owner's evidence is of limited value because it cannot support a nexus between the secondary considerations and the full scope of the challenged claims. *Rambus Inc. v. Rea*, 731 F.3d 1248, 1257–1258 (Fed. Cir. 2013) (citing 35 U.S.C. § 103).

Therefore, because the method for Julia®'s use is not reasonably commensurate with the claims of the challenged claims, we find that Petitioner has rebutted the presumption of nexus for the secondary considerations relating to Julia®. Also, as Petitioner points out, claim 1 encompasses many compounds other than efinaconazole used in Julia®. *See* Reply 18 (stating "in light of the breadth of claim 1, the evidence [of secondary considerations] represents only a

sliver of the claimed subject matter); Ex. 1510 ¶ 63 (stating "scope of claim 1 of the '506 patent is much broader than Jublia® not only in terms of the breadth and variation in the claimed compound, but also the formulation used in Jublia®, which is not part of the claims and is covered by at least five Orange Book listed patents that were filed about a decade or more after the '506 patent was first filed"); *In re Kao*, 639 F.3d at 1068 (indicating evidence of secondary considerations for one embodiment may not establish that the evidence is commensurate with the scope of the claims if no adequate basis is provided to support the conclusion that other embodiments falling within the claim will behave in the same manner). For this additional reason, the method for using Jublia® is not commensurate in scope with challenged claim 1.

Thus, we find that Petitioner rebuts the presumption of a nexus between the secondary considerations of Jublia® and the subject matter of challenged claims 1 and 2 because of the lack of commensurate scope between the claimed subject matter and the secondary considerations. Based upon that finding, we conclude that the secondary considerations presented by Patent Owner do not weigh in favor of a finding that the subject matter of the claims would not have been obvious. We also, however, address the substance of the evidence of secondary considerations.

(3) Unexpected result

Patent Owner asserts that in the face of long-felt, but unmet need,

> when Jublia® came on the market and demonstrated efficacy almost comparable to an oral treatment without the concomitant side effects, it represented a real and surprising advance in the ability to treat onychomycosis by topical application to the nail.
>
> Efinaconazole is the primary active ingredient in Jublia®, which was the first topical monotherapy treatment approved for onychomycosis. One other topical formulation existed at the time (Penlac®), but it required a comprehensive nail management system

> that included regularly seeing a healthcare professional to remove unattached infected nails. Jublia® does not require an inconvenient nail management system.

PO Resp. 61–62 (citations omitted); *see also* Ex. 1508 (Dr. Elewski stating that treatment with Penlac® also "required regular debridement of the nail").

Patent Owner's evidence, however, links the alleged unexpected results for topical use of efinaconazole with the unclaimed feature of being a monotherapy where nail management, such as debridement, is not required. *See* Ex. 1001, 17:33–18:32 (claims 1 and 2 employ the open transitional term "comprises").

Petitioner also provides evidence that we credit that Jublia®'s efficacy was only incremental over that of Penlac®. *See* Reply 20; Ex. 1504, 4 (FDA stating concerning efinaconazole solution for the treatment of onychomycosis that preliminary efficacy analysis "claims to show a primary efficacy response rate of about 16%, which is similar to at least one currently approved therapy" and "[a]pproximately 85% of subjects would fail to respond to your proposed treatment"); Ex. 1510 ¶ 72 (stating Jublia®'s clinical trials involved patients with less severe nail involvement than Penlac® and also utilized other topical antifungals for tinea pedis indicating "a higher efficacy rate for Jublia® could have reasonably been expected simply based on these study design differences"); *see also* Ex. 1510 ¶ 69 (stating "Jublia® is only indicated for patients having mild to moderate cases of onychomycosis, i.e. 'patients 18 years and older (18 to 70 years of age) with 20% to 50% clinical involvement of the target toenail, without dermatophytomas or lunula (matrix) involvement'").

We conclude that Patent Owner's evidence of unexpected results is weak and insufficient to support the nonobviousness of the challenged claims.

(4) Commercial success

Patent Owner states that "Jublia® saw over two million prescriptions in just its first two years on the market and sales revenue of more than $1 billion, accounting for 60% of total market revenue in the first full year the product was on sale. In fact, Jublia® almost singlehandedly shifted the market for onychomycosis treatment from oral to topical therapy." PO Resp. 63, (citing Ex. 2028 ¶¶ 9–10, 22).

Petitioner responds that blocking patents owned by Patent Owner render its evidence insufficient. Reply 19. Specifically, Petitioner states that

> PO ignores that its prior-issued U.S. Patent 5,620,994 ("'994 patent") covered the chemical compound genus of claim 1, fungicide compositions of those compounds, and methods of treating mycosis by their administration. Ex. 1007, claims 1, 5, 9. Regarding claim 2, the '994 patent claimed efinaconazole itself, *any* fungicide composition comprising efinaconazole, and a process of treating mycosis by administering it (Ex. 1007, claims 4, 8, 12), and U.S. Patent 5,962,476 ("'476 patent") covered fungicide compositions comprising efinaconazole, (Ex. 1505, claim 1).

Reply 19 (citations omitted).

We agree that even assuming Patent Owner's evidence of commercial success has a nexus to the challenged claims and is sufficiently supported,[14] it is

[14] Petitioner asserts that Mr. Thomas failed to consider whether previously-issued patents blocked potential competitors and failed to provide sufficient support for his assertions concerning sales data and marketing spend. Reply 21–23. We need not reach these additional issues because we find that assuming commercial success evidence, it is rendered weak by the '994 and '476 patents as discussed above.

weak in light of the Patent Owner's '994 and '476 patents. Petitioner has shown that the claims of the '994 and the '476 patents cover using the compounds of challenged claim 1 and, specifically, efinaconazole of challenged claim 2 for treating mycosis, of which onychomycosis is a particular type. *See* Ex. 1007, 17:50–18:57 (claims 1,4,5,8,9, 12); Ex. 1001, 9:32–39 (describing onychomycosis as a superficial mycosis); *see also* Ex. 1505, 19:36–20:35 (claiming fungicide compositions comprising efinaconazole). Because Patent Owner could preclude others from using the compounds of challenged claims 1 or 2 to treat mycosis, which includes onychomycosis, barring market entry before expiration of those patents, Patent Owner's evidence of commercial success is weak and insufficient to support the nonobviousness of the challenged claims. *See Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (patent barring entry supported a finding commercial success evidence was weak); *Galderma Labs, LP v. Tolmar, Inc.*, 737 F.3d 731, 740–41 (Fed. Cir. 2013) (finding "[w]here 'market entry by others was precluded due to blocking patents, the inference of non-obviousness of the asserted claims, from evidence of commercial success, is weak").

(5) Industry praise

Patent Owner states the following with regard to industry praise for Julia®.

> The favorable outcomes from Julia®'s clinical trials were applauded by the industry and generated significant anticipation for its release. *See, e.g.*, Ex. 2084, 3. Ex. 2027, ¶¶ 135–137. Efinaconazole was named a Top Ten Innovation in Podiatry in 2018, 1, written up in "Microbe" in 2014 (Ex. 2058, 267), and was nominated to the PRIX GALIEN award in 2015 (Ex. 2059, 2). This praise and recognitation reflected the features claimed in the '506 patent, i.e., efinaconazole's surprising efficacy in treating onychomycosis after topical treatment. Ex. 2017, 17; Ex. 2055, 171; Ex. 2027, ¶ 140.

PO Resp. 62.

Petitioner responds that the evidence of praise is due to the use of efinaconazole to topically treat mycosis, which is covered by an earlier issued patent and is merely the reporting of expected results. Reply 20. Petitioner also asserts that the praise itself is equivocal, and Dr. Elewski did not consider whether the source of the praise were paid consultants of Patent Owner. *Id*. at 20–21.

We agree with Petitioner that the praise cited by Patent Owner indicates the treatment of onychomycosis with efinaconazole shows promise, but is equivocal. *See, e.g.* Ex. 2084, 3 (stating Julia® "shows promise in comparison to the currently available topical prescription and over-the-counter options"); Ex. 2017, 17 (stating Julia® "appears to represent an important advance"). We also note that the authors of the pieces praising Julia® were associated with Patent Owner. *See* Ex. 2084, 2 (stating that author Dr. Gupta has been a clinical trials investigator for and served as a speaker or consultant for Valeant Canada); Ex. 2017, 8 (stating author Dr. Del Rosso serves as consultant and/or speaker for Valeant).

Therefore, we conclude that Patent Owner's evidence of industry praise is weak and insufficient to support the nonobviousness of the challenged claims.

(6) Long-felt, but unmet need

Patent Owner points to a desire in the late 1990s to treat onychomycosis topically with many different agents being considered, "but none had proven efficacy in the topical treatment of onychomysocis." PO Resp. 61 (citing Ex. 2027 ¶¶ 133–134).

Petitioner points out that Penlac® was FDA-approved in 1999 before Julia®. Petitioner again points to the FDA's comments concerning the similarity of efficacy response rates between Julia® and Penlac®, noting the following.

> Any efficacy difference between Jublia® and Penlac® is merely one of degree, not kind, and not probative of nonobviousness. Further, because Loceryl®, Trosyl®/Trosyd®, and Penlac® were approved and marketed in the 1990s , [Patent Owner's] assertions of failure and long-felt umet [need] should be rejected.

Reply 24. Petitioner concludes that Patent Owner "topically applied a known compound with known activity against known causes of onychomycosis and observed predictable success." *Id*.

We agree that Patent Owner ignores at least one other topical treatment for onychomycosis, Penlac® that has at least some recognized efficacy. *See* Ex. 1504, 4; Ex. 1510 ¶¶ 72 (comparing Penlac® to Jublia® and discussing FDA comments). We also agree with Petitioner that the difference between the efficacy of Jublia® and Penlac® would not tend to establish that there was a long-felt, but unmet need for a topical treatment for onychomycosis nor show failure of others.

Therefore, we conclude that Patent Owner's evidence of long-felt, but unmet need is weak and insufficient to support the nonobviousness of the challenged claims.

6. *Conclusion*

In sum, we find that the combinations of the Ogura with each of JP '639, the '367 patent, or Hay teach or suggest each and every element of claims 1 and 2. We also find that an ordinarily skilled artisan would have been motivated to combine Ogura with either JP '639, the '367 patent, or Hay, and would have had a reasonable expectation of success in achieving the claimed invention. We find that although Patent Owner showed a presumption of nexus between secondary considerations concerning Jublia® and the subject matter of the claims, Petitioner rebutted that presumption showing that the secondary considerations evidence is not commensurate in scope with the challenged claims. We also additionally find

that Patent Owner failed to persuasively show unexpected results, commercial success, industry praise, and long-felt, but unmet need for its product Jublia®. Even if such evidence of secondary considerations were shown, it would not outweigh the strong evidence presented for the first three *Graham* factors concerning the obviousness analysis. *See Wyer v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010) (stating secondary considerations of nonobviousness "simply cannot overcome" a strong case of obviousness) (citations omitted). Because of the breadth of the claims includes treatment of skin or visible mucosa using efinaconazole, we conclude that the inventions represent no more than "the predictable use of prior art elements according to their established functions," which cannot be overcome by secondary consideration evidence. *See KSR*, 550 U.S. at 417. After carefully considering the arguments and evidence we find that the record as a whole weighs in favor of a conclusion that the challenged claims would have been obvious.

III. CONCLUSION

After reviewing the information presented in the Petition and the Patent Owner Response, as well as the evidence of record, we determine that Petitioner has shown by a preponderance of the evidence that claims 1 and 2 of the '506 patent are unpatentable under 35 U.S.C. § 103(a) over the combinations of the Kaken Abstracts with each of JP '639, the '367 patent, or Hay.

IV. ORDER

Accordingly, it is

ORDERED that claims 1 and 2 of U.S. Patent No. 7,214,506 B2 have been shown by a preponderance of the evidence to be unpatentable; and

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

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