Paper 1, November 21, 2017

In the United States Patent and Trademark Office

Before the Patent Trial and Appeal Board

FLATWING PHARMACEUTICALS, LLC,
Petitioner,
v.
ANACOR PHARMACEUTICALS, INC.,
Patent Owner

U.S. Patent No. 9,566,290 to Baker *et al.*
Ser. No. 15/134,286, filed April 20, 2016
Issue Date: February 14, 2017

Title: BORON-CONTAINING SMALL MOLECULES

Inter Partes Review No. 2018-00170

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,566,290 UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. §§ 42.100 *et. seq*.

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EXHIBIT LIST

Pursuant to 37 C.F.R. § 42.63(e), petitioner provides the following exhibit list with the exhibit number, a brief description of each exhibit, and where applicable the short form used herein.

EXHIBIT[1]	DESCRIPTION	SHORT FORM
Ex. 1001	U.S. Patent No. 9,566,290	'290 Patent
Ex. 1002	Prosecution History of the '290 Patent	
Ex. 1003	Declaration of Stephen Kahl, Ph.D	Kahl Decl.
Ex. 1004	Curriculum Vitae of Stephen Kahl, Ph.D	
Ex. 1005	Declaration of S. Narasimha Murthy, Ph.D	Murthy Decl.
Ex. 1006	Curriculum Vitae of S. Narasimha Murthy, Ph.D	
Ex. 1007	Austin et al., PCT Pub. No. WO 1995/033754	*Austin*

[1] As indicated in Petitioner's mandatory disclosure of related matters, *infra* at xi, this petition is one of four that Petitioner has filed concurrently, requesting *inter partes* review of U.S. Patents Nos. 9,549,938 B2, 9,566,289 B2, 9,566,290 B2, and 9,572,823 B2. To avoid confusion, Petitioner has numbered the same or corresponding exhibits consistently across all four Petitions, and in each filing has omitted Exhibits not discussed in that Petition.

EXHIBIT[1]	DESCRIPTION	SHORT FORM
Ex. 1008	Brehove, U.S. Patent Pub. No. 2002/0165121	*Brehove*
Ex. 1009	Freeman et al., PCT Pub. No. WO 2003/009689	*Freeman*
Ex. 1010	Samour et al., U.S. Patent No. 6,224,887	*Samour*
Ex. 1011	*Intentionally omitted- Exhibit number not used*	
Ex. 1012	U.S. Patent No. 7,582,621	'621 Patent
Ex. 1013	Prosecution History of the '621 Patent	
Ex. 1014	Final Written Decision, *Coalition for Affordable Drugs X LLC v. Anacor Pharmaceuticals, Inc.*, IPR2015-01776 (P.T.A.B. Feb. 23, 2017), Paper 70	IPR '776, FWD
Ex. 1015	U.S. Patent No. 7,767,657	'657 Patent
Ex. 1016	Prosecution History of the '657 Patent	
Ex. 1017	Final Written Decision, *Coalition for Affordable Drugs X LLC v. Anacor Pharmaceuticals, Inc.*, IPR2015-01780 (P.T.A.B. Feb. 23, 2017), Paper 70	IPR '780, FWD
Ex. 1018	Final Written Decision, *Coalition for Affordable Drugs X LLC v. Anacor Pharmaceuticals, Inc.*, IPR2015-01785 (P.T.A.B. Feb. 23, 2017), Paper 70	IPR '785, FWD
Ex. 1019	U.S. Patent No. 4,202,894	'894 Patent
Ex. 1020	Murdan, Sudaxshina. "Drug delivery to the nail following topical application." *International journal of pharmaceutics* 236, no. 1 (2002): 1-26.	Murdan 2002
Ex. 1021	BioborJF® Specification Sheet (2015)	
Ex. 1022	BioborJF® Material Safety Data Sheet (2004)	
Ex. 1023	*Intentionally omitted- Exhibit number not used*	

EXHIBIT[1]	DESCRIPTION	SHORT FORM
Ex. 1024	*Intentionally omitted- Exhibit number not used*	
Ex. 1025	National Center for Biotechnology Information (NCBI), PubChem Compound Database, CID=6440876, *available at* https://pubchem.ncbi.nlm.nih.gov/compound/6440876 (retrieved on May 26, 2017)	
Ex. 1026	National Center for Biotechnology Information (NCBI), PubChem Compound Database, CID=3198, *available at* https://pubchem.ncbi.nlm.nih.gov/compound/3198 (retreived on May 26, 2017)	
Ex. 1027	National Center for Biotechnology Information (NCBI), PubChem Compound Database, CID=11499245, *available at* https://pubchem.ncbi.nlm.nih.gov/compound/11499245 (retrieved on May 26, 2017)	
Ex. 1028	Meds. & Healthcare Prods. Regulatory Agency, Curanail 5% Nail Lacquer (Amorolfine Hydrochloride) PL 10590/0049, UK Public Assessment Report (approved July 4, 2006)	
Ex. 1029	National Center for Biotechnology Information (NCBI), PubChem Compound Database, CID=22497760, *available at* https://pubchem.ncbi.nlm.nih.gov/compound/22497760 (retrieved on May 26, 2017)	
Ex. 1030	National Center for Biotechnology Information (NCBI), PubChem Compound Database, CID=61764, *available at* https://pubchem.ncbi.nlm.nih.gov/compound/61764 (retrieved on May 26, 2017)	
Ex. 1031	Mertin, Dirk, and Lippold, Bernhard C. "In-vitro permeability of the human nail and of a keratin membrane from bovine hooves: Prediction of the penetration rate of antimycotics through the nail plate and their efficacy." *Journal of pharmacy and pharmacology* 49, no. 9 (1997): 866–872	Mertin 1997

EXHIBIT[1]	DESCRIPTION	SHORT FORM
Ex. 1032	Groziak, Michael P. "Boron therapeutics on the horizon," *American journal of therapeutics* 8, no. 5 (2001): 321–328	Groziak 2001
Ex. 1033	National Center for Biotechnology Information (NCBI), PubChem Compound Database, CID=66827, available at https://pubchem.ncbi.nlm.nih.gov/compound/66827 (retrieved on May 26, 2017)	
Ex. 1034	National Center for Biotechnology Information (NCBI), PubChem Compound Database, CID=2775922, available at https://pubchem.ncbi.nlm.nih.gov/compound/2775922 (retrieved on May 26, 2017)	
Ex. 1035	*Intentionally omitted- Exhibit number not used*	
Ex. 1036	Alley, Michael R. *et al*. "Recent progress on the topical therapy of onychomycosis." *Expert Opinion on Investigational Drugs* 16, no. 2 (2007): 157-167	Alley 2007
Ex. 1037	Rock, Fernando L. *et al*. "An Antifungal agent inhibits an aminoacyl-tRNA synthetase by trapping tRNA in the editing site." *Science* 316 (2007):1759-1761	Rock 2007
Ex. 1038	Queller, Jenna N. & Bhatia, Neal. "The dermatologist's approach to onychomycosis," *Journal of Fungi* 1 (2015): 173-184	Queller 2015
Ex. 1039	Elewski, Boni E. *et al*. "Efficacy and safety of tavaborole topical solution 5%, a novel boron-based antifungal agent, for the treatment of toenail onychomycosis; Results from 2 randomized phase-III studies." *Journal of American Academic Dermatology* 73, no. 1 (2015): 62-69	Elewski 2015
Ex. 1040	FDA Medical Review of NDA 240-427	
Ex. 1041	FDA Clinical Pharmacology and Biopharmaceutics Review(s) of NDA 240-427	
Ex. 1042	NDA 240-427 Product Label	

EXHIBIT[1]	DESCRIPTION	SHORT FORM
Ex. 1043	Brief of Appellant-Patent Owner, Anacor Pharmaceuticals, Inc. v. Joseph Matal, No. 17-1947 (Fed. Cir. Aug. 4, 2017)	

MANDATORY NOTICES

Petitioner provides the following mandatory disclosures pursuant to 37 C.F.R. § 42.8, which are excluded from the petition type-volume limitations pursuant to § 42.24.

1. Real Parties-In-Interest, § 42.8(b)(1)

The real parties-in-interest are FlatWing Pharmaceuticals, LLC, Rajneesh Ahuja, and Wicker Pharmaceuticals, LLC (collectively "FlatWing" or "Petitioner").

2. Related Matters, § 42.8(b)(2).

There are no judicial matters pending that would affect, or be affected by, a decision in the proceeding.

Administrative matters that would or could affect or be affected by a decision in a proceeding instituted on this petition are United States Patent Applications Ser. No. 15/355,393 and Ser. No. 15/355,813.

This petition is one of four petitions that Petitioner has filed concurrently, requesting *inter partes* review of U.S. Patents Nos. 9,549,938 B2, 9,566,289 B2, 9,566,290 B2, and 9,572,823 B2. Docket numbers for those P.T.A.B. proceedings are not yet available, but each of the four would or could affect, or be affected by, a decision in any of the other three proceedings

In addition, although not currently subject to administrative proceedings that would affect or be affected by a decision in a proceeding instituted on this petition, issued patents which assert the same claim of priority as U.S. Patent No. 9,566,290 and have substantially the same specification are:

- U.S. Patent No. 7,582,621
- U.S. Patent No. 7,767,657
- U.S. Patent No. 8,039,451
- U.S. Patent No. 8,115,026
- U.S. Patent No. 8,440,642
- U.S. Patent No. 8,722,917
- U.S. Patent No. 8,889,656
- U.S. Patent No. 9,353,133
- U.S. Patent No. 9,549,938
- U.S. Patent No. 9,572,823
- U.S. Patent No. 9,566,289

3. Lead and Back-Up Counsel, § 42.8(b)(3)

The following are designated as lead counsel and back-up counsel, pursuant to 37 C.F.R. § 42.10. A Power of Attorney is being filed concurrently herewith.

Lead counsel is:

Philip D. Segrest, Jr. (Reg. No. 39,021)

Back-up counsel is:

Eric J. Rakestraw (Reg. No. 68,740).

4. Service Information, § 42.8(b)(4)

Papers concerning this matter should be served on the following:

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(iv) Telephone number

(312) 655-1500

(v) Facsimile Number

(312) 655-1501

INTRODUCTION

FlatWing requests *inter partes* review under 35 U.S.C. §§ 311–319 and cancellation of claims 1–12 of U.S. Patent No. 9,566,290 ("'290 patent," Ex. 1001). The Office is authorized to charge petition fees and deficiencies to Deposit Acct. No. 23-0920, Cust. ID No. 24628. The '290 patent which relates to a method of treating nail fungus by topical application is invalid over prior art which taught the use of the claimed compound as a fungicide for which a person of ordinary skill in the art ("POSITA") would have had a reasonable expectation of success.

GROUNDS FOR STANDING

Petitioner certifies pursuant to 37 C.F.R. § 42.104(a) that the '290 patent is available for *inter partes* review and that Petitioner is not estopped or barred from requesting *inter partes* review challenging the identified '290 patent claims on the grounds identified herein. Petitioner is a person who may petition for *inter partes* review under 37 C.F.R. § 42.101, and this petition is timely under 37 C.F.R. § 42.102.

BACKGROUND

I. Scope And Content Of The Prior Art

A. Boron-Containing Compounds In General.

Boron-containing compounds were well known to a POSITA before February 16, 2005. (Ex. 1003, Kahl Decl. ¶ 30.) Like other skilled artisans, Dr.

Kahl (one of petitioner's declarants) has been studying boron-containing compounds as therapeutic agents for over 45 years, including the administration of boron-containing compounds to humans as a treatment. (Ex. 1003, Kahl Decl. ¶ 30.)

Groziak 2001 (Ex. 1032) published a review of the then-current state of research and development concerning boron-based therapeutics for use in humans. (Ex. 1032, Groziak 2001 at 1–2[2]; Ex. 1003, Kahl Decl. ¶ 31.) In particular, Groziak 2001 recognized that it was "not at all surprising to find that most of the boron-based therapeutics currently on the horizon are either boronic acids themselves or boron heterocycles that are simply internally complexed versions of boronic acids." (Ex. 1032, Groziak 2001 at 2; Ex. 1003, Kahl Decl. ¶ 31.) Dr. Kahl explains that the statement in Groziak 2001 is correct, because boronic acids and boron heterocycles often share similar functional properties based on the unique chemical properties of boron itself. (Ex. 1003, Kahl Decl. ¶ 31.)

Boron-containing compounds are generally considered safe. (Ex. 1003, Kahl Decl. ¶ 32.) One notable exception is trialkylboranes, which are compounds with

[2] Throughout this Petition, page citations refer to the consecutive page numbers added in the exhibit label. Paragraph, column, and line number citations refer to the numbering system used in the original document.

the general formula BR_3 where R is an alkyl group. (Ex. 1003, Kahl Decl. ¶ 32.) Trialkylboranes can spontaneously combust under certain conditions. (Ex. 1003, Kahl Decl. ¶ 32.) The oxaboroles disclosed by the art discussed *infra* such as *Austin*[3] are **not** trialkylboranes, and a POSITA would recognize that the boron-containing compounds of *Austin* are generally considered safe. (Ex. 1003, Kahl Decl. ¶ 32.)

Dr. Kahl explained there is no reason a POSITA would have been discouraged from selecting an oxaborole as disclosed by *Austin* for consideration as a topical therapeutic in humans. (Ex. 1003, Kahl Decl. ¶ 33; *see also* Ex. 1014, IPR '776, FWD at 27; Ex. 1017, IPR '780, FWD at 33–34; Ex. 1018, IPR '785, FWD at 30.) As further explained *infra* and in Dr. Kahl's declaration (Ex. 1003), based on *Austin*'s disclosure of tavaborole[4] as one of three preferred anti-fungal compounds for the treatment of *Candida albicans*, a POSITA would (i) consider the compound as obvious to try as a starting point for developing a topical

[3] Ex. 1007, Austin *et al.*, PCT Pub. No. WO 1995/033754 ("*Austin*").

[4] Tavaborole is referred to as 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole in the '290 patent and as 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole in *Austin*, both of which are the same compound. *See, e.g.,* Ex. 1014, IPR '776, FWD at 7.

composition to treat fungal infections and (ii) have a reasonable expectation of success in doing so. (Ex. 1003, Kahl Decl. ¶ 33.)

B. Prior Art Patents And Printed Publications.

Not all boron-based compounds are bioactive. (Ex. 1003, Kahl Decl. ¶ 34.) If a molecule is known to be bioactive against a fungus, such as *Candida albicans* (which is a cause of onychomycosis), a POSITA would consider that molecule as obvious to try for therapeutic use in humans. (Ex. 1003, Kahl Decl. ¶ 34.) A POSITA would have been particularly motivated to try such a compound when other prior art (such as *Brehove*[5] and *Freeman*[6], *infra*) demonstrates that boron-based compounds are effective against the pathogens that cause onychomycosis, including *Candida albicans* and dermatophytes. (Ex. 1003, Kahl Decl. ¶ 34.)

1. *Austin*[7]

Austin (Ex. 1007) discloses just such bioactivity (making it obvious to try for therapeutic use in humans) with its three preferred compounds, in particular tavaborole. (Ex. 1007, *Austin* at 39; Ex. 1003, Kahl Decl. ¶ 35.) It is the exact same

[5] Ex. 1008, Brehove, U.S. Patent Pub. No. 2002/0165121 ("*Brehove*").

[6] Ex. 1009, Freeman *et al.*, PCT Pub. No. WO 2003/009689 ("*Freeman*").

[7] *Supra*, n.3.

compound claimed for use in the '290 Patent and was not novel in February 2005. (Ex. 1003, Kahl Decl. ¶ 35; Ex. 1005, Murthy Decl. ¶ 57.)

Austin not only discloses "5- and 6-fluoro or bromo-1,3 dihydro-1hydroxy-2,1-benzoxaborole" (i.e., tavaborole), it includes tavaborole among "[p]referred compounds" on the front page of the publication. (Ex. 1007, *Austin* at [57] (Abstract); Ex. 1003, Kahl Decl. ¶ 36; Ex. 1005, Murthy Decl. ¶ 57.) In Table 9, it reports the antifungal bioactivity of the 5-fluoro (Example 64), 5-bromo (Example 68), and 6-fluoro (Example 70) compounds. (Ex. 1007, *Austin* at 39; Ex. 1003, Kahl Decl. ¶ 36; Ex. 1005, Murthy Decl. ¶ 59.) Of the preferred compounds, tavaborole (5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole) demonstrated the lowest Minimum Inhibitory Concentration ("MIC") values, as low as five (5) parts per million ("ppm"), against several pathogens, including *Candida albicans*. (Ex. 1007, *Austin* at 39; Ex. 1003, Kahl Decl. ¶ 36; Ex. 1005, Murthy Decl. ¶ 60.) In other words, of the three preferred compounds tested, tavaborole inhibited the visible growth of *Candida albicans* (a fungus that causes onychomycosis, sometimes in conjunction with dermatophytes) at the lowest level of concentration. *Austin* further discloses that compounds containing an "oxaborole ring" are "particularly effective" as fungicides. (Ex. 1007, *Austin* at 3:35–40, 12:16–19, 39; Ex. 1005, Murthy Decl. ¶¶ 57, 62.)

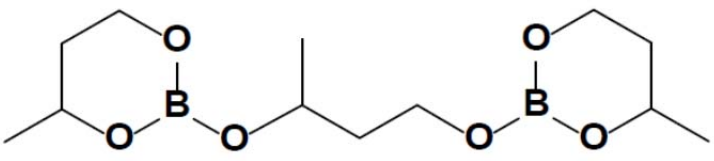
Austin also discloses preparation of benzoxaborole derivatives, specifically teaches tavaborole, even including its melting point and elemental analysis, and formulations including tavaborole. (Ex. 1007, *Austin* at 24:1–15, 25 [Table 5], and 38:15–26; Ex. 1005, Murthy Decl. ¶ 58.) *Austin* further teaches that the "concentration of the oxaborole in the biocide composition is . . . preferably from 1 to 50%, especially from 5 to 30% and more especially from 10 to 20% by weight relative to the total weight of the biocide composition." (Ex. 1007, *Austin* at 9:5–9; Ex. 1005, Murthy Decl. ¶ 60.) *Austin* provides that "oxaborole . . . is preferably formulated in a composition together with a carrier," carriers including "water or a water-miscible organic solvent," where "suitable water-miscible organic solvents are . . . alcohols such as ethanol or glycols such as . . . propylene glycol." (Ex. 1007, *Austin* at 8:11–38; Ex. 1005, Murthy Decl. ¶ 60.)

Thus, *Austin* discloses a biocide composition formulated with tavaborole as a preferred fungicide to effectively inhibit *Candida albicans* (which is one of the fungi that cause onychomycosis) and in carriers including water-miscible solvents, such as ethanol and propylene glycol, at preferred concentrations of 5 to 30% and 10 to 20% by weight relative to the total weight of the biocide composition. (Ex. 1007, *Austin* at 8:34–39, 9:5–9; Ex. 1005, Murthy Decl. ¶¶ 61, 63.) As of February 16, 2005, a POSITA would consider the preferred compound of *Austin*, which is the exact same compound recited in claims 1–12 of the '290 Patent, obvious to try

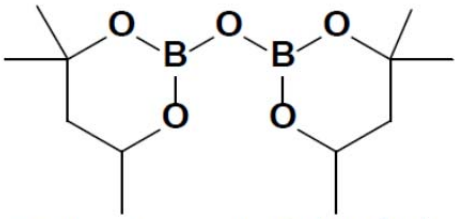
to successfully treat onychomycosis in humans based on its disclosed anti-fungal activity and structural similarities, e.g., boron-based cyclic compounds. (Ex. 1003, Kahl Decl. ¶ 45.)

2. *Brehove*[8]

Brehove is a U.S. patent application publication that disclosed the use of boron-containing compounds as anti-fungal agents to treat onychomycosis in humans more than a year before the priority date of February 16, 2005. (Ex. 1003, Kahl Decl. ¶ 37; Ex. 1005, Murthy Decl. ¶¶ 64–65.) *Brehove* disclosed the effective use of the following boron-containing compounds to treat onychomycosis in humans:



2,2'-(1-methyltrimethylene dioxy) bis (4-methyl-1, 3, 2-dioxaborinane)



2,2'-oxybis (4, 4, 6-trimethyl-1, 3, 2-dioxaborinane)

(Ex. 1003, Kahl Decl. ¶ 38.)

Brehove discloses the topical application of boron-based compounds to "treat and prevent the spread of nail infections or onychomycosis caused by

[8] *Supra*, n.5.

bacteria, fungi and other pathogens." (Ex. 1008, *Brehove* at [57] (Abstract), ¶ [0003]; Ex. 1005, Murthy Decl. ¶ 65.) *Brehove* states that "[o]nychomycosis is a nail disease of the toes and fingers typically caused by the organisms *Candida albicans*, *Tricophyton mentagrophytes*, *Tricophyton rubrum*, or *Epidermpophyton floccusum*." (Ex. 1008, *Brehove* ¶ [0005]; Ex. 1003, Kahl Decl. ¶ 39.). *Brehove* acknowledges that boron-based compounds "have long been known to exhibit biocidal activity." (Ex. 1008, *Brehove* ¶ [0007]; Ex. 1005, Murthy Decl. ¶ 65.) *Brehove* specifically discloses that these boron-based compounds are effective *in vitro* against *Candida albicans*, which is a cause of onychomycosis: "This invention also comprises a method of treating onychomycosis by topical application of a composition containing, as an active ingredient, at least one member selected from the group consisting of 2,2'-(1-methyltrimethylenedioxy) bis-(4-methyl-1,3,2-dioxaborinane) and 2,2'-oxybis (4,4,6-trimethyl-1, 3,2-dioxaborinane)." (Ex. 1008, *Brehove* ¶¶ [0017], [0032]–[0033], Table 1; Ex. 1003, Kahl Decl. ¶ 39.) *Brehove*, consistent with *Austin*, recognizes that formulations containing boron-based compounds have "powerful potency against *Candida albicans*. . . . effectively kill[ing] the most common pathogen causing onychomycosis." (Ex. 1008, *Brehove* ¶ [0018]; Ex. 1005, Murthy Decl. ¶ 65.) *Brehove* recognizes that *Trichophyton rubrum* and *Trichophyton mentagrophytes* are the common causes of onychomycosis, along with *Candida albicans*, and that

there was a motivation to try a topical application effective against the pathogens causing onychomycosis. (Ex. 1008, *Brehove* ¶¶ [0005], [0016]; Ex. 1005, Murthy Decl. ¶ 65.)

Brehove taught preparing topical compositions containing these boron-based compounds were "highly effective" to successfully treat humans suffering from onychomycosis. (*See, e.g.*, Ex. 1008, *Brehove* ¶¶ [0030]–[0038]; Ex. 1003, Kahl Decl. ¶ 40; Ex. 1005, Murthy Decl. ¶ 68.) This is the same pathogen inhibited in *Austin* with a boron-based compound. (Ex. 1003, Kahl Decl. ¶ 40.)

Not only did *Brehove* successfully treat humans with this boron-based compound, the compound was commercially sold as an industrial biocide for fuel under the trade name BioborJF®. (Exs. 1021, 1022; Ex. 1003, Kahl Decl. ¶ 40.) These compounds were previously sold commercially in antifungal additives for leaded motor fuels in order to improve combustion efficiency, and U.S. Patent No. 2,741,548 had taught their synthesis. (Ex. 1008, *Brehove* ¶¶ [0015], [0023]; Ex. 1005, Murthy Decl. ¶ 67.) These compounds had been used under the trade name BioborJF® as an antifungal fuel additive since 1965. (*See* Exs. 1021, 1022; Ex. 1005, Murthy Decl. ¶ 67.) The BioborJF® specification sheet explains:

BioborJF® was specially formulated and introduced in 1965 to one of the harshest and most safety-conscious industries in the world, the commercial and military jet aircraft industry. For over 45 years **BioborJF®** has maintained and even enhanced its position as the worldwide leader in the disinfection of microbial growth in both jet engines and jet fuel storage tanks, in addition to the marine diesel work boat and pleasure boat markets.

(Ex. 1021 at 1; Ex. 1005, Murthy Decl. ¶ 67.) BioborJF® is a recognized antifungal for industrial applications.

BioborJF® kills fungi, bacteria and **micro-organisms** which cause **fuel tank contamination...**

Plus

- **Disperses** and prevents sludge
- **Prevents** clogged filters
- **Adds** lubricity to low sulfur fuels, exceeding ASTM Standards
- **Recommended** by airframe and equipment manufacturers around the world **(See back for current list)**
- MIL-S-53021A

(Ex. 1021 at 1; Ex. 1005, Murthy Decl. ¶ 67.) The material safety datasheet for BioborJF® from January 1, 2004, discloses its active ingredients as 2,2'-(1-methyltrimethylene dioxy) bis-(4-methyl-1, 3, 2- dioxaborinane) and/or 2,2'-oxybis (4, 4, 6-trimethyl-1, 3, 2-dioxaborinane), the very same compounds used to treat onychomycosis in humans by *Brehove*:

2. COMPOSITION/INFORMATION ON INGREDIENTS

Common Name	CAS#	Approximate % (w/w)
Substituted dioxaborinanes	See below*	95.0
Naphtha	8030-30-6	4.5
Non-hazardous and other ingredients below reportable levels		Balance

*2,2' - (1-methyltrimethylenedioxy) bis - (4-methyl-1, 3, 2-dioxaborinane);
2,2' - oxybis (4, 4, 6 - trimethyl-1, 3, 2-dioxaborinane) (CAS No.: 8063-89-6).

(Ex. 1022 at 1; Ex. 1005, Murthy Decl. ¶ 66.)

Brehove specifically applied topical compositions containing the active ingredient in BioborJF® to five volunteers who presented with onychomycosis. (Ex. 1008, *Brehove* ¶¶ [0034]–[0038]; Ex. 1005, Murthy Decl. ¶ 69.) In all five examples, the topical application of the compositions directly to the infected nail, or cuticle surrounding the infected nail, effectively treated the onychomycosis with "[n]o skin irritation" seen or observed, and the patent stated "no side effects are evident." (Ex. 1008, *Brehove* ¶¶ [0022], [0030], [0034]–[0038]; Ex. 1005, Murthy Decl. ¶ 69.)

Brehove further describes a number of topical formulations of the boron-based compounds, including "[o]ne formulation [that] is conveniently applied nightly in a petroleum jelly or mineral oil base"; "[d]ilute compositions of the active compounds in alcohol or acetone base [that have] the ability to deliver concentrated active ingredient as the solvent evaporates"; and "[a]nother formulation [that] is conveniently applied once per week in a cellulose acetate lacquer base." (Ex. 1008, *Brehove* ¶ [0018]; Ex. 1005, Murthy Decl. ¶ 70)

Brehove provides that the active ingredient may be combined with a "penetration enhancer" that "increases the permeability of the skin to a drug," (Ex. 1008, *Brehove* ¶ [0027]; Ex. 1005, Murthy Decl. ¶ 71.) and, in at least some formulations, the "mineral oil, petroleum jelly and paraffin wax help protect the skin against irritation or drying and serve as a reservoir for the active ingredient permitting extended continuous diffusion and penetration into the nail." (Ex. 1008, *Brehove* ¶ [0025]; Ex. 1005, Murthy Decl. ¶ 71.)

Brehove also provides that the active fungicidal ingredient may be combined with an organic film former, and that "[m]any suitable film-forming polymers are known." (Ex. 1008, *Brehove* at ¶ [0026]; Ex. 1005, Murthy Decl. ¶ 72.)

Brehove teaches the effectiveness of its organo-boron compounds against *Candida albicans* at concentrations "between 0.1 wt% and 25 wt% of the composition." (Ex. 1008, *Brehove* ¶ [0032], Table 1, Claim 14; Ex. 1005, Murthy Decl. ¶ 73.)

Brehove further teaches application of its topical formulation once a day for the treatment of onychomycosis. (Ex. 1008, *Brehove* ¶ [0035]; Ex. 1005, Murthy Decl. ¶ 74.)

Thus, *Brehove* taught a boron-based industrial fungicide to treat humans. (Ex. 1003, Kahl Decl. ¶ 40.) This is real world proof that a POSITA would not be discouraged, and would in fact select a boron-based industrial fungicide for use in

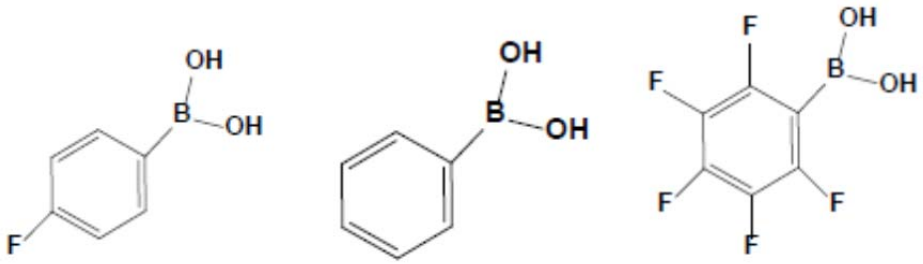
humans to treat onychomycosis. (Ex. 1003, Kahl Decl. ¶ 40.) It discloses topical formulations of boron-based compounds, which were previously used as leaded fuel additives, for application directly to the nail and surrounding skin of humans to effectively treat onychomycosis, which is typically caused by the organisms *Candida albicans*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*, or *Epidermophyton floccosum*. (Ex. 1008, *Brehove* ¶¶ [0005], [0018], [0034]-[0038]; Ex. 1005, Murthy Decl. ¶ 75.)

3. *Freeman*[9]

Freeman is an international patent application publication that discloses the use of boron-containing compounds as anti-fungal agents to treat onychomycosis safely and effectively in humans. (Ex. 1003, Kahl Decl. ¶ 37; Ex. 1005, Murthy Decl. ¶ 76.) It disclosed "methods and compositions for treating fungal infections, and more particularly, dermatophytoses or on[y]chomycosis of the fingernail and the toenail" with phenyl boronic acid and derivatives thereof. (Ex. 1009, *Freeman* ¶¶ [001], [0022]; Ex. 1005, Murthy Decl. ¶ 77.)

Freeman disclosed the effective use of the boron-containing compounds to treat onychomycosis in humans, including the following disclosed compounds:

[9] *Supra*, n.6.



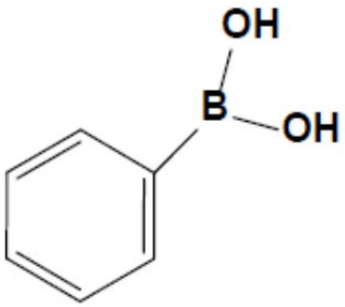
(Ex. 1009, *Freeman* ¶ [0062]; Ex. 1003, Kahl Decl. ¶ 41.)

Freeman states that "'Onychomycosis' has traditionally referred to a nondermatophytic infection of the nail. (Ex. 1009, *Freeman* ¶ [005]; Ex. 1003, Kahl Decl. ¶ 42.) Onychomycosis is now used as a general term to denote any fungal nail infection. (Ex. 1009, *Freeman* ¶ [005]; Ex. 1003, Kahl Decl. ¶ 42.) *Tinea unguium* specifically describes a dermatophytic invasion of the nail plate." (Ex. 1009, *Freeman* ¶ [005]; Ex. 1003, Kahl Decl. ¶ 42.) In addition, *Freeman* recognizes that, as a POSITA would have known, "[t]he dermatophyte species that most often causes onychomycosis in North America and parts of Europe are *T. rubrum*, *T. metagrophytes*, and *Epidermophyton floccosum* . . . . Both dermatophytes and non-dermatophytes, especially *Candida Sp.*, have been identified as etiologic agents of onychomycosis." (Ex. 1009, *Freeman* ¶ [008]; Ex. 1003, Kahl Decl. ¶ 42; Ex. 1005, Murthy Decl. ¶ 78.)

Freeman discloses the treatment of onychomycosis using boron-based compounds: "[i]t has now been discovered that phenyl boronic acid and derivatives thereof as well as related boronic acid compounds have fungicidal properties, and

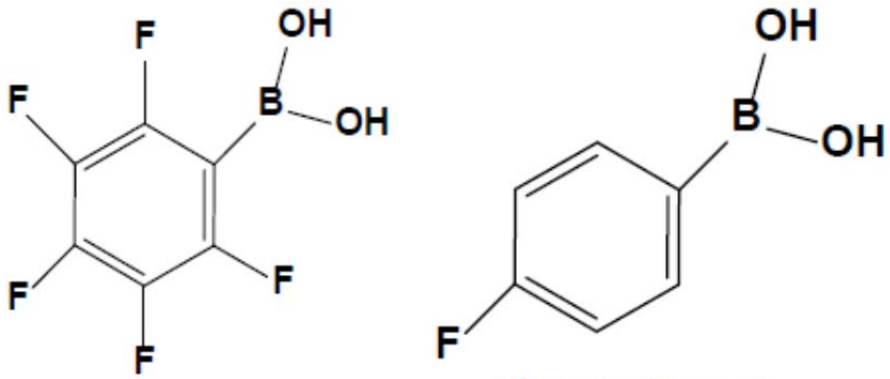
that these compounds are particularly useful in treating fungal infections." (Ex. 1009, *Freeman* ¶ [022]; Ex. 1003, Kahl Decl. ¶ 43; Ex. 1005, Murthy Decl. ¶ 79.) It also teaches that these compounds have been found to be "particularly useful in treating nail fungal infections." (Ex. 1009, *Freeman* ¶ [022]; Ex. 1003, Kahl Decl. ¶ 43; Ex. 1005, Murthy Decl. ¶ 79.)

Phenyl boronic acid ("PBA") is a common compound and has the following structure:



Phenyl Boronic Acid

(Ex. 1009, *Freeman* ¶¶ [0029]–[0034]; Ex. 1005, Murthy Decl. ¶ 79.) Along with PBA, *Freeman* discloses a pentafluoro PBA and a fluoro PBA, both derivatives of PBA, which have the following structures:



(Ex. 1009, *Freeman* ¶ [0062] ("R_1, R_2, R_3, R_4, and R_5" are all fluorine or "R_3" is fluorine and the remaining substituents are hydrogen.); Ex. 1005, Murthy Decl. ¶ 79.)

Freeman then specifically discloses that certain boron-based compounds are effective in vitro against *T. rubrum*, which is a cause of onychomycosis: "[i]t can readily be seen from the above that the PBA exhibited fungicidal effects on T. rubrum within the concentration range of 5–10 mg/ml tested." (Ex. 1009, *Freeman* ¶¶ [0033]–[0037]; Ex. 1003, Kahl Decl. ¶ 44; Ex. 1005, Murthy Decl. ¶ 80.) *Freeman* specifically discloses the topical administration of compositions containing PBA or its derivatives to the skin or nails of a human for the treatment of onychomycosis. (Ex. 1009, *Freeman* ¶ [0030] (disclosing "in the form of a buffered solution, lotion, or ointment. . . . once daily until cure"), ¶ [0068] ("The form of the cosmetic composition can be a powder, lotion, gel, spray, stick, cream,

ointment, liquid, emulsion, foam or aerosol."); *see also* Ex. 1009, *Freeman* ¶¶ [0053], [0064–65]; Ex. 1005, Murthy Decl. ¶ 80; Ex. 1003, Kahl Decl. ¶ 44.)

With respect to pharmaceutical formulations, *Freeman* provides

> "The pharmacologically active compounds of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, e.g., mammals including human beings. For example, the compounds of formula (I) can be employed in admixtures with conventional excipients, e.g., pharmaceutically acceptable carrier substances suitable for topical application which do not deleteriously react with the active compounds."

(Ex. 1009, *Freeman* ¶ [0037]; Ex. 1005, Murthy Decl. ¶ 81.) Specifically, *Freeman* describes "[s]uitable pharmaceutically acceptable carriers include but are not limited to water . . . alcohols . . . polyethylene glycols, etc." (Ex. 1009, *Freeman* ¶ [0038]; Ex. 1005, Murthy Decl. ¶ 81.)

Freeman discloses that in using phenylboronic acid derivatives in treating onychomycosis, "[t]he PBA compound will be present in the overall formulation in amounts ranging from about 0.1% to about 100% by weight, depending upon the use of the formulation. In most uses . . . ranges from about 2% to about 50% are most preferred. (Ex. 1009, *Freeman* ¶ [0064]; Ex. 1005, Murthy Decl. ¶ 82.)

Freeman therefore discloses the topical application of compositions including PBA, or derivatives thereof, directly to the skin or nail of a human with onychomycosis to effectively treat onychomycosis typically caused by the organisms *Candida albicans*, *Trichophyton mentagrophytes*, *Trichophyton rubrum*,

or *Epidermophyton floccosum*. (*See* Ex. 1009, *Freeman* ¶ [008]; Ex. 1005, Murthy Decl. ¶ 83.) Like *Brehove*, *Freeman* is real-world proof that a POSITA would not be discouraged, and would in fact select a boron-based compound for use in humans to treat onychomycosis. (Ex. 1003, Kahl Decl. ¶ 44.)

4. *Samour*[10]

Like *Brehove* and *Freeman*, *Samour* discloses a topical formulation for treating onychomycosis in humans, caused by dermatophytes, molds and *Candida*, including dermatophytes *Trichophyton rubrum* and *T. mentagrophytes*. (Ex. 1010, *Samour* at [57] (Abstract), col. 1:23–35; Ex. 1005, Murthy Decl. ¶ 84.) Specifically, *Samour* discloses "improvements in the physical properties (e.g., durability, water-resistance, flexibility) of water- insoluble adherent films . . . of [a] nail lacquer composition, as well as improved diffusion characteristics of active principle(s) included in the lacquer composition from the resulting film." (Ex. 1010, *Samour* col. 3:13–29; Ex. 1005, Murthy Decl. ¶ 84.)

In particular, *Samour* discloses topical fungicidal compositions including some or all of the following: "(a) at least one antifungal agent . . .; (b) penetration enhancing agent . . .; (c) water-insoluble, film-forming polymer; and (d) volatile solvent . . . ." (Ex. 1010, *Samour* col. 3:59–65; Ex. 1005, Murthy Decl. ¶ 85.)

[10] Ex. 1010, Samour et al., U.S. Patent No. 6,224,887 ("*Samour*").

Samour also discloses that its lacquer formulations may include "[o]ther conventional additives customarily present in cosmetic or medicinal nail lacquers . . . in their usual amounts as long as they do not interfere with the diffusion of the active principles and other parameters of the lacquer composition and dried-polymer-film." (Ex. 1010, *Samour* col. 10:57–62; Ex. 1005, Murthy Decl. ¶ 86). One such class of conventional additive identified by *Samour* is chelating agents. (Ex. 1010, *Samour* col. 10:62–65; Ex. 1005, Murthy Decl. ¶ 86).

In formulation, *Samour* provides that "amounts of active antifungal agent [e.g., econazole] . . . range . . . from about 0.5 to 20 percent by weight, preferably from about 1 to 10 percent, by weight." (Ex. 1010, *Samour* col. 12:9–14, col. 16:40–62; Ex. 1005, Murthy Decl. ¶ 87.)

Samour describes formulations including "[f]ilm-forming polymers . . . such as . . . methylvinyl ether copolymers sold . . . under the tradename Gantrez, e.g., . . . Gantrez ES-425 [i.e., poly(vinyl methyl ether-alt- maleic acid monobutyl ester)]." (Ex. 1010, *Samour* col. 7:54–62; *see* Ex. 1025; Ex. 1005, Murthy Decl. ¶¶ ¶ 86, 88.) *Samour* provides that "satisfactory results are obtained when the amount of film-forming polymer is in the range . . . preferably from about 15 to about 50 percent, especially from about 20 to 40 percent by weight of the total nail lacquer composition." (Ex. 1010, *Samour* col. 8:39–44; Ex. 1005, Murthy Decl. ¶ 88.) *Samour* further discloses that "[c]onventional plasticizers compatible (e.g.,

forming a homogenous film) with film-forming polymers may be included in the compositions of this invention," and that "[s]uitable plasticizers include . . . propylene glycol." (Ex. 1010, *Samour* col. 8:58–col. 9:4; Ex. 1005, Murthy Decl. ¶ 88.)

Samour also identifies a number of "physiologically safe organic solvents," including ethanol, especially anhydrous ethanol (EtOH), ethyl acetate, and mixtures thereof. (Ex. 1010, *Samour* col. 9:31–49; Ex. 1005, Murthy Decl. ¶ 89.)

Samour discloses its lacquer formulation as being suitable for once-a-day administration for nail treatment. (Ex. 1010, *Samour* col. 10:1–7, col. 11:16–27; Ex. 1005, Murthy Decl. ¶ 90).

In its Example 6, *Samour* discloses a lacquer formulation including 65% ethanol, 24% film-forming polymer (Eudragit RL), 6% Propylene Glycol, and 5% active fungicidal ingredient (econazole). (Ex. 1010, *Samour* col. 21:41–col. 22:18; Ex. 1005, Murthy Decl. ¶ 91).

In its Examples 7 and 8, *Samour* discloses lacquer formulations including 71% ethanol, 24% film-forming polymer (Eudragit RL), and 5% active fungicidal ingredient (econazole). (Ex. 1010, *Samour* col. 22:20–col. 24:22; Ex. 1005, Murthy Decl. ¶ 92.)

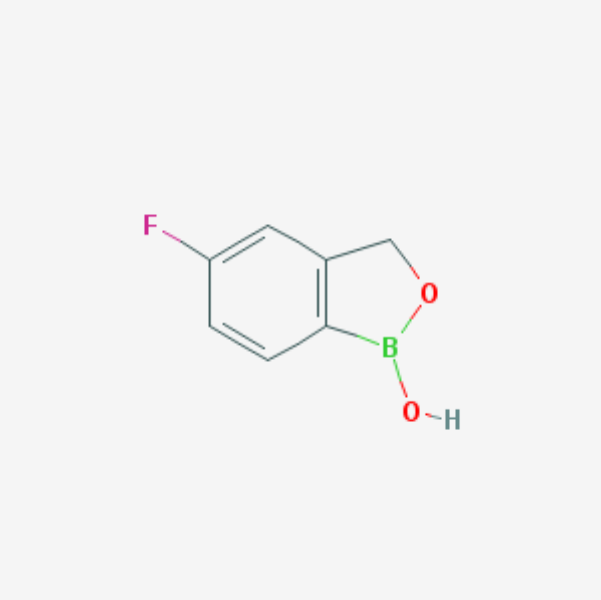
II. Level of Ordinary Skill in the Art

A person of ordinary skill in the art at the time of the alleged invention would have either a Master's or Ph.D. degree in chemistry, pharmacology, or biochemistry, and at least two years of experience in research, development, or production of pharmaceuticals. (Ex. 1005, Mertha Decl. ¶¶ 19–21; Ex. 1003, Kahl Decl. ¶ 22.) In addition, the prior art cited and discussed above is representative of the level of ordinary skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001). In previous *inter partes* review, the board determined that this art "is consistent with Petitioner's broader description of the level of ordinary skill in the art" and no "additional experience in mycology, clinical dermatology, medicinal chemistry, the development of drug candidates for treating onychomycosis, and the assessment of the toxicology, pharmacology, and clinical utility of drug candidates is required." (Ex. 1014, IPR '776, FWD at 6; Ex. 1017, IPR '780, FWD at 8; Ex. 1018, IPR '785, FWD at 8.) The Board also previously held that "Drs. Murthy and Kahl are qualified to testify as to the knowledge of a person of ordinary skill in the art." (Ex. 1017, IPR '780, FWD at 11; Ex. 1018, IPR '785, FWD at 11.)

III. The '290 Patent Prosecution History.

The '290 Patent describes treating fungal infections, including onychomycosis, via topical application of boron-containing small molecules to the

nail or skin of a human. (Ex. 1001, the '290 patent at [54] Title, [57] Abstract; Ex. 1003, Kahl Decl. ¶ 26; Ex. 1005, Murthy Decl. ¶ 22.) It specifically claims a method of treating an onychomycosis infection of a human toenail caused by *Trichophyton rubrum or Trichophyton mentagrophytes* (Ex. 1005, Murthy Decl. ¶ 22), including a step of topically administering a pharmaceutical composition including tavaborole (recited as 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole). (Ex. 1001, the '290 patent cols. 317–18; Ex. 1003, Kahl Decl. ¶ 25.) Tavaborole has the following structure:



(Ex. 1003, Kahl Decl. ¶ 25.)

During the prosecution of U.S. Patent Application No. 11/357,687 (Ex. 1013, the '687 file wrapper) which issued as U.S. Patent No. 7,582,621 (Ex. 1012, the '621 Patent), and to which the '290 Patent claims priority, the Examiner rejected the pending claims over *Austin* and the definition of "fungicide" from

Answers.com. (Ex. 1013, the '687 file wrapper at 53–55; Ex. 1003, Kahl Decl. ¶ 26; Ex. 1005, Murthy Decl. ¶ 49.) The Examiner noted that *Austin* discloses tavaborole for use as an industrial fungicide, and that the definition of fungicide from Answers.com taught that a fungicide can be used for agriculture or the pharmaceutical industry. (Ex. 1013, the '687 file wrapper at 55; Ex. 1003, Kahl Decl. ¶ 26; Ex. 1005, Murthy Decl. ¶ 49.)

In response to this rejection, the Patent Owner argued that a POSITA would not choose an industrial fungicide for human use because some fungicides are dangerous to humans. (Ex. 1013, the '687 file wrapper at 18–19; Ex. 1003, Kahl Decl. ¶ 27; Ex. 1005, Murthy Decl. ¶ 50.) The Patent Owner argued: "the art teaches that compounds that are useful for killing or inhibiting fungi may also harm animals" and "Answers.com thus does not provide a motivation to modify the teachings of *Austin* to use any particular oxaborole to treat an animal, and in fact teaches away from such modification." (Ex. 1013, the '687 file wrapper at 18–19; Ex. 1003, Kahl Decl. ¶ 27; Ex. 1005, Murthy Decl. ¶ 50.)

The Examiner relied on the Patent Owner's argument in deciding to allow the pending claims which ultimately issued as claims 1–12 the '621 Patent. (Ex. 1013, the '687 file wrapper at 6–7; Ex. 1003, Kahl Decl. ¶ 28; Ex. 1005, Murthy Decl. ¶ 50.)

The Patent Owner relied on the same argument during prosecution of application Ser. No. 11/505,591 (Ex. 1016, the ’591 application), which issued as the ’657 Patent (Ex. 1015). (Ex. 1016, the ’591 application at 24–25; Ex. 1003, Kahl Decl. ¶ 29; Ex. 1005, Murthy Decl. ¶¶ 52–56.) There again, the Examiner relied on the Patent Owner’s argument in deciding to allow the pending claims. (Ex. 1016, the ’591 application at 6–7; Ex. 1003, Kahl Decl. ¶ 29; Ex. 1005, Murthy Decl. ¶¶ 56.) The Board found all claims of the ’657 Patent to be obvious and unpatentable in IPR2015-01780 and IPR2015-01785 (Ex. 1017, IPR ’780, FWD at 60; Ex. 1018, IPR ’785, FWD at 58–59; Ex. 1005, Murthy Decl. ¶ 56).

U.S. Patent App. No. 11/505,591, which became the ’657 Patent, was filed on August 16, 2006. (Ex. 1015.) The first substantive Office Action rejected the pending claims over U.S. Patent No. 5,880,188 to Austin (“the ’188 Patent”) and Austin et al. (CAS:124:234024). (Ex. 1016, the ’591 application at 40–41.)

The Examiner rejected the pending claims in the ’591 application on the grounds that U.S. Patent No. 5,880,188 to Austin, which has substantially the same disclosure as *Austin* (Ex. 1007), discloses tavaborole as recited in the claims. (Ex. 1016, the ’591 application at 38–41; Ex. 1005, Murthy Decl. ¶ 53.) The Examiner correctly explained that “[o]ne having ordinary skill in the art would find the claims . . . prima facie obvious because one would be motivated to employ the compositions of Austin et al. to obtain [the] instant formulation comprising 1,3-

dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole and pharmaceutical acceptable excipient." (Ex. 1016, the '591 application at 41; Ex. 1005, Murthy Decl. ¶ 53.) The Examiner also correctly explained that "[t]he motivation to make the claimed compounds derived from the known compounds/compositions would possess similar activity (i.e., fungicide or treating fungal infection) to that which is claimed in the reference." (Ex. 1016, the '591 application at 41; Ex. 1005, Murthy Decl. ¶ 53.)

In response to this rejection, the Patent Owner argued that a POSITA would not choose an industrial fungicide for topical application to a human because some fungicides are dangerous to humans. (Ex. 1016, the '591 application at 24; Ex. 1005, Murthy Decl. ¶ 54.) Specifically, the Patent Owner argued that "one of skill in the art would not presumptively consider a compound to be suitable for administration to an animal, especially a human, merely because a compound has been shown to have antifungal effects in paint or aviation fuel." (Ex. 1016, the '591 application at 24; Ex. 1005, Murthy Decl. ¶ 54.) The Patent Owner also repeated arguments made during prosecution of the '621 Patent, stating "the art teaches that compounds that are useful for killing or inhibiting fungi may also harm animals, and thus teaches away from assuming that any fungicide can be used in a pharmaceutical formulation as claimed." (Ex. 1016, the '591 application at 25; Ex. 1005, Murthy Decl. ¶ 54.) Therefore, the Patent Owner again argued that

a POSITA would be discouraged from using an industrial fungicide for the topical treatment of fungal infections in humans. (Ex. 1016, the ’591 application at 23-25; Ex. 1005, Murthy Decl. ¶ 54.)

Additionally, in response to a rejection under Section 112, paragraph 1, the Patent Owner argued that the claims were “fully enabled by the specification coupled with knowledge in the art” and that “formulations may be made based on excipients, additives and methods known in the art.” (Ex. 1016, the ’591 application at 22; Ex. 1005, Murthy Decl. ¶ 55.)

The arguments made above were in applications to which the application that issued as the ’290 patent claimed priority and thus are part of the prosecution history of the ’290 patent. (Ex. 1001; Ex. 1003, Kahl Decl. ¶ 29.)

IDENTIFICATION OF THE CHALLENGE

Pursuant to 37 C.F.R. § 42.104(b), Petitioner provides the following statement of the precise relief requested for each claim challenged. Petitioner requests institution of *inter partes* review and a final written decision that claims 1–12 of the ’290 patent are invalid and unpatentable under 35 U.S.C. § 103, and cancellation of those claims. To prevail in *inter partes* review of the challenged claims, Petitioner must prove unpatentability by a preponderance of the evidence. 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d). This request shows a reasonable likelihood that the petitioner would prevail on at least one of the claims challenged in this

petition because the request shows that each limitation of at least one claim of the '290 patent are taught in the prior art. Each reference is non-redundant and has particular unique relevance. Petitioner's detailed statement of the reasons for the relief requested is set forth below.

I. The Claims Challenged

Pursuant to § 42.104(b)(1), Petitioner identifies the challenged claims as all 12 claims of the '290 patent. A listing of these claims is provided below:

> 1. A method of treating a human having onychomycosis of a toenail caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*, the method comprising:
>
> topically administering to the toenail a pharmaceutical composition comprising an amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole or a pharmaceutically acceptable salt thereof, effective to inhibit an aminoacyl tRNA synthetase in the *Trichophyton rubrum* or *Trichophyton mentagrophytes.*
>
> 2. The method of claim 1, wherein the pharmaceutical composition is in the form of a solution comprising 5% w/w of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole or a pharmaceutically acceptable salt thereof.
>
> 3. The method of claim 1, wherein the pharmaceutical composition further comprises ethanol and propylene glycol.
>
> 4. The method of claim 1, wherein the aminoacyl tRNA synthetase is leucyl tRNA synthetase.
>
> 5. The method of claim 4, wherein the pharmaceutical composition is in the form of a solution comprising 5% w/w of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole or a pharmaceutically acceptable salt thereof.
>
> 6. The method of claim 5, wherein the pharmaceutical composition further comprises ethanol and propylene glycol.
>
> 7. The method of claim 1, wherein the administering of the pharmaceutical composition occurs once a day.
>
> 8. The method of claim 6, wherein the administering of the pharmaceutical composition occurs once a day.

9. The method of claim 1, wherein the method inhibits an aminoacyl tRNA synthetase in *Trichophyton rubrum.*

10. The method of claim 1, wherein the method inhibits an aminoacyl tRNA synthetase in *Trichophyton mentagrophytes.*

11. The method of claim 6, wherein the method inhibits leucyl tRNA synthetase in *Trichophyton rubrum.*

12. The method of claim 6, wherein the method inhibits leucyl tRNA synthetase in *Trichophyton mentagrophytes.*

(Ex. 1001, the '290 patent, col. 321:25–col. 322:43.)

II. Specific Grounds And Art.

Pursuant to § 42.104(b)(2), Petitioner identifies the specific statutory grounds under 35 U.S.C. §§ 102 or 103 on which the challenge to the claim is based and the patents or printed publications relied upon for each ground as follows:

Ground I: Claims 1, 4, 7 & 9-10 of the '290 Patent are Obvious Over *Austin* in View of *Brehove*

Ground II: Claims 2-3, 5-6, 8 & 11-12 of the '290 Patent are Obvious Over *Austin* in View of *Brehove* and *Samour*

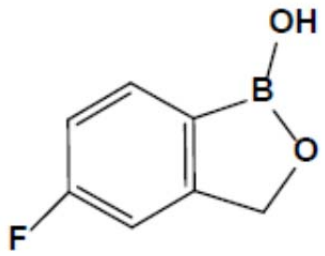
Ground III: Claims 1, 4, 7 & 9-10 of the '290 Patent are Obvious Over *Austin* in View of *Freeman*

Ground IV: Claims 2-3, 5-6, 8 & 11-12 of the '290 Patent are Obvious Over *Austin* in View of *Freeman* and *Samour*

III. Claim Construction

Pursuant to § 42.104(b)(3), Petitioner identifies how the challenged claim is to be construed as follows:

Claims 1–12 of the '290 Patent recite or depend from claims reciting the following compound: "1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole." (Ex. 1001, the '290 patent col. 321:25–col. 322:43.) 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole is disclosed in *Austin* as 5-fluoro-1,3 dihydro-1-hydroxy-2,1-benzoxaborole. (Ex. 1005, Murthy Decl. ¶¶ 35-46.) The compound of claims 1–12 has the following structure:



(*See* Ex. 1007, *Austin* at 24:5–14; *see also* Ex. 1027 at 1, 3; Ex. 1005, Murthy Decl. ¶ 93.) The '290 Patent discloses this structure as compound 1 with a formula of $C_7H_6BFO_2$ and a molecular weight of 151.93 Daltons. (Ex. 1001, the '290 patent col. 135:51-66; Ex. 1005, Murthy Decl. ¶ 93.)

Claims 1-12 of the '290 Patent recite or depend from claims reciting the term "inhibit." The '290 Patent defines "inhibiting" as "the partial or full blockade of an editing domain of a tRNA synthetase." (Ex. 1001, the '290 patent col. 13:48–50.; Ex. 1005, Murthy Decl. ¶ 94.)

IV. How the claims are unpatentable.

Pursaunt to § 42.104(b)(4), Petitioner identifies the following as its statement of how the construed claim is unpatentable under the statutory grounds identified in identification part II, *supra*, specifying where each element of the claim is found in the prior art patents or printed publications relied upon. This section also includes, as integral to the explanation of how the claims are unpatentable, petitioner's identification pursuaunt to 37 C.F.R. § 42.104(b)(5) of the exhibit number of the supporting evidence relied upon to support the challenge and the relevance of the evidence to the challenge raised, including identifying specific portions of the evidence that support the challenge.

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

"[I]t can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the claimed new invention does." *KSR*, 550 U.S. at 418. Moreover, a person of ordinary skill in the art must have had a reasonable expectation of success of doing so. *PAR Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014). Conclusive proof of efficacy is not required to show obviousness. *See Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success.").

All four grounds below use as a principal reference *Austin*, which Petitioner submits is analogous prior art. Prior art is analogous if it either (1) "is from the same field of endeavor, regardless of the problem addressed," or (2) "is reasonably pertinent to the particular problem with which the inventor is involved." *Unwired Planet, LLC v. Google Inc.*, 841 F.3d 995, 1000 (Fed. Cir. 2016) (quoting *In re Clay*, 966 F.2d 656, 658–59 (Fed. Cir. 1992)); *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). "A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem." *In re ICON Health & Fitness, Inc.*, 496 F.3d 1374, 1380–81 (Fed. Cir. 2007); *see also*, *Innovation Toys, LLC v. MGA Entm't,*

Inc., 637 F.3d 1314, 1321 (Fed. Cir. 2011). *Austin* logically would have commended itself to the problem facing the inventors of the ’823 patent. *See Scientific Plastic Products, Inc. v. Biotage AB*, 766 F.3d 1355 (Fed. Cir. 2014); *see also ICON*, 496 F.3d at 1379–80 (holding that reference may be reasonably pertinent as analogous art where the matter it deals with logically would have commended itself to the inventor’s attention). (*See also* Ex. 1014, IPR ’776, FWD at 12; Ex. 1017, IPR ’780, FWD at 19–22; Ex. 1018, IPR ’785, FWD at 19–22.)

A. Explanation Of Ground 1 For Unpatentability: Claims 1, 4, 7 & 9–10 of the ’290 Patent are Obvious Over *Austin* in View of *Brehove*

It would have been obvious to a POSITA to combine the known, effective antifungal boron-containing compound disclosed in *Austin* with the topical application of pharmaceutical compositions including boron-containing antifungal compounds for the treatment of onychomycosis as taught by *Brehove*. The substitution of tavaborole for the active ingredient of *Brehove* is nothing more than a simple substitution of one known elements for another according to their established functions. *See KSR*, 550 U.S. at 401. This combination renders Claims 1, 4, 7 & 9–10 of the ’290 Patent obvious.

1. All Elements of Claims 1, 4, 7 & 9–10 are Obvious Over *Austin* in View of *Brehove*

a. Independent Claim 1

All limitations of Claim 1 of the ’290 Patent would have been obvious over

Austin in view of *Brehove*. The prior art "must be read, not in isolation, but for what it fairly teaches in combination with the prior art as whole." *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986). As the Board has previously found, *Austin* and *Brehove* together suggest administering to a human a therapeutically effective amount of tavaborole. (*See* Ex. 1014, IPR2015-01776 FWD at 18; Ex. 1017, IPR '780, FWD at 28.)

The preamble is "**A method of treating a human having onychomycosis of a toenail caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes***." This preamble recites no essential structure or steps necessary for understand the claim and therefore does not provide limitations on the claim. Regardless, all parts of the preamble are disclosed by *Austin* and *Brehove* as fully described for the limitations in the claim body below.

The method of Claim 1 recites "**topically administering to the toenail a pharmaceutical composition comprising an amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole or a pharmaceutically acceptable salt thereof . . . .**" 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole is specifically disclosed as an effective fungicide in *Austin*. (Ex. 1007, *Austin* at (57) [Abstract], 3:35–40; Ex. 1005, Murthy Decl. ¶ 97.) *Brehove* discloses topical application of pharmaceutical compositions containing boron-containing compounds, and specifically teaches such application to the "entire toenail" of a human. (Ex. 1008, *Brehove* ¶¶ [0034]–

[0038], Ex. 1005, Murthy Decl. ¶ 102.) Combining the compound of *Austin* with the topical application and pharmaceutical composition of *Brehove* renders this limitation obvious and it would have been obvious to combine these compounds specifically for the treatment of onychomycosis caused by *T. rubrum* or *T. mentagrophytes. Austin* teaches that the 5-fluoro benzoxaborole is inhibitory against *Candida albicans* in vitro (Ex. 1007, *Austin* at 35–39; Ex. 1005, Murthy Decl. ¶ 98), and *Brehove* identifies *T. rubrum* and *T. mentagrophytes* as typical causes of onychomycosis (Ex. 1008, *Brehove* ¶ [0005]; Ex. 1005, Murthy Decl. ¶ 100). *Brehove* discloses its topical formulations containing organo-boron compounds as inhibiting *Candida albicans* in vitro and treating onychomycosis in vivo and describes its formulations as effective in curing onychomycosis caused by "bacteria, fungi or other pathogens." (Ex. 1008, *Brehove* ¶¶ [0003], [0032–33].) A POSITA understood inhibitory activity against yeasts such as *Candida albicans* to be predictive of antifungal activity against dermatophytes, including *T. rubrum* and *T. mentagrophytes*. (Ex. 1005, Murthy Decl. ¶ 99.) Therefore, it would have been obvious for a POSITA to use the tavaborole compound taught by *Austin* as the active fungicidal ingredient in the topically applied pharmaceutical formulation of *Brehove* in order to treat onychomycosis caused by *T. rubrum* or *T. mentagrophytes*.

Moreover, the Board has previously held that a POSITA would combine the

teachings of *Austin* and *Brehove* to treat *T. rubrum* or *T. mentagrophytes* caused onychomycosis, stating that a POSITA "would have expected that Austin's tavaborole would share similar functional features with the compounds in Brehove that effectively treat onychomycosis caused by microorganisms other than *Candida albicans*, and thus would have had a reasonable expectation of success in combining Austin and Brehove to effectively treat infections [caused by *T. rubrum* or *T. mentagrophytes*]." (Ex. 1017, IPR '780, FWD at 35–37.)

The method of Claim 1 further requires the claimed claimed topical administration to be "**effective to inhibit an aminoacyl tRNA synthetase in the *Trichophyton rubrum* or *Trichophyton mentagrophytes***." Inhibition of leucyl tRNA synthetase (a type of aminoacyl tRNA synthetase) is the very mechanism by which tavaborole treats the pathogens that cause onychomycosis and this limitation is therefore a necessary, inherent outcome of the topical application of tavaborole for the treatment of onychomycosis. (Ex. 1005, Murthy Decl. ¶¶ 103–04.) This understanding of tavaborole's mechanism of action is extensively supported by the relevant scientific literature. (*See* Ex. 1038, Queller 2015 at 6 ("Tavaborole is a novel, boron-based topical agent approved for the treatment of onychomycosis caused by *T. rubrum* and *T. mentagrophytes*. Tavaborole inhibits leucyl-tRNA-synthetase, resulting in inhibition of fungal protein synthesis and extinction of fungal cell growth.") (citations omitted); *see also* Ex. 1036, Alley 2007 at 8; Ex.

1037, Rock 2007 at 1; Ex. 1039, Elewski 2015 at 2; Ex. 1005, Murthy Decl. ¶ 105.) Further, Patent Owner themselves identified aminoacyl tRNA synthetase as the mechanism of action of tavaborole in submitting its New Drug Application No. 240–427 to the Food and Drug Administration. (*See* Ex. 1040 at 36; Ex. 1041 at 5; Ex. 1042 at 5; Ex. 1005, Murthy Decl. ¶ 106.) Thus, as leucyl tRNA synthetase inhibition of the pathogens that cause onychomycosis is the mechanism of action by which tavaborole treats onychomycosis, leucyl tRNA synthetase is a necessary component of such treatment. Such an inherently present limitation is obvious even where the inherency is not disclosed in the prior art. (Ex. 1005, Murthy Decl. ¶ 105.) Multiple Federal Circuit decisions have held that where a claim limitation covers nothing more than an inherent property of an obvious pharmaceutical formulation, such a limitation "adds nothing of patentable consequence." *In re Huai-Hung Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) ("[T]he claimed 'food effect' adds nothing of patentable consequence."); *see also Alcon Research, Ltd. v. Apotex, Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012) ("[T]his claim language does not impose any additional requirement . . ."); *In re Kubin*, 561 F.3d 1351, 1357–58 (Fed. Cir. 2009) ("[N]ot an additional requirement imposed by the claims . . . but rather a property necessarily present . . .").

b. Dependent Claims 4, 7 & 9–10

Claim 4 depends from Claim 1 and further requires "**wherein the aminoacyl**

tRNA synthetase is leucyl tRNA synthetase." As explained above for Claim 1, the mechanism of action by which tavaborole treats onychomycosis is the inhibition of leucyl tRNA synthetase in onychomycosis-causing pathogens and is therefore inherent to using tavaborole for such treatment. (Ex. 1005, Murthy Decl. ¶ 125–26.)

Claim 7 depends from Claim 1 and further requires "**wherein the administering of the pharmaceutical composition occurs once a day**." *Brehove* provides multiple examples of applying its topical formulation to the entire nail once a day for the effective treatment of onychomycosis. (Ex. 1008, *Brehove* ¶¶ [0035]–[0037]; Ex. 1005, Murthy Decl. ¶¶ 128–29.)

Claim 9 depends from Claim 1 and further requires "**wherein the method inhibits an aminoacyl tRNA synthetase in *Trichophyton rubrum***." As explained above for Claim 1, the mechanism of action by which tavaborole treats onychomycosis is the inhibition of leucyl tRNA synthetase, a type of aminoacyl tRNA synthetase, in onychomycosis-causing pathogens and it would have been obvious to use the tavaborole compound of *Austin* as the active fungicidal ingredient in a topically applied pharmaceutical composition as taught by *Brehove* to treat onychomycosis caused by *T. rubrum*. (Ex. 1005, Murthy Decl. ¶¶ 129–30.)

Claim 10 depends from Claim 1 and further requires "**wherein the method inhibits an aminoacyl tRNA synthetase in *Trichophyton mentagrophytes***." As

explained above for Claim 1, the mechanism of action by which tavaborole treats onychomycosis is the inhibition of leucyl tRNA synthetase, a type of aminoacyl tRNA synthetase, in onychomycosis-causing pathogens and it would have been obvious to use the tavaborole compound of *Austin* as the active fungicidal ingredient in a topically applied pharmaceutical composition as taught by *Brehove* to treat onychomycosis caused by *T. mentagrophytes*. (Ex. 1005, Murthy Decl. ¶¶ 131–32.)

2. A POSITA Would Have Had Reason to Combine *Austin* and *Brehove*

A POSITA would have had numerous reasons to combine the teachings of *Austin* and *Brehove*, i.e., use the tavaborole compound of *Austin* in a topical application for treatment of onychomycosis as taught by *Brehove*. (*See* Ex. 1005, Murthy Decl. ¶¶ 108–113, 133.) The Board has previously held that a person of ordinary skill in the art "would have had reason to use Austin's tavaborole in Brehove's formulation for topical treatment of nail infections such as onychomycosis," (Ex. 1017, IPR '780, FWD at 28), and that "Austin and Brehove together suggest administering to a human a therapeutically effective amount of tavaborole." (Ex. 1014, IPR '776 FWD at 18.)

First, both *Austin* and *Brehove* teach the use of boron-containing compounds as effective fungicides. (Ex. 1005, Murthy Decl. ¶ 110.) *Austin* specifically teaches that oxaboroles are particularly effective against microorganisms such as yeasts

and fungi. (Ex. 1007, *Austin* at 3:35–40.) *Brehove* teaches that organo-boron compounds have long been known to exhibit biocidal activity and teaches the use of such compounds in topical applications for the treatment of onychomycosis without skin irritation or noticeable side effects. (Ex. 1008, *Brehove* ¶¶ [0007], [0017]–[0018], Ex. 1005, Murthy Decl. ¶ 110.)

Second, both *Austin* and *Brehove* teach efficacy of boron-containing compounds against onychomycosis-causing yeast, i.e., *Candida albicans*. (Ex. 1005, Murthy Decl. ¶ 110.) *Austin* discloses the high fungicidal potency of tavaborole, disclosing that an *in vitro* MIC of 5 ppm against numerous types of fungi, including *Candida albicans*. (Ex. 1007, *Austin* at 35–39.) Similarly, *Brehove* teaches its topical application of boron-containing compounds to inhibit *Candida albicans* among other bacteria, fungi and other pathogens that cause onychomycosis. (Ex. 1008, *Brehove* ¶¶ [0003], [0017]–[0018].) It was known in the art that antifungal activity against yeasts such as *Candida albicans* is predictive of similar efficacy against dermatophytes such as *T. rubrum and T. mentagrophytes*. (Ex. 1005, Murthy Decl. ¶ 110.) A POSITA would therefore be motivated to combine the effective antifungal, tavaborole, taught by *Austin* with the topical composition taught by *Brehove* to arrive at a safe and convenient topical application effective against all primary causes of onychomycosis: *Candida albicans*, *T. rubrum, and T. mentagrophytes*. (*Id*.)

Third, a person would have been motivated to replace the active fungicidal ingredient used in the topical compositions of *Brehove* with the tavaborole compound taught by *Austin* because of tavaborole's lower molecular weight. (Ex. 1005, Murthy Decl. ¶¶ 111–12.) While *Brehove* treats onychomycosis using 2,2'-(1-methyltrimethylene dioxy) bis-(4-methyl-1,3,2-dioxaborinane) and 2,2'-oxybis (4,4,6-trimethyl-1,3,2-dioxaborinane) as the active ingredients in its compositions, these compounds having respective molecular weights of 285.9 and 269.9 Daltons, the tavaborole molecule has a significantly lower molecular weight of 151.93 Daltons. (Ex. 1005, Murthy Decl. ¶¶ 111–12.) It was known in the art that smaller, lower molecular weight molecules are more effective at penetrating the human nail barrier and therefore have a greater likelihood of penetrating the entire nail and reaching the underlying nail plate at lower concentrations. (*Id*.) Therefore, a POSITA, aware of the fungicidal properties of boron-containing compounds in general and tavaborole in particular, would be motivated to use tavaborole as an active ingredient in the topical compositions of *Brehove* as it is a lower molecular weight boron-containing molecule and would therefore be more effective at penetrating the nail plate thereby leading to improved efficacy and safety of the composition at lower concentrations of the active ingredient. (*Id*.)

Finally, the Board has already previously held that a POSITA would have been motivated to combine the teachings of *Austin* and *Brehove* for the treatment

of onychomycosis. (Ex. 1014, IPR '776, FWD at 18–23.) The Board stated that "the combination of the structural similarities *and* the similar fungicidal activity against *C. albicans* would have led a [POSITA] to combine Brehove's method of treating onychomycosis using Austin's tavaborole instead of BioBor" and that, due to tavaborole's low molecular weight and demonstrated efficacy against *C. albicans*, tavaborole was *Austin*'s "first and best compound to select for treatment of onychomycosis." (*Id.* at 21–22; *see also* Ex. 1017, IPR '780, FWD at 28, 37–38.)

Thus, a POSITA would have had ample reason to combine the tavaborole compound of *Austin* with the topical method of treating onychomycosis taught by *Brehove.*

3. A POSITA Would Have Had a Reasonable Expectation of Success in Combining *Austin* and *Brehove*

A POSITA would have had a reasonable expectation of success in using the tavaborole compound of *Austin* in the method of treating onychomycosis through topical application of a composition including an organo-boron compound as taught by *Brehove* for the following reasons: 1) boron-containing compounds were well known in the art as effective biocides and the boron-containing compounds of *Brehove* and *Austin* share common structural features, indicating similar fungicidal activity; 2) the preferred tavaborole compound of *Austin* is taught to have similar fungicidal activity with the active ingredient compounds used in the method of

Brehove; 3) the tavaborole compound of *Austin* has a lower molecular weight than the active ingredient compounds used in the method of *Brehove*; 4) *Brehove* demonstrates that an industrial boron-based biocide such as the tavaborole compound of *Austin* can be incorporated as an active ingredient in a safe and effective topical application for treatment of onychomycosis. (Ex. 1005, Murthy Decl. ¶¶ 114–24, 134; *see also* Ex. 1014, IPR '776 FWD at 28; Ex. 1017, IPR '780, FWD at 37–38.)

A POSITA was aware that boron-based compounds are effective fungicides. *Brehove* teaches that "organo-boron compounds have long been known to exhibit biocidal activity." (Ex. 1008, *Brehove* ¶ [0007].) The specific boron-based compounds applied as the active fungicidal ingredient in the method of *Brehove* are boron heterocycles, as is the tavaborole compound disclosed as one of three preferred antifungal compounds of *Austin*. (Ex. 1007, *Austin* at (57) [Abstract]; Ex. 1005, Murthy Decl. ¶ 115–17.) Due to this structural similarity, a POSITA would have an expectation that the tavaborole compound would exhibit similar antifungal activity and would be an effective active ingredient for use in the method of treatment of *Brehove*. (Ex. 1005, Murthy Decl. ¶ 115–17.)

In addition to structural similarity, *Brehove* and *Austin* disclose similar fungicidal activity in their respective compounds. *Austin* teaches the tavaborole as one of three preferred compounds. (Ex. 1007, *Austin* at (57) [Abstract], col. 6:5–

10.) *Austin* teaches MICs as low as 5 ppm of tavaborole against *Candida albicans* as well as numerous other fungi in vitro. (*Id*. at 35–39.) *Brehove* similarly teaches effectiveness of its preferred boron-containing compounds at killing *Candida albicans* at concentrations of 0.1% by weight. (Ex. 1008, *Brehove* ¶¶ [0032]–[0033].) In addition it was known to a POSITA that antifungal activity against yeasts such as *Candida albicans* is a predictor of similar activity against dermatophytes such as *T. rubrum* and *T. mentagrophytes*. (Ex. 1005, Murthy Decl. ¶ 118; Ex. 1014, IPR ’776 FWD at 30–31.) Therefore, as the Board has previously held, a POSITA would have had a reasonable expectation that tavaborole, which shares fungicidal activity with the compounds of *Brehove*, would share other functional activity, including suitability for incorporation as an active ingredient into a safe and effective formulation for topical treatment of the primary onychomycosis-causing pathogens. (Ex. 1014, IPR ’776, FWD at 30-31; Ex. 1017, IPR ’780, FWD at 37.)

A POSITA would further have a reasonable expectation of success in using tavaborole as the active ingredient in the method disclosed by *Brehove* due to tavaborole’s low molecular weight. (*See* Ex. 1014, IPR ’776, FWD at 24.) While *Brehove* treats onychomycosis using 2,2’-(1-methyltrimethylene dioxy) bis-(4-methyl-1,3,2-dioxaborinane) and 2,2’-oxybis (4,4,6-trimethyl-1,3,2-dioxaborinane) as the active ingredients in its compositions, these compounds having respective

molecular weights of 285.9 and 269.9 Daltons, the tavaborole molecule has a significantly lower molecular weight of 151.93 Daltons. (Ex. 1005, Murthy Decl. ¶¶ 119-20.) Therefore, a POSITA would have a reasonable expectation that the tavaborole molecule of *Austin* would be an effective active ingredient in a topical application for the treatment of onychomycosis as taught by *Brehove* as it would allow the active ingredient of the composition to effectively penetrate the nail plate. (Ex. 1005, Murthy Decl. ¶¶ 119–20.) Indeed, the Board has previously held that a POSITA "would have had a reasonable expectation that administering tavaborole topically would penetrate the nail." (Ex. 1014, IPR '776, FWD at 24; Ex. 1017, IPR '780, FWD at 30–31.)

Finally, a POSITA would not be discouraged from applying a fungicide initially used for industrial applications as an active ingredient in a topically applied pharmaceutical composition. The concentration of an active ingredient in such a composition is readily adjustable for topical application to humans based on routine experimentation. (Ex. 1005, Murthy Decl. ¶¶ 121–23.) The level of skill of a POSITA was high and a POSITA would have had a reasonable expectation of successfully determining via well-known techniques a therapeutically effective amount of tavaborole for use in a topical application for treatment of onychomycosis. (Ex. 1005, Murthy Decl. ¶¶ 121–22.) Further, there are multiple examples of industrial biocides being applied for use in topical pharmaceutical

formulations. For example, the boron-containing active ingredient compounds of *Brehove* were themselves used in an industrial biocide, BioborJF®, before being applied in *Brehove's* pharmaceutical compositions. (Ex. 1005, Murthy Decl. ¶¶ 101, 123.) Another such example is amorolfine hydrochloride, used in the topically applied LOCERYL®, which was previously used for agricultural applications. (Ex. 1005, Murthy Decl. ¶ 123.) Thus, a POSITA would have a reasonable expectation of success of replacing the boron-containing active ingredients of *Freeman* with tavaborole, despite its use as an industrial fungicide. Indeed, the Board has previously held that a POSITA "would have recognized that industrial fungicides may have therapeutic uses, including in some cases, topically treating a human for *C. albicans*." (Ex. 1014, IPR '776, FWD at 13.)

Thus, as the Board has previously found, a POSITA would have had a reasonable expectation of success of using the preferred tavaborole compound of *Austin* as the active fungicidal compound in the method of topical application of a pharmaceutical composition for the treatment of onychomycosis as taught by *Brehove*. (Ex. 1014, IPR '776, FWD at 23 (holding that that a POSITA "would have had a reasonable expectation of success in combining Austin and Brehove"); Ex. 1017, IPR '780, FWD at 30 (same).)

B. Explanation Of Ground 2 For Unpatentability: Claims 2–3, 5–6, 8 & 11–12 of the '290 Patent are Obvious Over *Austin* in View of *Brehove* and *Samour*

It would have been obvious to a POSITA to combine the topical application of a boron-containing compound for treatment of onychomycosis as taught by *Brehove* with the specific antifungal active ingredient of tavaborole taught by *Austin* in further combination with the effective and durable nail lacquer formulation for topical treatment of onychomycosis taught by *Samour*. The substitution of the active ingredient of *Samour* with a boron-based compound for use in a topical application for treatment of onychomycosis as generally taught by *Brehove* and for tavaborole as specifically taught by *Austin* is nothing more than a simple substitution of known elements for one another according to their established functions. *See KSR.*, 550 U.S. at 401. This combination renders Claims 2–3, 5–6, 8 & 11–12 of the '290 Patent obvious.

1. All Elements of Claims 2–3, 5–6, 8 & 11–12 are Obvious Over *Austin* in View of *Brehove* and *Samour*

Claim 2 depends from Claim 1 and further requires that "**the pharmaceutical composition is in the form of a solution comprising 5% w/w of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole or a pharmaceutically acceptable salt thereof**." *Austin* teaches a preferred concentration of tavaborole of "especially from 5 to 30% . . . by weight relative to the total weight of the biocide composition." (Ex. 1007, *Austin* at 9:5–9.) *Brehove* teaches that its active organo-

boron compound "[m]ost preferably . . . constitutes between about 0.1 wt % and 25 wt % of the composition." (Ex. 1008, *Brehove* ¶ [0028].) It would have been obvious to a POSITA to include tavaborole as an active ingredient in the pharmaceutical composition at a concentration of 5% as this value is within the range of preferred concentrations of active ingredient disclosed by both *Austin* and *Brehove*. Further, *Samour* specifically teaches a topically applied pharmaceutical composition with 5% w/w active antifungal ingredient. (Ex. 1010, *Samour* col. 22:20–24:23 (Example 7 & 8 disclosing numerous pharmaceutical compositions with 5% by weight econazole).) Therefore, it would have been obvious to provide such topical composition with 5% w/w tavaborole active ingredient. (Ex. 1005, Murthy Decl. ¶¶ 139–41.)

Claim 3 depends from Claim 1 and further requires "**wherein the pharmaceutical composition further comprises ethanol and propylene glycol**." *Austin* teaches that its disclosed oxaborole compound is "preferably formulated in a composition together with a carrier" and that such a carrier may be "alcohols such as ethanol or glycols such as . . . propylene glycol." (Ex. 1007, *Austin* at 8:34–38.) *Brehove* teaches its pharmaceutical composition as containing a "volatile solvent such as alcohol." (Ex. 1008, *Brehove* ¶ [0025].) *Samour* teaches a topical lacquer solution for treatment of onychomycosis including a film-forming polymer, a suitable plasticizer such as propylene glycol, and an organic solvent such as

ethanol. (Ex. 1010, *Samour* col. 8:58–64, col. 9:31–48.) Further, *Samour* provides numerous examples of lacquer formulations including both ethanol and propylene glycol. (*See, e.g.*, *id.* at col. 21:41–22:18 (Example 6, compound 303A consisting of an antifungal active ingredient (econazole), a film forming polymer (Eudragit), propylene glycol, and ethanol), col. 23:52–24:42 (Examples 8 & 9, compound 353B consisting of an antifungal compound, polymer, penetration enhancer (2-n-nonyl-1,3-dioxolane), propylene glycol, and ethanol); Ex. 1005, Murthy Decl. ¶¶ 148–49.)

Claim 5 depends from Claim 4 and further requires that "**the pharmaceutical composition is in the form of a solution comprising 5% w/w of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole or a pharmaceutically acceptable salt thereof**." Claim 4 would have been obvious based on the combination of *Austin* and *Brehove*, as discussed above. The additional limitation of Claim 5 requiring 5% by weight of tavaborole would have been obvious in further view of the teachings of *Samour* as described above for Claim 2. (Ex. 1005, Murthy Decl. ¶¶ 150–52.)

Claim 6 depends from Claim 5 and further requires that the "**pharmaceutical composition further comprises ethanol and propylene glycol.**" This further limitation is obvious in view of *Austin*, *Brehove*, and *Samour* as explained for Claim 3 above. (Ex. 1005, Murthy Decl. ¶¶ 153–56.)

Claim 8 depends from Claim 6 and further requires that "**the administering of the pharmaceutical composition occurs once a day**." *Brehove* provides multiple examples of applying its topical formulation to the entire nail once a day for the effective treatment of onychomycosis. (Ex. 1008, *Brehove* ¶¶ [0035]–[0037], Ex. 1005, Murthy Decl. ¶¶ 157–59.) *Samour* also teaches that for topical application for the treatment of onychomycosis, films having short release periods "may be desirable since many individuals are accustomed to and prefer treatments requiring applications of a drug on a daily basis. (Ex. 1010, *Samour* col. 10:1–7, col. 25:61–63; Ex. 1005, Murthy Decl. ¶ 160.)

Claim 11 depends from Claim 6 and further requires "**wherein the method inhibits leucyl tRNA synthetase in *Trichophyton rubrum***." As explained above for Claim 1, the mechanism of action by which tavaborole treats onychomycosis is the inhibition of leucyl tRNA synthetase in onychomycosis-causing pathogens and it would have been obvious to use the tavaborole compound of *Austin* as a boron-based active fungicidal ingredient (per *Brehove*) in a topically applied pharmaceutical nail lacquer as taught by *Samour* to treat onychomycosis caused ty *T. rubrum*. (Ex. 1005, Murthy Decl. ¶¶ 161–62.)

Claim 12 depends from Claim 6 and further requires "**wherein the method inhibits leucyl tRNA synthetase in *Trichophyton mentagrophytes***." As explained above for Claim 1, the mechanism of action by which tavaborole treats

onychomycosis is the inhibition of leucyl tRNA synthetase in onychomycosis-causing pathogens and it would have been obvious to use the tavaborole compound of *Austin* as a boron-based active fungicidal ingredient (per *Brehove*) in a topically applied pharmaceutical nail lacquer as taught by *Samour* to treat onychomycosis caused ty *T. mentagrophytes*. (Ex. 1005, Murthy Decl. ¶¶ 163–64.)

2. A POSITA Would Have Had Reason to Combine *Austin*, *Brehove*, and *Samour* and Would Have had a Reasonable Expectation of Success in Combining the Same

Samour teaches a topically applied pharmaceutical composition for the treatment of onychomycosis in the form of a nail lacquer having improved physical properties (e.g., durability, water-resistance, flexibility, improved diffusion) for carrying an active fungicidal ingredient for the treatment of onychomycosis. (Ex. 1010, *Samour* col. 3:59–65, col. 22:20–24:23.) A POSITA would have combined the improved composition of *Samour* with *Brehove*'s teaching of using a boron-based fungicidal active ingredient in topically applied pharmaceutical compositions for onychomycosis treatment along with *Austin*'s specific disclosure of tavaborole as an effective boron-based fungicide. A POSITA would have had reason to combine and would have had a reasonable expectation of success in combining *Austin, Brehove,* and *Samour* for all the reasons discussed above for *Austin* and *Brehove* alone. (Ex. 1005, Murthy Decl. ¶¶ 142–143, 146, 165–66; *see also* Ex. 1017, IPR '780, FWD at 43–44.)

Further, formulating pharmaceutical compositions, and the amount of active ingredient therein, was well known in the art of topical pharmaceuticals and involves nothing more than routine experimentation based on well-known protocols. (Ex. 1005, Murthy Decl. ¶ 143.) *Samour* discloses its pharmaceutical compositions as having its fungicidal active ingredient in ranges similar to those disclosed in *Austin* and *Brehove,* and *Samour* specifically teaches pharmaceutical compositions including 5% by weight of an active fungicidal compound. (Ex. 1010, *Samour* col. 22:20–24:23; Ex. 1005, Murthy Decl. ¶ 143.) A POSITA would therefore reasonably expect that a nail lacquer formulation according to *Samour* using 5% tavaborole as its active ingredient would be similarly effective in treating onychomycosis. (Ex. 1005, Murthy Decl. ¶ 143–44.)

A POSITA would be motivated to use tavaborole as the active ingredient in the topical pharmaceutical composition of *Samour* due to its low molecular weight of 151.93 Daltons. (Ex. 1001, the '290 patent, col. 135:1–66.) The preferred antifungal of *Samour*, econazole, has a molecular weight of 381.68 Daltons. (Ex. 1005, Murthy Decl. ¶ 145.) A POSITA would therefore be motivated to use the lower molecular weight tavaborole as the active ingredient of the topical compositions taught by *Samour* as a POSITA understood that lower molecular weight fungicidal compounds are more effective at penetrating the nail plate and delivering the active ingredient to the pathogen-infected area. (Ex. 1005, Murthy

Decl. ¶ 145.) This lower molecular weight would also give a POSITA a reasonable expectation of success that such compositions including tavaborole would effectively treat onychomycosis, including such caused by *T. rubrum* and *T. mentagrophytes*, when topically applied. (Ex. 1005, Murthy Decl. ¶ 147; Ex. 1017, IPR ’780, FWD at 44.)

Thus, as the Board has previously held, a POSITA would have had a motivation to combine *Austin*, *Brehove*, and *Samour* and would have had a reasonable expectation of success in doing so. (Ex. 1005, Murthy Decl. ¶¶ 142–47; Ex. 1017, IPR ’780, FWD at 42–44 (stating that a POSITA “would be motivated to substitute tavaborole for the higher molecular weight compound in Samour . . . and would have a reasonable expectation of success in doing so.”).)

C. Explanation Of Ground 3 For Unpatentability: Claims 1, 4, 7 & 9–10 of the ’290 Patent are Obvious Over *Austin* in View of *Freeman*

It would have been obvious to a POSITA to combine the known, effective antifungal boron-containing compound disclosed in *Austin* with the topical application of pharmaceutical compositions including boron-containing antifungal compounds for the treatment of onychomycosis as taught by *Freeman*. The substitution of tavaborole for the active ingredient of *Freeman* is nothing more than a simple substitution of one known elements for another according to their established functions. *See KSR*, 550 U.S. at 401. This combination renders Claims

1, 4, 7 & 9–10 of the ’290 Patent obvious.

1. All Elements of Claims 1 & 4–6 are Obvious Over *Austin* in View of *Freeman*

a. Independent Claim 1

All limitations of Claim 1 of the ’290 Patent would have been obvious over *Austin* in view of *Freeman*. The preamble claims “**a method of delivering a compound, in a human, from a dorsal layer of a nail plate to a nail bed to treat onychomycosis caused by Trichophyton rubrum or Trichophyton mentagrophytes**.” The preamble claims “**A method of treating a human having onychomycosis of a toenail caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes***.” This preamble recites no essential structure or steps necessary for understand the claim and therefore does not provide limitations on the claim. Regardless, all parts of the preamble are disclosed by *Austin* and *Freeman* as fully described for the limitations in the claim body below.

The method of Claim 1 requires “**topically administering to the toenail a pharmaceutical composition comprising an amount of 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole or a pharmaceutically acceptable salt thereof . . . .**” 1,3-dihydro-5-fluoro-1-hydroxy-2,1-benzoxaborole is specifically disclosed as an effective fungicide in *Austin*. (Ex. 1007, *Austin* at (57) [Abstract], 3:35–40; Ex. 1005, Murthy Decl. ¶ 169.) *Freeman* discloses topical application to human finger or toenails of pharmaceutical compositions containing boron-containing

compounds for the treatment of onychomycosis. (Ex. 1009, *Freeman* ¶¶ [001], [0022].) Therefore, combining the compound of *Austin* with the method of topical application of a pharmaceutical composition with a boron-containing compound for the treatment of onychomycosis taught by *Freeman* renders this limitation obvious and it would have been obvious to combine these compounds specifically for the treatment of onychomycosis caused by *T. rubrum* or *T. mentagrophytes*. *Austin* teaches that the 5-fluoro benzoxaborole is inhibitory against *Candida albicans* in vitro (Ex. 1007, *Austin* at 35–39; Ex. 1005, Murthy Decl. ¶ 170), and *Freeman* identifies *T. rubrum* and *Candida* species yeasts as common causes of onychomycosis (Ex. 1009, *Freeman* ¶ [008].). *Freeman* discloses its topical formulation containing organo-boron compounds as inhibiting both *T. rubrum* and *Candida* species in vitro. (Ex. 1009, *Freeman* ¶¶ [0030]–[0037].) Further, A POSITA understood inhibitory activity against yeasts such as *Candida albicans* to be predictive of antifungal activity against dermatophytes, including *T. rubrum* and *T. mentagrophytes*. (Ex. 1005, Murthy Decl. ¶ 171; Ex. 1014, IPR ’776, FWD at 30–31.) Therefore, it would have been obvious for a POSITA to use the tavaborole compound taught by *Austin* as the active fungicidal ingredient in the topically applied pharmaceutical formulation of *Freeman* in order to treat onychomycosis caused by *T. rubrum* or *T. mentagrophytes*.

Moreover, the Board has previously held that a POSITA would combine the

teachings of *Austin* and *Freeman* to treat *T. rubrum* or *T. mentagrophytes* caused onychomycosis, stating that a POSITA "would have expected that Austin's tavaborole would share similar functional features with the compounds in *Freeman* that effectively treat onychomycosis caused by microorganisms other than the *Candida* species, and thus would have had a reasonable expectation of success in combining *Austin* and *Freeman* to effectively treat infections [caused by *T. rubrum* or *T. mentagrophytes*]." (Ex. 1018, IPR '785, FWD at 32–35; *see also* Ex. 1014, IPR '776, FWD at 30-31.)

The method of Claim 1 further requires the claimed claimed topical administration to be "**effective to inhibit an aminoacyl tRNA synthetase in the *Trichophyton rubrum* or *Trichophyton mentagrophytes***." As explained for Ground 1 above, inhibition of leucyl tRNA synthetase, which is a type of aminoacyl tRNA synthetase, is the mechanism of action by which tavaborole treats the pathogens that cause onychomycosis and is therefore a necessary and inherent aspect of using tavaborole to topically treat such pathogens. This limitation is therefore obvious based on the combination of *Austin* and *Freeman*. (Ex. 1005, Murthy Decl. ¶¶ 176–80.)

b. Dependent Claims 4, 7 & 9–10

Claim 4 depends from Claim 1 and further requires "**wherein the aminoacyl tRNA synthetase is leucyl tRNA synthetase**." As explained above for Claim 1,

the mechanism of action by which tavaborole treats onychomycosis is the inhibition of leucyl tRNA synthetase in onychomycosis-causing pathogens and this limitation is therefore inherent to using tavaborole for such treatment. (Ex. 1005, Murthy Decl. ¶¶ 199–200.)

Claim 7 depends from Claim 1 and further requires "**wherein the administering of the pharmaceutical composition occurs once a day**." *Freeman* provides "[g]enerally, the compositions are applied topically once daily until cure." (Ex. 1009, *Freeman* ¶ [0030], Ex. 1005, Murthy Decl. ¶¶ 201–02.)

Claim 9 depends from Claim 1 and further requires "**wherein the method inhibits an aminoacyl tRNA synthetase in *Trichophyton rubrum***." As explained above for Claim 1, the mechanism of action by which tavaborole treats onychomycosis is the inhibition of leucyl tRNA synthetase, a type of aminoacyl tRNA synthetase, in onychomycosis-causing pathogens and it would have been obvious to use the tavaborole compound of *Austin* as the active fungicidal ingredient in a topically applied pharmaceutical composition as taught by *Freeman* to treat onychomycosis caused by *T. rubrum*. (Ex. 1005, Murthy Decl. ¶¶ 203–04.)

Claim 10 depends from Claim 1 and further requires "**wherein the method inhibits an aminoacyl tRNA synthetase in *Trichophyton mentagrophytes***." As explained above for Claim 1, the mechanism of action by which tavaborole treats onychomycosis is the inhibition of leucyl tRNA synthetase, a type of aminoacyl

tRNA synthetase, in onychomycosis-causing pathogens and it would have been obvious to use the tavaborole compound of *Austin* as the active fungicidal ingredient in a topically applied pharmaceutical composition as taught by *Freeman* to treat onychomycosis caused by *T. mentagrophytes*. (Ex. 1005, Murthy Decl. ¶¶ 205–06.)

2. A POSITA Would Have Had Reason to Combine *Austin* and *Freeman*

A POSITA would have had numerous reasons to combine the teachings of *Austin* and *Freeman*, i.e., use the tavaborole compound of *Austin* in a topical application for treatment of onychomycosis as taught by *Freeman*. (*See* Ex. 1005, Murthy Decl. ¶¶ 181–87, 207.)

First, both *Austin* and *Freeman* teach the use of boron-containing compounds as effective fungicides. (Ex. 1005, Murthy Decl. ¶ 182.) *Austin* specifically teaches that oxaboroles are particularly effective against microorganisms such as yeasts and fungi. (Ex. 1007, *Austin* at 3:35–40.) *Freeman* discloses the topical application of pharmaceutical compositions including boron-containing PBA and its derivatives for the treatment of onychomycosis. (Ex. 1009, *Freeman* ¶¶ [008], [0030]–[0037].) The tavaborole of *Austin* is structurally similar to the PBA active ingredient of *Freeman* and a POSITA would therefore expect tavaborole to exhibit similar fungicidal activity when used in the pharmaceuticals formulations disclosed by *Freeman*. (Ex. 1005, Murthy Decl. ¶¶ 182, 185; *see also*

Ex. 1014, IPR ’776, FWD at 40; Ex. 1018, IPR ’785, FWD at 31, 35.)

Second, both *Austin* and *Freeman* teach efficacy of boron-containing compounds against onychomycosis-causing yeast, i.e., *Candida* species, or *T. Rubrum*. (Ex. 1005, Murthy Decl. ¶¶ 184–85.) *Austin* discloses the high fungicidal potency of tavaborole, disclosing that an *in vitro* MIC of 5 ppm against numerous types of fungi, including *Candida albicans*. (Ex. 1007, *Austin* at 35–39.) Similarly, *Freeman* teaches its topical application of boron-containing compounds to inhibit *Candida* species as well as *T. rubrum*. Ex. 1009, *Freeman* ¶¶ [0030]–[0037]. It was known in the art that antifungal activity against yeasts such as *Candida albicans* is predictive of similar efficacy against dermatophytes such as *T. rubrum and T. mentagrophytes*. (Ex. 1005, Murthy Decl. ¶ 192; *see also* Ex. 1014, IPR ’776, FWD at 30-31.) A POSITA would therefore be motivated to combine the effective antifungal, tavaborole, taught by *Austin* with the topical application of a boron-containing compound taught by *Freeman* to arrive at a topical application effective against all primary causes of onychomycosis: *Candida albicans*, *T. rubrum, and T. mentagrophytes*.

Third, a person would have been motivated to replace the active fungicidal ingredient used in the topical compositions of *Freeman* with the tavaborole compound taught by *Austin* because of tavaborole’s low molecular weight. (Ex. 1005, Murthy Decl. ¶¶ 186–87.) *Freeman* treats onychomycosis using PBA and

pentafluoro PBA as the active ingredients in its compositions, these compounds having respective molecular weights of 121.9 and 211.89 Daltons, and the tavaborole molecule has a similar molecular weight of 151.93 Daltons. (Ex. 1005, Murthy Decl. ¶¶ 186–87.) It was known in the art that smaller, lower molecular weight molecules are more effective at penetrating the human nail barrier and therefore have a greater likelihood of penetrating the entire nail and reaching the underlying nail plate at lower concentrations. (Ex. 1005, Murthy Decl. ¶ 186.) Therefore, a POSITA, aware of the fungicidal properties of boron-containing compounds in general and tavaborole in particular, would be motivated to use tavaborole as an active ingredient in the topical compositions of *Freeman* as it is a low molecular weight boron-containing molecule and would therefore be effective at penetrating the nail plate thereby leading to improved efficacy and safety of the composition at low concentrations of the active ingredient. (Ex. 1005, Murthy Decl. ¶¶ 186–87.).

Finally, the Board has already previously held that a POSITA would have been motivated to combine the teachings of *Austin* and *Freeman* for the treatment of onychomycosis. (Ex. 1014, IPR ’776, FWD at 38–41.) The Board stated that a POSITA “would have had a reason to modify Freeman to administer Austin’s tavaborole instead of PBA in light of the similar chemical structure and the similar activity against *Candida* species.” (*Id.* at 40; *see also* Ex. 1018, IPR ’785, FWD at

26, 35.)

Thus, a POSITA would have had ample reason to combine the tavaborole compound of *Austin* with the topical method of treating onychomycosis taught by *Freeman.*

3. A POSITA Would Have Had a Reasonable Expectation of Success in Combining *Austin* and *Freeman*

A POSITA would have had a reasonable expectation of success in using the tavaborole compound of *Austin* in the method of treating onychomycosis through topical application of a composition including an organo-boron compound as taught by *Freeman* for the following reasons: 1) boron-containing compounds were well known in the art as effective biocides and the boron-containing compounds of *Freeman* and *Austin* share common structural features, indicating similar fungicidal activity; 2) the preferred tavaborole compound of *Austin* is taught to have similar fungicidal activity with the active ingredient compounds used in the method of *Freeman*; and 3) the tavaborole compound of *Austin* has similar molecular weight as the active ingredient compounds used in the method of *Freeman*. (Ex. 1005, Murthy Decl. ¶¶ 188–98, 208.)

A POSITA was aware that boron-based compounds are effective fungicides. *Freeman* teaches that "phenyl boronic acid and derivatives thereof as well as related boronic acid compounds have fungicidal properties." (Ex. 1009, *Freeman* ¶ [0022].) The specific boron-based compounds applied as the active fungicidal

ingredient in the method of *Freeman* are cyclic boron compounds, as is the tavaborole compound disclosed as one of three preferred antifungal compounds of *Austin*. (Ex. 1007, *Austin* at (57) [Abstract]; Ex. 1005, Murthy Decl. ¶¶ 189–91.) Due to this structural similarity, a POSITA would have an expectation that the tavaborole compound would exhibit similar antifungal activity and would be an effective active ingredient for use in the method of treatment of *Freeman*. (Ex. 1005, Murthy Decl. ¶¶ 189–91.)

In addition to structural similarity, *Freeman* and *Austin* disclose similar fungicidal activity in their respective compounds. *Austin* teaches the tavaborole as one of three preferred compounds. (Ex. 1007, *Austin* at (57) [Abstract], col. 6:5–10.) *Austin* teaches MICs as low as 5 ppm of tavaborole against *Candida albicans* as well as numerous other fungi in vitro. (*Id*. at 35–39.) *Freeman* similarly teaches effectiveness of its preferred boron-containing compounds at killing *Candida* species yeasts as well as *T. rubrum* and various other fungi in vitro. (Ex. 1009, *Freeman* ¶¶ [0031]–[0037].) In addition it was known to a POSITA that antifungal activity against yeasts such as *Candida albicans* is a predictor of similar activity against dermatophytes such as *T. rubrum* and *T. mentagrophytes*. (Ex. 1005, Murthy Decl. ¶ 192.) Therefore, a POSITA would have had a reasonable expectation that tavaborole, which shares fungicidal activity with the compounds of *Freeman*, would share other functional activity, including suitability for

incorporation as an active ingredient into an effective formulation for topical treatment of the primary onychomycosis-causing pathogens. (Ex. 1005, Murthy Decl. ¶ 192.)

A POSITA would further have a reasonable expectation of success in using tavaborole as the active ingredient in the method disclosed by *Freeman* due to tavaborole's low molecular weight. *Freeman* treats onychomycosis using PBA and pentafluoro PBA as the active ingredients in its compositions, these compounds having respective molecular weights of 121.9 and 211.89 Daltons, and the tavaborole molecule has a similar molecular weight of 151.93 Daltons. (Ex. 1005, Murthy Decl. ¶¶ 193–94.) Therefore, a POSITA would have a reasonable expectation that the tavaborole molecule of *Austin* would be an effective active ingredient in a topical application for the treatment of onychomycosis as taught by *Freeman* as it would allow the active ingredient of the composition to effectively penetrate the nail plate. (Ex. 1005, Murthy Decl. ¶¶ 193–94.) Indeed, the Board has previously held that a POSITA "would have had a reasonable expectation that administering tavaborole topically would penetrate the nail." (Ex. 1014, IPR '776, FWD at 24; Ex. 1017, IPR '780, FWD at 30-31.)

Thus, as the Board has previously found, a POSITA would have had a reasonable expectation of success of using the preferred tavaborole compound of *Austin* as the active fungicidal compound in the method of topical application of a

pharmaceutical composition for the treatment of onychomycosis as taught by *Freeman*. (Ex. 1014, IPR ’776, FWD at 38–41 (stating that a POSITA “would have had a reason to combine Austin and Freeman with a reasonable expectation of success.”); *see also* Ex. 1018, IPR ’785, FWD at 26, 35.)

D. Explanation Of Ground 4 For Unpatentability: Claims 2–3, 5–6, 8 & 11–12 of the ’290 Patent are Obvious Over *Austin* in View of *Freeman* and *Samour*

The reasons for and results of combining *Samour* with *Austin* in view of *Freeman* are substantially the same as the reasons for combining it with *Austin* in view of *Brehove* set forth in Ground II and discussed in subheading B, at 46–52, *supra*. The analysis of *Austin* and of *Samour* in that discussion fully applies here, and is incorporated by reference as part of the basis for this Ground.

With regard to the “solvent system” language of Claim 4, *Freeman* fully substitutes for *Brehove*, *supra*, because it discloses that the active compound may be formulated in a pharmaceutically acceptable vehicle comprising “a powder, lotion, gel, spray, stick, cream, ointment, liquid, emulsion, foam or aerosol. The active PBA compound can be incorporated into a liquid in dissolved form or colloidal form. The liquid can be a solvent, partial solvent, or non-solvent. Since the active PBA compounds are water-soluble, water is a preferred solvent.” (Ex. 1009 at ¶ [0065].)

With regard to the concentration recited in Claim 2, *Freeman* fully

substitutes for *Breehove*, *supra*¸ because *Freeman* teaches that for the pharmaceutical compositions containing its active boron-containing compound, "ranges from about 2% to about 50% are most preferred." (Ex. 1009, *Freeman* ¶ [0038].)

With regard to the administering once a day language in Claim 8, *Freeman* fully substitutes for *Brehove*, *supra*, because it discloses that "[g]enerally, the compositions are applied topically once daily until cure." (Ex. 1009, *Freeman* ¶ [0030], Ex. 1005, Murthy Decl. ¶¶ 231–34.)

The remaining analysis, applying *Austin* and *Samour* to the rest of the limitations of Claims 2–3, 5–6, 8 & 11–12 is substantially the same to the analysis above for those same claims and references, as is the analysis of the motivation to combine and likelihood of success.

Thus, as the Board has previously held, a POSITA would have had a motivation to combine *Austin*, *Freeman*, and *Samour* and would have had a reasonable expectation of success in doing so. (Ex. 1018, IPR '785, FWD at 41–43 (stating that a POSITA "would have been motivated to substitute tavaborole for the higher molecular weight compound in Samour . . . and would have a reasonable expectation of success in doing so.").)

E. No Secondary Considerations Overcome This Strong Showing of Obviousness.

Factual inquiries for an obviousness determination include secondary considerations based on evaluation and crediting of objective evidence of nonobviousness. *Graham*, 383 U.S. at 17–18. The totality of the evidence submitted, including objective evidence of nonobviousness, may lead to a conclusion that the challenged claims would not have been obvious to one of ordinary skill in the art. *In re Piasecki*, 745 F.2d 1468, 1471–72 (Fed. Cir. 1984). However, "secondary considerations of nonobviousness . . . simply cannot overcome a strong prima facie case of obviousness." *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (Fed. Cir. 2010); *Ryko Mfg. Co. v. Nu–Star, Inc.*, 950 F.2d 714, 719 (Fed. Cir. 1991) (the weight of secondary considerations may be of insufficient weight to override a determination of obviousness based on primary considerations); *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988) (secondary considerations "must be considered, [but] they do not control the obviousness conclusion" (citations omitted)).

For example, Patent Owner cannot show any unexpected results over the closest prior art. *See Kao Corp. v. Unilever United States, Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) ("[w]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art.") (*quoting In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed.

Cir. 1991)). Nor can Patent Owner identify any long felt need in comparison to other already available treatments, with evidence showing that the need was a persistent one was recognized by those of ordinary skill in the art. *See In re Gershon*, 372 F.2d 535, 539 (CCPA 1967). Petitioner reserves the right to offer evidence to rebut any alleged secondary considerations Patent Owner seeks to assert.

CONCLUSION

For the foregoing reasons, Petitioner submits that there is a reasonable likelihood that it will prevail with respect to at least one of the claims challenged as unpatentable over the prior art cited herein. Accordingly, Petitioner respectfully requests *inter partes* review of claims 1–12 of the '290 patent.

Respectfully submitted,

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CERTIFICATION OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), the undersigned hereby certifies that the word count for the Petition for *Inter Partes Review* of U.S. Patent No. 9,566,290 filed in this proceeding on November 21, 2017, totals 13,695 words, which is less than the 14,000 allowed under 37 C.F.R. § 42.24(a)(i).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.105, Petitioner certifies that this *Petition for Inter Partes Review* and supporting evidence was served by Federal Express®, on November 21, 2017, to the Patent Owner owner of U.S. Patent No. 9,566,290, Anacor Pharmaceuticals, Inc., at their correspondence address of record according to USPTO PAIR:

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