

On behalf of **Padagis Israel Pharmaceuticals Ltd;
Padagis US LLC; and Padagis, LLC**

By:

Carol Pitzel Cruz (Reg. No. 61,224)
KNOBBE, MARTENS, OLSON & BEAR, LLP
925 Fourth Ave., Ste. 2500
Seattle WA 98104
Telephone: (206) 405-2000

Brian Barnes (Reg. No. 75,805)
KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 Main Street, 14th Floor
Irvine, CA 92614

Andrea Cheek (Reg. No. 65,642)
KNOBBE, MARTENS, OLSON & BEAR,
LLP
1717 Pennsylvania Ave. N.W.
Ste. 900
Washington D.C. 20006
Telephone: (202) 640-6400

Email: PadagisIPR482@knobbe.com

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

**PADAGIS ISRAEL PHARMACEUTICALS LIMITED;
PADAGIS US LLC; AND PADAGIS, LLC**
Petitioners,

v.

BAUSCH HEALTH US, LLC
Patent Owner.

IPR2023-01114
Patent No. 11,311,482

**PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 11,311,482**

TABLE OF CONTENTS

	Page No.
I. SUMMARY OF THE ARGUMENT	1
II. STATE OF THE ART.....	4
A. Topical Tazarotene Treatments For Acne.....	4
B. Local Skin Irritation Associated With Tazarotene.....	6
C. Prior Art Lotion Vehicles For Formulating Tazarotene.....	7
D. Prosecution Of Related Patent Owner’s Related Applications.....	12
1. The ’576 Application	12
2. The ’871 Application	15
III. THE ’482 PATENT	16
A. Overview	16
B. Prosecution History	26
C. The Critical Date	26
IV. STATEMENT AND RELIEF REQUESTED.....	27
A. IPR Grounds	27
B. The Asserted References Are Prior Art	28
C. The Asserted References Are Analogous Art	30
V. THE BOARD SHOULD NOT DENY INSTITUTION UNDER 35 U.S.C. § 325(D).....	30

TABLE OF CONTENTS
(cont'd)

	Page No.
VI. LEVEL OF ORDINARY SKILL	34
VII. CLAIM CONSTRUCTION	35
VIII. PROPOSED GROUNDS FOR UNPATENTABILITY	35
A. Grounds 1-3: Claims 1-11 Would Have Been Obvious Over WO '001 and Kircik, Chim, or Anderson	35
1. Claim 1	37
a. Preamble	37
i. Anderson	37
ii. Kircik.....	38
iii. Chim	38
b. Composition of tazarotene at .045% as sole active ingredient.....	39
i. Anderson	41
ii. Kircik.....	43
iii. Chim	44
c. Oil-in-water emulsion lotion	45
d. Oil phase	45
e. Aqueous phase	46
f. Polymeric emulsifier.....	47

TABLE OF CONTENTS
(cont'd)

	Page No.
2. Claim 2	49
3. Claim 3	49
4. Claims 4-6	49
a. Anderson	50
b. Kircik	50
c. Chim	51
5. Claim 7	51
6. Claim 8	52
7. Claims 9-10	53
8. Claim 11	55
B. Ground 4: Claims 1-11 Would Have Been Obvious Over WO '001 and Anderson in Combination with Shalita	57
1. Claims 4-6	59
C. Ground 5: Claims 1-11 Would Have Been Obvious Over the '824 Publication and the Tazorac® Label	59
1. Claim 1	61
a. Preamble	61
b. Composition of tazarotene at 0.045% as sole active ingredient	61
c. Oil-in-water emulsion lotion	64

TABLE OF CONTENTS

(*cont'd*)

	Page No.
d. Oil phase	66
e. Aqueous phase	67
f. Polymeric emulsifier.....	68
2. Claim 2	70
3. Claim 3	70
4. Claims 4-6	70
5. Claim 7	71
6. Claim 8	72
7. Claims 9-10	73
8. Claim 11	74
D. Grounds 6: Claims 1-11 Would Have Been Obvious Over the '824 Publication and the Tazorac® Label in view of Anderson	75
E. Grounds 7-9: Claims 1-11 Would Have Been Obvious Over the '824 Publication and the IDP-118 Study in view of Anderson, Kircik, or Chim.....	76
1. Claim 1	78
a. Preamble	78
b. Composition of tazarotene at 0.045% as sole active ingredient.....	78
i. Anderson	79

TABLE OF CONTENTS

(*cont'd*)

	Page No.
ii. Kircik.....	79
iii. Chim	79
c. Remaining Limitations	79
2. Claims 2-3, 7-11.....	82
3. Claims 4-6	82
IX. SECONDARY CONSIDERATIONS	82
X. THE BOARD SHOULD NOT DENY INSTITUTION UNDER 35 U.S.C. §314(A).....	84
XI. MANDATORY NOTICES UNDER 37 C.F.R. §42.8(A)(1).....	85
A. Real Party-In-Interest (37 C.F.R. §42.8(b)(1))	85
B. Related Matters (37 C.F.R. §42.8(b)(2)).....	85
C. Lead and Backup Counsel (37 C.F.R. §42.8(b)(3))	86
D. Service Information Under 37 C.F.R. §42.8(b)(4).....	86
XII. FEES.....	87
XIII. GROUNDS FOR STANDING UNDER 37 C.F.R. §42.104	87
XIV. CONCLUSION.....	87

TABLE OF AUTHORITIES

Page No(s).

<i>Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH,</i> IPR2019-01469, Paper 6 (P.T.A.B. Feb. 13, 2020) (precedential)	31
<i>Bausch Health Ireland Ltd. v. Padagis Israel Pharms. Ltd.,</i> No. 22-4248 (MCA) (AME), Dkt. 1	85
<i>Becton, Dickinson and Co. v. B. Braun Melsungen AG,</i> IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017)	32
<i>Comcast Cable Commc’ns LLC v. Promptu Sys. Corp.,</i> IPR2018-00342, Paper 13 (P.T.A.B. July 19, 2018)	32
<i>Galderma Labs., L.P. v. Tolmar, Inc.,</i> 737 F.3d 731 (Fed. Cir. 2013)	<i>passim</i>
<i>Lite-On Technology Corp. v. Sensor Elec. Tech., Inc.,</i> IPR2022-00780, Paper 11 (P.T.A.B. Oct. 28, 2022)	32
<i>Microsoft Corp. v. Surfcast, Inc.,</i> IPR2022-00590, Paper 9 (P.T.A.B. Oct. 7, 2022)	33
<i>In re Nilssen,</i> 851 F.2d 1401 (Fed. Cir. 1988)	30
<i>Phillips v. AWH Corp.,</i> 415 F.3d 1303 (Fed. Cir. 2005)	35
<i>Unwired Planet, LLC v. Google Inc.,</i> 841 F.3d 995 (Fed. Cir. 2016)	30

OTHER AUTHORITIES

35 U.S.C. § 102	28, 29, 30
35 U.S.C. § 314	84

TABLE OF AUTHORITIES
(cont'd)

	Page No.
35 U.S.C. § 325	30, 31, 33
37 C.F.R. §42.100	35
MPEP §2153.01	29

TABLE OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 11,311,482 (“ ’482 patent ”)
1002	Prosecution History of the ’482 patent
1003	Declaration of Dr. Robert Schwartz
1004	Curriculum Vitae of Dr. Robert Schwartz
1005	Declaration of Dr. Narasimha Murthy
1006	Curriculum Vitae of Dr. Narasimha Murthy
1007	International Patent Publication WO 2016/205001 (“ WO ’001 ”)
1008	Topical Tazarotene in Acne Vulgaris: Treatment Approaches, CUTIS 2004;74 (suppl 4): 16-21 (“ Anderson ”)
1009	Kircik, L., Tretinoin Microsphere Gel Pump 0.04% Versus Tazarotene Cream 0.05% in the Treatment of Mild-to-Moderate Facial Acne Vulgaris, J. of Drugs in Dermatology, 2009;8(7): 650-654 (“ Kircik ”)
1010	Chim, C., Acne Vulgaris, ACSAP 2016 Book 2, pp. 7 – 22 (“ Chim ”)
1011	Shalita et al., Tazarotene Gel is Safe and Effective in the Treatment of Acne Vulgaris, CUTIS, 1999;63(6): 349-354 (“ Shalita ”)
1012	U.S. Patent Pub. No. US 2012/0129824 (“ ’824 publication ”)
1013	Prescribing Information for Tazorac® Cream (December 2013) (“ Tazorac® Label ”)
1014	ClinicalTrials.gov, “A Phase 2 Dosing Ranging, Evaluator-Blinded Study to Evaluate the Safety of Topical IDP-118” (“ IDP-118 Study ”)
1015	IQVIA Sales Data For 0.05% Tazarotene For The Indication Of Acne Vulgaris, February 2017-January 2018 (“ IQVIA ”)

Exhibit No.	Description
1016	Declaration of James Booydegraaf
1017	Prescribing Information for FABIOR® Foam (May 2012) (“ Fabior® Label ”)
1018	Eichenfield et al., Evidence-Based Recommendations for the Diagnosis and Treatment of Pediatric Acne, Pediatrics 2013;131(Suppl. 3): S163 – S186 (“ Eichenfield ”)
1019	Zaenglein et al., Guidelines of care for the management of acne vulgaris, J. Am. Acad. Dermatol. 2016;74(5): 945-973 (“ Zaenglein ”)
1020	Gregoriou et al., Use of tazarotene foam for the treatment of acne vulgaris, Clinical, Cosmetic and Investigational Dermatology 2014;7 165–170 (“ Gregoriou ”)
1021	Kober, M-M. et al., Acneiform Eruptions in Dermatology: A Differential Diagnosis, 19-25 (2014) (“ Kober ”)
1022	Dosik et al., Cumulative Irritation Potential of Adapalene 0.1% Cream and Gel Compared With Tazarotene Cream 0.05% and 0.1%, CUTIS 2005;75 289-293 (“ Dosik ”)
1023	Patel et al., Novel microemulsion-based gel formulation of tazarotene for therapy of acne, Pharm. Dev. Technol, 2016;21(8): 921-932 (“ Patel ”)
1024	U.S. Pat. Appl. Pub. No. US 2012/0328670 (“ 670 publication ”)
1025	Kircik, L., Importance of Vehicles in Acne Therapy, J. of Drugs in Dermatology, 201;10(6): s18-s23 (“ Kircik 2011 ”)
1026	Bausch Health Companies, Inc. Duobrii® Citizen Petition (May 28, 2021)
1027	Arazlo Webpage, <i>available at</i> https://www.arazlo.com/hcp
1028	Arazlo Vehicle Webpage, <i>available at</i> https://www.arazlo.com/hcp/vehicle

Exhibit No.	Description
1029	Prosecution History of U.S. Pat. App. No. 16/179,576
1030	'482 patent and '576 application claim comparison chart
1031	Singh et al., Dosage Forms: Non-Parenteral in Encyclopedia of Pharmaceutical Technology, 2002 (“ Singh ”)
1032	U.S. Patent Pub. No. 2012/0328670 (“ Donello ”)
1033	<i>Bausch Health Ireland Ltd. v. Padagis Israel Pharms. Ltd.</i> , Case No. 2:20-cv-05426, Testimony of Dr. Radhakrishnan Pillai (Oct. 4, 2022) (“ Pillai Trial Testimony ”)
1034	Prescribing Information for DIFFERIN® Lotion (April 2013) (“ Differin® Label ”)
1035	Tegeli et al., Pemulen as a Versatile Emulsifier, International Journal of Drug Formulation & Research, 2011;2(1): 52-63 (“ Tegeli ”)
1036	Federal Court Management Statistics, U.S. District Courts (March 31, 2023)
1037	NDA 20600 Tazorac 0.05% and 0.01% Medical Review Part 3 (May 17, 1996) <i>available at</i> https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/20600_TAZORAC%200.05%25%20AND%200.1%25_MEDR_P3.PDF
1038	National Medical and Treatment Audit Diagnosis Allocation Fact Sheet, <i>available at</i> https://www.iqvia.com/-/media/iqvia/pdfs/us/fact-sheet/national-medical-and-treatment-audit-diagnosis-allocation.pdf (“ NMTA Fact Sheet ”)
1039	Eastman et al., Assessing Attributes of Topical Vehicles for the Treatment of Acne, Atopic Dermatitis, and Plaque Psoriasis, CUTIS, 2014; 94: 46-53. (“ Eastman ”)
1040	Russell, J., Topical Therapy for Acne, Am Fam Physician 2000; 61(2):357-365. (“ Russell ”)

Exhibit No.	Description
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1044	Ismail et al., Subchronic and Chronic Toxicity of Tazarotene Gel Following Topical Administration in Hanford Miniswine, 16 Int’l. J. Tox. 571 (1997). (“ Ismail ”)
1045	Gennaro, A. (1990). Remington’s Pharmaceutical Sciences (18th ed., pp. 257-309). Mack Publishing Company. (“ Remington’s ”)
1046	Fiume et al., Int. J. Toxicol. 2012 Jul-Aug (“ Fiume ”)
1047	Prosecution History of U.S. Pat. App. No. 17/366,871
1048	WO 2012/087443

Petitioners Padagis Israel Pharmaceuticals Ltd., Padagis US LLC, and Padagis, LLC (“Petitioner”) request *inter partes* review (“IPR”) of claims 1-11 of U.S. Patent No. 11,311,482 (“the ’482 patent”) assigned to Bausch Health US, LLC (“Patent Owner”).

I. SUMMARY OF THE ARGUMENT

The ’482 patent claims an obvious method of treating acne vulgaris with a known retinoid—tazarotene. In fact, tazarotene had been used to treat that disease for nearly two decades before the patent’s priority date. The ’482 patent claims tazarotene in a lotion vehicle that is expressly disclosed in the prior art. The *exact same* tazarotene formulation was taught by a single prior art reference, including the specific concentrations for every ingredient in the formulation. The only question then is whether a person of ordinary skill in the art (“POSITA”) would have found it obvious to use that prior art tazarotene lotion to treat acne, as dermatologists had been doing for nearly two decades with a nearly identical concentration of the same drug. The answer is unequivocally yes. The prior art was replete with evidence that nearly the same concentration of tazarotene (0.05%) was both safe and effective for treating acne and was commonly used to do so.

The Federal Circuit held a similar patent claiming a retinoid composition for treating acne to be obvious in highly similar circumstances in *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013). There, the asserted patent claimed a

pharmaceutical composition of the retinoid adapalene at a concentration of 0.3% that is “effective for the treatment of acne.” *Id.*, 734. “[T]he sole dispute between the parties [was] whether it was obvious to use a 0.3% adapalene composition for the treatment of acne.” *Id.*, 737. The court held that it would have been obvious to do so given that the prior art disclosed: (1) topical adapalene compositions for treating acne in a preferred range of 0.01%-1%; (2) an animal model study showing that 0.3% adapalene was suitable for treating acne; (3) “that 0.03% and 0.1% adapalene products were suitable for the treatment of acne and that 0.3% adapalene products were suitable for the treatment of other conditions without intolerable irritability”; and (4) “that dermatologists desired acne treatments that came in varying concentrations.” *Id.*, 737 (internal quotations omitted). The analysis in *Galderma* is highly instructive as to Petitioners’ invalidity grounds herein and reinforces the obviousness of the ’482 patent.

For example, *Galderma* rejected the district court’s finding that the prior art taught away from a 0.3% adapalene composition because it showed that increasing the concentration of adapalene would increase irritability. *Galderma Labs., L.P.*, 737 F.3d at 738. The court noted that the prior art did not “indicate that increasing the concentration to 0.3% would be unproductive, nor . . . indicate in any way that the side effects would be serious enough to dissuade the development of a 0.3% adapalene product.” *Id.*, 739. The court further noted that a “teaching that a

composition may be optimal or standard does not criticize, discredit, or otherwise discourage investigation into other compositions.” *Id.* *Galderma* also rejected the plaintiff’s argument that the asserted patent was non-obvious due to unexpected results because the claimed 0.3% adapalene composition presented similar side effects as the lower-concentration 0.1% commercial compositions. *Galderma Labs., L.P.*, 737 F.3d at 739. The court held that while “this result was unexpected, it does not constitute an unexpected result that is probative of nonobviousness” because “where an unexpected increase in efficacy is measured by a small percentage, as here, and the evidence indicates that skilled artisans were capable of adjusting the percentage, the result constitutes a difference in degree, not kind.” *Id.* This holding squarely applies to Patent Owner’s arguments for unexpected results during prosecution of the ’482 patent and its related application. *See infra* § VIII. Like *Galderma*, the clinical results Patent Owner relies on merely demonstrate a difference in degree, not in kind, and therefore cannot demonstrate that the claimed methods would not have been obvious. *Id.*

Like *Galderma*, this Petition “presents an obviousness case that is both straightforward and potent.” *Galderma Labs., L.P.*, 737 F.3d at 736. “At the time of the [alleged] invention, [tazarotene] was a known compound and the prior art [relied on herein] disclose[d] topical [tazarotene] compositions for the purpose of treating acne” at 0.05% – the same or nearly the same concentration as the claimed

“about” 0.045%. *Id.* The “specific inactive ingredients of the [challenged] claims are” also expressly disclosed by the prior art at the same concentrations recited in the claims. *Id.* Therefore, the Board should find that challenged claims 1-11 of the ’482 patent unpatentable as obvious in view of the prior art.

II. STATE OF THE ART

A. Topical Tazarotene Treatments For Acne

Prior to May 2017 (the ’482 patent’s critical date), tazarotene was FDA-approved and commercially available in multiple topical dosage forms (i.e., vehicles) and at two different concentrations – 0.05% and 0.1%. (*See* Ex. 1013, Indications and Usage; Ex. 1017; Ex. 1010, 13, Tables 1-3; Ex. 1003, ¶33; Ex. 1005, ¶30.) Tazarotene was approved for topical use in 1997 and had been approved for treating acne in both cream and foam dosage forms at 0.1% since at least 2013. (*See* Ex. 1013, Indications and Usage; Ex. 1017.) The 0.05% tazarotene concentration was also submitted to the FDA for the indication of acne in 1996, but the FDA did not approve 0.05% tazarotene for that indication. (*See* Ex. 1037, 100; Ex. 1013, Indications and Usage.) Nevertheless, in clinical practice, 0.05% tazarotene

formulations were commonly prescribed and used to treat acne “off-label”¹ prior to May 2017. This is reflected by both prior art literature and by third-party market data collected on 0.05% tazarotene sales prior to May 2017. (*See, e.g.*, Ex. 1008, 17-21 (2004 article with dermatologists disclosing their use of topical 0.05% tazarotene to treat acne); Ex. 1010, Table 1-3 (2016 article listing tazarotene cream and gel 0.05% as an “Available Prescription Option[] to Treat Acne Vulgaris”); Ex. 1018, 168 (2013 article disclosing that “because acne routinely presents in patients younger than 12 years of age, topical retinoids are widely used off-label in this age group”); Ex. 1015²; Ex. 1016; Ex. 1003, ¶34.) Use of 0.05% tazarotene to treat acne was also supported by multiple clinical studies, which reported that 0.05% tazarotene compositions provided statistically significant improvements in treating acne. (Ex. 1011, 351 (0.05% tazarotene gel provided statistically significantly better efficacy than placebo); Ex. 1009, 651-652 (0.05% tazarotene provided statistically

¹ “Off-label” refers to prescription of pharmaceuticals by physicians to treat indications other than those listed on the FDA-approved labeling for the drug. (Ex. 1003, ¶34.)

² Petitioner has submitted a PDF copy of Ex. 1015. Petitioner is happy to provide the Board with a native Microsoft Excel version of the exhibit if the Board would prefer such a version.

significant reductions in acne lesions from baseline levels); Ex. 1003, ¶34.)

Two other retinoids, tretinoin and adapalene, were also used topically to treat acne prior to May 2017. (Ex. 1008; Ex. 1010, 13.) Clinical studies suggested that tazarotene was superior to both tretinoin and adapalene. (Ex. 1010, 13; *see also* Ex. 1019, 952; Ex. 1020, 166; Ex. 1021, 20.) Also, unlike tretinoin and adapalene, tazarotene was FDA approved for the treatment of psoriasis in addition to acne. (*See, e.g.,* Ex. 1013, Indications and Usage; Ex. 1003, ¶32.)

B. Local Skin Irritation Associated With Tazarotene

Although it was efficacious, tazarotene was also known to cause concentration-dependent skin irritation when treating both psoriasis and acne, which could be severe. (Ex. 1010, 13; Ex. 1013, Sections 5.2, 14, 16.1; Ex. 1003, ¶35; Ex. 1005, ¶31.) Because this irritation was concentration-dependent, one recognized means of reducing irritation was using a lower concentration of tazarotene, such as the 0.05% formulations. (Ex. 1022, 290-293; Ex. 1013, Sections 5.2, 14, 16.1; Ex. 1010, 13; Ex. 1008, 17-21; Ex. 1011, 354; Ex. 1003, ¶¶37-38; Ex. 1005, ¶32.) Another recognized method for reducing irritation was to have patients apply a moisturizer along with the tazarotene product. (*See* Ex. 1010, 13; Ex. 1008, 17-21; Ex. 1017, Dosage and Administration; Ex. 1013, Section 17, Patient Counseling Information; Ex. 1003, ¶39; Ex. 1005, ¶33.) A third recognized approach for addressing irritation was development of new vehicle formulations that increased

the penetration of tazarotene into the skin, allowing for greater efficacy with a lower concentration. (*See* Ex. 1023, 921; Ex. 1010, 13; Ex. 1024, [0017]-[0018]; Ex. 1025, 20; Ex. 1003, ¶40; Ex. 1005, ¶34.) The prior art demonstrated that POSITAs were actively pursuing different formulations and formulation types for topical retinoids, including tazarotene, to address irritation. (*See* Ex. 1023, 921; Ex. 1024, [0017]-[0018]; Ex. 1017.)

C. Prior Art Lotion Vehicles For Formulating Tazarotene

The prior art provided lotion vehicles that would have enabled POSITAs to formulate effective, lower-concentration tazarotene compositions. Both WO 2016/205001 (“WO ’001”) and U.S. Patent Pub. No. US 2012/0129824 (the “’824 publication”) disclosed topical formulations that allowed reduced concentrations of active ingredients to be applied, while maintaining similar efficacy to higher concentrations of those active ingredients. (Ex. 1003, ¶¶41-43; Ex. 1005, ¶¶35-44.)

WO ’001 disclosed topical compositions and methods for treating psoriasis with tazarotene and halobetasol propionate. (*See* Ex. 1007, [002].) One of the disclosed compositions is a lotion containing 0.045% tazarotene as the sole active ingredient. (*Id.*, Table 4.) That lotion discloses *every* component of the tazarotene composition described and claimed in the ’482 patent. *See infra* §VII.A. The only thing missing from WO ’001’s disclosure compared to the ’482 patent is using the composition to treat acne. However, as discussed above, POSITAs would have

known that tazarotene was used and approved for treating both acne and psoriasis and that patients in both groups suffered from skin irritation due to tazarotene. *Supra* §II.B. Thus, POSITAs developing tazarotene formulations for acne would have looked to prior art dealing with psoriasis, particularly prior art such as WO '001 that disclosed methods for formulating lower-concentration tazarotene formulations. (See Ex. 1003, ¶¶41-43; Ex. 1005, ¶39.)

The '824 publication disclosed topical vehicle formulations for corticosteroids that preferentially enhance the penetration of the active ingredient into the skin, rather than through the skin into systemic circulation. (Ex. 1012, [0016].) The formulations accomplish this via a “liquid oil component” comprising a dicarboxylic acid ester, which dissolves the corticosteroid and enhances its delivery. (*Id.*) The formulations allowed the concentration of the steroid to be significantly reduced, by as much as five times, while maintaining the same potency as higher-dose formulations. (*Id.*, [0035], [0037]-[0040], Tables 1 & 3.) One such formulation in the '824 publication discloses *every* component of the tazarotene composition described and claimed in the '482 patent, except for tazarotene. See *infra* §VII.C. Importantly, like halobetasol propionate, the active ingredient in the '824 publication's formulations, tazarotene is also a lipophilic molecule and would have been expected to be soluble in the same liquid oil component ingredients disclosed in the '824 publication. (Ex. 1005, ¶41.)

WO '001 was not the only prior art reference to disclose a 0.045% tazarotene lotion. The IDP-118 Study disclosed a phase II clinical trial comparing treatment of psoriasis with a 0.01% halobetasol propionate/0.045% tazarotene combination lotion against treatment with two monotherapy lotions, one comprising 0.01% halobetasol propionate and the other comprising **0.045% tazarotene**. (Ex. 1014, Arms and Interventions.) As noted above, POSITAs would have looked to prior art for treating psoriasis with topical tazarotene when developing formulations for acne because tazarotene was the only topical retinoid used and approved for treating both indications and skin irritation was seen in patients with both indications. (Ex. 1003, ¶¶42-43; Ex. 1005, ¶43.) In view of the IDP-118 Study, which used a 0.045% tazarotene lotion to treat psoriasis, POSITAs would have investigated treating acne with the same or a similar lotion and would have sought an appropriate vehicle for such a lotion. (Ex. 1003, ¶43; Ex. 1005, ¶43.) That investigation would have driven POSITAs directly to WO '001 and the '824 publication. (*Id.*)

WO '001 not only disclosed a vehicle for a 0.045% tazarotene lotion, it also disclosed vehicles for the 0.01% halobetasol/0.045% tazarotene combination and the 0.01% halobetasol monotherapy treatments disclosed in the IDP-118 Study. (*See* Ex. 1007, Table 4; Ex. 1005, ¶44.) The only other prior art reference to disclose a vehicle for a 0.01% halobetasol lotion is the '824 publication. (*See* Ex. 1012, Tables 1&4; Ex. 1005, ¶44.) Notably, the inactive ingredients in the 0.045% tazarotene

lotion disclosed in WO '001 and Formulation 4A in the '824 publication are identical. (*Compare* Ex. 1007, Table 4 *with* Ex. 1012, Table 4.) They are also identical to the inactive ingredients of Composition A described and claimed in the '482 patent.

WO '001					
Table 4					
Compositions for Clinical Studies					
Ingredient	Function	Concentration (wt%)			
		IDP-118 (Present Invention)	Placebo (Vehicle)	Halobeta- sol propio- nate only	Tazaro- tene only
Halobetasol propionate, micronized	Active Ingredient	0.01	0	0.01	0
Tazarotene	Active Ingredient	0.045	0	0	0.045
Diethyl sebacate	Emollient & Solvent	2.97	2.97	2.97	2.97
Light mineral oil	Emollient & Solvent	8.03	8.03	8.03	8.03
Sorbitan monooleate	Surfactant/ Emulsifying Agent	0.1	0.1	0.1	0.1
Sorbitol solution, 70%	Humectant	10.7	10.7	10.7	10.7
Methyl paraben	Antimicrobial Preservative	0.17	0.17	0.17	0.17
Propyl paraben	Antimicrobial Preservative	0.03	0.03	0.03	0.03
Edetate disodium dihydrate	Chelating Agent	0.05	0.05	0.05	0.05
Carbomer copolymer type B (Pemulen TM TR-1)	Emulsifying Agent	0.4	0.4	0.4	0.4
Carbomer homopolymer type A (Carbomer 981)	Thickener	0.6	0.6	0.6	0.6
Sodium hydroxide	pH-adjusting agent	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5
Purified water	Solvent	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

'824 publication		
TABLE 4		
Ingredients	% w/w	
	Formula 4A	Formula 4B
Halobetasol Propionate	0.01	0.025
Diethyl Sebacate	2.97	2.90
Light Mineral Oil	8.03	2.90
Sorbitan Monooleate	0.10	0.10
Sorbitol Solution, 70%	10.7	10.7
Disodium Edetate, Dihydrate	0.05	0.05
Pemulen TR-1	0.40	0.40
Carbopol 981	0.60	0.60
Methylparaben	0.17	0.17
Propylparaben	0.03	0.03
Sodium Hydroxide, q. s.	pH 4.0-6.0	pH 4.0-6.0
Purified Water, q.s. ad	100	100

'482 patent

TABLE 2

Some Emulsion Compositions of the Present Invention for Treating Acne

Ingredient	Function	Concentration (wt. %)			Composition A
		Range 1	Range 2	Range 3	
Tazarotene	Retinoid	0.02-0.049	0.03-0.049	0.04-0.049	0.045
Diethyl sebacate	Liquid Oil & Solvent	1-5	2-4	2.5-3.5	2.97
Light mineral oil	Liquid Oil & Co-Solvent	5-15	5-10	7.5-8.5	8.03
Sorbitan monooleate	Surfactant/Emulsifying Agent	0.01-1	0.02-0.5	0.05-0.2	0.1
Sorbitol solution, 70%	Humectant	5-15	7-12	10-11	10.7
Methyl paraben	Antimicrobial Preservative ⁽¹⁾	0.05-0.3	0.1-0.3	0.1-0.2	0.17
Propyl paraben	Antimicrobial Preservative ⁽¹⁾	0.01-0.1	0.01-0.05	0.02-0.04	0.03
Edetate disodium dihydrate	Chelating Agent ⁽¹⁾	0.02-0.1	0.02-0.7	0.03-0.06	0.05
Carbomer copolymer type B (e.g., Pemulen™ TR-1)	Emulsifying Agent	0.1-1	0.2-0.7	0.3-0.5	0.4
Carbomer homopolymer type A (e.g., Carbomer 981)	Thickener	0.2-1.5	0.3-1	0.5-0.7	0.6
Sodium hydroxide, 10% Solution	pH-adjusting Agent ⁽¹⁾	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5
Purified water	Carrier	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

Note:

⁽¹⁾These ingredients are broadly classified as Pharmaceutical Aids.

(Compare Ex. 1007, Table 4 and Ex. 1012, Table 4 with Ex. 1001, Table 2.)

Despite arguing during prosecution that the efficacy and side effect profiles of the claimed 0.045% tazarotene composition in the '482 patent were unexpected, Patent Owner has elsewhere publicly represented that the *prior art* vehicle delivery system disclosed by WO '001 and the '824 publication (referred to by Patent Owner as the "PRISMATREX system" or "polymeric emulsion technology") is a key component to the efficacy and side effects observed with Arazlo®, a commercial product embodying the '482 patent. (See Ex. 1026, 8 ("The PRISMATREX System is functional: it delivers an effective dose of HP from a strength that is 5 times lower

than that in competitor HP products and an effective dose of TAZ at a strength that is similar to or lower than that in competitor TAZ products.”), 9-18; Ex. 1027; Ex. 1028.) Given that the delivery system Patent Owner claims to have such an impact on the efficacy and side effects of Arazlo® was disclosed in the prior art, Patent Owner cannot claim that the predictable benefits of using that delivery system in a tazarotene composition for treating acne would have been unexpected.

The prior art would have led POSITAs directly to the tazarotene compositions claimed in the '482 patent prior to May 2017. The prior art also would have motivated POSITAs to use those tazarotene compositions to treat acne with a reasonable expectation of success, which would have yielded predictable results. Therefore, the challenged claims are unpatentable.

D. Prosecution Of Related Patent Owner's Related Applications

1. The '576 Application

U.S. Pat. App. No. 16/179,576 (“’576 application”) was filed on November 2, 2018. The ’576 application, like the ’482 patent, is a continuation in part of App. No. 15/977,088. The pending claims of the ’576 application recite topical compositions for treating acne that are similar to the compositions recited in the method claims of the ’482 patent as demonstrated in the chart comparing pending independent claim 1 of the ’576 application with claim 1 of the ’482 patent:

Claim 1 of the '482 Patent	Claim 1 of the '576 Application (as of December 8, 2022 Amendment)
1. A method of treating acne vulgaris, the method comprising topically applying a pharmaceutical composition once per day to an affected area of a body of a subject suffering from acne vulgaris, wherein: the composition comprises tazarotene at a concentration of about 0.045 percent by weight of the composition as a sole active pharmaceutical ingredient the composition is an oil-in-water emulsion lotion comprising an oil phase and an aqueous phase; the oil phase comprises a dicarboxylic acid ester and a mineral oil at a total concentration of 10-12 percent by weight of the composition; the aqueous phase comprises water and a carbomer homopolymer, wherein the concentration of the carbomer homopolymer is 0.5-0.7 percent by weight of the composition; and the composition further comprises a polymeric emulsifier at a concentration of 0.3-0.5 percent by weight of the composition.	1. (Previously presented) A topical pharmaceutical composition for treating acne, comprising: a sole active pharmaceutical ingredient consisting of tazarotene at a concentration of 0.045 percent by weight of the composition; wherein said composition is an oil-in-water emulsion lotion comprising an oil phase and an aqueous phase, wherein the oil phase comprises a dicarboxylic acid ester and a mineral oil, wherein the aqueous phase comprises water and a carbomer homopolymer, wherein the composition further comprises a polymeric emulsifier, and wherein the tazarotene is in solution in the oil phase.

(Ex. 1029, 35; Ex. 1001, claim 1.)

The Examiner has finally rejected all pending claims of the '576 application

as obvious over the combination of the '824 publication and the Tazorac® Label. (Ex. 1029, 1-20.) The Examiner noted that Applicant's argument that POSITAs would not expect to achieve effective delivery of tazarotene from a composition formulated for delivery of halobetasol propionate had "been fully considered but has not been found persuasive [because] the formulation for delivery as applicants assert is the very same formulation as instant claimed. Therefore, it would have been obvious to substitute tazarotene in [the] same [lotion] formulation." (*Id.*, 4.) The Examiner also rejected Applicants' arguments regarding unexpected results because Applicants failed to compare the claimed 0.045% tazarotene composition to the 0.05% tazarotene composition disclosed in the Tazorac® Label. (*Id.*, 5-6.)

Regarding the claimed concentration of tazarotene – 0.045% – the Examiner found that "[t]he amounts of active agents to be used, the pharmaceutical forms, e.g., tablets, etc; mode of administration, flavors, surfactant are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration." (*Id.*, 11.) The Examiner further concluded that "it is obvious to vary and/or optimize the amount of tazarotene provided in the composition, according to the guidance provided by Tazarac, to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.)." (*Id.*, 12.) Finally, regarding the intended use recited in the preamble of the pending claims, the Examiner concluded that the

intended use was not limiting. (*Id.*, 15.)

2. The '871 Application

U.S. Application No. 17/366,871 (the "'871 application") was filed on July 2, 2021 and shares a substantively identical specification as the prior art WO '001 reference. (*Compare* Ex. 1047, 367-412 *with* Ex. 1007.) Like, WO '001, the '871 application discloses halobetasol propionate and tazarotene compositions for treating psoriasis. (*See* Ex. 1047, 367-412.) However, independent claim 1 of the '871 application recites a pharmaceutical composition that is similar to the finally rejected claims of the '576 application. (Ex. 1047, 61; Ex. 1029, 35-36.) Dependent claim 2 of the '871 application requires using that composition to treat psoriasis. (Ex. 1047, 61.)

Like the '576 application, the Examiner rejected the pending claims of the '871 application over, *inter alia*, the '824 publication³ and the Tazorac® Label. (Ex. 1047, 155-163.) In response, Applicants made the same unexpected results arguments as presented for the '576 application. (*Id.*, 60-75.) Applicants even submitted the same declaration by Dr. Gordon Dow that was submitted for the '576 application, which asserts that the 0.045% tazarotene composition exhibited

³ The Examiner asserted Dow (WO 2012/087443), which is the PCT publication of the '824 publication. (*See* Ex. 1048.)

unexpected results based on the clinical trial data relating to the treatment of acne disclosed in the '576 application. (*Id.*) Unlike the Examiner for the '576 application, however, the Examiner for the '871 application allowed the claims over the prior art following Applicant's unexpected results arguments. (*Id.*, 8-15.)⁴

The inconsistent patentability decisions reached by different examiners on the same evidence and arguments for the '576 and '871 applications highlights the substantial questions regarding the patentability of the tazarotene formulation claimed in the '482 patent and the need for the Board to address the patentability issues raised in this Petition.

III. THE '482 PATENT

A. Overview

The '482 patent describes topical compositions of tazarotene for treating skin diseases, such as acne and psoriasis, in an oil-in-water emulsion vehicle that forms a lotion. (Ex. 1001, Abstract, 2:42-44.) Tazarotene is included at a concentration less than 0.05 wt %. (*Id.*, 2:48-53.) The oil-in-water emulsion vehicle includes an oil phase and an aqueous phase. (*Id.*, 2:65-3:1.) The oil phase includes a "liquid oil component" comprising "one or more materials that are practically insoluble or insoluble in water and which are liquid at room temperature." (*Id.*, 4:38-40.) The

⁴ The '871 application has issued as U.S. Patent No. 11,679,116.

liquid oil component may comprise a dicarboxylic acid ester, such as diethyl sebacate, and light mineral oil. (*Id.*, 4:58-61, 5:5-25.) The oil-in-water emulsion vehicle may include additional excipients such as “liquid oils, waxes viscosity-modifying agents, thickening agents, gelling agents, alcohols, surfactants, chelating agents, buffers, preservatives, humectants, emollients, stabilizers, diluents, dispersing agents, emulsifiers, wetting agents, stabilizers, pH adjusters, solvents or cosolvents.” (*Id.*, 3:5-12.) Additionally, “polymeric emulsifiers such as those known under the trade name PemulenTM . . . may be used.” (*Id.*, 4:10-12.)

The '482 patent provides example formulations in Tables 1-2:

TABLE 1

Compositions of the Present Invention for Treating Skin Diseases			
Ingredient	Concentration (wt %)		
	Range 1	Range 2	Range 3
Tazarotene or Tazarotenic Acid Compound	0.01-0.049	0.02-0.045	0.03-0.045
Emollient, Solvent, and/or Thickener	0.5-40	1-25	2-20
Emulsifier	0.25-10	0.5-7	1-5
Humectant	0-15	2-12	3-10
Polymeric Thickener	0.05-2	0.1-1.5	0.3-1
Pharmaceutical Aids	q.s.	q.s.	q.s.
Purified water	q.s. to 100	q.s. to 100	q.s. to 100

TABLE 2

Some Emulsion Compositions of the Present Invention for Treating Acne					
Ingredient	Function	Concentration (wt %)			
		Range 1	Range 2	Range 3	Composition A
Tazarotene	Retinoid	0.02-0.049	0.03-0.049	0.04-0.049	0.045
Diethyl sebacate	Liquid Oil & Solvent	1-5	2-4	2.5-3.5	2.97
Light mineral oil	Liquid Oil & Co-Solvent	5-15	5-10	7.5-8.5	8.03
Sorbitan monooleate	Surfactant/Emulsifying Agent	0.01-1	0.02-0.5	0.05-0.2	0.1
Sorbitol solution, 70%	Humectant	5-15	7-12	10-11	10.7
Methyl paraben	Antimicrobial Preservative ⁽¹⁾	0.05-0.3	0.1-0.3	0.1-0.2	0.17
Propyl paraben	Antimicrobial Preservative ⁽¹⁾	0.01-0.1	0.01-0.05	0.02-0.04	0.03
Edetate disodium dihydrate	Chelating Agent ⁽¹⁾	0.02-0.1	0.02-0.7	0.03-0.06	0.05
Carbomer copolymer type B (e.g., Pemulen™ TR-1)	Emulsifying Agent	0.1-1	0.2-0.7	0.3-0.5	0.4
Carbomer homopolymer type A (e.g., Carbomer 981)	Thickener	0.2-1.5	0.3-1	0.5-0.7	0.6
Sodium hydroxide, 10% Solution	pH-adjusting Agent ⁽¹⁾	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5
Purified water	Carrier	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

(*Id.*, Tables 1-2.)

The '482 patent also discloses three clinical studies conducted with Composition A (Table 2) in acne patients. In the first study, patients were treated with either Composition A, a placebo lotion, commercially available 0.1% tazarotene cream (Tazorac® 0.1% cream), or a placebo cream once daily for twelve weeks. (*Id.*, 7:25-59.) Efficacy was measured by the improvement in the Evaluator's Global Severity Score (EGSS), and the numbers of inflammatory and non-inflammatory lesions were also assessed. (*Id.*, 7:60-8:5.) Efficacy results of the first study are disclosed in Tables 3-7:

TABLE 3

Baseline Characteristics - Inflammatory Lesions and Non-inflammatory lesions			
	Combined Placebo N = 69	Composition A N = 69	Tazorac ® 0.1% Cream N = 72
Inflammatory Lesions			
Mean (SD)	27.2 (5.49)	28.3 (6.0)	27.3 (5.95)
Median	26.0	27.0	26.0
Non-inflammatory Lesions			
Mean (SD)	36.6 (13.17)	37.6 (14.70)	36.6 (13.31)
Median	34.0	34.0	34.0

TABLE 4

EGSS (Clear or Almost Clear) by Visit (ITT)			
	Combined Placebo N = 69	Composition A N = 69	Tazorac ® 0.1% Cream N = 72
Week 2	0%	0%	0%
Week 4	0%	1.4%	1.4%
Week 8	4.3%	7.2%	5.6%
Week 12	10.1%	18.8%	16.7%

TABLE 5

Inflammatory Lesions by Visit Absolute Change from Baseline			
	Combined Placebo N = 69	Composition A N = 69	Tazorac ® 0.1% Cream N = 72
Week 2	-4.7	-2.9	-2.4
Week 4	-7.2	-5.8	-7.8
Week 8	-10.9	-13.2	-12.0
Week 12	-14.0	-18.1	-16.8

TABLE 6

Treatment % Success (ITT) at 12 Weeks			
	Combined Placebo N = 69	Composition A N = 69	Tazorac ® 0.1% Cream N = 72
EGSS - Clear or Almost Clear Inflammatory Lesions	10.1%	18.8%	16.7%
Absolute Change	-14.0	-18.1	-16.8
% Change	-51.41%	-63.75%	-59.99%
Non-inflammatory Lesions			
Absolute Change	-13.1	-21.6	-20.3
% Change	-35.18%	-56.86%	-54.09%

TABLE 7

Treatment % Success (PP)			
	Combined Placebo N = 57	Composition A N = 54	Tazorac ® 0.1% Cream N = 56
EGSS - Clear or Almost Clear Inflammatory Lesions	12.3%	20.4%	16.1%
Non-inflammatory Lesions	-14.2	-18.3	-18.2
	-11.8	-20.8	-21.9

(*Id.*, Tables 3-7.) Tolerability was also assessed, and the results are disclosed in Figures 4A-C:

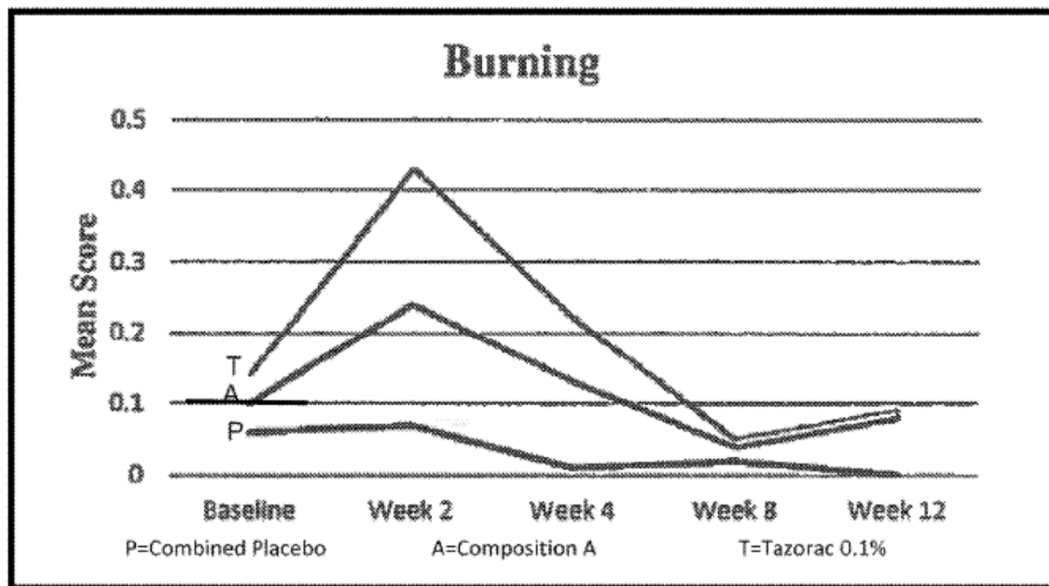


FIG. 4A

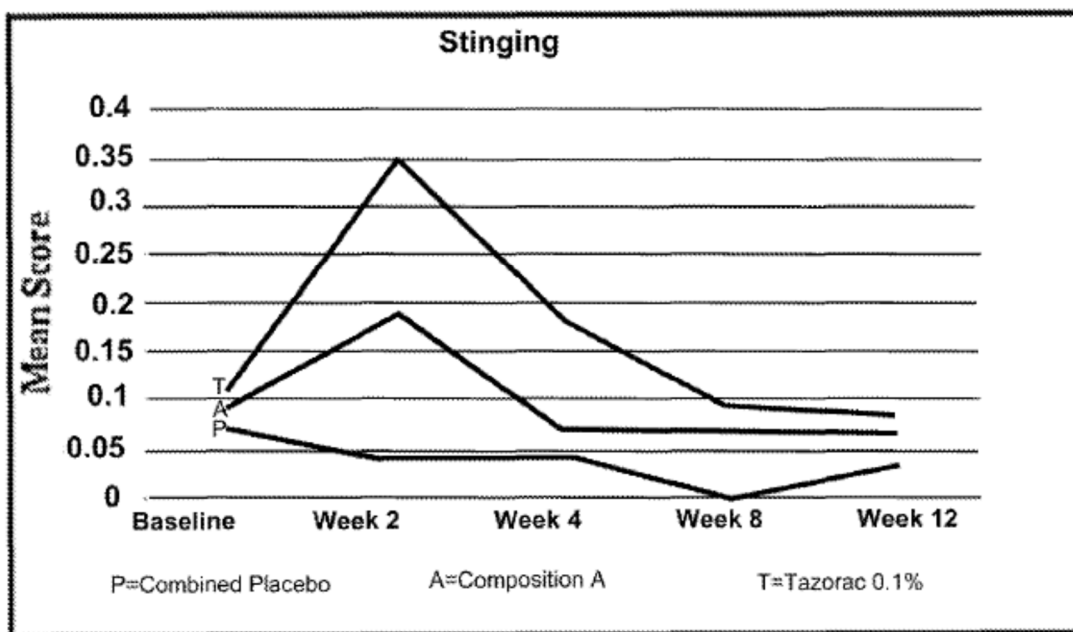


FIG. 4B

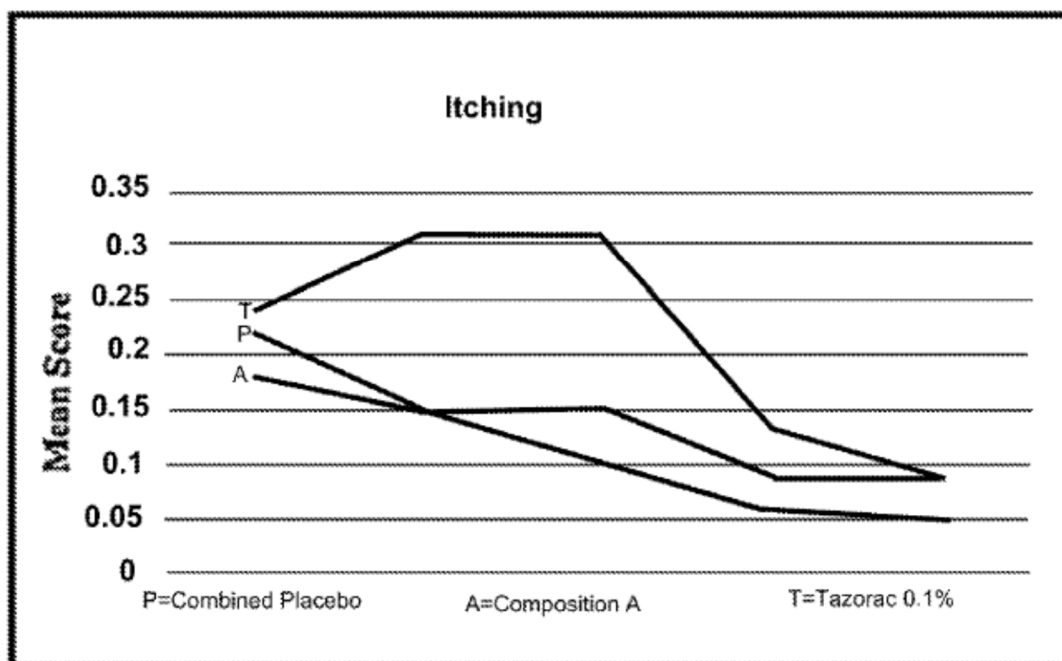


FIG. 4C

(*Id.*, Figs. 4A-C.)

The '482 patent also discloses two larger, phase-3 clinical studies in acne patients where patients applied either Composition A (Table 2) or placebo lotion once daily for twelve weeks. (*Id.*, 10:29-57.) Efficacy, cutaneous safety, and tolerability were measured via the same means as the first study, and the results are disclosed in Tables 10-13:

TABLE 10

EGSS (Clear or Almost Clear) at Week 12 (ITT)				
	Study 301		Study 302	
	Composition A Lotion N = 402	Placebo Lotion N = 411	Composition A Lotion N = 397	Placebo Lotion N = 404
Week 12	25.5% (p < 0.001)	13.0%	29.6% (p < 0.001)	17.3

TABLE 11

Inflammatory and Non-Inflammatory Lesions Absolute Changes from Baseline at Week 12				
	Study 301		Study 302	
	Composition A Lotion N = 402	Placebo Lotion N = 411	Composition A Lotion N = 397	Placebo Lotion N = 404
Inflammatory Lesions	-15.6 (p < 0.001)	-12.4	-16.7 (p < 0.001)	-13.4
Non-inflammatory Lesions	-21.0 (p < 0.001)	-16.4	-24.6 (p < 0.001)	-16.6

TABLE 12

Treatment Success (Per-Protocol Basis)				
	Study 301		Study 302	
	Composition A Lotion N = 402	Placebo Lotion N = 411	Composition A Lotion N = 397	Placebo Lotion N = 404
EGSS - Clear or Almost Clear	26.8%	14.4%	30.6%	18.3%
Inflammatory Lesions	-15.8	-12.4	-16.4	-13.4
Non-inflammatory Lesions	-21.3	-16.3	-24.1	-15.4

TABLE 13

Cutaneous Safety and Tolerability				
	Study 301		Study 302	
	Composition A Lotion N = 387	Placebo Lotion N = 392	Composition A Lotion N = 392	Placebo Lotion N = 399
<u>Scaling</u>				
Moderate	4	2	6	1
Severe	0	0	1	0
<u>Erythema</u>				
Moderate	7	8	13	6
Severe	0	0	1	0
<u>Hypopigmentation</u>				
Moderate	1	1	0	0
Severe	0	0	0	0
<u>Hyperpigmentation</u>				
Moderate	7	9	8	17
Severe	1	2	0	1
<u>Itching</u>				
Moderate	4	2	4	4
Severe	0	0	0	0
<u>Burning</u>				
Moderate	2	0	5	0
Severe	0	0	2	0
<u>Stinging</u>				
Moderate	1	1	3	0
Severe	0	0	1	0

(*Id.*, 10:64-12:32, Tables 10-13.)

B. Prosecution History

The Examiner issued two non-final office actions and two final office actions during prosecution of the '482 patent⁵, all of which rejected the pending claims as obvious. (Ex. 1002, 134-152, 179-191, 210-221, 296-306.) The first non-final office action rejected the claims as obvious over the combination of Fabior® and Singh and the combination of Fabior® and Fiume. (*Id.*, 296-306.) The Examiner's final three office actions rejected the claims as obvious over the combination of WO '001 and Donello. (*Id.*, 134-152, 179-191, 210-221.) Chim, Anderson, and the IDP-118 Study (all discussed in this Petition) were not of-record during prosecution of the '482 patent.

C. The Critical Date

The '482 patent issued from U.S. Patent Application Serial No. 16/179,561 ("the '561 Application"), which was filed on November 02, 2018, and is a continuation in part of U.S. Application Serial No. 15/977,088, filed on May 11, 2018, which claims priority to U.S. Provisional Application Serial No. 62/505,421,

⁵ On March 14, 2023, the Patent Office issued a certificate of correction, deleting the term "carbomer polymer type B" from claims 9-11 and replacing it with the term "carbomer copolymer type B." (Ex. 1002, 1.)

which was filed on May 12, 2017. Accordingly, the earliest effective filing date of the '482 patent is May 12, 2017.

IV. STATEMENT AND RELIEF REQUESTED

A. IPR Grounds

Petitioner asserts the following grounds of unpatentability:

Ground	Claims Challenged	AIA 35 U.S.C. §	References
1	1-11	103	WO '001 + Anderson
2	1-11	103	WO '001 + Kircik
3	1-11	103	WO '001 + Chim
4	1-11	103	WO '001 + Anderson + Shalita
5	1-11	103	'824 Publication + Tazorac® Label
6	1-11	103	'824 Publication + Tazorac® Label + Anderson
7	1-11	103	'824 Publication + Anderson + IDP-118
8	1-11	103	'824 Publication + Kircik + IDP-118
9	1-11	103	'824 Publication + Chim + IDP-118

B. The Asserted References Are Prior Art

The following references are prior art under AIA §102(a)(1):

- (1) WO '001 (Ex. 1007) published on December 22, 2016;
- (2) Anderson (Ex. 1008) published in 2004;
- (3) Kircik (Ex. 1009) published in 2009;
- (4) Chim (Ex. 1010) published in 2016;
- (5) Shalita (Ex. 1011) published in 1999;
- (6) '824 Publication (Ex. 1012) published on May 24, 2012;
- (7) The Tazorac® Label (Ex. 1013) published in 2013;
- (8) IDP-118 (Ex. 1014) published on January 24, 2014.

WO '001 was asserted by the Examiner during prosecution of the '482 patent, and Applicants did not contest, and thus admitted, the prior art status of WO '001 during prosecution. (*See* Ex. 1002, 79-85, 164-172, 202-207.) To the extent Patent Owner contends that WO '001 is not prior art because it falls within the exception set out in AIA 35 U.S.C. § 102(b)(1), Patent Owner cannot make such a showing. WO '001 and the '482 patent share one common inventor – Dr. Rhadakrishnan Pillai. (Ex. 1001; Ex. 1007.) However, Dr. Pillai is only one of three named inventors on WO '001, and the other two named inventors on WO '001 are *not* inventors of the '482 patent. (*Id.*)

Regarding the prior art exception in AIA § 102(b)(1), the MPEP provides that “[w]hat evidence is necessary to show that the disclosure is by the inventor or a joint inventor requires case-by-case treatment, depending upon whether it is apparent from the disclosure itself or the patent application specification that the disclosure is by the inventor or a joint inventor.” MPEP §2153.01(a). The MPEP further explains that “[i]f . . . the application names fewer joint inventors than a publication (e.g., the application names as joint inventors A and B, and the publication names as authors A, B and C), it would not be readily apparent from the publication that it is by the inventor (i.e., the inventive entity) or a joint inventor and the publication would be treated as prior art under AIA 35 U.S.C. 102(a)(1).” MPEP §2153.01(a). That is the situation for WO ’001.

The evidence demonstrates that the 0.045% tazarotene-only formulation disclosed in WO ’001 upon which Petitioners rely was *not* made by either inventor of the ’482 patent. Dr. Pillai has publicly testified under oath that he was not involved in any formulation aspects of developing the Duobrii® product, which embodies the halobetasol propionate-tazarotene combination formulation disclosed in WO ’001. (Ex. 1033, 105:10-15.) Dr. Pillai further testified under oath that he was “not the formulation person” on the Duobrii® project and did not formulate any prototypes of the Duobrii® product. (*Id.*, 143:6-144:2.) This evidence demonstrates the 0.045% tazarotene-only formulation disclosed in WO ’001 did not originate from

Dr. Pillai. Arturo Angel, the other named inventor on the '482 patent, is not identified as an inventor on WO '001, demonstrating that the formulation of the 0.045% tazarotene-only formulation disclosed in WO '001 did not originate from Mr. Angel. Accordingly, § 102(b)(1) does not apply to the disclosures in WO '001 upon which Petitioners rely.

C. The Asserted References Are Analogous Art

The asserted references are analogous art that is usable in an obviousness combination. *Unwired Planet, LLC v. Google Inc.*, 841 F.3d 995, 1000 (Fed. Cir. 2016). Each reference is from the same field as the '482 patent, e.g., treatment of skin diseases through application of topical compositions, including retinoids. The references are also pertinent to the problem the inventor was focused on, e.g., the topical treatment of skin disorders, such as acne and psoriasis. As analogous art, a POSITA is presumed to have been aware of these references. *In re Nilssen*, 851 F.2d 1401, 1403 (Fed. Cir. 1988).

V. THE BOARD SHOULD NOT DENY INSTITUTION UNDER 35 U.S.C.

§ 325(D)

The Board applies a two-part framework to determine whether to exercise discretion to deny institution under 35 U.S.C. § 325(d): (1) whether the same or substantially same prior art or arguments were previously presented to the Patent Office; and (2) if either condition in the first part is satisfied, whether the petition

has demonstrated that the Patent Office erred in a manner material to the patentability of the challenged claims. *Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential). Here, Anderson, Chim, and the IDP-118 Study, relied upon in this Petition, were not cited during prosecution of the '482 patent, and thus the same art or arguments presented herein were not previously before the Patent Office. For this reason, the Board should not exercise its discretion to deny institution under 35 U.S.C. § 325(d).

Although Kircik and Shalita, which were before the Examiner, disclosed clinical studies investigating the use of 0.05% tazarotene for treating acne, Anderson and Chim, which were not before the examiner, evidence that prior art use of 0.05% tazarotene for treating acne was not limited to experimental clinical studies. Rather, Anderson and Chim show that in real-world clinical practice, over a more than ten-year period before the priority date of the '482 patent, POSITAs were commonly prescribing and using compositions with 0.05% tazarotene as the sole active ingredient to treat acne. This is direct evidence that POSITAs considered compositions with a nearly identical concentration of tazarotene as that claimed in the '482 patent to be efficacious for treating acne, confirming that POSITAs would have been motivated to use the prior art 0.045% tazarotene compositions to treat acne and would have reasonably expected success in doing so. This additional

evidence and the motivation it would have provided POSITAs is not cumulative and warrants reconsideration of the prior art, such as WO '001, that was before the Examiner during prosecution. *See Becton, Dickinson and Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph).

Likewise, the IDP-118 Study is not cumulative of the prior art submitted to and/or considered by the Examiner. The IDP-118 Study discloses a phase II clinical study for psoriasis that includes a 0.01% halobetasol propionate/0.045% tazarotene combination lotion, 0.01% halobetasol propionate lotion and **0.045% tazarotene lotion**. (Ex. 1014, Arms and Interventions, emphasis added.) As detailed below, the IDP-118 Study would have motivated POSITAs to investigate treating acne with the same or a similar tazarotene lotion and would have driven them to the lotion vehicles disclosed in WO '001 and the '824 publication. *Infra* §VII.E.

Additionally, the Board should not deny institution based on the citation of the '824 Publication, Shalita, and Kircik on an IDS because, as shown below, the references render the challenged claims unpatentable, and the Examiner never applied them during prosecution. (Ex. 1002); *see e.g., Comcast Cable Commc'ns LLC v. Promptu Sys. Corp.*, IPR2018-00342, Paper 13 (P.T.A.B. July 19, 2018) (declining to deny institution under §325(d) because prior art was not applied); *Lite-On Technology Corp. v. Sensor Elec. Tech., Inc.*, IPR2022-00780, Paper 11 at 30-

32 (P.T.A.B. Oct. 28, 2022); *Microsoft Corp. v. Surfcaster, Inc.*, IPR2022-00590, Paper 9 at 13-16 (P.T.A.B. Oct. 7, 2022). Accordingly, to the extent that the references relied on herein were before the Examiner during prosecution, this Petition demonstrates that the Examiner materially erred in allowing the challenged claims over those references.

In order to overcome a rejection over WO '001, Patent Owner argued during prosecution that the efficacy and tolerability results of the clinical studies disclosed in the '482 patent demonstrated that the claimed tazarotene formulations provided unexpected results. (Ex. 1002, 81-84, 167-170, 205-206). However, as explained below, the results disclosed in the '482 patent would not have been unexpected to POSITAs in May 2017, at least in light of the real-world clinical practice disclosed in at least Chim and Anderson. *Infra* §VIII. Further, even if the efficacy and tolerability results would have been unexpected, they merely represent a difference in degree from the expected results, not a difference in kind, and, therefore, they are not probative of nonobviousness. *See, e.g., Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013) (“[W]here an unexpected increase in efficacy is measured by a small percentage, as here, and the evidence indicates that skilled artisans were capable of adjusting the percentage, the result constitutes a difference in degree, not kind.”). Consequently, Patent Owner’s statements during prosecution should not form a basis to deny institution under §325(d).

The Board should also decline to deny institution under §325(d) because the Examiner was not informed of the decade-plus of off-label use of compositions comprising 0.05% tazarotene for the treatment of acne prior to May 12, 2017. That evidence directly undermines Patent Owner’s prosecution arguments regarding unexpected results and the alleged lack of motivation and reasonable expectation of success for using compositions comprising 0.045% tazarotene for treating acne. The significance of this omission is also reflected in the Examiner’s reasons for allowance, which stated “Applicants amendment of claims to recite tazarotene as a sole active agent renders the obviousness rejection moot . . . [b]ecause Dow teaches that tazarotene and halobetasol is synergistic[] and there is no motivation to administer tazarotene alone in view of [WO ’001].” (Ex. 1002, 55). The Examiner was not made aware of the common practice of physicians to prescribe 0.05% tazarotene compositions for treating acne prior to May 12, 2017, as demonstrated by Anderson in 2004, Chim in 2016, and the IQVIA data for 2017-2018, which would have strongly motivated POSITAs to use the 0.045% tazarotene lotion in WO ’001 to treat acne. These references are not cumulative of the prior art submitted to and/or considered by the Examiner, as explained above.

VI. LEVEL OF ORDINARY SKILL

A POSITA in May 2017 would have been a dermatologist with several years of experience in treating skin disorders, such as acne and psoriasis, with topical

medications and/or a formulation scientist having a PhD or equivalent experience relating to the development of topical compositions useful for the treatment of skin disorders. One of skill in the art may have worked as part of a multi-disciplinary team of scientists and medical professionals, including both a dermatologist and a formulation scientist, and, therefore, would have drawn from the knowledge and skills of the team as a whole to solve a given problem.

VII. CLAIM CONSTRUCTION

All claim terms should receive their plain and ordinary meaning as understood by a POSITA at the time of filing and in accordance with the specification and the prosecution history. 37 C.F.R. §42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005). Petitioner does not believe that any claim terms require express construction.

VIII. PROPOSED GROUNDS FOR UNPATENTABILITY

A. Grounds 1-3: Claims 1-11 Would Have Been Obvious Over WO '001 and Kircik, Chim, or Anderson

WO '001 disclosed a 0.045% tazarotene lotion that is *identical* to the composition disclosed and claimed in the '482 patent. (*See* Ex. 1007, Table 4.) Therefore, the only question is whether POSITAs would have found it obvious to use that 0.045% tazarotene lotion to treat acne, rather than psoriasis. The answer is unequivocally yes. Using tazarotene to treat acne was far from inventive in May

2017. The prior art provided ample motivation for POSITAs to do so with a reasonable expectation of success.

Anderson, Kircik, and Chim all disclose that topical compositions containing nearly the same concentration of tazarotene (0.05%) as that in WO '001 (0.045%) were effectively used to treat acne prior to May 2017. POSITAs would have found those references consistent with their knowledge of off-label use of 0.05% tazarotene for treating acne for more than a decade before May 2017. *Supra* §II.A. Moreover, POSITAs would have known that tazarotene, unlike the two other known retinoids, was approved and used to treat both acne and psoriasis. *Id.* POSITAs would also have known that local skin irritation was a significant issue associated with using tazarotene to treat either disease and would have looked to formulations used for both indications for solutions to the irritation problem. *Id.* Therefore, POSITAs developing tazarotene therapies would have been motivated to investigate prior art dealing with the treatment of both diseases using tazarotene and would have been motivated to combine the teachings of references dealing with acne with those dealing with psoriasis and vice versa. (Ex. 1003, ¶¶32, 42-43; Ex. 1005, ¶39.)

Accordingly, claims 1-11 of the '482 patent would have been obvious to POSITAs in May 2017 in view of WO '001 in combination with Anderson, Kircik, or Chim as further described below. (Ex. 1003, ¶¶64-66; Ex. 1005, ¶65.)

1. Claim 1

WO '001 in combination with Anderson, Kircik, or Chim renders claim 1 obvious. (Ex. 1003, ¶¶67; Ex. 1005, ¶¶66.)

a. Preamble

To the extent the preamble is limiting, Anderson, Kircik, and Chim each disclose “[a] method of treating acne vulgaris, the method comprising topically applying a pharmaceutical composition once per day to an affected area of a body of a subject suffering from acne vulgaris.” (Ex. 1003, ¶¶68-72; Ex. 1005, ¶¶68-74.)

i. Anderson

Anderson disclosed that “topical tazarotene is efficacious and well tolerated in a variety of patients with acne.” (Ex. 1008, 16.) In the article, the authors described their clinical use of topical tazarotene as an acne treatment for a broad-spectrum of patients. (*Id.*) Anderson discloses that Dr. Valerie Callender “initiates treatment with tazarotene 0.05% cream applied every night” and then “[a]fter 2 or 3 weeks, she switches patients to a stronger concentration.” (*Id.*, 17.) Anderson discloses that Dr. Lee Zane “thinks that topical tazarotene can be a useful part of the treatment regimen and that tazarotene 0.05% cream fits well into the retinoid ladder in moderate to severe inflammatory acne or comedonal acne, with every-other-night dosing (advancing to nightly, as tolerated).” (*Id.*, 20.) Anderson discloses that Dr. Emil Tanghetti “starts treatment with lower-strength tazarotene cream or gel and

increases (or decreases) the strength according to tolerability.” (*Id.*) According to Dr. Tanghetti, “[p]atients with sensitive skin show increased tolerability with tazarotene 0.05% cream.” (*Id.*)

ii. Kircik

Kircik disclosed the results of a clinical study comparing tretinoin microsphere gel 0.04% deliver by pump (“TMG PUMP”) to tazarotene cream 0.05% in the treatment of mild-to-moderate facial acne. (Ex. 1009, 650-651.) Subjects topically applied either TMG PUMP or tazarotene cream 0.05% once daily for 12 weeks. (*Id.*, 651.)

iii. Chim

Chim disclosed that “[s]ubstantial evidence supports the use of [topical retinoids] across all stages of acne severity.” (Ex. 1010, 13.) Chim disclosed that the three available topical retinoids for treating acne—tazarotene, tretinoin, and adapalene—were available in various formulations, which Chim lists in Table 1-3. (*Id.*, 14, Table 1-3.) Chim teaches that “[d]osing of [topical retinoids] should start at the lowest concentration a few times a week and be titrated to nightly, as tolerated.” (*Id.*, 13.) Chim lists 0.05% tazarotene compositions as “Available Prescription Options to Treat Acne Vulgaris.”

Table 1-3. Available Prescription Options to Treat Acne Vulgaris				
Drugs	Available Formulations (Concentrations)	Dose	Common Adverse Effects	Place in Therapy
Topical Retinoids				
Adapalene	Cream (0.1%) Gel (0.1%, 0.3%) Lotion (0.1%)	Once daily (cream, gel: daily in the evening)	Dryness, erythema, photosensitivity, pruritus, scaling, stinging	Any stage
Tazarotene	Cream (0.05%, 0.1%) Foam (0.1%) Gel (0.05%, 0.1%)	Once daily in the evening		
Tretinoin	Cream (0.025%, 0.05%, 0.1%) Gel (0.01%, 0.025%) Micronized gel (0.04%, 0.08%, 0.1%)	Once daily in the evening		

(*Id.*, Table 1-3.)

b. Composition of tazarotene at .045% as sole active ingredient

WO '001 discloses “wherein the composition comprises tazarotene at a concentration of about 0.045 percent by weight of the composition as a sole active pharmaceutical ingredient.” (Ex. 1003, ¶¶73-74; Ex. 1005, ¶¶76-77.) WO '001 discloses a topical pharmaceutical composition wherein the sole active ingredient is tazarotene at a concentration of 0.045%.

WO '001

Ingredient	Function	Concentration (wt%)			
		IDP-118 (Present Invention)	Placebo (Vehicle)	Halobeta- sol propio- nate only	Tazaro- tene only
Halobetasol propionate, micronized	Active Ingredient	0.01	0	0.01	0
Tazarotene	Active Ingredient	0.045	0	0	0.045
Diethyl sebacate	Emollient & Solvent	2.97	2.97	2.97	2.97
Light mineral oil	Emollient & Solvent	8.03	8.03	8.03	8.03
Sorbitan monooleate	Surfactant/ Emulsifying Agent	0.1	0.1	0.1	0.1
Sorbitol solution, 70%	Humectant	10.7	10.7	10.7	10.7
Methyl paraben	Antimicrobial Preservative	0.17	0.17	0.17	0.17
Propyl paraben	Antimicrobial Preservative	0.03	0.03	0.03	0.03
Edetate disodium dihydrate	Chelating Agent	0.05	0.05	0.05	0.05
Carbomer copolymer type B (Pemulen TM TR-1)	Emulsifying Agent	0.4	0.4	0.4	0.4
Carbomer homopolymer type A (Carbomer 981)	Thickener	0.6	0.6	0.6	0.6
Sodium hydroxide	pH-adjusting agent	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5
Purified water	Solvent	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

(Ex. 1007, Table 3; Table 4; Ex. 1003, ¶74; Ex. 1005, ¶76.) POSITAs would have been motivated to use the 0.045% tazarotene composition disclosed in WO '001 to treat acne through once daily topical application in view of the teachings of Anderson, Kircik, or Chim. (Ex. 1003, ¶¶73-82; Ex. 1005, ¶¶76-89.)

i. Anderson

Anderson disclosed the clinical use of 0.05% tazarotene compositions to treat acne by practicing dermatologists. (Ex. 1008, 17-21.) Anderson disclosed that Dr. Valerie Callender “initiates treatment with tazarotene 0.05% cream applied every night” and then “[a]fter 2 or 3 weeks, she switches patients to a stronger concentration.” *Id.*, 17. Anderson disclosed that according to Dr. Emil Tanghetti, “[p]atients with sensitive skin show increased tolerability with tazarotene 0.05% cream.” (*Id.*, at 20.) Anderson disclosed that, according to Dr. Lee Zane, “topical tazarotene can be a useful part of the treatment regimen and that tazarotene 0.05% cream fits well into the retinoid ladder in moderate to severe inflammatory acne or comedonal acne.” (*Id.*, 20.) Anderson further discloses that according to Dr. Zane, “in those patients with very oily skin and widespread comedones that required repeated extraction procedures, topical tazarotene 0.05% or 0.1% cream—or gel if tolerated—can be particularly useful for minimizing comedonal burden.” (*Id.*, 21.)

Anderson’s teachings on the clinical use of 0.05% tazarotene compositions to treat acne would have motivated POSITAs to use the 0.045% tazarotene composition disclosed by WO ’001 with a reasonable expectation of success. (Ex. 1003, ¶¶75-77; Ex. 1005, ¶¶79-80.) POSITAs would have been motivated to combine the teachings of WO ’001, which focused on treating psoriasis with tazarotene compositions, and Anderson, which focused on treating acne with tazarotene,

because POSITAs would have known that tazarotene was the only topical retinoid used and approved by the FDA for treating both indications. (Ex. 1003, ¶78; Ex. 1005, ¶80.) Patent Owner's own arguments during prosecution of the '871 application confirm this. The '871 application discloses and claims methods of treating psoriasis with a topical tazarotene composition, but Patent Owner relied on clinical trial data on treating acne with the claimed composition to traverse the Examiner's rejection, demonstrating that POSITAs would have looked to information regarding either disease when dealing with topical tazarotene treatments. (*See* Ex. 1047, 60-75.)

Additionally, POSITAs would have known that local skin irritation was a common side effect when treating either psoriasis or acne with topical tazarotene, and, therefore, POSITAs would have been motivated to look to formulations used for treating either disease to address the irritation issue while maintaining efficacy. (Ex. 1003, ¶78; Ex. 1005, ¶80) POSITAs would have recognized that WO '001 provides one such formulation. *Id.* POSITAs also would have been motivated to use vehicles that included moisturizing ingredients, such as the lotion vehicle in WO '001, which included known moisturizers mineral oil and sorbitol, for formulating tazarotene to reduce its irritation, providing a further motivation to combine WO '001 with Anderson. (Ex. 1003, ¶78; Ex. 1005, ¶80; *see also* Ex. 1025, 20.)

ii. Kircik

Kircik disclosed a clinical study comparing tretinoin microsphere gel 0.04% delivered by pump to tazarotene cream 0.05% in the treatment of mild-to-moderate facial acne. (Ex. 1009, 650-651.) Kircik disclosed that tazarotene 0.05% cream produced a 36.86, 64.54, and 70.06% reduction in total inflammatory lesions at weeks 4, 8, and 12, respectively, and a 37.26, 58.94, and 75.50% reduction in total non-inflammatory lesions at weeks 4, 8, and 12, all of which were statistically significant. (*Id.*, 651-52, Figs. 1-2.)

Kircik's teachings of the efficacy of a 0.05% tazarotene composition in the topical treatment of acne would have motivated POSITAs to use the 0.045% tazarotene composition disclosed by WO '001 with a reasonable expectation of success. POSITAs also would have been aware that topical compositions comprising 0.05% tazarotene were commonly prescribed by physicians prior to May 2017. (Ex. 1003, ¶¶34, 79; Ex. 1005, ¶84; *see also* Ex. 1015.) Given this common practice and the efficacy results disclosed in Kircik, POSITAs would have reasonably expected a topical composition with a similar concentration of tazarotene, such as the 0.045% tazarotene composition in WO '001, to be efficacious in treating acne. (Ex. 1003, ¶80; Ex. 1005, ¶¶83-84.) POSITAs would have been motivated to combine the teachings of WO '001, which focused on treating psoriasis with tazarotene compositions, and Kircik, which focused on treating acne with

tazarotene, for the same reasons explained in the previous section regarding WO '001 and Anderson. (*Supra* §VII.A.1.a.i.)

iii. **Chim**

Chim disclosed that “[s]ubstantial evidence supports the use of [topical retinoids] across all stages of acne severity.” (Ex. 1010, 7.) Chim teaches that “[d]osing of [topical retinoids] should start at the lowest concentration a few times a week and be titrated to nightly, as tolerated.” (*Id.*, 13.) Table 1-3 in Chim is titled “Available Prescription Options to Treat Acne Vulgaris,” and it lists tazarotene cream 0.05% and gel 0.05% as available prescription options to treat acne. (*Id.*, Table 1-3.) Chim disclosed that clinical studies had suggested that tazarotene is more effective than adapalene and tretinoin. (*Id.*) Chim also teaches that topical retinoids “are limited by their adverse effects, which may result in nonadherence or discontinuation” and teaches that irritation can be managed through application of moisturizers or by “dosing or choice of vehicle.” (*Id.*)

Chim’s teaching that dosing of topical retinoids, like tazarotene, should start at the lowest concentration due to tolerability concerns would have motivated POSITAs to use a lower-concentration tazarotene composition, such as the 0.045% tazarotene lotion in WO '001, to treat acne. (*Id.*, 13; Ex. 1003, ¶¶81-82; Ex. 1005, ¶¶86-89.) Chim’s teachings of the efficacy and irritation benefits of a 0.05% tazarotene composition in the topical treatment of acne would have further motivated

POSITAs to use the 0.045% tazarotene lotion disclosed by WO '001 with a reasonable expectation of success for the same reasons explained above with respect to Kircik and Anderson. (*Supra* §§ VII.A.1.b.i.-ii.) POSITAs would have been motivated to combine the teachings of WO '001, which focused on treating psoriasis with tazarotene compositions, and Kircik, which focused on treating acne with tazarotene, for the same reasons explained in the previously regarding WO '001 and Anderson. (*Supra* § VII.A.1.b.i.)

c. Oil-in-water emulsion lotion

WO '001 discloses “wherein the composition is an oil-in-water emulsion lotion comprising an oil phase and an aqueous phase.” WO '001 discloses an oil-in-water emulsion lotion comprising an oil phase and an aqueous phase and 0.045% tazarotene. (Ex. 1007, [0038], [0054]-[0060], Table 4; Ex. 1003, ¶¶83-85; Ex. 1005, ¶¶90-91.)

d. Oil phase

WO '001 discloses “wherein the oil phase comprises a dicarboxylic acid ester and a mineral oil at a total concentration of 10-12 percent by weight of the composition.” WO '001 discloses a 0.045% tazarotene composition comprising an oil phase containing 2.97 weight % diethyl sebacate and 8.03 weight % light mineral oil.

WO '001

Ingredient	Function	Concentration (wt%)			
		IDP-118 (Present Invention)	Placebo (Vehicle)	Halobeta- sol propio- nate only	Tazaro- tene only
Halobetasol propionate, micronized	Active Ingredient	0.01	0	0.01	0
Tazarotene	Active Ingredient	0.045	0	0	0.045
Diethyl sebacate	Emollient & Solvent	2.97	2.97	2.97	2.97
Light mineral oil	Emollient & Solvent	8.03	8.03	8.03	8.03
Sorbitan monooleate	Surfactant/ Emulsifying Agent	0.1	0.1	0.1	0.1
Sorbitol solution, 70%	Humectant	10.7	10.7	10.7	10.7
Methyl paraben	Antimicrobial Preservative	0.17	0.17	0.17	0.17
Propyl paraben	Antimicrobial Preservative	0.03	0.03	0.03	0.03
Edetate disodium dihydrate	Chelating Agent	0.05	0.05	0.05	0.05
Carbomer copolymer type B (Pemulen TM TR-1)	Emulsifying Agent	0.4	0.4	0.4	0.4
Carbomer homopolymer type A (Carbomer 981)	Thickener	0.6	0.6	0.6	0.6
Sodium hydroxide	pH-adjusting agent	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5
Purified water	Solvent	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

(Ex. 1007, [0054]-[0060], Table 4; Ex. 1003, ¶¶86-88; Ex. 1005, ¶¶92-93.) Diethyl sebacate is a dicarboxylic acid ester. (Ex. 1005, ¶93; Ex. 1007, [0050].)

e. Aqueous phase

WO '001 discloses “wherein the aqueous phase comprises water and a carbomer homopolymer, wherein the concentration of the carbomer homopolymer is 0.5-0.7 percent by weight of the composition.” WO '001 discloses a 0.045%

tazarotene composition containing water, q.s. to 100 weight % and 0.6 weight % carbomer homopolymer type A.

WO '001

Ingredient	Function	Concentration (wt%)			
		IDP-118 (Present Invention)	Placebo (Vehicle)	Halobeta- sol propio- nate only	Tazaro- tene only
Halobetasol propionate, micronized	Active Ingredient	0.01	0	0.01	0
Tazarotene	Active Ingredient	0.045	0	0	0.045
Diethyl sebacate	Emollient & Solvent	2.97	2.97	2.97	2.97
Light mineral oil	Emollient & Solvent	8.03	8.03	8.03	8.03
Sorbitan monooleate	Surfactant/ Emulsifying Agent	0.1	0.1	0.1	0.1
Sorbitol solution, 70%	Humectant	10.7	10.7	10.7	10.7
Methyl paraben	Antimicrobial Preservative	0.17	0.17	0.17	0.17
Propyl paraben	Antimicrobial Preservative	0.03	0.03	0.03	0.03
Edetate disodium dihydrate	Chelating Agent	0.05	0.05	0.05	0.05
Carbomer copolymer type B (Pemulen™ TR-1)	Emulsifying Agent	0.4	0.4	0.4	0.4
Carbomer homopolymer type A (Carbomer 981)	Thickener	0.6	0.6	0.6	0.6
Sodium hydroxide	pH-adjusting agent	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5
Purified water	Solvent	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

(Ex. 1007, [0054]-[0060], Table 4; Ex. 1003, ¶¶89-91; Ex. 1005, ¶¶94-95.)

f. Polymeric emulsifier

WO '001 discloses “wherein the composition further comprises a polymeric emulsifier at a concentration of 0.3-0.5 percent by weight of the composition.” WO

'001 discloses a 0.045% tazarotene composition containing 0.4 weight % carbomer copolymer type B.

WO '001

Ingredient	Function	Concentration (wt%)			
		IDP-118 (Present Invention)	Placebo (Vehicle)	Halobeta- sol propio- nate only	Tazaro- tene only
Halobetasol propionate, micronized	Active Ingredient	0.01	0	0.01	0
Tazarotene	Active Ingredient	0.045	0	0	0.045
Diethyl sebacate	Emollient & Solvent	2.97	2.97	2.97	2.97
Light mineral oil	Emollient & Solvent	8.03	8.03	8.03	8.03
Sorbitan monooleate	Surfactant/ Emulsifying Agent	0.1	0.1	0.1	0.1
Sorbitol solution, 70%	Humectant	10.7	10.7	10.7	10.7
Methyl paraben	Antimicrobial Preservative	0.17	0.17	0.17	0.17
Propyl paraben	Antimicrobial Preservative	0.03	0.03	0.03	0.03
Edetate disodium dihydrate	Chelating Agent	0.05	0.05	0.05	0.05
Carbomer copolymer type B (Pemulen™ TR-1)	Emulsifying Agent	0.4	0.4	0.4	0.4
Carbomer homopolymer type A (Carbomer 981)	Thickener	0.6	0.6	0.6	0.6
Sodium hydroxide	pH-adjusting agent	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5
Purified water	Solvent	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

(Ex. 1007, [0054]-[0060], Table 4; Ex. 1003, ¶¶92-94; Ex. 1005, ¶¶96-98.)

Carbomer copolymer type B is a polymeric emulsifier. (Ex. 1005, ¶94; Ex. 1001, 4:10-14.)

2. Claim 2

Claim 2 recites “[t]he method of claim 1, wherein the dicarboxylic acid ester in the oil phase is diethyl sebacate.” WO ’001 discloses the limitations of claim 2 for the reasons explained in claim 1. (*Supra* §VII.A.1.d.) Therefore, WO ’001 in combination with Anderson, Kircik, or Chim renders claim 2 obvious.

3. Claim 3

Claim 3 recites “[t]he method of claim 1, wherein the oil phase comprises diethyl sebacate and light mineral oil.” Ex. 1001, 14:58-59. WO ’001 discloses the limitations of claim 3 for the reasons explained in claim 1. (*Supra* §VII.A.1.d.) Therefore, WO ’001 in combination with Anderson, Kircik, or Chim renders claim 3 obvious.

4. Claims 4-6

Claims 4-6 recite the method of claim 1, wherein the application is carried out for at least eight weeks (claim 4), at least twelve weeks (claim 5), or twelve weeks (claim 6). WO ’001 disclosed a halobetasol and tazarotene composition that may be applied for a period of twelve weeks or longer. (*See* Ex. 1007, [0084].) Therefore, WO ’001 in combination with Anderson, Kircik, or Chim renders claims 4-6 obvious. (Ex. 1003, ¶¶99-105; Ex. 1005, ¶¶104-110.)

a. Anderson

Anderson disclosed that several practicing dermatologists used 0.05% tazarotene compositions to treat acne as of 2004 and would have motivated POSITAs to use the 0.045% tazarotene lotion in WO '001 to treat acne. (*Supra* §VII.A.1.b.i.) POSITAs would have been motivated to carry out that treatment for a period of at least 12-weeks or longer because such a treatment period was common with topical retinoid therapies, including tazarotene, prior to May 2017. (Ex. 1003, ¶102; Ex. 1013, Clinical Studies (disclosing 12-week treatment of acne with topical tazarotene); Ex. 1017, Clinical Studies (disclosing 12-week treatment of acne with topical tazarotene); Ex. 1034, Clinical Studies (disclosing 12-week treatment of acne with topical adapalene).) A 12-week treatment period encompasses the 8-week, at least 12-week, and 12-week treatment period recited in claims 4-6. (Ex. 1003, ¶102.)

b. Kircik

Kircik disclosed treatment of acne vulgaris with once daily application of tazarotene 0.05% cream for 12 weeks. (Ex. 1009, 651.) Kircik disclosed that tazarotene 0.05% cream produced a 36.86, 64.54, and 70.06% reduction in total inflammatory lesions at weeks 4, 8, and 12, respectively, and a 37.26, 58.94, and 75.50% reduction in total non-inflammatory lesions at weeks 4, 8, and 12, all of which were statistically significant. (*Id.*, 651-52, Figs. 1-2.) These teachings would have motivated POSITAs to use the 0.045% tazarotene composition in WO '001 to

treat acne for a period of up to 12-weeks or longer. (Ex. 1003, ¶¶103-104; *see also supra* §§VII.A.1.a.ii.; VII.A.1.b.ii.) The 12-week treatment period disclosed in Kircik encompasses the 8-week, at least 12-week, and 12-week treatment period recited in claims 4-6. (Ex. 1003, ¶104.)

c. Chim

Chim teaches that “[b]est results [with treating acne with topical retinoids] may be expected in about 3 months.” (Ex. 1010, 13.) This teaching would have motivated POSITAs to use the WO ’001’s 0.045% tazarotene lotion for at least 12-weeks (i.e., about 3 months) or longer, which encompasses the 8-week, at least 12-week, and 12-week treatment period recited in claims 4-6. (Ex. 1003, ¶ 105.)

5. Claim 7

WO ’001 discloses “wherein the tazarotene is in solution in the oil phase of the oil-in-water emulsion lotion.” WO ’001 discloses a tazarotene-only oil-in-water emulsion lotion composition containing 0.045 weight % tazarotene, wherein the tazarotene is in solution in the oil phase of the oil-in-water emulsion. (Ex. 1007, [0038], [0054]-[0060], Table 4; Ex. 1003, ¶¶106-108; Ex. 1005, ¶¶111-113.) Therefore, WO ’001 in combination with Anderson, Kircik, or Chim renders claim 7 obvious. (Ex. 1003, ¶¶106-108; Ex. 1005, ¶¶111-113.)

6. Claim 8

WO '001 discloses “wherein the composition has a pH of about 4 to about 6.”

WO '001 discloses a 0.045% tazarotene only composition wherein the composition has a pH of 5.5 ± 0.5 .

WO '001

Ingredient	Function	Concentration (wt%)			
		IDP-118 (Present Invention)	Placebo (Vehicle)	Halobeta- sol propio- nate only	Tazaro- tene only
Halobetasol propionate, micronized	Active Ingredient	0.01	0	0.01	0
Tazarotene	Active Ingredient	0.045	0	0	0.045
Diethyl sebacate	Emollient & Solvent	2.97	2.97	2.97	2.97
Light mineral oil	Emollient & Solvent	8.03	8.03	8.03	8.03
Sorbitan monooleate	Surfactant/ Emulsifying Agent	0.1	0.1	0.1	0.1
Sorbitol solution, 70%	Humectant	10.7	10.7	10.7	10.7
Methyl paraben	Antimicrobial Preservative	0.17	0.17	0.17	0.17
Propyl paraben	Antimicrobial Preservative	0.03	0.03	0.03	0.03
Edetate disodium dihydrate	Chelating Agent	0.05	0.05	0.05	0.05
Carbomer copolymer type B (Pemulen TM TR-1)	Emulsifying Agent	0.4	0.4	0.4	0.4
Carbomer homopolymer type A (Carbomer 981)	Thickener	0.6	0.6	0.6	0.6
Sodium hydroxide	pH-adjusting agent	q.s. to pH of 5.5 ± 0.5	q.s. to pH of $5.5 \pm$ 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of $5.5 \pm$ 0.5
Purified water	Solvent	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

(Ex. 1007, [0059], Table 4; Ex. 1003, ¶¶109-111; Ex. 1005, ¶¶114-116.) Therefore, WO '001 in combination with Anderson, Kircik, or Chim renders claim 8 obvious. (Ex. 1003, ¶¶109-111; Ex. 1005, ¶¶114-116.)

7. Claims 9-10

WO '001 in combination with Anderson, Kircik, or Chim renders claims 9-10 obvious. Claim 9 recites “[t]he method of claim 1, wherein the composition consists essentially of: 0.045 weight % tazarotene; diethyl sebacate; light mineral oil; sorbitan monooleate; sorbitol solution, 70%; methylparaben; propylparaben; edetate disodium dihydrate; carbomer polymer type B; carbomer homopolymer type A; sodium hydroxide; purified water.” Claim 10 recites “[t]he method of claim 1, wherein the composition consists essentially of: 0.045 weight % tazarotene; 2.5-3.5 weight % diethyl sebacate; 7.5-8.5 weight % light mineral oil; 0.05-0.2 weight % sorbitan monooleate; 10-11 weight % sorbitol solution, 70%; 0.1-0.2 weight % methylparaben; 0.02-0.04 weight % propylparaben; 0.03-0.06 weight % edetate disodium dihydrate; 0.3-0.5 weight % carbomer polymer type B; 0.5-0.7 weight % carbomer homopolymer type A; sodium hydroxide, q.s. to pH 5.5±0.5; and purified water, q.s. to 100 weight %.” WO '001 discloses the limitations recited in claims 9 and 10. (Ex. 1003, ¶¶112-114; Ex. 1005, ¶¶117-119.)

WO '001 discloses a tazarotene only formulation comprising 0.045 weight % tazarotene, 2.97 weight % diethyl sebacate, 8.03 weight % light mineral oil, 0.1

weight % sorbitan monooleate, 10.7 weight % sorbitol solution, 70%, 0.17 weight % methylparaben, 0.03 weight % propyl paraben, 0.05 weight % edetate disodium dihydrate, 0.4 weight % carbomer copolymer type B, 0.6 weight % carbomer homopolymer type A, sodium hydroxide, q.s. to pH of 5.5 ± 0.5 , and purified water, q.s. to 100.

WO '001

Ingredient	Function	Concentration (wt%)			
		IDP-118 (Present Invention)	Placebo (Vehicle)	Halobeta- sol propio- nate only	Tazaro- tene only
Halobetasol propionate, micronized	Active Ingredient	0.01	0	0.01	0
Tazarotene	Active Ingredient	0.045	0	0	0.045
Diethyl sebacate	Emollient & Solvent	2.97	2.97	2.97	2.97
Light mineral oil	Emollient & Solvent	8.03	8.03	8.03	8.03
Sorbitan monooleate	Surfactant/ Emulsifying Agent	0.1	0.1	0.1	0.1
Sorbitol solution, 70%	Humectant	10.7	10.7	10.7	10.7
Methyl paraben	Antimicrobial Preservative	0.17	0.17	0.17	0.17
Propyl paraben	Antimicrobial Preservative	0.03	0.03	0.03	0.03
Edetate disodium dihydrate	Chelating Agent	0.05	0.05	0.05	0.05
Carbomer copolymer type B (Pemulen™ TR-1)	Emulsifying Agent	0.4	0.4	0.4	0.4
Carbomer homopolymer type A (Carbomer 981)	Thickener	0.6	0.6	0.6	0.6
Sodium hydroxide	pH-adjusting agent	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5
Purified water	Solvent	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

(Ex. 1007, Table 4; Ex. 1003, ¶113; Ex. 1005, ¶118.) Therefore, WO '001 in combination with Kircik, Chim, or Anderson renders claims 9 and 10 obvious. (Ex. 1003, ¶¶112-114; Ex. 1005, ¶¶117-119.)

8. Claim 11

Claim 11 is an independent claim that recites a method for treating acne vulgaris through topical application of a composition that “consists essentially of: 0.045 weight % tazarotene; 2.97 weight % diethyl sebacate; 8.03 weight % light mineral oil; 0.1 weight % sorbitan monooleate; 10.7 weight % sorbitol solution, 70%; 0.17 weight % methylparaben; 0.03 weight % propylparaben; 0.05 weight % edetate disodium dihydrate; 0.4 weight % carbomer polymer type B; 0.6 weight % carbomer homopolymer type A; sodium hydroxide, q.s. to pH 5.5 ± 0.5 ; and purified water, q.s. to 100 weight %.” WO '001 in combination with Anderson, Kircik, or Chim renders claim 11 obvious. (Ex. 1003, ¶¶116-118; Ex. 1005, ¶¶121-123.)

WO '001 discloses a tazarotene only formulation comprising 0.045 weight % tazarotene, 2.97 weight % diethyl sebacate, 8.03 weight % light mineral oil, 0.1 weight % sorbitan monooleate, 10.7 weight % sorbitol solution, 70%, 0.17 weight % methylparaben, 0.03 weight % propylparaben, 0.05 weight % edetate disodium dihydrate, 0.4 weight % carbomer copolymer type B, 0.6 weight % carbomer homopolymer type A, sodium hydroxide, q.s. to pH of 5.5 ± 0.5 , and purified water, q.s. to 100.

WO '001

Ingredient	Function	Concentration (wt%)			
		IDP-118 (Present Invention)	Placebo (Vehicle)	Halobeta- sol propio- nate only	Tazaro- tene only
Halobetasol propionate, micronized	Active Ingredient	0.01	0	0.01	0
Tazarotene	Active Ingredient	0.045	0	0	0.045
Diethyl sebacate	Emollient & Solvent	2.97	2.97	2.97	2.97
Light mineral oil	Emollient & Solvent	8.03	8.03	8.03	8.03
Sorbitan monooleate	Surfactant/ Emulsifying Agent	0.1	0.1	0.1	0.1
Sorbitol solution, 70%	Humectant	10.7	10.7	10.7	10.7
Methyl paraben	Antimicrobial Preservative	0.17	0.17	0.17	0.17
Propyl paraben	Antimicrobial Preservative	0.03	0.03	0.03	0.03
Edetate disodium dihydrate	Chelating Agent	0.05	0.05	0.05	0.05
Carbomer copolymer type B (Pemulen™ TR-1)	Emulsifying Agent	0.4	0.4	0.4	0.4
Carbomer homopolymer type A (Carbomer 981)	Thickener	0.6	0.6	0.6	0.6
Sodium hydroxide	pH-adjusting agent	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5	q.s. to pH of 5.5 ± 0.5
Purified water	Solvent	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100

(Ex. 1007, Table 4; Ex. 1003, ¶117; Ex. 1005, ¶122.) To the extent the preamble of claim 11 is limiting, POSITAs would have been motivated to use the 0.045% tazarotene composition in WO '001 to treat acne with a reasonable expectation of success in view of Kircik, Chim, and Anderson for the reasons explained in claim 1. (*Supra* §VII.A.1.a.)

B. Ground 4: Claims 1-11 Would Have Been Obvious Over WO '001 and Anderson in Combination with Shalita

As explained in Grounds 1-3, WO '001 and Anderson render claims 1-11 of the '482 patent obvious. (*Supra* §VII.A.). Shalita would have provided POSITAs with even further motivation to use the 0.045% tazarotene lotion from WO '001 to treat acne. (Ex. 1003, ¶¶120-125; Ex. 1005, ¶¶125-130.)

Shalita disclosed a 12-week multicenter, double-blind, vehicle-controlled study of tazarotene 0.1% and 0.05% gel in the treatment of acne. (Ex. 1011, 350.) Shalita disclosed that treatment with 0.05% tazarotene gel was significantly more effective than treatment with vehicle gel in terms of both reduction in lesion count and treatment success rate. (*Id.*, 351, Figs. 1-2.) Shalita also disclosed that irritation caused by topical tazarotene treatment “[is] consistent with the known effects of topical retinoids” and “can be managed in ways similar to other retinoids: reducing treatment to every other day until skin ‘hardens’ to the retinoid; reducing the strength of the treatment, from 0.1% gel to 0.05% gel until the skin adjusts; or a combination of the two.” (*Id.*, 354.)

Shalita’s teachings of the efficacy and irritation benefits of a 0.05% tazarotene composition in the topical treatment of acne would have further motivated POSITAs to use the 0.045% tazarotene composition disclosed by WO '001 with a reasonable expectation of success. (Ex. 1003, ¶¶120-122; Ex. 1005, ¶127.) This is particularly

true given Anderson's teachings regarding the clinical use of 0.05% tazarotene to treat acne (*supra* §VII.A.1.b.i.) and the POSITA's awareness that topical compositions comprising 0.05% tazarotene were commonly prescribed by physicians prior to May 2017. (Ex. 1003, ¶122; *see also* Ex. 1015.) Given this common practice and the efficacy results disclosed in Shalita, POSITAs would have reasonably expected a topical composition with a similar concentration of tazarotene, such as the 0.045% tazarotene composition in WO '001, to be efficacious in treating acne. (Ex. 1003, ¶122; Ex. 1005, ¶127.) POSITAs would have understood that the difference in concentration between the 0.05% and 0.045% tazarotene compositions is minor and would have expected that difference to have little, if any, impact on the efficacy of the treatment. (Ex. 1003, ¶122; Ex. 1005, ¶127.)

Shalita would have also given POSITAs a reasonable expectation that the 0.045% tazarotene composition in WO '001 would cause less irritation than higher concentrations of tazarotene, for example 0.1%, providing further motivation to use that composition to treat acne. (Ex. 1003, ¶123; Ex. 1005, ¶127.) POSITAs would have been motivated to combine the teachings of WO '001, which focused on treating psoriasis with tazarotene compositions, with Anderson and Shalita, which focused on treating acne with tazarotene, for the reasons explained in Grounds 1-3 for WO '001 and Anderson. (*Supra* §VII.A.1.b.i.) Accordingly, claims 1-11 of the

'482 patent would have been obvious over WO '001 in combination with Anderson and Shalita. (Ex. 1003, ¶¶120-125; Ex. 1005, ¶¶125-128.)

1. Claims 4-6

Shalita would have also provided POSITAs further motivation to use the 0.045% tazarotene formulation from WO '001 to treat acne for the length of time recited in claims 4-6 of the '482 patent. (Ex. 1003, ¶125; Ex. 1005, ¶¶129-130.)

Shalita discloses treatment of acne vulgaris with once daily application of tazarotene 0.05% gel for 12 weeks. (Ex. 1011, 350.) Shalita teaches that treatment with 0.05% tazarotene gel was statistically significantly more effective than vehicle at decreasing noninflammatory and total lesion count at week 12 and provided a statistically significantly higher success rate than vehicle at week 8. (*Id.*, 351, Figs. 1-2.) These teachings would have further motivated POSITAs to use the 0.045% tazarotene composition in WO '001 to treat acne for a period of up to twelve weeks or longer. (Ex. 1003, ¶125; Ex. 1005, ¶129; *see also supra* VII.A.1.b.i.) The 12-week treatment period disclosed in Shalita encompasses the 8-week, at least 12-week, and 12-week treatment period recited in claims 4-6. (Ex. 1003, ¶125.)

C. Ground 5: Claims 1-11 Would Have Been Obvious Over the '824

Publication and the Tazorac® Label

The '824 publication disclosed a lotion vehicle that is *identical* to the composition disclosed and claimed in the '482 patent, with the exception of the

active ingredient – 0.045% tazarotene. (See Ex. 1012, Table 4; Ex. 1003, ¶127; Ex. 1005, ¶131.) POSITAs would have found it obvious to replace the active ingredient in the '824 publication's formulations with 0.045% tazarotene in view of the Tazorac Label®, consistent with the Examiner's final rejection during prosecution of the related '576 application.⁶ (*Supra* §II.D.1.) The only remaining question is whether POSITAs would have found it obvious to use the 0.045% tazarotene lotion to treat acne. Given that POSITAs would have known that 0.05% tazarotene compositions, including the 0.05% concentration of Tazorac®, were commonly prescribed and used to treat acne prior to May 2017, POSITAs would have found it obvious to use a composition with a nearly identical tazarotene concentration – 0.045% – to treat the same condition. (See Ex. 1003, ¶137.) That would have been particularly so for a tazarotene composition formulated in the '824 publication's lotion vehicle, which was taught to enable greater penetration of the active ingredient into the skin, allowing for better efficacy even when the concentration of the active ingredient is greatly reduced. (Ex. 1003, ¶138; Ex. 1005, ¶¶131, 142.) Accordingly, claims 1-11 of the '482 patent would have been obvious to POSITAs in May 2017 in view of the

⁶ As explained above, the Examiner issued a similar rejection for Patent Owner's related '871 application, but the Examiner then concluded that the *prima facie* case of obviousness was overcome by secondary considerations. (*Supra* §II.D.2.)

'824 publication in combination with the Tazorac® label as further described below. (Ex. 1003, ¶¶126-130; Ex. 1005, ¶¶131-133.)

1. Claim 1

The '824 publication and the Tazorac® Label render claim 1 obvious. (Ex. 1003, ¶131; Ex. 1005, ¶134.)

a. Preamble

The Tazorac® label discloses a method of treating acne vulgaris by applying the pharmaceutical composition once per day to an affected area of a body of a subject suffering from acne vulgaris. (Ex. 1013, Indications and Usage; Ex. 1003, ¶133; Ex. 1005, ¶¶135-136.)

b. Composition of tazarotene at 0.045% as sole active ingredient

POSITAs would have been motivated to replace the active ingredient in the lotion disclosed by the '824 publication with 0.045% tazarotene in view of the Tazorac® Label and knowledge of a POSITA in May 2017. (Ex. 1003, ¶¶135-139; Ex. 1005, ¶¶137-145.) The Tazorac® Label disclosed topical tazarotene compositions with two different concentrations of tazarotene: 0.1% and 0.05%. (Ex. 1013.) As the Examiner concluded for the related '576 application, “it would have been obvious to substitute tazarotene instead of halobetasol propionate [in the lotion of the '824 publication] because both agents are known in the art to treat skin

disorder[s] and the composition for delivery [in the '824 publication] is the same” as the composition claimed in the '482 patent. (Ex. 1029, 4.) As the Examiner also explained in the '576 application final rejection, the Tazorac® Label discloses tazarotene compositions with 0.05% and 0.1% tazarotene, and “[t]he amounts of active agents to be used . . . are all deemed obvious since they are all within the knowledge of the skilled pharmacologist and represent conventional formulations and modes of administration.” (*Id.*, 11.) Thus, like the Examiner concluded in the '576 application, “it is obvious to vary and/or optimize the amount of tazarotene provided in the composition, according to the guidance provided by Tazorac, to provide a composition having” about 0.045% tazarotene as claimed in claim 1 of the '482 patent. (*Id.*, 12.)

POSITAs would have been further motivated to select a tazarotene concentration of about 0.045% in view of the Tazorac® Label’s teaching that the “0.1% was associated with a greater degree of local irritation than the 0.05% cream.” (Ex. 1013, Adverse Reactions; Ex. 1003, ¶136; Ex. 1005, ¶¶137-138.) POSITAs would have been motivated to minimize local skin irritation to improve patient compliance and would have recognized lowering the concentration of tazarotene in the formulation as one means for doing so in view of the Tazorac Label® and the POSITA’s general knowledge regarding tazarotene treatments. (Ex. 1003, ¶; Ex. 1005, ¶138; *see also* Ex. 1022, 293; Ex. 1010, 13.)

POSITAs would have been motivated to use the 0.045% tazarotene lotion resulting from the combination of the Tazorac® Label and the '824 publication to treat acne and would have had a reasonable expectation of success in doing so. (Ex. 1003, ¶¶132-136; Ex. 1005, ¶¶137-145.) As explained previously, POSITAs also would have been aware that topical compositions comprising 0.05% tazarotene were commonly prescribed by physicians prior to May 2017 to treat acne. (Ex. 1003, ¶34; *see also* Ex. 1015.) POSITAs would have understood that the difference in concentration between the 0.05% and 0.045% tazarotene compositions is minor and would have expected that difference to have little, if any, impact on the efficacy of the treatment. Ex. 1003, ¶¶36, 137; Ex. 1005, ¶139.) Moreover, the '824 publication teaches that its lotion vehicle improves the penetration of the active ingredient into the patient's skin, which allows for the compositions to have the same or better efficacy even when the concentration of the active ingredient is greatly reduced. (Ex. 1012, [0035], [0037]-[0040], Tables 1 & 3; Ex. 1003, ¶138; Ex. 1005, ¶142.) Thus, POSITA's would have had an even greater expectation of success in treating acne with 0.045% tazarotene formulated in the lotion vehicle disclosed in the '824 publication. (Ex. 1003, ¶138; Ex. 1005, ¶142.)

c. **Oil-in-water emulsion lotion**

The Patent Office has already concluded that the '824 publication discloses an “oil-in-water emulsion lotion comprising an oil phase and an aqueous phase” in the related '576 application. (*Supra* §II.D.)

The '824 publication disclosed oil-in-water emulsion vehicle formulations containing a “liquid oil component” comprising a dicarboxylic acid ester, such as diethyl sebacate, that is used to formulate topical corticosteroid compositions.

'824 publication

TABLE 4		
Ingredients	% w/w	
	Formula 4A	Formula 4B
Halobetasol Propionate	0.01	0.025
Diethyl Sebacate	2.97	2.90
Light Mineral Oil	8.03	2.90
Sorbitan Monooleate	0.10	0.10
Sorbitol Solution, 70%	10.7	10.7
Disodium Edetate, Dihydrate	0.05	0.05
Pemulen TR-1	0.40	0.40
Carbopol 981	0.60	0.60
Methylparaben	0.17	0.17
Propylparaben	0.03	0.03
Sodium Hydroxide, q. s.	pH 4.0-6.0	pH 4.0-6.0
Purified Water, q.s. ad	100	100

(Ex. 1012, [0012], Tables 1 & 4.) The '824 publication disclosed that the “liquid oil component” comprising a dicarboxylic acid ester dissolves the corticosteroid, and that the disclosed vehicle provides enhanced delivery of the steroid into the skin,

rather than through the skin into systemic circulation. (*Id.*, [0016]; Ex. 1005, ¶131.) The '824 publication disclosed example formulations with the corticosteroid halobetasol propionate wherein the potency of the formulation is maintained when the concentration of halobetasol propionate is reduced from 0.05% to as low as 0.01%. (Ex. 1012, [0035], [0037]-[0040], Tables 1 & 3.) The '824 publication also disclosed a method for manufacturing example lotion formulations with 0.01% halobetasol propionate. (*Id.* at [0041]-[0045], Table 4.)

POSITAs would have been motivated to use the oil-in-water emulsion vehicle disclosed in the '824 publication to formulate a topical composition of tazarotene at a concentration of about 0.045%, consistent with the Examiner's final rejection of Patent Owner's related '576 application. (Ex. 1005, ¶147; Ex. 1029, 1-20.) POSITAs would have been particularly motivated to investigate Formulation 4A as a vehicle for a composition of 0.045% tazarotene because unlike many of the other vehicles disclosed in the '824 publication, Formulation 4A does not contain propylene glycol, an ingredient that was known to cause irritation and dryness. (Ex. 1012, Table 4; Ex. 1005, ¶144.) Additionally, POSITAs would have known that tazarotene is a lipophilic molecule, and it would have been a matter of routine experimentation and optimization to determine that tazarotene would be soluble in the oil-phase of the vehicles disclosed in the '824 publication. (Ex. 1005, ¶143.)

POSITAs would have also known that application of moisturizers was known to help alleviate the irritation caused by tazarotene therapy. (Ex. 1003, ¶¶39, 142; Ex. 1005, ¶141; *see also, e.g.*, Ex. 1010, 13.) Formulation 4A in the '824 publication would have been particularly attractive to POSITAs developing a topical formulation of tazarotene because it includes several known moisturizing ingredients, including mineral oil and sorbitol, which would have been expected to help alleviate the irritation from the tazarotene. (*See* Ex. 1012, Table 4; Ex. 1005, ¶144.) Formulation 4A includes a higher concentration of the moisturizing ingredient mineral oil than Formulation 4B. (*See* Ex. 1012, Table 4; Ex. 1005, ¶144.)

d. Oil phase

Formulation 4A of the '824 publication disclosed an oil-in-water emulsion that includes an oil phase comprising diethyl sebacate at 2.97% and light mineral oil at 8.03% by weight of the composition.

'824 publication

TABLE 4		
Ingredients	% w/w	
	Formula 4A	Formula 4B
Halobetasol Propionate	0.01	0.025
Diethyl Sebacate	2.97	2.90
Light Mineral Oil	8.03	2.90
Sorbitan Monooleate	0.10	0.10
Sorbitol Solution, 70%	10.7	10.7
Disodium Edetate, Dihydrate	0.05	0.05
Pemulen TR-1	0.40	0.40
Carbopol 981	0.60	0.60
Methylparaben	0.17	0.17
Propylparaben	0.03	0.03
Sodium Hydroxide, q. s.	pH 4.0-6.0	pH 4.0-6.0
Purified Water, q.s. ad	100	100

(Ex. 1012, Table 4; Ex. 1003, ¶¶146-148; Ex. 1005, ¶¶148-149.) POSITAs would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion lotion vehicles of the '824 publication, particularly Formulation 4A, with a reasonable expectation of success for the reasons described previously. (*Supra* §VII.C.1.c.)

e. Aqueous phase

Formulation 4A of the '824 publication disclosed a vehicle for an oil-in-water emulsion lotion comprising an aqueous phase that comprises water and Carbopol 981 (Carbomer Homopolymer Type A) at 0.60% by weight of the composition.

'824 publication

TABLE 4		
Ingredients	% w/w	
	Formula 4A	Formula 4B
Halobetasol Propionate	0.01	0.025
Diethyl Sebacate	2.97	2.90
Light Mineral Oil	8.03	2.90
Sorbitan Monooleate	0.10	0.10
Sorbitol Solution, 70%	10.7	10.7
Disodium Edetate, Dihydrate	0.05	0.05
Pemulen TR-1	0.40	0.40
Carbopol 981	0.60	0.60
Methylparaben	0.17	0.17
Propylparaben	0.03	0.03
Sodium Hydroxide, q. s.	pH 4.0-6.0	pH 4.0-6.0
Purified Water, q.s. ad	100	100

(Ex. 1012, Table 4; Ex. 1003, ¶¶146-148; Ex. 1005, ¶¶150-151.) POSITAs would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion lotion vehicles of the '824 publication, particularly Formulation 4A, with a reasonable expectation of success for the reasons described previously. (*Supra* §VII.C.1.c.)

f. Polymeric emulsifier

Formulation 4A of the '824 publication disclosed a vehicle for an oil-in-water emulsion lotion comprising Pemulen TR-1 at 0.40% by weight of the composition.

'824 publication

TABLE 4		
Ingredients	% w/w	
	Formula 4A	Formula 4B
Halobetasol Propionate	0.01	0.025
Diethyl Sebacate	2.97	2.90
Light Mineral Oil	8.03	2.90
Sorbitan Monooleate	0.10	0.10
Sorbitol Solution, 70%	10.7	10.7
Disodium Edetate, Dihydrate	0.05	0.05
Pemulen TR-1	0.40	0.40
Carbopol 981	0.60	0.60
Methylparaben	0.17	0.17
Propylparaben	0.03	0.03
Sodium Hydroxide, q. s.	pH 4.0-6.0	pH 4.0-6.0
Purified Water, q.s. ad	100	100

(Ex. 1012, Table 4; Ex. 1003, ¶¶149-151; Ex. 1005, ¶¶152-154.) The '824 publication disclosed that Pemulen is a polymeric emulsifier. (Ex. 1012, [0024]; Ex. 1005, ¶153.) The use of Pemulen polymeric emulsifiers in topical formulations with Carbopol was well known in the prior art. (Ex. 1005, ¶154; *see also* Ex. 1035.) POSITAs would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion lotion vehicles of the '824 publication, particularly Formulation 4A, with a reasonable expectation of success for the reasons described previously. (*Supra* §VII.C.1.c.)

2. Claim 2

The '824 publication discloses the limitations of claim 2 for the reasons explained in claim 1. (*Supra* §VII.C.1.d.) Therefore, the combination of the '824 publication and the Tazorac® Label render claim 2 obvious. (Ex. 1003, ¶152; Ex. 1005, ¶155.)

3. Claim 3

The '824 publication discloses the limitations of claim 3 for the reasons explained in claim 1. (*Supra* §VII.C.1.d.) Therefore, the combination of the '824 publication and the Tazorac® Label render claim 3 obvious. (Ex. 1003, ¶153; Ex. 1005, ¶156.)

4. Claims 4-6

In multiple clinical trials disclosed in the Tazorac® Label, the treatment was carried out for 12 weeks. (Ex. 1013, Clinical Studies.) POSITAs would have therefore found it obvious to use the 0.045% tazarotene lotion resulting from the combination of the '824 publication and the Tazorac® Label for at least 12 weeks or longer. (Ex. 1003, ¶¶154-155; Ex. 1005, ¶¶157-159.) Because 12-weeks encompasses “at least 8 weeks” as well as “at least 12 weeks,” the Tazorac® Label in combination with the '824 publication renders claims 4-6 obvious. (Ex. 1003, ¶155; Ex. 1005, ¶158.)

5. Claim 7

Formulation 4A of the '824 publication disclosed an oil-in-water emulsion that includes an oil phase comprising diethyl sebacate at 2.97% and light mineral oil at 8.03% by weight of the composition.

'824 publication

TABLE 4		
Ingredients	% w/w	
	Formula 4A	Formula 4B
Halobetasol Propionate	0.01	0.025
Diethyl Sebacate	2.97	2.90
Light Mineral Oil	8.03	2.90
Sorbitan Monooleate	0.10	0.10
Sorbitol Solution, 70%	10.7	10.7
Disodium Edetate, Dihydrate	0.05	0.05
Pemulen TR-1	0.40	0.40
Carbopol 981	0.60	0.60
Methylparaben	0.17	0.17
Propylparaben	0.03	0.03
Sodium Hydroxide, q. s.	pH 4.0-6.0	pH 4.0-6.0
Purified Water, q.s. ad	100	100

(Ex. 1012, Table 4; Ex. 1003, ¶156; Ex. 1005, ¶¶160-163.) POSITAs would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion lotion vehicles of the '824 publication, particularly Formulation 4A, with a reasonable expectation of success for the reasons described previously. (*Supra* §VII.C.1.c.) Therefore, the '824 publication and the Tazorac® Label renders claim 7 obvious. (Ex. 1003, ¶156; Ex. 1005, ¶¶160-163.)

6. Claim 8

Formulation 4A of the '824 publication disclosed an oil-in-water emulsion with a pH of 4.0-6.0.

'824 publication

TABLE 4		
Ingredients	% w/w	
	Formula 4A	Formula 4B
Halobetasol Propionate	0.01	0.025
Diethyl Sebacate	2.97	2.90
Light Mineral Oil	8.03	2.90
Sorbitan Monooleate	0.10	0.10
Sorbitol Solution, 70%	10.7	10.7
Disodium Edetate, Dihydrate	0.05	0.05
Pemulen TR-1	0.40	0.40
Carbopol 981	0.60	0.60
Methylparaben	0.17	0.17
Propylparaben	0.03	0.03
Sodium Hydroxide, q. s.	pH 4.0-6.0	pH 4.0-6.0
Purified Water, q.s. ad	100	100

(Ex. 1012, Table 4; Ex. 1003, ¶¶157-159; Ex. 1005, ¶¶164-166.) POSITAs would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion lotion vehicles of the '824 publication, particularly Formulation 4A in Table 4, with a reasonable expectation of success for the reasons described previously. (*Supra* §VII.C.1.c.) Therefore, the '824 publication in combination with the Tazorac® Label renders claim 8 obvious. (Ex. 1003, ¶¶157-159; Ex. 1005, ¶¶164-166.)

7. Claims 9-10

Formula 4A of the '824 publication disclosed each of the limitations recited in claims 9 and 10 except for 0.045% tazarotene.

'824 publication

TABLE 4		
Ingredients	% w/w	
	Formula 4A	Formula 4B
Halobetasol Propionate	0.01	0.025
Diethyl Sebacate	2.97	2.90
Light Mineral Oil	8.03	2.90
Sorbitan Monooleate	0.10	0.10
Sorbitol Solution, 70%	10.7	10.7
Disodium Edetate, Dihydrate	0.05	0.05
Pemulen TR-1	0.40	0.40
Carbopol 981	0.60	0.60
Methylparaben	0.17	0.17
Propylparaben	0.03	0.03
Sodium Hydroxide, q. s.	pH 4.0-6.0	pH 4.0-6.0
Purified Water, q.s. ad	100	100

(Ex. 1012, Table 4; Ex. 1003, ¶¶161-162; Ex. 1005, ¶¶168-169.) POSITAs would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion lotion vehicles of the '824 publication, particularly Formulation 4A, with a reasonable expectation of success for the reasons described previously. (*Supra* §VII.C.1.c.) Therefore, the '824 publication in combination with the Tazorac® Label renders claims 9-10 obvious. (Ex. 1003, ¶¶161-162; Ex. 1005, ¶¶168-169.)

8. Claim 11

Formula 4A of the '824 publication disclosed each of the limitations recited in claim 11, except for 0.045% tazarotene.

'824 publication

TABLE 4		
Ingredients	% w/w	
	Formula 4A	Formula 4B
Halobetasol Propionate	0.01	0.025
Diethyl Sebacate	2.97	2.90
Light Mineral Oil	8.03	2.90
Sorbitan Monooleate	0.10	0.10
Sorbitol Solution, 70%	10.7	10.7
Disodium Edetate, Dihydrate	0.05	0.05
Pemulen TR-1	0.40	0.40
Carbopol 981	0.60	0.60
Methylparaben	0.17	0.17
Propylparaben	0.03	0.03
Sodium Hydroxide, q. s.	pH 4.0-6.0	pH 4.0-6.0
Purified Water, q.s. ad	100	100

(Ex. 1012, Table 4; Ex. 1003, ¶¶165-166; Ex. 1005, ¶172.) POSITAs would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion lotion vehicles of the '824 publication, particularly Formulation 4A, with a reasonable expectation of success for the reasons described previously. (*Supra* § VII.C.1.c.) To the extent the preamble of claim 11 is limiting, POSITAs would have been motivated to treat acne with once daily application of a composition comprising 0.045% tazarotene with a reasonable expectation of success for the reasons discussed

previously. (*Supra* § VII.B.1.) Therefore, the '824 publication in combination with the Tazorac® Label renders claim 11 obvious. (Ex. 1003, ¶¶164-166; Ex. 1005, ¶¶171-174.)

D. Grounds 6: Claims 1-11 Would Have Been Obvious Over the '824

Publication and the Tazorac® Label in view of Anderson

As explained in Ground 5, the '824 publication and the Tazorac® Label render claims 1-11 of the '482 patent obvious. (*Supra* §VII.C.) Anderson would have provided POSITAs with even further motivation to use the 0.045% tazarotene lotion resulting from the combination of the '824 publication and the Tazorac® Label to treat acne. (Ex. 1003, ¶¶167-169; Ex. 1005, ¶¶175-178.)

As explained previously, Anderson disclosed the clinical use of 0.05% tazarotene compositions to treat acne by practicing dermatologists, who described 0.05% tazarotene compositions as “a useful part of the treatment regimen . . . [that] fits well into the retinoid ladder in moderate to severe inflammatory acne or comedonal acne.” (*Supra* §§VII.A.1.a.i., VII.A.1.b.i.) Anderson’s teachings for 0.05% tazarotene, and the POSITA’s knowledge of the use and prescription of 0.05% tazarotene for treating acne, would have provided POSITAs with further motivation and expectation of success in using a composition with a similar concentration of tazarotene – 0.045% – to treat the same disease. (Ex. 1003, ¶168; Ex. 1005, ¶¶176-178.) Accordingly, claims 1-11 of the '482 patent would have

been obvious over the '824 Publication and the Tazorac® Label in view of Anderson. (Ex. 1003, ¶¶167-169; Ex. 1005, ¶¶176-178.)

E. Grounds 7-9: Claims 1-11 Would Have Been Obvious Over the '824 Publication and the IDP-118 Study in view of Anderson, Kircik, or Chim

Given the known irritation profile of commercially available 0.1% tazarotene compositions and the common off-label use of the 0.05% tazarotene compositions, POSITAs in May 2017 would have been looking to find lower-concentration tazarotene compositions for treating acne. (Ex. 1003, ¶170; Ex. 1005, ¶179.) In conducting that search, POSITAs would have become aware of the IDP-118 Study. The IDP-118 Study disclosed a phase two clinical trial for psoriasis involving four treatment arms: (1) a combination lotion containing 0.045% tazarotene and 0.01% halobetasol propionate (the active ingredient disclosed in the '824 publication); (2) a 0.045% tazarotene monotherapy lotion; (3) a 0.01% halobetasol propionate monotherapy lotion; and (4) a placebo lotion. (Ex. 1014, Arms and Interventions.) As explained above, POSITAs would have known that tazarotene was used and approved for treating both acne and psoriasis and would have therefore been interested in exploring the 0.045% tazarotene monotherapy lotion in the IDP-118 Study for acne. (Ex. 1003, ¶¶32, 43, 170; Ex. 1005, ¶¶30, 39, 43, 186.) POSITAs would have then looked for a vehicle for the 0.045% tazarotene monotherapy lotion

in the IDP-118 Study, and that investigation would have led the POSITA directly to the '824 publication.

The '824 publication is the only prior art reference other than WO '001 that discloses a vehicle for a 0.01% halobetasol lotion. Given that the IDP-118 study disclosed a 0.045% tazarotene lotion in the same vehicle as a 0.01% halobetasol lotion, POSITAs would have been motivated to investigate the 0.01% halobetasol formulations in the '824 publication as vehicles for a 0.045% tazarotene lotion. (Ex. 1003, ¶170; Ex. 1005, ¶180.) The '824 publication disclosed a lotion vehicle that is *identical* to the composition disclosed and claimed in the '482 patent, with the exception of the active ingredient – 0.045% tazarotene, and the Patent Office has already determined that it would have been obvious to replace the active ingredient in that vehicle with 0.045% tazarotene. (*Supra* §II.D.) That conclusion is reinforced by the IDP-118 Study, which was not before the Patent Office when it concluded that formulating 0.045% tazarotene in the '824 publication's lotion vehicle was obvious.

The only remaining question is whether POSITAs would have found it obvious to use the 0.045% tazarotene lotion to treat acne. That answer is unequivocally yes for the same reasons explained above. The prior art provided ample motivation for POSITAs to use a 0.045% tazarotene composition to treat acne with a reasonable expectation of success. Accordingly, claims 1-11 of the '482

patent would have been obvious over the '824 Publication and the IDP-118 Study in further combination with Anderson, Kircik, or Chim as further described below. (Ex. 1003, ¶¶170-171; Ex. 1005, ¶¶179-181.)

1. Claim 1

The '824 publication and the IDP-118 Study in view of Anderson, Kircik, or Chim renders claim 1 obvious. (Ex. 1003, ¶¶172-187; Ex. 1005, ¶¶182-194.)

a. Preamble

To the extent the preamble is limiting, Anderson, Kircik, and Chim disclose that limitation as explained in Grounds 1-3. (*Supra* §VII.A.1.a.)

b. Composition of tazarotene at 0.045% as sole active ingredient

The IDP-118 Study disclosed a phase two clinical trial for psoriasis involving four treatment arms: (1) a combination lotion containing 0.045% tazarotene and 0.01% halobetasol propionate; (2) a 0.045% tazarotene monotherapy lotion; (3) a 0.01% halobetasol propionate monotherapy lotion; and (4) a placebo lotion. (Ex. 1014, Arms and Interventions.)

POSITAs would have been motivated to use the 0.045% tazarotene lotion disclosed in the IDP-118 Study to treat acne through once daily topical application with the '824 publication in view of the teachings of Anderson, Kircik, or Chim. (Ex. 1003, ¶¶174-175; Ex. 1005, ¶¶185-190.)

i. Anderson

Anderson's teachings on the clinical use of 0.05% tazarotene compositions to treat acne would have motivated POSITAs to use the 0.045% tazarotene composition disclosed by WO '001 with a reasonable expectation of success for the same reasons explained in Grounds 1-3. (*Supra* §VII.A.1.b.i.)

ii. Kircik

Kircik's teachings of the efficacy of a 0.05% tazarotene composition in the topical treatment of acne would have motivated POSITAs to use the 0.045% tazarotene composition disclosed by the IDP-118 Study with a reasonable expectation of success for the same reasons explained in Grounds 1-3. (*Supra* §VII.A.1.b.ii.)

iii. Chim

Chim's teachings of the efficacy and irritation benefits of a 0.05% tazarotene composition in the topical treatment of acne would have motivated POSITAs to use the 0.045% tazarotene composition disclosed by the IDP-118 Study with a reasonable expectation of success for the same reasons explained in Grounds 1-3. (*Supra* §VII.A.1.b.iii.)

c. Remaining Limitations

The '824 publication discloses the remaining limitations of claim 1 as explained in Ground 5. (*Supra* §VII.C.1.) As the Patent Office concluded for Patent

Owner's related '576 application, POSITAs would have been motivated to use the vehicle disclosed in the '824 publication to formulate a topical composition of tazarotene at a concentration of about 0.045%. (*See* Ex. 1029, 1-20.) The IDP-118 Study would have provided additional motivation. (Ex. 1003, ¶¶176-187; Ex. 1005, ¶¶191-194.)

The IDP-118 Study disclosed a phase II clinical trial comparing treatment of psoriasis with a lotion comprising a combination of 0.01% halobetasol propionate and 0.045% tazarotene against treatment with two monotherapy lotions, one comprising 0.01% halobetasol propionate and the other comprising 0.045% tazarotene. (Ex. 1014, Arms and Interventions.) As explained previously, POSITAs would have known that tazarotene was the only topical retinoid approved to treat both acne and psoriasis, and therefore, POSITAs developing topical formulations of tazarotene for treatment of acne would have been motivated to turn to prior art relating to psoriasis. (*Supra* §VII.A.1.b.i.) Given that the IDP-118 study disclosed a 0.045% tazarotene lotion in the same vehicle as a 0.01% halobetasol lotion, POSITAs would have been motivated to investigate the 0.01% halobetasol formulations in the '824 publication as vehicles for a 0.045% tazarotene lotion. (Ex. 1003, ¶¶178-181; Ex. 1005, ¶¶186-190.) As noted above, the '824 publication and WO '001 are the only prior art references disclosing lotion formulations comprising

0.01% halobetasol propionate, one of the treatments disclosed in the IDP-118 Study. (*Supra* §II.C.)

The '824 publication disclosed two examples of formulations with 0.01% halobetasol propionate, Formulation C in Table 1 and Formulation 4A in Table 4, and POSITAs would have been motivated to investigate both formulations as vehicles for a composition of 0.045% tazarotene. (Ex. 1012, Tables 1 & 4; (Ex. 1003, ¶180; Ex. 1005, ¶188.) POSITAs would have been particularly motivated to investigate Formulation 4A as a vehicle for a composition of 0.045% tazarotene because Formulation 4A does not contain propylene glycol, an ingredient that was known to cause irritation and dryness. (Ex. 1012, Table 4; Ex. 1005, ¶188.) Additionally, POSITAs would have known that tazarotene is a lipophilic molecule, and it would have been a matter of routine experimentation and optimization to determine that tazarotene would be soluble in the oil-phase of the vehicles disclosed in the '824 publication. (Ex. 1005, ¶41.)

POSITAs would have also known that application of moisturizers was known to help alleviate the irritation caused by tazarotene therapy. (*See, e.g.*, Ex. 1010, 13; Ex. 1003, ¶39; Ex. 1005, ¶¶33, 144.) Formulation 4A in the '824 publication would have been particularly attractive to POSITAs developing a topical formulation of tazarotene because it includes several known moisturizing ingredients and does not include propylene glycol as explained in Ground 5 above. (*Supra* §VII.C.1.c.)

2. Claims 2-3, 7-11

The '824 publication discloses the limitations of claims 2-3 and 7-11 for the reasons explained in Ground 5. (*Supra* §VII.C.) POSITAs would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion lotion vehicles of the '824 publication, particularly Formulation 4A, with a reasonable expectation of success for the reasons described previously. (*Supra* §VII.C.1.c.) Therefore, the '824 publication and the IDP-118 Study in combination with Kircik, Chim, or Anderson renders claims 2-3 and 7-11 obvious. (Ex. 1003, ¶¶188-189, 191-201; Ex. 1005, ¶¶195-196, 198-207.)

3. Claims 4-6

The '824 publication and the IDP-118 study in combination with Anderson, Kircik, or Chim renders claims 4-6 obvious for the same reasons explained in Grounds 1-3. (*Supra* §VII.A.4.)

IX. SECONDARY CONSIDERATIONS

Patent Owner bears the burden of demonstrating any secondary considerations of nonobviousness. Patent Owner cannot meet its burden here.

The clinical data in the '482 patent does not demonstrate unexpected results at least because the results would not have been unexpected by POSITAs, particularly given that compositions comprising 0.05% tazarotene were frequently prescribed and used to treat acne prior to May 2017. (Ex. 1003, ¶34.) Additionally,

as explained above, the prior art disclosed that one could successfully reduce the concentration of an active ingredient using a vehicle formulation that is identical to the claimed formulations of the '482 patent. (*Supra* §VII.C.) Moreover, given the small sample sizes of patients included in the first clinical study in the '482 patent and the lack of any statistical analysis demonstrating that any of the reported results were not likely due to random chance, POSITAs would not be able to conclude the data disclosed in the patents demonstrates that the 0.045% tazarotene lotion provided greater and/or similar efficacy in treating acne as the 0.1% tazarotene cream, as Patent Owner incorrectly asserted during prosecution. (Ex. 1003, ¶203.) Finally, even if the results disclosed in the '482 patent would have been unexpected, they merely represent a difference in degree, not a difference in kind, and therefore are not probative of nonobviousness. *Galderma Labs., L.P.*, 737 F.3d at 739 (“[W]here an unexpected increase in efficacy is measured by a small percentage, as here, and the evidence indicates that skilled artisans were capable of adjusting the percentage, the result constitutes a difference in degree, not kind.”).

Patent Owner cannot demonstrate that the challenged claims solved a long-felt but unmet need for a lower-concentration tazarotene formulation at least because compositions comprising nearly the same concentration of tazarotene as that recited in the challenged claims were commonly used to treat acne prior to May 2017. (*Supra* §II.A.) Patent Owner also cannot demonstrate failure of others or skepticism

for similar reasons. Patent Owner has not presented any evidence regarding commercial success.

Petitioner reserves its right to respond to any evidence of secondary considerations asserted by Patent Owner.

X. THE BOARD SHOULD NOT DENY INSTITUTION

UNDER 35 U.S.C. §314(A)

The Board should not exercise its discretion to deny institution under 35 U.S.C. § 314(a) based on the pending district court litigation between Petitioners and Patent Owner for several reasons. First, the district court has not set a trial date in the district court litigation and based on the median time to trial in the District of New Jersey for 2022—52.9 months—a trial will not likely take place before the deadline for the Board’s Final Written Decision. (*See* Ex. 1036; *see also* June 21, 2022 Interim Procedure for Discretionary Denials, U.S.P.T.O. (“Interim Procedure”).) Second, the litigation is still in fact discovery, and unlike many Hatch-Waxman cases, there is no 30-month stay in effect for the litigation, making the likelihood of a stay of the litigation following institution much more likely. Third, the Petition presents compelling challenges that would plainly lead to a conclusion that one or more of the challenged claims is unpatentable by a preponderance of the evidence. (*See* Interim Procedure, 4.) Finally, if the Board believes it necessary, Petitioner is willing to file a *Sotera* Stipulation in the district court litigation

providing that Petitioner agrees it will not pursue the same grounds as in the Petition or any grounds that could have reasonably been raised in the Petition in the event that this IPR is instituted. (*See id.*, 7.)

XI. MANDATORY NOTICES UNDER 37 C.F.R. §42.8(A)(1)

The following mandatory notices are provided as part of this Petition.

A. Real Party-In-Interest (37 C.F.R. §42.8(b)(1))

Padagis Israel Pharmaceuticals Ltd.; Padagis US LLC; and Padagis, LLC are the real parties in interest.

B. Related Matters (37 C.F.R. §42.8(b)(2))

Patent Owner filed suit against Petitioner alleging infringement of the '482 patent in the United States District Court for the District of New Jersey on June 24, 2022. *See Bausch Health Ireland Ltd. v. Padagis Israel Pharms. Ltd.*, No. 22-4248 (MCA) (AME), Dkt. 1, Complaint (June 24, 2022). The district court litigation is still in fact discovery. The parties have agreed that claim construction proceedings are not necessary in the district court litigation. The district court has not set a trial date.

Petitioner is not aware of any other judicial or administrative matter that would affect, or be affected by, a decision in this proceeding.

C. Lead and Backup Counsel (37 C.F.R. §42.8(b)(3))

Petitioner provides the following designation of counsel, all of whom are included in Customer No. 20,995 identified in Petitioner's Power of Attorney.

Lead Counsel	Back-up Counsel
Carol Pitzel Cruz (Reg. No. 61,224) Carol.Pitzel.Cruz@knobbe.com <u>Postal and Hand-Delivery Address:</u> Knobbe, Martens, Olson & Bear, LLP 925 Fourth Ave., Ste. 2500 Seattle WA 98104 Telephone: (206) 405-2000 Facsimile: (206) 405-2001	Andrea Cheek (Reg. No. 65,642) Andrea.Cheek@knobbe.com <u>Postal and Hand-Delivery Address:</u> Knobbe, Martens, Olson & Bear, LLP 1717 Pennsylvania Ave. N.W. Ste. 900 Washington D.C. 20006 202-640-6441 - Direct Telephone: (202) 640-6400 Facsimile: (202) 640-6401
Brian Barnes (Reg. No. 75,805) Brian.Barnes@knobbe.com <u>Postal and Hand-Delivery Address:</u> Knobbe, Martens, Olson & Bear, LLP 2040 Main Street, 14th Floor Irvine, CA 92614 Telephone: (949) 760-0404 Facsimile: (949) 760-9502	

D. Service Information Under 37 C.F.R. §42.8(b)(4)

Please address all correspondence to lead counsel and back-up counsel at the addresses shown above. Petitioner also consents to electronic service by email to PadagisIPR482@knobbe.com.

XII. FEES

The fee for this petition has been paid. Additional fees may be charged to Deposit Account No. 11-1410.

XIII. GROUNDS FOR STANDING UNDER 37 C.F.R. §42.104

Petitioner certifies that the '482 patent is available for IPR and that Petitioner is not barred or estopped from requesting IPR challenging the claims on the identified grounds.

XIV. CONCLUSION

For the reasons above, Petitioner has established a reasonable likelihood of prevailing in showing that the challenged claims are unpatentable as anticipated or obvious and, therefore, requests that the Board institute an *inter partes* review and cancel the claims.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: June 21, 2023

By: /Carol Pitzel Cruz/
Carol Pitzel Cruz (Reg. No. 61,224)
Andrea Cheek (Reg. No. 65,642)
Brian Barnes (Reg. No. 75,805)

Attorneys for Petitioners
PADAGIS ISRAEL PHARMACEUTICALS LTD;
PADAGIS US LLC; AND PADAGIS, LLC

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that the foregoing **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,311,482**, exclusive of the parts exempted as provided in 37 C.F.R. §42.24(a), contains 13,879 words and therefore complies with the type-volume limitations of 37 C.F.R. §42.24(a).

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: June 21, 2023

By: /Carol Pitzel Cruz/
Carol Pitzel Cruz (Reg. No. 61,224)

Attorneys for Petitioners
PADAGIS ISRAEL PHARMACEUTICALS LTD;
PADAGIS US LLC; AND PADAGIS, LLC

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 11,311,482** and **EXHIBITS 1001-1048** are being served via Federal Express overnight mail on counsel of record for U.S. Patent 11,311,482 as addressed below:

112120 - Bausch Health / Kilpatrick Townsend & Stockton LLP
Mailstop: IP Docketing - 22
1100 Peachtree Street
Suite 2800
Atlanta, GA 30309

Dated: June 21, 2023

By: /Carol Pitzel Cruz/
Carol Pitzel Cruz (Reg. No. 61,224)

Attorneys for Petitioners
PADAGIS ISRAEL PHARMACEUTICALS LTD;
PADAGIS US LLC; AND PADAGIS, LLC