

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

**DECLARATION OF DR. NARASIMHA MURTHY
IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 11,311,482**

TABLE OF CONTENTS

Page No.

I. SUMMARY OF THE ARGUMENT	1
A. Engagement	1
B. Experience and Qualifications	2
C. Topics of Opinions	3
D. Materials Considered.....	4
II. APPLICABLE LEGAL STANDARDS	4
A. Claim Construction	4
B. Anticipation	4
C. Obviousness.....	5
D. Person of Ordinary Skill in the Art	8
III. BACKGROUND	10
A. Tazarotene was a Well-Known Drug for Treating Acne Prior to May 2017.....	10
B. Prior Art Lotion Vehicles For Formulating Tazarotene.....	14
IV. THE '482 PATENT	21
A. Summary of the '482 Patent.....	21
B. The Challenged Claims	~~3130~~
C. Prosecution History	~~3130~~
V. PROSECUTION OF THE RELATED '567 APPLICATION	~~3231~~
VI. SUMMARY OF IPR GROUNDS	~~3735~~

TABLE OF CONTENTS (*cont'd*)

	Page No.
VII. GROUNDS 1-3: CLAIMS 1-11 OBVIOUS OVER WO '001 AND KIRCIK, CHIM, OR ANDERSON.....	<u>3836</u>
A. Claim 1	<u>3937</u>
1. Preamble.....	<u>3937</u>
a. Anderson.....	<u>3937</u>
b. Kircik	<u>4139</u>
c. Chim	<u>4240</u>
2. Composition of Tazarotene at 0.045% as Sole Active Ingredient	<u>4442</u>
a. Anderson.....	<u>4543</u>
b. Kircik	<u>4745</u>
c. Chim	<u>4946</u>
3. Oil-in-water emulsion lotion.....	<u>5249</u>
4. Oil Phase	<u>5349</u>
5. Aqueous Phase	<u>5551</u>
6. Polymeric Emulsifier	<u>5753</u>
B. Claim 2	<u>5854</u>
C. Claim 3	<u>5955</u>
D. Claims 4-6	<u>5955</u>
1. Anderson	<u>6056</u>
2. Kircik.....	<u>6056</u>

TABLE OF CONTENTS

(cont'd)

	Page No.
3. Chim.....	<u>6157</u>
E. Claim 7	<u>6258</u>
F. Claim 8	<u>6359</u>
G. Claims 9-10	<u>6561</u>
H. Claim 11	<u>6763</u>
VIII. GROUND 4: CLAIMS 1-11 WOULD HAVE BEEN OBVIOUS OVER WO '001 AND ANDERSON IN COMBINATION WITH SHALITA	<u>6965</u>
A. Claims 4-6	<u>7167</u>
IX. GROUND 5: CLAIMS 1-11 WOULD HAVE BEEN OBVIOUS OVER THE '824 PUBLICATION AND THE TAZORAC® LABEL.....	<u>7268</u>
A. Claim 1	<u>7470</u>
1. Preamble.....	<u>7470</u>
2. Composition of Tazarotene at 0.045% as Sole Active Ingredient	<u>7571</u>
a. The Tazorac® Label	<u>7671</u>
b. The '824 Publication	<u>7772</u>
3. Oil-in-Water Emulsion Lotion.....	<u>7975</u>
4. Oil Phase	<u>8075</u>
5. Aqueous Phase	<u>8277</u>
6. Polymeric Emulsifier	<u>8378</u>

TABLE OF CONTENTS
(cont'd)

	Page No.
B. Claim 2	<u>8580</u>
C. Claim 3	<u>8580</u>
D. Claims 4-6	<u>8580</u>
E. Claim 7	<u>8681</u>
F. Claim 8	<u>8782</u>
G. Claims 9-10	<u>8984</u>
H. Claim 11	<u>9085</u>
 X. GROUND 6: CLAIMS 1-11 WOULD HAVE BEEN OBVIOUS OVER THE '824 PUBLICATION AND THE TAZORAC® LABEL IN VIEW OF ANDERSON.....	 <u>9388</u>
 XI. 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.....	 <u>9489</u>
A. Claim 1	<u>9691</u>
1. Preamble.....	<u>9792</u>
2. Composition of Tazarotene at 0.045% as Sole Active Ingredient	 <u>9792</u>
3. Oil-in-Water Emulsion Lotion.....	<u>10095</u>
4. Oil Phase	<u>10196</u>
5. Aqueous Phase	<u>10196</u>
6. Polymeric Emulsifier	<u>10196</u>
B. Claim 2	<u>10297</u>

TABLE OF CONTENTS
(cont'd)

	Page No.
C. Claim 3	<u>10297</u>
D. Claim 4-6.....	<u>10398</u>
E. Claim 7	<u>10398</u>
F. Claim 8	<u>10398</u>
G. Claims 9-10	<u>10499</u>
H. Claim 11	<u>105100</u>
XII. SECONDARY CONSIDERATIONS.....	<u>106101</u>
XIII. CONCLUSION	<u>108103</u>

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 ”)

Exhibit No.	Description
1015	IQVIA Sales Data For 0.05% Tazarotene For The Indication Of Acne Vulgaris, February 2017-January 2018 (“ IQVIA ”)
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)

Exhibit No.	Description
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
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 ”)

Exhibit No.	Description
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 ”)
1041	Draelos, Z., Therapeutic Moisturizers, Dermatologic Aspects of Cosmetics 2000;18(4): 597-607. (“ Draelos ”)
1042	Rawlings, A.V. & Lombard, K. J., A review on the extensive skin benefits of mineral oil, International Journal of Cosmetic Science, 2012;34: 511-518. (“ Rawlings ”)
1043	Lubrizol, Pharmaceutical Bulletin No. 8, Emulsification Properties, October 29, 2008. (“ Bulletin ”)
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

I, Dr. Narasimha Murthy, do hereby declare:

I. SUMMARY OF THE ARGUMENT

A. Engagement

1. I have been retained on behalf of Padagis Israel Pharmaceuticals Ltd., Padagis US LLC, and Padagis LLC (collectively, “Padagis” or “Petitioner”) to provide my opinions regarding the patentability of claims 1-11 of U.S. Patent No. 11,311,482 (“the ’482 patent”). For the reasons discussed herein, I have concluded that claims 1-11 of the ’482 patent are unpatentable because the prior art references would have rendered them obvious.

2. I understand that this Declaration supports Padagis’s Petition for the above-captioned *inter partes* review (“IPR”) of the ’482 patent. I have reviewed the Petition and agree with the unpatentability arguments contained therein.

3. I reserve the right to supplement, change, clarify, or modify my opinions should additional information and/or documentation become available to me. I also reserve the right to submit a rebuttal declaration in response to any expert declaration(s) submitted on behalf of the owner of the ’482 patent, Bausch Health US, LLC (“Bausch” or “Patent Owner”).

4. I am being compensated at my customary hourly rate for my work in this matter, and I am being reimbursed at cost for my expenses. My compensation

in no way depends upon the substance of my opinions or the outcome of this proceeding. I have no financial interest in any of the parties to this proceeding.

B. Experience and Qualifications

5. My experience and qualifications are summarized in my *curriculum vitae*, a copy of which is included as Exhibit 1006.

6. I am a pharmaceutical formulation specialist with extensive experience in topical products. I am the current Chief Scientific Officer at Topical Products Testing, LLC, in Oxford, Mississippi. Previously, I was a professor of Pharmaceutics and Drug Delivery at the University of Mississippi. I had been involved in pharmaceutics in academia for 27 years until I moved to my current role in the private sector.

7. I earned my Bachelor of Pharmacy degree from Bangalore University in India in 1992. I then went on to earn my Master of Pharmacy in Pharmaceutics from Bangalore University in 1994. In 2002, I graduated from Bangalore University with my PhD in Pharmaceutics. From 2002-2005, I was a Postdoctoral Research Associate for Molecular and Cellular Biophysics at Roswell Park Cancer Institute in Buffalo, New York.

8. I am currently the Associate Editor of *Clinical Pharmacology: Advances and Applications* and have published over 160 peer reviewed articles in the area of pharmaceutical formulation, many of which involve the analysis of

pharmaceutical topical treatments of skin diseases. I have been provided about \$10 million in research grants to conduct pharmaceutical formulations studies, many of which deal with the composition of topical products. I have authored multiple chapters in academic textbooks concerning drug delivery systems and have received many awards for my work as a pharmaceutical scientist in the field of drug formulation.

9. In addition to my written publications, I have given many speeches and seminars on the topic of topical formulations and how they can be optimized, dermal delivery systems, and bioequivalence with topical formulations, among other subjects.

C. Topics of Opinions

10. I offer opinions in this Declaration on the following general topics:

- The subject matter described and claimed in the '482 patent;
- The level of ordinary skill in the art pertaining to the '482 patent;
- The teachings of the prior art; and
- Whether claims 1-11 of the '482 patent would have been obvious to a person of ordinary skill in the art at the time of the alleged invention in view of the prior art.

11. I also provide background information on the formulation of topical pharmaceutical products, including oil-in-water emulsions.

D. Materials Considered

12. In preparing this Declaration, I have considered the materials referenced in this Declaration and those identified in the attached list of exhibits.

13. I also have relied on my education, training, and experience, and my knowledge of pertinent literature in the field of the '482 patent.

II. APPLICABLE LEGAL STANDARDS

A. Claim Construction

14. In determining whether a patent claim is unpatentable in view of the prior art, the Patent Office construes the claim by giving the claim its ordinary and customary (i.e., plain and ordinary) meaning ascribed to it by a person of ordinary skill in the art at the time of the invention, consistent with the specification and prosecution history. For the purposes of my analysis and opinions, and to the extent necessary, I have construed each claim term in accordance with its ordinary and customary meaning under the required standard.

B. Anticipation

15. I have been instructed that a claim is “anticipated” if a prior art reference describes, either expressly or inherently, each limitation of the claim. I understand that this description must be recognizable to a person of ordinary skill in the art at the time of the alleged invention.

16. I understand that an element is “inherent in,” and therefore taught by, the prior art, if it necessarily flows from the explicit disclosure of the prior art. The fact that a certain result or characteristic may be present in the prior art is not sufficient to establish inherency. However, if the result or characteristic is necessarily present based upon the explicit disclosure in the prior art, it is inherent in the prior art and is therefore disclosed.

C. Obviousness

17. I have been instructed that a claim is “obvious” if the claimed subject matter as a whole would have been obvious to a person of ordinary skill in the art at the time of the alleged invention. An obviousness analysis takes into account the scope and content of the prior art, the differences between the claimed subject matter and the prior art, and the level of ordinary skill in the art at the time of the invention.

18. In determining the scope and content of the prior art, I understand that a reference is considered analogous (i.e., appropriate) prior art if it falls within the field of the inventor’s endeavor. In addition, a reference is pertinent prior art if it is reasonably pertinent to the particular problem with which the inventor was involved. A reference is reasonably pertinent if it logically would have commended itself to an inventor’s attention in considering the problem. If a reference relates to the same problem as the claimed invention, that supports use of the reference as prior art in an obviousness analysis.

19. The prior art references applied in this Declaration are analogous art that is usable in an obviousness combination. The references are from the same field as the '482 patent, e.g., topical formulations containing lipophilic active ingredients (e.g. retinoids and corticosteroids) as the active ingredient. The references are also pertinent to the problem the inventor was focused on, e.g., treating skin diseases, such as acne vulgaris and psoriasis.

20. To assess the differences between the prior art and the claimed subject matter, I have been instructed that the law requires the claimed invention to be considered as a whole. This “as a whole” assessment requires showing that one of ordinary skill in the art at the time of invention, confronted by the same problems as the inventor and with no knowledge of the claimed invention, would have selected the elements from the prior art and combined them in the claimed manner.

21. I am also informed that the law recognizes several rationales for combining references or modifying a reference to show obviousness of claimed subject matter. Some of these rationales include:

- combining prior art elements according to known methods to yield predictable results;
- simple substitution of one known element for another to obtain predictable results;

- a predictable use of prior art elements according to their established functions;
- applying a known technique to a known device (method or product) ready for improvement to yield predictable results;
- choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; and
- some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

22. A prior art reference may also suggest a limitation of the claims. In that case, even if the prior art reference does not explicitly or inherently disclose the limitation, the motivation to modify the prior art reference to include the limitation may exist within the prior art reference. Thus, the limitation would have been obvious over that prior art reference alone. This is the case if a person of ordinary skill in the art would have had a simple design choice or a finite number of identified, predictable solutions, for example, and if the modification furthers the goals of the prior art reference.

23. I have also been informed that the obviousness analysis must be performed from the perspective of a person of ordinary skill in the art at the time of the alleged invention. This is to avoid using impermissible hindsight in the analysis.

The claims of the patent must not be used to provide a road map for obviousness; instead, the claims would have been obvious if a person of ordinary skill in the art would have been motivated to combine the teachings of the prior art to arrive at the claimed invention and had a reasonable expectation of success in doing so.

24. An obviousness analysis also must consider whether there are additional factors that would indicate that the invention would not have been obvious. These factors include whether there was: (i) a long-felt need in the industry; (ii) any unexpected results; (iii) skepticism of the invention; (iv) a teaching away from the invention; (v) commercial success; (vi) praise by others for the invention; and (vii) copying by others. I am not aware of any evidence that would suggest that claims 1-11 of the '482 patent would have been non-obvious, as further explained in §§ VII. – XI. below.

D. Person of Ordinary Skill in the Art

25. It is my understanding that when interpreting the claims of the '482 patent, I must do so based on the perspective of a person of ordinary skill in the art at the relevant priority date. I have been instructed to assume for the purposes of my opinions that the relevant priority date of the '482 patent is May 12, 2017. I have been informed that all of the references relied upon in this Declaration qualify as prior art under that priority date.

26. I am informed that the person of ordinary skill in the art is a hypothetical person who is presumed to have known the relevant art at the time of the invention. This is a person of ordinary creativity, not an automaton.

27. I am informed that in determining the level of ordinary skill in the art, several factors are considered. Those factors may include: (i) the type of problems encountered in the art; (ii) prior art solutions to those problems; (iii) the rapidity with which innovations are made; (iv) the sophistication of the technology; and (v) the educational level of active workers in the field. A person of ordinary skill in the art must have the capability of understanding the scientific principles applicable to the pertinent art.

28. Based on my review of the specification and claims of the '482 patent, it is my opinion that a person of ordinary skill in the art 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.

29. I would have met this definition of a person of ordinary skill in the art in May 2017. At that time, I held a PhD in Pharmaceutics and had more than fourteen years of post-doctoral experience in the field of topical drug formulation, including development of topical formulations for treatment of skin disorders.

III. BACKGROUND

A. Tazarotene was a Well-Known Drug for Treating Acne Prior to May 2017

30. Although I am not a dermatologist or a clinician, the prior art disclosed that topical retinoids, including the drug tazarotene, were well known for treating acne vulgaris prior to May 2017. *See* Ex. 1010 (Chim) at 13; Ex. 1018 (Eichenfield) at 168; Ex. 1032 (Donello) at claims 11-12. The prior art also disclosed that tazarotene was approved for the treatment of psoriasis in addition to acne. *See* Ex. 1013 (Tazorac® Label) at Indications and Usage. Tazarotene was commercially available in multiple topical dosage forms (also referred to as vehicles) and at two different concentrations – 0.05% and 0.1% – prior to May 2017. *See id.*; Ex. 1017 (Fabior® Label); Ex. 1010 (Chim) at 13, Table 1-3. As I discuss below, several additional prior art references disclose treating acne with 0.05% tazarotene compositions, in both cream and gel vehicles. *See* Ex. 1008 (Anderson); Ex. 1009 (Kircik); Ex. 1010 (Chim); Ex. 1011 (Shalita). These teachings are not surprising. It is common for topical pharmaceutical compositions to be developed and

commercialized in multiple vehicles and multiple dosage strengths (i.e., concentrations). Indeed, the prior art teaches that two other topical retinoids, tretinoin and adapalene, which were also used for treating acne were similarly available in multiple vehicles and concentrations prior to May 2017. *See* Ex. 1010 (Chim) at Table 1-3.

31. The prior art also teaches that tazarotene was known to cause local skin irritation when used in topical compositions prior to May 2017. Ex. 1010 (Chim) at 13; *see also* Ex. 1018 (Eichenfield) at 169; Ex. 1013 (Tazorac® Label) at Sections 5.2, 14, 16.1. The prior art taught that this irritation was dose (i.e., concentration) dependent. Ex. 1013 (Tazorac® Label) at Sections 5.2, 14, 16.1; Ex. 1018 (Eichenfield) at 169. Because the commercial formulations of tazarotene available in May 2017, including Tazorac® Cream, were known to cause patients irritation, persons of ordinary skill in the art would have been motivated to develop new tazarotene formulations to reduce the irritation. *See* Ex. 1013 (Tazorac® Label) at Sections 5.2, 14, 16.1. A person of ordinary skill in the art in May 2017 would have known of several means for addressing this type of dose-dependent local side effect.

32. First, an ordinarily skilled formulator would have known that irritation can be addressed by reducing the dose (i.e., concentration) of the tazarotene applied to the skin. *See, e.g.*, Ex. 1022 (Dosik) at 290-293; Ex. 1013 (Tazorac® Label) at Sections 5.2, 14, 16.1; Ex. 1018 (Eichenfield) at 169; Ex. 1011 (Shalita) at 354; Ex.

1010 (Chim) at 13. For example, Dosik, a 2005 article, published the results of a clinical study comparing the irritation potential of tazarotene 0.05% cream versus 0.1% tazarotene cream. Ex. 1022 (Dosik) at 289. Dosik reported that the 0.1% tazarotene cream was significantly more irritating than the 0.05% cream. *Id.* at 293. The FDA labeling for Tazorac® Cream, the commercial tazarotene product, similarly instructed that patients who cannot tolerate treatment with 0.1% tazarotene cream be switched to 0.05% tazarotene cream because it produced less irritation in clinical studies. Ex. 1013 (Tazorac® Label) at Sections 5.2, 14, 16.1. Additional prior art medical journals also reflected this approach, suggesting that treatment for acne with topical retinoids be initiated with the “lowest strength” available to minimize irritation. Ex. 1018 (Eichenfield) at 169; *see also* Ex. 1011 (Shalita) at 354. Formulators would have also been aware of means for reducing the concentration of a topically applied drug while preserving its efficacy, as I explain further below. *Infra* § VII. – XI.

33. Second, an ordinarily skilled formulator would have known that the irritation caused by tazarotene could be reduced through the concurrent application of moisturizers to the patient’s skin. *See* Ex. 1010 (Chim) at 13; Ex. 1018 (Eichenfield) at 169; Ex. 1017 (Fabior® Label) at Dosage and Administration; Ex. 1013 (Tazorac® Label) at Patient Counseling Information. Given this knowledge, formulators would have been motivated to re-formulate tazarotene in vehicle

formulations that included moisturizing ingredients within the vehicle itself, which could reduce or eliminate the need for application of a separate moisturizing agent, making the treatment more convenient and effective. *See, e.g.*, Ex. 1025 (Kircik 2011) at 18 (disclosing that for topical retinoids, the “aim of formulators has been reducing irritation, enhancing therapeutic outcomes and promoting patient adherence to therapy” and teaching that formulators achieved those objectives by “incorporating ingredients into the formulation vehicle that repair the impaired epidermal barrier and offset the irritating effects of drugs.”). Formulators would have also been motivated to explore different types of vehicles for tazarotene than the commercial gel and cream formulations, which were known to cause irritation. *See* Ex. 1013 (Tazorac® Label) at Sections 5.2, 14, 16.1. One such type of vehicle that would have been attractive to a formulator in May 2017 was a lotion. The prior art taught several advantages to lotion formulations, including that lotions were generally considered to be moisturizing vehicles that are preferred by patients. Ex. 1039 (Eastman) at 47, 49. This would be particularly true for lotions that did not include propylene glycol, an ingredient known to cause dryness and irritation. *See, e.g.*, Ex. 1040 (Russell) at 3 (“lotions contain propylene glycol and thus may have burning or drying effects”).

34. Third, formulators would have been aware of methods for formulating tazarotene in new vehicle formulations that could increase the penetration of

tazarotene into the skin, allowing for greater efficacy with a lower concentration of tazarotene. *See* Ex. 1010 (Chim) at 13; Ex. 1025 (Kircik 2011) at 20. Indeed, the prior art disclosed two such formulations, the formulations in WO '001 and the '824 publication discussed below, that would have been particularly attractive to an ordinarily skilled formulator.

B. Prior Art Lotion Vehicles For Formulating Tazarotene

35. The prior art provided lotion vehicles that would have enabled an ordinarily skilled formulator to formulate effective, lower-concentration tazarotene compositions. Both the WO '001 and the '824 publication disclosed vehicles that formulators would have recognized as enabling reduced concentrations of active ingredients to be applied topically for treatment of skin disorders, while still maintaining the efficacy of higher concentrations of those active ingredients.

36. WO '001 disclosed topical compositions and methods for treating psoriasis with tazarotene and halobetasol propionate. *See* Ex. 1007 (WO '001) at [002]. One of the compositions disclosed in WO '001 is a lotion containing 0.045% tazarotene as the sole active ingredient. *Id.* at Table 4. Notably, that lotion formulation is identical to the tazarotene composition described and claimed in the '482 patent:

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

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

Table 4					
Compositions for Clinical Studies					
Ingredient	Function	Concentration (wt%)			
		IDP-118 (Present Invention)	Placebo (Vehicle)	Halobetasol propionate only	Tazarotene 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

Compare Ex. 1001 ('482 patent) at Table 2 with Ex. 1007 (WO '001) at Table 4. Given that WO '001 teaches that 0.045% tazarotene was successfully formulated in the vehicle disclosed in Table 4, an ordinarily skilled formulator would have been highly motivated to use that vehicle to formulate a tazarotene composition with a lower concentration (about 0.05%) tazarotene.

37. Additionally, formulators would have recognized that several of the ingredients in the vehicle disclosed in Table 4 of WO '001 were known to have moisturizing properties, including diethyl sebacate, light mineral oil, and sorbitol. Ex. 1041 (Draelos) at 598-599, Tables 1 & 2; *see also* Ex. 1042 (Rawlings) at 512-515. Formulators would have also been aware that lotions, such as the WO '001's lotion vehicle, are generally considered to be moisturizing vehicles that are preferred by patients. Ex. 1039 (Eastman) at 47, 49. This knowledge would have provided

formulators with further motivation to use the vehicle described in WO '001 to formulate a lower-concentration (about 0.05%) tazarotene composition. *See, e.g.,* Ex. 1025 (Kircik 2011) at s18 (disclosing that the “aim of formulators [for topical retinoids] has been reducing irritation, enhancing therapeutic outcomes and promoting patient adherence” and teaching that formulators achieved those objectives by “incorporating ingredients into the formulation vehicle that repair the impaired epidermal barrier and offset the irritating effects of drugs.”).

38. The 0.045% tazarotene formulation in WO '001 also uses a Pemulen emulsifier to formulate tazarotene. *See* Ex. 1007 (WO '001) at Table 4. The prior art taught numerous advantages of using Pemulen emulsifiers, including the Pemulen TR-1 used in WO '001, for topical pharmaceutical formulations. For example, the prior art taught that Pemulen emulsifiers provide efficient suspension and stabilization of insoluble materials; they can be used “with almost any oil phase”; they have high stability; they require low concentrations, typically only 0.1-0.3%; they do not cause irritation; they provide rapid release of the oil phase onto the patient’s skin, helping to provide rapid delivery of the active into the patient’s skin; and they can enable new dosage forms for insoluble materials. *See* Ex. 1035 (Tegeli) at 56-57; Ex. 1043 (Bulletin) at 2-3. Formulators would have been aware of these teachings, and they would have provided further motivation to use the vehicle disclosed in WO '001 to formulate a 0.045% tazarotene composition.

39. Additionally, as I noted above, formulators in May 2017 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* ¶¶ 30-33. Thus, formulators 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.

40. Another exemplary lotion vehicle that enables formulation of effective topical compositions with reduced concentrations of the active ingredient is provided by U.S. Patent Pub. No. US 2012/0129824 (the "'824 publication"). The '824 publication disclosed topical vehicle formulations for corticosteroids that preferentially enhance the penetration of the active agent into the skin, rather than through the skin into systemic circulation. Ex. 1012 ('824 publication) at [0016]. The formulations of the '824 publication accomplish this via a "liquid oil component" comprising a dicarboxylic acid ester, which dissolves the corticosteroid and enhances its delivery. *Id.* The '824 publication's 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.* at [0035], [0037]-[0040], Tables 1 & 3. The '824 publication's formulations also used Pemulen emulsifiers as part of the lotion vehicles, which were known to provide several advantages as I discussed previously. *Supra* ¶ 38.

41. Importantly, like halobetasol propionate, the active ingredient in the '824 publication's formulations, tazarotene is also a lipophilic molecule and formulators would have expected tazarotene to be soluble in the same liquid oil component ingredients disclosed in the '824 publication. *See, e.g.*, Ex. 1044 (Ismail) at 573; Ex. 1045 (Remington's) at 271. Given this knowledge and the '824 publication's teachings of the benefits of its formulations in enabling lower concentrations of the active ingredient to be used while maintaining efficacy, ordinarily skilled formulators would have been highly motivated to use the '824 publication's formulations to develop lower-concentration tazarotene formulations. As I explained above, using a lower concentration of tazarotene was a known means for reducing irritation, and formulators seeking to formulate an effective lower-concentration tazarotene composition would have looked to vehicles used to formulate lower-concentration compositions for other drugs with similar hydrophobicity, such as the '824 publication.

42. The '824 publication provides several examples of lotion formulations that enable lower concentrations of the active ingredient to be used. Formulators would have been motivated to investigate all of those exemplary formulations for formulating a lower-concentration tazarotene product and would have been particularly drawn to Formula 4A in Table 4. Unlike many of the other examples in the '824 publication, Formula 4A does not include propylene glycol as an ingredient.

See Ex. 1012 ('824 publication) at Table 4. As I explained above, propylene glycol was known to cause irritation, so formulators would have been motivated to avoid using that ingredient when formulating a tazarotene composition with reduced irritation. See, e.g., Ex. 1040 (Russell) at 3. Formula 4A also contains a relatively high concentration of moisturizing ingredients, such as diethyl sebacate, light mineral oil, and sorbitol, providing further motivation to use it as a vehicle for formulating tazarotene. See *supra* ¶ 37. As I've illustrated in the comparison below, Formula 4A in the '824 publication is identical to the tazarotene composition described and claimed in the '482 patent, except for the tazarotene active ingredient:

'482 patent						'824 publication		
TABLE 2						TABLE 4		
Some Emulsion Compositions of the Present Invention for Treating Acne						% w/w		
Ingredient	Function	Concentration (wt %)				Ingredients	Formula 4A	Formula 4B
		Range 1	Range 2	Range 3	Composition A			
Tazarotene	Retinoid	0.02-0.049	0.03-0.049	0.04-0.049	0.045	Halobetasol Propionate	0.01	0.025
Diethyl sebacate	Liquid Oil & Solvent	1-5	2-4	2.5-3.5	2.97	Diethyl Sebacate	2.97	2.90
Light mineral oil	Liquid Oil & Co-Solvent	5-15	5-10	7.5-8.5	8.03	Light Mineral Oil	8.03	2.90
Sorbitan monooleate	Surfactant/Emulsifying Agent	0.01-1	0.02-0.5	0.05-0.2	0.1	Sorbitan Monooleate	0.10	0.10
Sorbitol solution, 70%	Humectant	5-15	7-12	10-11	10.7	Sorbitol Solution, 70%	10.7	10.7
Methyl paraben	Antimicrobial Preservative ⁽¹⁾	0.05-0.3	0.1-0.3	0.1-0.2	0.17	Disodium Edetate, Dihydrate	0.05	0.05
Propyl paraben	Antimicrobial Preservative ⁽¹⁾	0.01-0.1	0.01-0.05	0.02-0.04	0.03	Pemulen TR-1	0.40	0.40
Edetate disodium dihydrate	Chelating Agent ⁽¹⁾	0.02-0.1	0.02-0.7	0.03-0.06	0.05	Carbopol 981	0.60	0.60
Carbomer copolymer type B (e.g., Pemulen™ TR-1)	Emulsifying Agent	0.1-1	0.2-0.7	0.3-0.5	0.4	Methylparaben	0.17	0.17
Carbomer homopolymer type A (e.g., Carbomer 981)	Thickener	0.2-1.5	0.3-1	0.5-0.7	0.6	Propylparaben	0.03	0.03
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	Sodium Hydroxide, q. s.	pH 4.0-6.0	pH 4.0-6.0
Purified water	Carrier	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	Purified Water, q.s. ad	100	100

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

Compare Ex. 1001 ('482 patent) at Table 2 with Ex. 1012 ('824 publication) at Table 4.

43. The prior art IDP-118 Study would have provided even further motivation for an ordinarily skilled formulator to look to the vehicles in WO '001 and the '824 publication when developing a lower-concentration tazarotene

composition. 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 (IDP-118 Study) at Arms and Interventions. As I explained above, formulators would have looked to prior art relating to tazarotene compositions used to treat psoriasis when developing formulations of tazarotene for treating acne since tazarotene was approved for treating both indications and skin irritation was seen in patients with both indications. *Supra* ¶ 39. Formulators would have been aware of the 0.045% tazarotene lotion disclosed in the IDP-118 Study and would have sought an appropriate vehicle for such a lotion. That investigation would have driven an ordinarily skilled formulator in May 2017 directly to WO '001 and the '824 publication.

44. Formulators would have been driven to WO '001 because it not only disclosed a vehicle for a 0.045% tazarotene lotion, but it also disclosed vehicles for the other two treatments disclosed in the IDP-118 Study, the 0.01% halobetasol/0.045% tazarotene combination and the 0.01% halobetasol monotherapy. *See* Ex. 1007 (WO '001) at Table 4. Formulators would have understood that in a clinical trial such as the IDP-118 Study, all four treatment arms would have been formulated in the same vehicle to ensure that comparisons among

the arms could be attributed to differences in the active ingredients and not the vehicle. Given this knowledge, formulators would have been motivated to investigate references that disclose vehicles for both 0.01% halobetasol compositions as well as 0.045% tazarotene compositions, and they would have found that the '824 publication discloses a vehicle for a 0.01% halobetasol lotion. The IDP-118 Study's disclosure of a 0.01% halobetasol lotion formulated in the same vehicle as a 0.045% tazarotene lotion would have given formulators a strong motivation to use the '824 publication's formulations as a vehicle for a 0.045% tazarotene composition.

IV. THE '482 PATENT

A. Summary of the '482 Patent

45. The '482 patent describes topical compositions of the retinoid tazarotene in an oil-in-water emulsion vehicle that forms a lotion for treating skin diseases, such as acne and psoriasis. Ex. 1001 ('482 patent) at Abstract, 2:42-44. The tazarotene is included at a concentration less than 0.05 wt %. *Id.* at 2:48-53. The oil-in-water emulsion vehicle includes an oil phase and an aqueous phase. *Id.* at 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.* at 4:38-40. The liquid oil component may comprise a dicarboxylic acid ester, such as diethyl sebacate, and light mineral oil. *Id.* at 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.* at 3:5-12. Additionally, “polymeric emulsifiers such as those known under the trade name Pemulen™ . . . may be used.” *Id.* at 4:10-12. The ’482 patent provides example formulations encompassed by the alleged inventions 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. at Tables 1-2.

46. The '482 patent also discloses three clinical studies in acne patients conducted with Composition A (Table 2). 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.* at 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.* at 7:60-8:5. The 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 -	12.3%	20.4%	16.1%
Clear or Almost Clear			
Inflammatory Lesions	-14.2	-18.3	-18.2
Non-inflammatory Lesions	-11.8	-20.8	-21.9

Id. at Tables 3-7. Tolerability was also assessed based on burning, stinging, or itching reported by the subjects, and cutaneous safety was assessed by scaling, erythema, hypo-pigmentation and hyper-pigmentations as evaluated by the investigator. *Id.* at 9:34-36. The tolerability results are disclosed in Figures 4A-C:

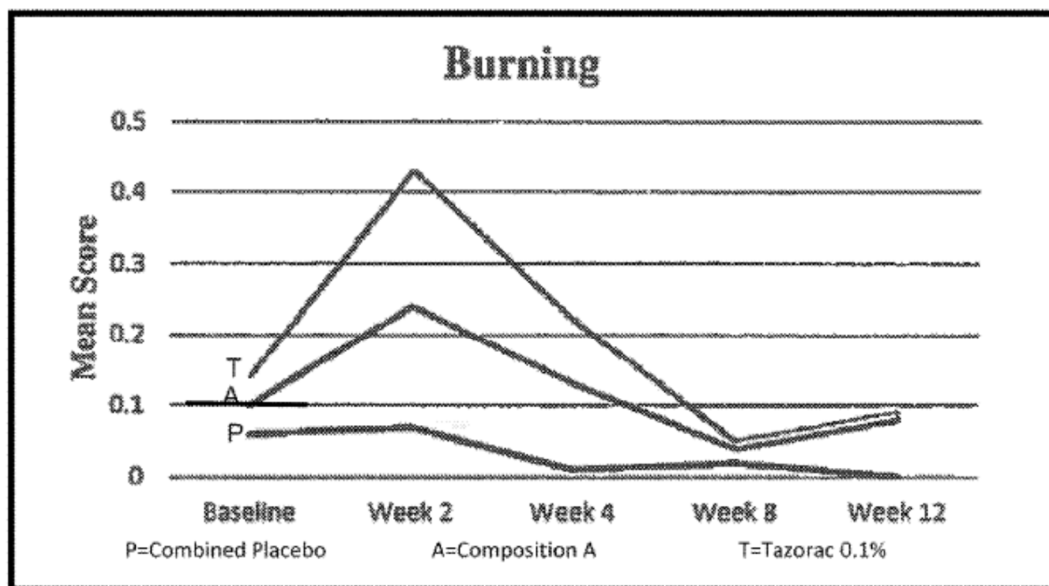


FIG. 4A

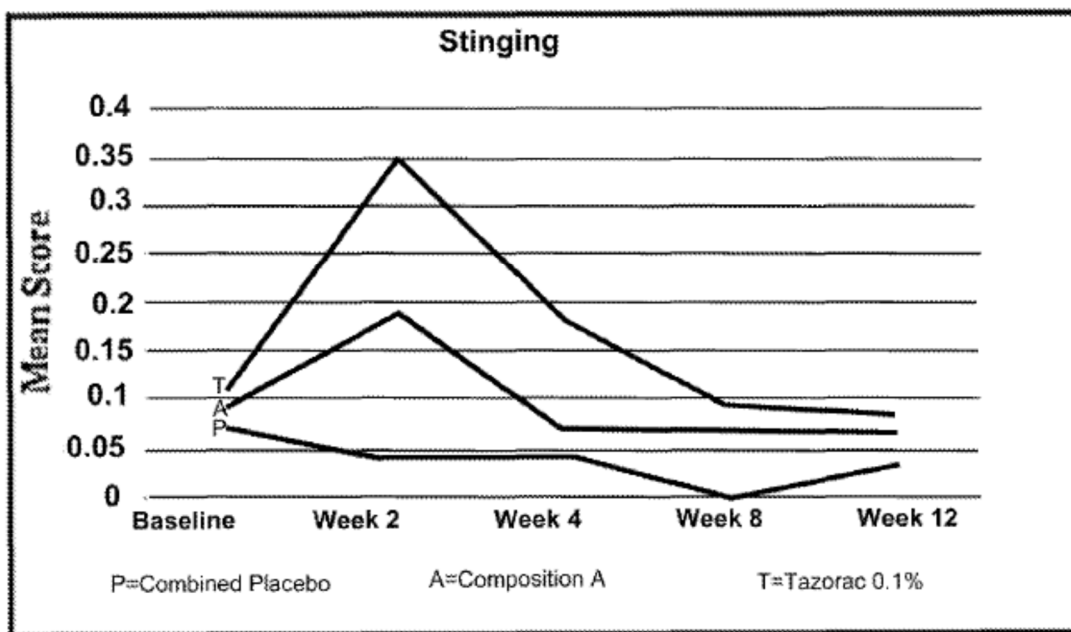


FIG. 4B

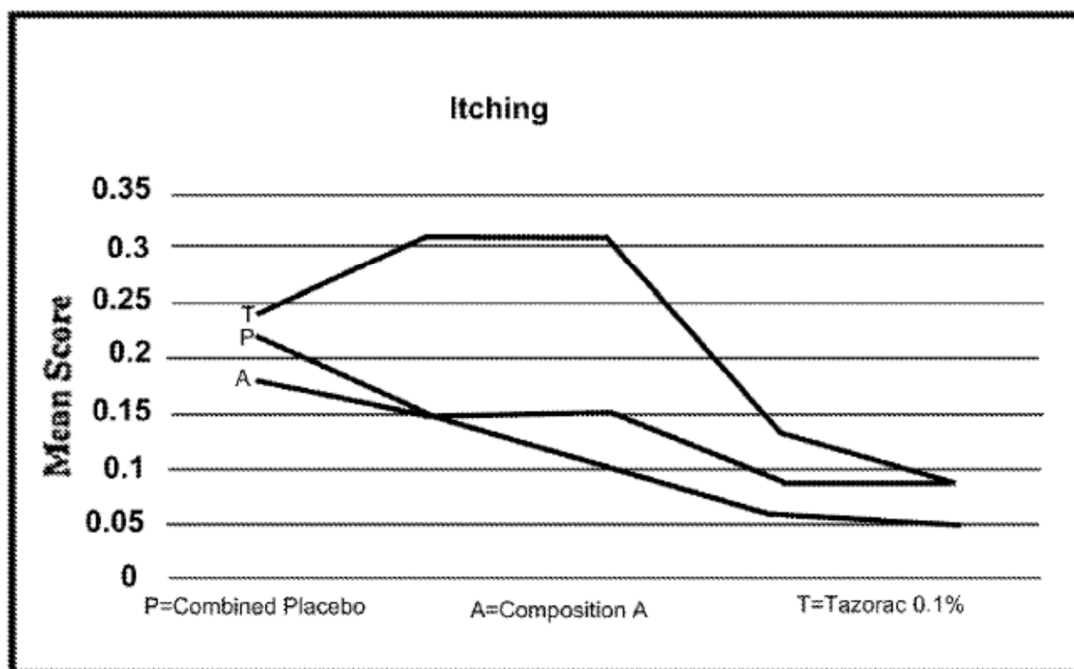


FIG. 4C

Id. at Figs. 4A-C.

47. 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.* at 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	Placebo	Composition	Placebo
	A Lotion	Lotion	A Lotion	Lotion
	N = 402	N = 411	N = 397	N = 404
EGSS -	26.8%	14.4%	30.6%	18.3%
Clear or Almost Clear				
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	Placebo	Composition	Placebo
	A Lotion	Lotion	A Lotion	Lotion
	N = 387	N = 392	N = 392	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. at 10:64-12:32, Tables 10-13.

B. The Challenged Claims

48. The challenged claims include claims 1-11 of the '482 patent. Claims 1 and 11 are independent claims.

49. Claim 1 is illustrative (but not representative) of some of the limitations in the challenged claims. Claim 1 states:

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.

C. Prosecution History

50. I have reviewed the '482 patent's prosecution history. During prosecution, the Patent Examiner issued two non-final office actions and two final office actions.

51. In the first non-final office action, the Examiner rejected the pending claims over the FDA labeling for Fabior® lotion both alone and in combination with two additional prior art references, Singh (Ex. 1031) and Fiume (Ex. 1046). *See* Ex.

1002 ('482 patent prosecution history excerpt) at 296-306.

52. In the first final office action, the Examiner rejected the pending claims over WO '001 (Ex. 1007) and Donello (Ex. 1032). *See* Ex. 1002 ('482 patent prosecution history excerpt) at 210-221.

53. In the second non-final office action, the Examiner again rejected the pending claims over WO '001 and Donello. *Id.* at 179-191.

54. In the second final office action, the Examiner maintained the rejection of the pending claims over WO '001 and Donello. *Id.* at 134-152.

55. The Patent Office issued a Certificate of Correction for the '482 patent on March 14, 2023 that replaced the term “carbomer polymer type B” in claims 9-11 with the term “carbomer copolymer type B.” My opinions herein are provided for the claims of the '482 patent as-corrected in the March 14, 2023 Certificate of Correction.

V. PROSECUTION OF PATENT OWNER'S RELATED APPLICATIONS

A. The '576 Application

56. I have also reviewed the prosecution history of U.S. Pat. App. No. 16/179,576 (“'576 application”), which I understand from counsel claims priority to the same patent application as the '482 patent. The specification of the '576 application and the '482 patent are substantively identical, and the claims are also

very similar, as illustrated in the chart comparing pending independent claim 1 of the '576 application with claim 1 of the '482 patent below:

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. 1001 ('482 patent) at claim 1; Ex. 1029, ('576 application prosecution history) at 25-36.

57. I understand that the Patent 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 ('576 application prosecution history) at 1-20. In that rejection, 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.* at 4. It is also my opinion that persons of ordinary skill in the art would have found it obvious to replace the halobetasol propionate in the compositions of the '824 publication with tazarotene, as I explain in further detail below. *Infra* §§ IX. – XI.

58. Regarding the claimed concentration of tazarotene in the '576 application – 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.* at 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 Tazorac, to provide a composition having the desired properties such as the desired (ratios, concentrations, percentages, etc.).” *Id.* at 12. It is also my opinion that optimizing the amounts of the active ingredient in a topical pharmaceutical composition, including tazarotene, was within the knowledge of an ordinarily skilled pharmacologist in May 2017. As I explain below, it is also my opinion that the compositions claimed in the ’482 patent represent conventional formulations and modes of administration that would have been well known to an ordinarily skilled formulator in May 2017.

59. I understand that the Examiner also rejected the Applicants’ arguments regarding unexpected results because the Applicants failed to compare the claimed 0.045% tazarotene composition to the 0.05% tazarotene composition disclosed in the Tazorac® Label. *Id.* at 5-6.

B. The ’871 Application

60. I have also reviewed the prosecution history of U.S. Application No. 17/366,871 (the “’871 application”), which shares a substantively identical specification as the prior art WO ’001 reference. *Compare* Ex. 1047 (’871 application prosecution history) at 367-412 *with* Ex. 1007 (WO ’001). Like, WO ’001, the ’871 application discloses halobetasol propionate and tazarotene

compositions for treating psoriasis. *See* Ex. 1047 ('871 application prosecution history) at 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. *Compare id.* at 61 with Ex. 1029 ('576 application prosecution history) at 35-36.

61. I understand that like the '576 application, the Patent Examiner had rejected the pending claims of the '871 application as obvious over the combination of the '824 publication¹ and the Tazorac® Label. Ex. 1047 ('871 application prosecution history) at 155-163. Also like the '576 application, I understand that in response, the Applicants argued that the claims would not have been obvious due to unexpected results based on the clinical trial data relating to the treatment of acne that is disclosed in the '576 application. *Id.* at 60-75. Unlike the Patent 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.* at 8-15.

62. Thus, it appears that different Patent Examiners have reached different, inconsistent conclusions on the same evidence and arguments for the '576 and '871 applications.

¹ The Examiner asserted Dow (WO 2012/087443) during prosecution of the '871 application, which I understand from counsel to be the PCT publication of the '824 publication. *See* Ex. 1048 (WO 2021/087443).

VI. SUMMARY OF IPR GROUNDS

63. I have identified the following grounds of unpatentability in this Declaration:

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

64. I have been asked to review the prior art from the view of a formulator and opine on the validity of the challenged claims of the '482 patent. I have reviewed the expert declaration of Dr. Robert Schwartz and I understand that Dr. Schwartz has opined on the prior art from the view of a Physician. I understand that Dr.

Schwartz has concluded that the clinical treatment of acne with tazarotene would have been obvious to a person of ordinary skill in the art in view of the prior art combinations described in Grounds 1-9. *See* Ex. 1003 (Schwartz Decl.). As explained herein, Dr. Schwartz's opinions that the claims of the '482 patent would have been obvious over the prior art are consistent with my own opinions.

**VII. GROUNDS 1-3: CLAIMS 1-11 OBVIOUS OVER WO '001 AND
KIRCIK, CHIM, OR ANDERSON**

65. As I discussed previously, persons of ordinary skill in the art in May 2017 would have been motivated to develop new topical tazarotene formulations with less irritating side effects. *Supra* § III. Persons of ordinary skill in the art would have looked to WO '001 as providing one such formulation. WO '001 disclosed topical pharmaceutical compositions for treating psoriasis. *See* Ex. 1007 (WO '001) at [0002]. WO '001 discloses a lotion formulation that includes 0.045% tazarotene at the sole active ingredient, which is a slightly lower concentration than the commercial 0.05% Tazorac® compositions. *Id.* at Table 4. That lotion is ***identical*** to the composition disclosed and claimed in the '482 patent and therefore discloses or renders obvious every formulation limitation of claims 1-11 of the '482 patent, as I explain further below. *See id.* As I discuss below, the Anderson, Kircik, and Chim articles further disclosed treating acne using tazarotene formulations with nearly the same concentration of tazarotene, 0.05%, as the concentration disclosed by WO

'001, 0.045%. Thus, it is my opinion that claims 1-11 would have been obvious in view of WO '001 in combination with Anderson, Kircik, or Chim. My opinions are further confirmed by the expert declaration of Dr. Schwartz, a dermatologist who is an expert in the field of treating acne, as I explain below.

A. Claim 1

66. In my opinion, claim 1 of the '482 patent would have been obvious over WO '001 in combination with Anderson, Kircik, or Chim.

1. Preamble

67. The preamble of Claim 1 recites “[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.”

68. The preamble relates to the treatment of acne vulgaris with a topical composition. I understand that Dr. Schwartz has provided an expert declaration and opines that Anderson, Kircik, and Chim each disclose this limitation. *See* Ex. 1003 (Schwartz Decl.) at ¶ 69. This aligns with my understanding of those references, which I provide from the perspective of a formulator.

a. Anderson

69. Anderson is a review article in a medical journal on the treatment of acne with topical tazarotene. *See* Ex. 1008 (Anderson). In my opinion, an ordinarily skilled formulator would commonly look to articles in medical journals, such as

Anderson, discussing the clinical use of the active ingredient(s) that the formulator was developing. Anderson disclosed that “topical tazarotene is efficacious and well tolerated in a variety of patients with acne.” *Id.* at 16. In the article, the authors described their clinical use of topical tazarotene as an acne treatment for a broad-spectrum of patients. *See id.* at 16-21. One of the physicians consulted for Anderson, Dr. Valerie Callender, stated that she “initiates treatment with tazarotene 0.05% cream applied every night” and then “after 2 or 3 weeks, she switches patients to a stronger concentration.” *Id.* at 17. Another physician, 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. A third physician, Dr. Emil Tanghetti, indicated that he “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.* Thus, as reflected by Anderson, treating acne by topically applying a tazarotene composition once per day to an affected area of a body was known in the prior art.

70. My opinions regarding Anderson are further confirmed by the expert declaration submitted by Dr. Schwartz, an expert in the field of treating acne. I have

read Dr. Schwartz's declaration, and I understand that Dr. Schwartz opines that Anderson disclosed treating acne by topically applying tazarotene once per day to the affected areas of the body. Ex. 1003 (Schwartz Decl.) at ¶ 70. I agree with Dr. Schwartz's analysis of Anderson.

b. Kircik

71. Kircik is an article from a medical journal published in 2009 that disclosed the results of a clinical study comparing tretinoin microsphere gel 0.04% deliver by pump ("TMP PUMP") to tazarotene cream 0.05% in the treatment of mild-to-moderate facial acne. Ex. 1009 (Kircik) at 650-651. As I explained in the preceding section, ordinarily skilled formulators would have looked to medical journal articles like Kircik when developing formulations for a particular active ingredient. Kircik disclosed that subjects in the study applied either TMP PUMP or tazarotene cream 0.05% once daily for 12 weeks. *Id.* at 651. Kircik reported 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.* at 651-52, Figs. 1-2. Thus, Kircik teaches topically treating acne by applying a tazarotene composition once per day to an affected area of a body.

72. My opinions regarding Kircik are further confirmed by the expert declaration submitted by Dr. Schwartz, an expert in the field of treating acne. I have read Dr. Schwartz's declaration, and I understand that Dr. Schwartz opines that Kircik disclosed treating acne by topically applying tazarotene once per day to the affected areas of the body. Ex. 1003 (Schwartz Decl.) at ¶ 71. I agree with Dr. Schwartz's analysis of Kircik.

c. Chim

73. Chim is a medical journal article authored by Dr. Christine Chim, who holds a doctorate in pharmacy, providing a review of acne vulgaris and various known treatments for that disease. Ex. 1010 (Chim) at 7. In my opinion, an ordinarily skilled formulator developing formulations for treating a certain disease, such as acne, would commonly look to articles in medical journals, such as Chim, discussing known treatment options for that disease. Chim disclosed that the three available topical retinoids for treating acne, tazarotene, tretinoin, and adapalene are available in various formulations, which Chim lists in Table 1-3. *Id.* at 13 Table 1-3. Table 1-3 is entitled "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.

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. at Table 1-3. Chim also 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.* at 13. Thus, like Anderson and Kircik, Chim teaches treating acne by topically applying a tazarotene composition once per day to an affected area of a body.

74. My opinions regarding Chim are further confirmed by the expert declaration submitted by Dr. Schwartz, an expert in the field of treating acne. I have read Dr. Schwartz’s declaration, and I understand that Dr. Schwartz opines that Chim disclosed treating acne by topically applying tazarotene once per day to the affected areas of the body. Ex. 1003 (Schwartz Decl.) at ¶ 72. I agree with Dr. Schwartz’s analysis of Chim.

2. Composition of Tazarotene at 0.045% as Sole Active Ingredient

75. Claim 1 next recites “wherein the composition comprises tazarotene at a concentration of about 0.045 percent by weight of the composition as a sole active pharmaceutical ingredient.”

76. WO '001 discloses a topical formulation that includes 0.045% tazarotene as the sole active ingredient in the formulation. Ex. 1007 (WO '001) at Table 4; *see also* [0054]-[0060] (describing preparation of oil-in-water emulsion lotion containing same inactive ingredients as tazarotene-only composition in Table 4); [0038] (teaching that topical pharmaceutical compositions of the present invention can be prepared in various dosage forms, including oil-in-water emulsions, including lotions).

77. I understand that Dr. Schwartz has provided an expert declaration and has opined that a clinician would have would have been motivated to treat acne vulgaris with a composition comprising 0.045% tazarotene and that such a clinician would have reasonably expected success in doing so. *See* Ex. 1003 (Schwartz Decl.) at ¶¶ 73-74. This aligns with my understanding of the state of topical compositions and my analysis of the prior art available in May 2017. As I discuss in detail below, the Anderson, Kircik, and Chim references all taught that acne could be effectively treated with topical tazarotene compositions containing nearly the same

concentration of tazarotene, 0.05%, as the concentration of tazarotene in WO '001, 0.045%.

a. Anderson

78. As I explained previously, Anderson disclosed the clinical treatment practices of several practicing dermatologists and teaches that several of the dermatologists used 0.05% tazarotene compositions to treat acne as of 2004. *Supra* § VII.A.1.a. For example, Dr. Valerie Callender, stated that she “initiates treatment with tazarotene 0.05% cream applied every night” and then “after 2 or 3 weeks, she switches patients to a stronger concentration.” *Id.* at 17. Another physician, 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.* at 20. A third physician, Dr. Emil Tanghetti, indicated that he “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.*

79. The concentration of tazarotene in the 0.05% compositions disclosed by Anderson is nearly identical to the 0.045% concentration disclosed in WO '001. In my opinion, an ordinarily skilled formulator would expect the minor difference

in concentration between those compositions to have little, if any, effect on the efficacy of the composition.

80. As I explained above, a person of ordinary skill in the art would have known tazarotene was used and approved for treating both psoriasis and acne. Therefore, an ordinarily skilled formulator seeking to develop tazarotene compositions for treating acne would have been motivated to look to references disclosing tazarotene compositions used for treating either disease. Accordingly, it is my opinion that a person of ordinary skill in the art 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 compositions, and the combined teachings of the references would have motivated one skilled in the art to use the 0.045% tazarotene composition disclosed in WO '001 to treat acne due to the similar tazarotene concentrations disclosed in the two references. Additionally, as I noted above, formulators in May 2017 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* ¶¶ 30-33. Thus, formulators 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. As I also explained above, persons of ordinary skill in the

art 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. *See* Ex. 1007 (WO '001) at Table 4; Ex. 1041 (Draelos) at 598-599, Tables 1 & 2; *see also* Ex. 1042 (Rawlings) at 512-515; *supra* ¶ 37.

81. My opinions regarding Anderson are further confirmed by the expert declaration submitted by Dr. Schwartz, an expert in the field of treating acne. I have read Dr. Schwartz's declaration, and I understand that Dr. Schwartz opines that Anderson would have motivated a person of ordinary skill in the art to use WO '001's 0.045% tazarotene lotion to treat acne with a reasonable expectation of success. Ex. 1003 (Schwartz Decl.) at ¶¶ 75-78. I agree with Dr. Schwartz's analysis of Anderson.

b. Kircik

82. As I explained previously, 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 [Kircik] at 650-651. Kircik reported 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.* at 651-52, Figs. 1-2.

83. As with Anderson, the concentration of tazarotene in the 0.05% compositions disclosed by Kircik is nearly identical to the 0.045% concentration disclosed in WO '001. In my opinion, an ordinarily skilled formulator would expect the minor difference in concentration between those compositions to have little, if any, effect on the efficacy of the composition.

84. As I explained above, a person of ordinary skill in the art would have known tazarotene was used and approved for treating both psoriasis and acne. Therefore, an ordinarily skilled formulator seeking to develop tazarotene compositions for treating acne would have been motivated to look to references disclosing tazarotene compositions used for treating either disease. Accordingly, it is my opinion that a person of ordinary skill in the art 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 compositions, and the combined teachings of the references would have motivated one skilled in the art to use the 0.045% tazarotene composition disclosed in WO '001 to treat acne due to the similar tazarotene concentrations disclosed in the two references. Additionally, as I noted above, formulators in May 2017 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* ¶¶ 30-33. Thus, formulators 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. As I also explained above, persons of ordinary skill in the art 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 Kircik. *See* Ex. 1007 (WO '001) at Table 4; Ex. 1041 (Draelos) at 598-599, Tables 1 & 2; *see also* Ex. 1042 (Rawlings) at 512-515; *supra* ¶ 37.

85. My opinions regarding Kircik are further confirmed by the expert declaration submitted by Dr. Schwartz, an expert in the field of treating acne. I have read Dr. Schwartz's declaration, and I understand that Dr. Schwartz opines that Kircik would have motivated a person of ordinary skill in the art to use WO '001's 0.045% tazarotene lotion to treat acne with a reasonable expectation of success. Ex. 1003 (Schwartz Decl.) at ¶¶ 79-80. I agree with Dr. Schwartz's analysis of Kircik.

c. Chim

86. As I explained previously, Chim disclosed that "[s]ubstantial evidence supports the use of [topical retinoids] across all stages of acne severity." Ex. 1010

Chim at 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.

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. at Table 1-3. 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 also 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.* at 13. A person of ordinary skill in the art would have known that the lowest concentration of tazarotene available at the time was 0.05%. *See id.* at Table 1-3.

87. As with Anderson and Kircik, the concentration of tazarotene in the 0.05% compositions disclosed by Chim is nearly identical to the 0.045% concentration disclosed in WO '001. In my opinion, an ordinarily skilled formulator

would expect the minor difference in concentration between those compositions to have little, if any, effect on the efficacy of the composition.

88. As I explained above, a person of ordinary skill in the art would have known tazarotene was used and approved for treating both psoriasis and acne. Therefore, an ordinarily skilled formulator seeking to develop tazarotene compositions for treating acne would have been motivated to look to references disclosing tazarotene compositions used for treating either disease. Accordingly, it is my opinion that a person of ordinary skill in the art would have been motivated to combine the teachings of WO '001, which focused on treating psoriasis with tazarotene compositions, and Chim, which focused on treating acne with topical compositions including tazarotene, and the combined teachings of the references would have motivated one skilled in the art to use the 0.045% tazarotene composition disclosed in WO '001 to treat acne due to the similar tazarotene concentrations disclosed in the two references. Additionally, as I noted above, formulators in May 2017 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* ¶¶ 30-33. Thus, formulators 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. As I also explained

above, persons of ordinary skill in the art 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 Chim. *See* Ex. 1007 (WO '001) at Table 4; Ex. 1041 (Draelos) at 598-599, Tables 1 & 2; *see also* Ex. 1042 (Rawlings) at 512-515; *supra* ¶ 37.

89. My opinions regarding Chim are further confirmed by the expert declaration submitted by Dr. Schwartz, an expert in the field of treating acne. I have read Dr. Schwartz's declaration, and I understand that Dr. Schwartz opines that Chim would have motivated a person of ordinary skill in the art to use WO '001's 0.045% tazarotene lotion to treat acne with a reasonable expectation of success. Ex. 1003 (Schwartz Decl.) at ¶¶ 81-82. I agree with Dr. Schwartz's analysis of Chim.

3. Oil-in-water emulsion lotion

90. Claim 1 next recites "wherein the composition is an oil-in-water emulsion lotion comprising an oil phase and an aqueous phase." WO '001 discloses this limitation.

91. The tazarotene only lotion disclosed in Table 4 of WO '001 is an oil-in-water emulsion lotion which contains 0.045% tazarotene. Ex. 1007 (WO '001) at Table 4; *see also id.* at [0054]-[0060] (describing preparation of oil-in-water

emulsion lotion containing same inactive ingredients as tazarotene-only composition in Table 4).

4. Oil Phase

92. Claim 1 next recites “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 this limitation.

93. WO ’001 disclosed a 0.045% tazarotene only composition 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 (WO '001) at Table 4; *see also id.* at [0054]-[0060] (describing preparation of oil-in-water emulsion lotion containing same inactive ingredients as tazarotene-only composition in Table 4, in which the diethyl sebacate and light mineral oil are part of the oil phase). Diethyl sebacate is a dicarboxylic acid ester. *See, e.g., id.* at

[0050]. WO '001 teaches that the diethyl sebacate and light mineral oil are part of the oil phase of the lotion. *Id.* at [0057].

5. Aqueous Phase

94. Claim 1 next recites “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 this limitation.

95. WO '001 disclosed a 0.045% tazarotene composition containing an aqueous phase that included 0.6 weight % Carbopol® 981.

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 (WO '001), Table 4; *see also id.* at [0055] (describing preparation of the aqueous phase of the oil-in-water emulsion lotion that includes Carbopol® 981 (i.e., carbomer homopolymer type A) as part of the aqueous phase). Carbopol® 981 is also known as carbomer homopolymer type A. *See, e.g., id.* at [0041], Table 4.

6. Polymeric Emulsifier

96. Lastly, Claim 1 recites “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 this limitation.

97. WO '001 disclosed 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 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 (WO '001) at Table 4. Carbomer copolymer type B (also known under the trade name Pemulen TR-1) is a polymeric emulsifier. *See* Ex. 1001 ('482 patent) at 4:10-14 (“In addition, polymeric emulsifiers such as those known under the trade name Pemulen™ (The Lubrizol Corporation, Wickliffe, Ohio) may be used.”).

98. The prior art taught numerous advantages of using Pemulen TR-1 as an emulsifier for a topical pharmaceutical formulation, including that it provides efficient suspension and stabilization of insoluble materials; they can be used “with almost any oil phase”; they have high stability; they require low concentrations, typically only 0.1-0.3%; they do not cause irritation; they provide rapid release of the oil phase onto the patient’s skin, helping to provide rapid delivery of the active into the patient’s skin; and they can enable new dosage forms for insoluble materials. *See* Ex. 1035 (Tegeli) at 56-57; Ex. 1043 (Bulletin) at 2-3. Formulators would have been aware of these teachings, and they would have provided further motivation to use the vehicles disclosed in the WO '001 that include Pemulen TR-1 to formulate a 0.045% tazarotene composition.

B. Claim 2

99. Claim 2 recites “[t]he method of claim 1, wherein the dicarboxylic acid ester in the oil phase is diethyl sebacate.”

100. WO '001 discloses the limitations of claim 2 for the reasons I explained in claim 1. *Supra* § VII.A.2. Therefore, it is my opinion that claim 2 of the '482 patent would have been obvious over WO '001 in combination with Anderson, Kircik, or Chim.

C. Claim 3

101. Claim 3 recites “[t]he method of claim 1, wherein the oil phase comprises diethyl sebacate and light mineral oil.”

102. WO '001 discloses the limitations of claim 3 for the reasons I explained in claim 1. *Supra* § VII.A.2. Therefore, it is my opinion that claim 2 of the '482 patent would have been obvious over WO '001 in combination with Anderson, Kircik, or Chim.

D. Claims 4-6

103. 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).

104. As I discussed above, Anderson, Kircik, and Chim all disclose treating acne with topical tazarotene compositions containing 0.05% tazarotene. *Supra* §§ VII.A.1-2. Those references also teach carrying out those treatments for the lengths of time recited in claims 4-6, as I explain below.

105. I understand that Dr. Schwartz has opined that the limitations of claims 4-6 would have been obvious to a person of ordinary skill in the art over WO '001 in combination with Anderson, Kircik, or Chim. *See* Ex. 1003 (Schwartz Decl.) at ¶¶ 99-101. Indeed, as shown below, WO '001 in combination with Anderson, Kircik, or Chim renders Claims 4-6 obvious.

1. Anderson

106. As I explained above, Anderson disclosed that several practicing dermatologists used 0.05% tazarotene compositions to treat acne as of 2004. *Supra* §§ VII.A.1.a. – VII.2.a. I have read Dr. Schwartz's declaration, and I understand that Dr. Schwartz opines that treating acne with topical tazarotene over a 12-week treatment period was common with topical retinoid therapies, including tazarotene, prior to May 2017, and would have been part of the standard of care for acne to an ordinarily skilled physician. Ex. 1003 (Schwartz Decl.) at ¶ 102. A 12-week treatment period encompasses the 8-week, at least 12-week, and 12-week treatment periods recited by claims 4-6. Accordingly, based on Dr. Schwartz's testimony, it is my opinion that claims 4-6 would have been obvious over WO '001 and Anderson.

2. Kircik

107. As I explained previously, Kircik disclosed treatment of acne vulgaris with once daily application of tazarotene 0.05% cream for 12 weeks. Ex. 1009 (Kircik) at 651. The twelve-week treatment period disclosed in Kircik encompasses

the 8-week, at least 12-week, and 12-week treatment periods recited by claims 4-6. Accordingly, it is my opinion that claims 4-6 would have been obvious over WO '001 and Kircik.

108. My opinion is further confirmed by the expert declaration submitted by Dr. Schwartz, an expert in the field of treating acne. I have read Dr. Schwartz's declaration, and I understand that Dr. Schwartz opines that Kircik would have motivated a person of ordinary skill in the art to use WO '001's 0.045% tazarotene lotion to treat acne for a period of 12 weeks. Ex. 1003 (Schwartz Decl.) at ¶¶ 103-104. I agree with Dr. Schwartz's analysis of Kircik.

3. Chim

109. Chim teaches that "[b]est results [with treating acne with topical retinoids] may be expected in about 3 months." Ex. 1010 (Chim) at 13. This teaching would have motivated persons of ordinary skill in the art to use WO '001's 0.045% tazarotene lotion to treat acne for at least twelve weeks (i.e., about 3 months), which encompasses the 8-week, at least 12--eek, and 12 week treatment periods recited in claims 4-6. Accordingly, it is my opinion that claims 4-6 would have been obvious over WO '001 and Chim.

110. My opinion is further confirmed by the expert declaration submitted by Dr. Schwartz, an expert in the field of treating acne. I have read Dr. Schwartz's declaration, and I understand that Dr. Schwartz opines that Chim would have

motivated a person of ordinary skill in the art to use WO '001's 0.045% tazarotene lotion to treat acne for a period of 12 weeks. Ex. 1003 (Schwartz Decl.) at ¶ 105. I agree with Dr. Schwartz's analysis of Chim.

E. Claim 7

111. Claim 7 recites "wherein the tazarotene is in solution in the oil phase of the oil-in-water emulsion lotion." WO '001 discloses this limitation.

112. 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 (WO '001) at [0038], [0054]-[0060], Table 4. WO '001 teaches that during preparation of the oil-in-water emulsion lotions, tazarotene is added to the phase and the mixture is "agitated until a solution [is] achieved." *Id.* at [0057]. Formulators would understand from this teaching that tazarotene was in solution in the oil phase of the oil-in-water emulsion. That teaching is not surprising. Formulators would have reasonably expected tazarotene, which is a lipophilic molecule, to be soluble in the oil phase of the oil-in-water emulsion disclosed in WO '001. *See, e.g.*, Ex. 1044 (Ismail) at 573; Ex. 1045 (Remington's) at 271. Additionally, it would have been a matter of routine optimization for a formulator to determine the solubility of tazarotene in the oil-phase of the lotion vehicle disclosed by WO '001. Indeed, solubility experiments to

determine the solubility of the active ingredient within the vehicle are performed during development of nearly every topical pharmaceutical formulation.

113. Therefore, it is my opinion that claim 7 of the '482 patent would have been obvious over WO '001 in combination with Anderson, Kircik, or Chim.

F. Claim 8

114. Claim 8 recites “wherein the composition has a pH of about 4 to about 6.” WO '001 discloses this limitation.

115. WO '001 discloses that the 0.045% tazarotene only 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 ± 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 (WO '001) at [0059], Table 4. WO '001 teaches that during preparation of the oil-in-water emulsion, “an appropriate amount of the sodium hydroxide solution was added incrementally to obtain a pH of 5.5 ± 0.5.” *Id.* at [0059].

116. Therefore, it is my opinion that claim 8 of the '482 patent would have been obvious over WO '001 in combination with Anderson, Kircik, or Chim.

G. Claims 9-10

117. 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 both the claim 9 limitation and the claim 10 limitation.

118. 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 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 (WO '001) at Table 4.

119. Because the clinical limitations of claims 9 and 10 would have been obvious in view of WO '001 in combination with Anderson, Kircik, or Chim, as explained previously in claim 1 and by Dr. Schwartz in his declaration, it is my

opinion that claims 9 and 10 of the '482 patent would have been obvious over WO '001 in combination with Anderson, Kircik, or Chim. *See* Ex. 1003 (Schwartz Decl.) at ¶¶ 112-114; *supra* § VII.A.2.

H. Claim 11

120. Claim 11 is an independent claim that recites “[a] method of treating acne vulgaris, the method comprising topically applying a pharmaceutical composition to an affected area of a body of a subject suffering from acne vulgaris; wherein the composition 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%.”

121. The preamble of claim 11 is rendered obvious over WO '001 in combination with Anderson, Kircik, or Chim as discussed previously in Claim 1 and as expounded on further in Dr. Schwartz’s declaration. *See* Ex. 1003 (Schwartz Decl.) at ¶¶ 115-116; *supra* §§ VII.A.1-2.

122. 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 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 (WO '001) at Table 4.

123. Because the treatment of acne using a 0.045% tazarotene concentration like the one in claim 11 would have been obvious in view of WO '001 in combination with Anderson, Kircik, or Chim as explained previously in claim 1 and by Dr. Schwartz in his declaration, it is my opinion that claim 11 of the '482 patent would have been obvious over WO '001 in combination with Anderson, Kircik, or Chim. *See* Ex. 1003 (Schwartz Decl.) at ¶¶ 115-116; *supra* § VII.A.2.

**VIII. GROUND 4: CLAIMS 1-11 WOULD HAVE BEEN OBVIOUS OVER
WO '001 AND ANDERSON IN COMBINATION WITH SHALITA**

124. As explained in Grounds 1-3, WO '001 and Anderson discloses or renders obvious the limitations of claims 1-11 of the '482 patent. *Supra* § VII.

125. Shalita provides even further motivation to use the 0.045% tazarotene lotion from WO '001 to treat acne.

126. Shalita is an article published in a medical journal in 1999 that discloses the results of a 12-week multicenter, double-blind, vehicle-controlled study of tazarotene 0.1% and 0.05% gel in the treatment of acne. Ex. 1011 (Shalita) at 350. As I explained in the previously, ordinarily skilled formulators would have looked to medical journal articles like Shalita when developing formulations for a particular active ingredient. 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.* at 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.* at 354.

127. Based on my review, it is my opinion that Shalita would have provided a person of ordinary skill in the art with even further motivation to use WO ’001’s 0.045% tazarotene lotion to treat acne with a reasonable expectation of success, particularly when combined with Anderson’s teachings regarding the use of 0.05% tazarotene compositions in clinical practice. As I explained previously, an ordinarily skilled formulator would expect the minor difference in concentration between those compositions to have little, if any, effect on the efficacy of the composition. Further, Shalita’s teachings regarding the relative irritation profiles of the 0.1% tazarotene gel and the 0.05% tazarotene gel would have also provided persons of ordinary skill in the art 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. *See id.* at 354. My opinions regarding Shalita are further confirmed by the expert declaration submitted by Dr. Schwartz, an expert in the field of treating acne. I have read Dr. Schwartz’s declaration, and I understand that Dr. Schwartz opines that

Shalita would have provided a person of ordinary skill in the art with additional motivation to use WO '001's 0.045% tazarotene lotion to treat acne with a reasonable expectation of success. Ex. 1003 (Schwartz Decl.) at ¶¶ 120-123. I agree with Dr. Schwartz's analysis of Shalita.

128. Accordingly, claims 1-11 of the '482 patent would have been obvious over WO '001 in combination with Anderson and Shalita.

A. Claims 4-6

129. Shalita would have also provided persons of ordinary skill in the art with 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. Shalita discloses treatment of acne vulgaris with once daily application of tazarotene 0.05% gel for 12 weeks. Ex. 1011 (Shalita) at 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.* at 351, Figs. 1-2. These teachings would have provided persons of ordinary skill in the art with additional motivation 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 (Schwartz Decl.) at ¶ 123; *see also supra* VII.D. 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.

130. My opinions regarding Shalita are further confirmed by the expert declaration submitted by Dr. Schwartz, an expert in the field of treating acne. I have read Dr. Schwartz's declaration, and I understand that Dr. Schwartz opines that Shalita would have provided a person of ordinary skill in the art with additional motivation to use WO '001's 0.045% tazarotene lotion to treat acne for at least 12 weeks. Ex. 1003 (Schwartz Decl.) at ¶¶ 124-125. I agree with Dr. Schwartz's analysis of Shalita.

**IX. GROUND 5: CLAIMS 1-11 WOULD HAVE BEEN OBVIOUS OVER
THE '824 PUBLICATION AND THE TAZORAC® LABEL**

131. As I discussed previously, persons of ordinary skill in the art in May 2017 would have been motivated to develop new topical tazarotene formulations with less irritating side effects, and two known means for doing so was to reduce the concentration of tazarotene in the formulation and include moisturizing ingredients within the vehicle. *Supra* § III. The '824 publication would have provided persons of ordinary skill in the art with exemplary lotion vehicles enabling both of those means. The '824 publication disclosed oil-in-water lotion emulsion vehicles for formulating corticosteroid compositions that were able to maintain potency even when the concentration of the corticosteroid was significantly reduced, by as much

as five times. *See* Ex. 1012 ('824 publication) at [0035]. The '824 publication achieved this through use of lotion vehicles containing a “liquid oil component” comprising a dicarboxylic acid ester that dissolves the active ingredient, enabling enhanced delivery of the active ingredient into the skin, rather than through the skin into systemic circulation. *Id.* at [0016]. These vehicles also included several known ingredients that were known to have moisturizing effects, such as diethyl sebacate, light mineral oil, and sorbitol, making them particularly attractive for formulating an irritating active ingredient such as tazarotene. *See id.* at Table 4. One such vehicle disclosed by the '824 publication is **identical** to the vehicle of the tazarotene composition disclosed and claimed in the '482 patent.

'482 patent						'824 publication		
TABLE 2						TABLE 4		
Some Emulsion Compositions of the Present Invention for Treating Acne						% w/w		
Ingredient	Function	Concentration (wt %)				Ingredients	Formula 4A	Formula 4B
		Range 1	Range 2	Range 3	Composition A			
Tazarotene	Retinoid	0.02-0.049	0.03-0.049	0.04-0.049	0.045	Halobetasol Propionate	0.01	0.025
Diethyl sebacate	Liquid Oil & Solvent	1-5	2-4	2.5-3.5	2.97	Diethyl Sebacate	2.97	2.90
Light mineral oil	Liquid Oil & Co-Solvent	5-15	5-10	7.5-8.5	8.03	Light Mineral Oil	8.03	2.90
Sorbitan monooleate	Surfactant/Emulsifying Agent	0.01-1	0.02-0.5	0.05-0.2	0.1	Sorbitan Monooleate	0.10	0.10
Sorbitol solution, 70%	Humectant	5-15	7-12	10-11	10.7	Sorbitol Solution, 70%	10.7	10.7
Methyl paraben	Antimicrobial Preservative ⁽¹⁾	0.05-0.3	0.1-0.3	0.1-0.2	0.17	Disodium Edetate, Dihydrate	0.05	0.05
Propyl paraben	Antimicrobial Preservative ⁽¹⁾	0.01-0.1	0.01-0.05	0.02-0.04	0.03	Pemulen TR-1	0.40	0.40
Edetate disodium dihydrate	Chelating Agent ⁽¹⁾	0.02-0.1	0.02-0.7	0.03-0.06	0.05	Carbopol 981	0.60	0.60
Carbomer copolymer type B (e.g., Pemulen™ TR-1)	Emulsifying Agent	0.1-1	0.2-0.7	0.3-0.5	0.4	Methylparaben	0.17	0.17
Carbomer homopolymer type A (e.g., Carbomer 981)	Thickener	0.2-1.5	0.3-1	0.5-0.7	0.6	Propylparaben	0.03	0.03
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	Sodium Hydroxide, q. s.	pH 4.0-6.0	pH 4.0-6.0
Purified water	Carrier	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	Purified Water, q.s. ad	100	100

Compare Ex. 1001 ('482 patent) at Table 2 with Ex. 1012 ('824 publication) at Table 4. The '824 publication therefore discloses every formulation limitation of claims 1-11 of the '482 patent except for the active ingredient – 0.045% tazarotene.

132. The Tazorac® Label discloses topical creams comprising either 0.1% or 0.05% tazarotene that are applied once daily. Ex. 1013 (Tazorac® Label). The Tazorac® Label disclosed that the most common adverse reactions associated with treatment are pruritus, erythema, and burning, and the 0.1% Tazorac® Cream produced a greater degree of local irritation than the 0.05% Tazorac® Cream. *See id.* at Adverse Reactions. The Tazorac® Label instructs that patients may use moisturizers during application of Tazorac® to help alleviate the irritation. *Id.* at Patient Counseling Information.

133. Based on my review of the prior art and my experience as a formulator, it is my opinion that the '824 publication in combination with the Tazorac® Label discloses or renders obvious all of the limitations of claim 1-11 of the '482 patent. My opinions are further confirmed by the expert declaration of Dr. Schwartz, a dermatologist who is an expert in the field of treating acne, as I explain below.

A. Claim 1

134. In my opinion, the '824 publication in combination with the Tazorac® label renders claim 1 obvious.

1. Preamble

135. The preamble of Claim 1 recites “[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.”

136. 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 (Tazorac® Label) at Indications and Usage. My opinions regarding the Tazorac® Label are further confirmed by the expert declaration submitted by Dr. Schwartz, an expert in the field of treating acne. I have read Dr. Schwartz’s declaration, and I understand that Dr. Schwartz opines that the Tazorac® Label disclosed treating acne by topically applying tazarotene once per day to the affected areas of the body. Ex. 1003 (Schwartz Decl.) at ¶ 133. I agree with Dr. Schwartz’s analysis of the Tazorac® Label.

2. Composition of Tazarotene at 0.045% as Sole Active Ingredient

137. Claim 1 next recites “wherein the composition comprises tazarotene at a concentration of about 0.045 percent by weight of the composition as a sole active pharmaceutical ingredient.” I understand that Dr. Schwartz has opined that an ordinarily skilled clinician would have been motivated to use a composition of tazarotene with a similar or lower concentration as the 0.05% composition disclosed in the Tazorac® Label, such as 0.045% tazarotene, to treat acne. Ex. 1003 (Schwartz Decl.) at ¶¶ 135-137. This aligns with my understanding of the state of topical compositions and my analysis of the prior art available before May 2017. From the perspective of a skilled formulator, the treatment of acne with a topical composition

of tazarotene would have been obvious over the '824 publication in combination with the Tazorac® Label.

a. The Tazorac® Label

138. The Tazorac® label disclosed topical tazarotene compositions with two different concentrations of tazarotene: 0.1% and 0.05%. Ex. 1013 (Tazorac® Label) at Indications and Usage. In my opinion, an ordinarily skilled formulator would have been 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." *Id.* at Adverse Reactions. This would have led those skilled in the art to investigate treating acne with lower concentrations of tazarotene, such as 0.05%. An ordinarily skilled formulator would have arrived at a concentration of "about 0.045%" tazarotene through routine optimization, consistent with the Examiner's final rejection of Patent Owner's related '576 application. *Supra* §V.A.

139. In my opinion, an ordinarily skilled formulator 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.

140. My opinions regarding the Tazorac® Label are further confirmed by the expert declaration submitted by Dr. Schwartz, an expert in the field of treating

acne. I have read Dr. Schwartz's declaration, and I understand that Dr. Schwartz opines that the Tazorac® Label would have motivated a person of ordinary skill in the art to treat acne with a topical composition comprising tazarotene at a concentration of about 0.045% with a reasonable expectation of success. Ex. 1003 (Schwartz Decl.) at ¶¶ 135-137. I agree with Dr. Schwartz's analysis of the Tazorac® Label.

b. The '824 Publication

141. In my opinion, an ordinarily skilled formulator would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion vehicles disclosed in the '824 publication, particularly Formula 4A in Table 4, for several reasons.

142. First, 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 ('824 publication) at [0035], [0037]-[0040], Tables 1 & 3. Thus, an ordinarily skilled formulator seeking to formulate an effective lower-concentration tazarotene composition would have been highly motivated to use the lotion vehicles disclosed in the '824 publication to achieve greater penetration of tazarotene into the patient's skin, allowing for efficacy to be maintained even when the concentration of tazarotene is reduced. And given these

teachings, persons of ordinary skill in the art 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.

143. Second, formulators would have known that tazarotene, like halobetasol propionate, is a lipophilic molecule. *See, e.g.*, Ex. 1044 (Ismail) at 573; Ex. 1045 (Remington's) at 271. Therefore, formulators would have reasonably expected tazarotene would be soluble in the oil phase of the oil-in-water emulsions disclosed in the '824 publication, providing further motivation to use those vehicles to formulate tazarotene compositions. Additionally, it would have been a matter of routine optimization for a formulator to determine the solubility of tazarotene in the oil-phase of the lotion vehicles disclosed by the '824 publication. Indeed, solubility experiments to determine the solubility of the active ingredient within the vehicle are performed during development of nearly every topical pharmaceutical formulation.

144. Third, formulators would have recognized that Formulation 4A in the '824 publication includes several known moisturizing ingredients, including mineral oil and sorbitol, which would have been expected to help alleviate the irritation from tazarotene. *See* Ex. 1012 ('824 publication) at Table 4; *see also* Ex. 1041 (Draelos) at 598-599, Tables 1 & 2; *see also* Ex. 1042 (Rawlings) at 512-515. Notably, Formulation 4A includes a higher concentration of the moisturizing ingredient

mineral oil than Formulation 4B. Ex. 1012 ('824 publication) at Table 4. Additionally, unlike several of the other vehicles disclosed in the '824 publication, Formulation 4A in Table 4 of the '824 publication does not include propylene glycol as an ingredient in the formulation. *See* Ex. 1012 ('824 publication) at Tables 1, 4. Propylene glycol was known to induce irritation, which would potentially exacerbate the irritation of tazarotene, and therefore, formulators would have been motivated to use a formulation that did not include that ingredient when formulating tazarotene. *See, e.g.,* Ex. 1040 (Russell) at 3 (“lotions contain propylene glycol and thus may have burning or drying effects”).

145. Fourth, the prior art disclosed that “[l]otions can be used with any skin type, and they spread well over hair-bearing skin.” *Id.* at 3. This would have provided formulators with further motivation to use the lotion vehicles disclosed in the '824 publication, including Formula 4A, to formulate a 0.045% tazarotene composition.

3. Oil-in-Water Emulsion Lotion

146. Claim 1 next recites “wherein the composition is an oil-in-water emulsion lotion comprising an oil phase and an aqueous phase.” The '824 publication discloses this limitation.

147. The '824 publication disclosed oil-in-water emulsion vehicle formulations containing an aqueous phase and an oil phase comprising a

dicarboxylic acid ester, such as diethyl sebacate, that is used to formulate topical corticosteroid compositions. Ex. 1012 ('824 publication) at [0041]-[0043] (describing preparation of aqueous phase and oil phase), Tables 1 & 4. An ordinarily skilled formulator would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion lotion vehicles disclosed in the '824 publication, particularly Formula 4A, for the reasons I explained previously. *Supra* § IX.A.2.

4. Oil Phase

148. Claim 1 next recites “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.” The '824 publication discloses this limitation.

149. The '824 publication disclosed a vehicle comprising an oil-in-water emulsion lotion comprising an oil phase that comprises a dicarboxylic acid ester and a mineral oil at a total concentration of 10-12 percent 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 ('824 publication) at Table 4. Formula 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. *Id.* Diethyl sebacate is a dicarboxylic acid ester. *See, e.g., id.* at [0019]. The '824 publication discloses that the diethyl sebacate and the light mineral oil are included in the oil phase of Formula 4A. *Id.* at [0043]. A person of ordinary skill would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion lotion vehicles of the '824 publication, particularly Formulation 4A, for the reasons I explained previously. *Supra* § IX.A.2.

5. Aqueous Phase

150. Claim 1 next recites “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.” The ’824 publication discloses this limitation.

151. The ’824 publication discloses oil-in-water emulsion lotion vehicles that include an aqueous phase comprising water and Carbopol 981 (also known as carbomer homopolymer type A) at 0.60% by weight.

’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 (’824 publication) at [0042], Table 4. A person of ordinary skill would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion

lotion vehicles of the '824 publication, particularly Formulation 4A, for the reasons I explained previously. *Supra* § IX.A.2.

6. Polymeric Emulsifier

152. Lastly, claim 1 recites “wherein the composition further comprises a polymeric emulsifier at a concentration of 0.3-0.5 percent by weight of the composition.” The '824 publication discloses this limitation.

153. The '824 publication disclosed a vehicle for an oil-in-water emulsion lotion comprising Pemulen TR-1 (also known as carbomer copolymer type B) 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 ('824 publication) at Table 4. The '824 publication disclosed that Pemulen is a polymeric emulsifier. *Id.* at [0024]; *see also* Ex. 1001 ('482 patent) at 4:10-14 (“In addition, polymeric emulsifiers such as those known under the trade name Pemulen™ (The Lubrizol Corporation, Wickliffe, Ohio) may be used.”). A person of ordinary skill would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion lotion vehicles of the '824 publication, particularly Formulation 4A, for the reasons I explained previously. *Supra* § IX.A.2.

154. The prior art taught numerous advantages of using Pemulen TR-1 as an emulsifier for a topical pharmaceutical formulation, including that it provides efficient suspension and stabilization of insoluble materials; they can be used “with almost any oil phase”; they have high stability; they require low concentrations, typically only 0.1-0.3%; they do not cause irritation; they provide rapid release of the oil phase onto the patient’s skin, helping to provide rapid delivery of the active into the patient’s skin; and they can enable new dosage forms for insoluble materials. *See* Ex. 1035 (Tegeli) at 56-57; Ex. 1043 (Bulletin) at 2-3. Formulators would have been aware of these teachings, and they would have provided further motivation to use the vehicles disclosed in the '824 publication that include Pemulen TR-1, such as Formula 4A, to formulate a 0.045% tazarotene composition.

B. Claim 2

155. Claim 2 recites “[t]he method of claim 1, wherein the dicarboxylic acid ester in the oil phase is diethyl sebacate.” The ’824 publication discloses the limitations of claim 2 for the reasons explained in claim 1. *Supra* IX.A.2. Therefore, it is my opinion that claim 2 of the ’482 patent would have been obvious over the ’824 publication in combination with the Tazorac® Label.

C. Claim 3

156. Claim 3 recites “[t]he method of claim 1, wherein the oil phase comprises diethyl sebacate and light mineral oil.” The ’824 publication discloses the limitations of claim 3 for the reasons explained in Claim 1. *Supra* VII.A.4. Therefore, it is my opinion that claim 3 of the ’482 patent would have been obvious over the ’824 publication in combination with the Tazorac® Label.

D. Claims 4-6

157. 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). The ’824 publication in combination with the Tazorac® Label renders claims 4-6 obvious.

158. In multiple clinical trials disclosed in the Tazorac® Label, the treatment with topical tazarotene was carried out for 12 weeks. Ex. 1013 (Tazorac label) at 14, Clinical Studies. Based on these teachings, it is my opinion that persons of

ordinary skill in the art 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 12 weeks. 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.

159. My opinions regarding the Tazorac® Label are further confirmed by the expert declaration submitted by Dr. Schwartz, an expert in the field of treating acne. I have read Dr. Schwartz’s declaration, and I understand that Dr. Schwartz opines that the Tazorac® Label would have motivated a person of ordinary skill in the art to treat acne with a topical composition comprising tazarotene at a concentration of about 0.045% for 12 weeks. Ex. 1003 (Schwartz Decl.) at ¶¶ 154-155. I agree with Dr. Schwartz’s analysis of the Tazorac® Label.

E. Claim 7

160. Claim 7 recites “wherein the tazarotene is in solution in the oil phase of the oil-in-water emulsion lotion.” The '824 publication discloses this limitation or renders it obvious.

161. 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. Ex. 1012 ('824 publication) at [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.* at [0016].

162. As I explained previously in claim 1, formulators would have known that tazarotene, like halobetasol propionate, is a lipophilic molecule. *See, e.g.*, Ex. 1044 (Ismail) at 573; Ex. 1045 (Remington’s) at 271. Therefore, formulators would have reasonably expected tazarotene would be soluble in the oil phase of the oil-in-water emulsions disclosed in the ’824 publication, providing further motivation to use those vehicles to formulate tazarotene compositions. Additionally, it would have been a matter of routine optimization for a formulator to determine the solubility of tazarotene in the oil-phase of the lotion vehicles disclosed by the ’824 publication. Indeed, solubility experiments to determine the solubility of the active ingredient within the vehicle are performed during development of nearly every topical pharmaceutical formulation.

163. Therefore, it is my opinion that claim 7 of the ’482 patent would have been obvious over the ’824 publication in combination with the Tazorac® Label.

F. Claim 8

164. Claim 8 recites “wherein the composition has a pH of about 4 to about 6.” The ’824 publication discloses the limitations of claim 8.

165. 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 ('824 publication) at Table 4. The '824 publication further teaches that during preparation of the oil-in-water emulsion vehicle, “an appropriate amount of the sodium hydroxide solution is added incrementally to obtain a pH of 5.5-0.5.” *Id.* at [0045]. A person of ordinary skill would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion lotion vehicles of the '824 publication, particularly Formulation 4A, for the reasons I explained previously. *Supra* § IX.A.2.

166. Therefore, it is my opinion that claim 8 of the '482 patent would have been obvious over the '824 publication in combination with the Tazorac® Label.

G. Claims 9-10

167. 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%.”

168. 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 ('824 publication) Table 4.

169. Because the clinical limitations (the usage of 0.045% tazarotene to treat acne) of claims 9 and 10 would have been obvious in view of the '824 publication in combination with the Tazorac® Label as explained in claim 1 and as expounded on by Dr. Schwartz, it is my opinion that claims 9 and 10 of the '482 patent would have been obvious over the '824 publication in combination with the Tazorac® Label. *See supra* § IX.A.1-2; Ex. 1003 (Schwartz Decl.) at ¶ 161.

H. Claim 11

170. Claim 11 is an independent claim that recites “[a] method of treating acne vulgaris, the method comprising topically applying a pharmaceutical

composition to an affected area of a body of a subject suffering from acne vulgaris; wherein the composition 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%.”

171. The preamble of claim 11 is rendered obvious over the Tazorac® Label as discussed previously in Claim 1 and as expounded on further in Dr. Schwartz’s declaration. *See supra* § IX.A.1.-2.; Ex. 1003 (Schwartz Decl.) at ¶ 164.

172. Formula 4A of the ’824 publication disclosed each of the formulation 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 ['824 publication], Table 4.

173. The use of 0.045% tazarotene is rendered obvious over the combination of the '824 publication and the Tazorac® Label as discussed previously in Claim 1 and as expounded on further in Dr. Schwartz's declaration. *See supra* § IX.A.1.-2.; Ex. 1003 (Schwartz Decl.) at ¶¶ 164-166.

174. Therefore, it is my opinion that claim 11 of the '482 patent would have been obvious over the '824 publication in combination with the Tazorac® Label.

X. GROUND 6: CLAIMS 1-11 WOULD HAVE BEEN OBVIOUS OVER
THE '824 PUBLICATION AND THE TAZORAC® LABEL IN VIEW OF
ANDERSON

175. As I explained in Ground 5, it is my opinion that the '824 publication and the Tazorac® Label render claims 1-11 of the '482 patent obvious. *Supra* § IX.

176. Anderson provides even further motivation to use the vehicle disclosed in the '824 publication in combination with a 0.045% tazarotene concentration to treat acne.

177. As I explained previously, Anderson discloses an article on the clinical treatment of acne vulgaris with topical tazarotene. *Supra* § VII.A.1.a. 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.” *Id.* As I explained previously, an ordinarily skilled formulator 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. Accordingly, claims 1-11 of the '482 patent would have been obvious over the '824 Publication and the Tazorac® Label in view of Anderson.

178. My opinions regarding Anderson are further confirmed by the expert declaration submitted by Dr. Schwartz, an expert in the field of treating acne. I have read Dr. Schwartz's declaration, and I understand that Dr. Schwartz opines that Anderson would have further motivated a person of ordinary skill in the art to use a composition comprising 0.045% tazarotene lotion to treat acne with a reasonable expectation of success, particularly when combined with the teachings of the '824 publication and the Tazorac® Label. Ex. 1003 (Schwartz Decl.) at ¶¶ 167-169. I agree with Dr. Schwartz's analysis of Anderson.

XI. 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

179. As I discussed previously, persons of ordinary skill in the art in May 2017 would have been motivated to develop new topical tazarotene formulations with less irritating side effects, and two known means for doing so was to reduce the concentration of tazarotene in the formulation and include moisturizing ingredients within the vehicle. *Supra* § III. As I also explained previously, the '824 publication disclosed oil-in-water emulsion vehicles that enabled significantly lower concentrations of the active ingredient to achieve similar potency as much high concentration compositions, including one such vehicle that is *identical* to the

composition disclosed and claimed in the '482 patent except for the active ingredient.

'482 patent						'824 publication		
TABLE 2						TABLE 4		
Some Emulsion Compositions of the Present Invention for Treating Acne						% w/w		
Ingredient	Function	Concentration (wt %)				Ingredients	Formula 4A	Formula 4B
		Range 1	Range 2	Range 3	Composition A			
Tazarotene	Retinoid	0.02-0.049	0.03-0.049	0.04-0.049	0.045	Halobetasol Propionate	0.01	0.025
Diethyl sebacate	Liquid Oil & Solvent	1-5	2-4	2.5-3.5	2.97	Diethyl Sebacate	2.97	2.90
Light mineral oil	Liquid Oil & Co-Solvent	5-15	5-10	7.5-8.5	8.03	Light Mineral Oil	8.03	2.90
Sorbitan monooleate	Surfactant/Emulsifying Agent	0.01-1	0.02-0.5	0.05-0.2	0.1	Sorbitan Monooleate	0.10	0.10
Sorbitol solution, 70%	Humectant	5-15	7-12	10-11	10.7	Sorbitol Solution, 70%	10.7	10.7
Methyl paraben	Antimicrobial Preservative ⁽¹⁾	0.05-0.3	0.1-0.3	0.1-0.2	0.17	Disodium Edetate, Dihydrate	0.05	0.05
Propyl paraben	Antimicrobial Preservative ⁽¹⁾	0.01-0.1	0.01-0.05	0.02-0.04	0.03	Pemulen TR-1	0.40	0.40
Edetate disodium dihydrate	Chelating Agent ⁽¹⁾	0.02-0.1	0.02-0.7	0.03-0.06	0.05	Carbopol 981	0.60	0.60
Carbomer copolymer type B (e.g., Pemulen™ TR-1)	Emulsifying Agent	0.1-1	0.2-0.7	0.3-0.5	0.4	Methylparaben	0.17	0.17
Carbomer homopolymer type A (e.g., Carbomer 981)	Thickener	0.2-1.5	0.3-1	0.5-0.7	0.6	Propylparaben	0.03	0.03
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	Sodium Hydroxide, q. s.	pH 4.0-6.0	pH 4.0-6.0
Purified water	Carrier	q.s. to 100	q.s. to 100	q.s. to 100	q.s. to 100	Purified Water, q.s. ad	100	100

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

Supra § IX. It is my opinion that an ordinarily skilled formulator would have been motivated to formulate a 0.045% tazarotene composition in the oil-in-water emulsion vehicles of the '824 publication for the reasons I explained in Ground 5.

Id. The IDP-118 Study would have provided even further motivation to do so.

180. 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 (IDP-118 Study) at Arms and Interventions. Because persons of ordinary skill in the art would have been motivated to use lower-concentration (e.g., about 0.05%) tazarotene compositions for treating acne, they would have recognized the 0.045%

tazarotene monotherapy lotion in the IDP-118 Study as an attractive option for treating acne. An ordinarily skill formulator would have looked for a vehicle for the 0.045% tazarotene monotherapy lotion in the IDP-118 Study, and that investigation would have led them to the '824 publication, which is one of the only references disclosing formulations for a 0.01% halobetasol propionate lotion, one of the other treatment arms in the IDP-118 Study.

181. As I explained in Grounds 1-3, Anderson, Kircik, and Chim all disclose that topical compositions containing nearly the same concentration of tazarotene as that in the IDP-118 Study (0.05%) were effectively used to treat acne prior to May 2017. Accordingly, it is my opinion that 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 explained below. My opinions are further confirmed by the expert declaration of Dr. Schwartz, an expert in the field of topical drug formulation, as I explain below.

A. Claim 1

182. In my opinion, the '824 publication and the IDP-118 Study in view of Anderson, Kircik, or Chim renders claim 1 obvious.

1. Preamble

183. The preamble of Claim 1 recites “[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.”

184. Anderson, Kircik, and Chim disclose this limitation as explained in Grounds 1-3. *Supra* § VII.A.1.

2. Composition of Tazarotene at 0.045% as Sole Active Ingredient

185. Claim 1 next recites “wherein the composition comprises tazarotene at a concentration of about 0.045 percent by weight of the composition as a sole active pharmaceutical ingredient.” I understand that Dr. Schwartz has opined that an ordinarily skilled clinician would have been motivated to use a composition of tazarotene with a similar or lower concentration as the 0.05% composition disclosed in the Tazorac® Label, such as 0.045% tazarotene, to treat acne. Ex. 1003 (Schwartz Decl.) at ¶¶ 174-175. This aligns with my understanding of the state of topical compositions and my analysis of the prior art available before May 2017. From the perspective of a skilled formulator, the treatment of acne with a topical composition of tazarotene would have been obvious over the ’824 publication in combination with the IDP-118 Study and Anderson, Kircik, or Chim. In my opinion, an ordinarily skilled formulator would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion vehicles disclosed in the ’824 publication, particularly

Formula 4A in Table 4, for the reasons I explained in Ground 5. *Supra* § IX. The IDP-118 Study would have provided an ordinarily skilled formulation with even further motivation to do so.

186. 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 (IDP-118 Study) at Arms and Interventions. Based on my personal experience, it is my opinion that formulators would have looked to information regarding the clinical use of the active ingredient(s) that they are developing a formulation for, including information on ClinicalTrials.gov. And as I noted previously, formulators would have known that tazarotene was approved for treating both acne and psoriasis, and would have therefore been motivated to look to references dealing with the treatment of either indication, including the IDP-118 Study, when developing topical tazarotene formulations. *Supra* § III.

187. Formulators would have understood that in a clinical trial such as the IDP-118 Study, all four treatment arms would have been formulated in the same vehicle to ensure that comparisons among the arms could be attributed to differences in the active ingredients. Given this knowledge, formulators would have been

motivated to investigate vehicles for both 0.01% halobetasol compositions as well as 0.045% tazarotene compositions, and that investigation would have led formulators to the '824 publication, which discloses vehicles for a 0.01% halobetasol lotion. The IDP-118 Study's disclosure of a 0.01% halobetasol lotion formulated in the same vehicle as a 0.045% tazarotene lotion would have reinforced the formulator's motivation and reasonable expectation of success for using the '824 publication's vehicles, including Formula 4A, for a 0.045% tazarotene composition.

188. The '824 publication disclosed two examples of formulations with 0.01% halobetasol propionate, Formulation C in Table 1 and Formulation 4A in Table 4. *See* Ex. 1012 ('824 publication) at Table 1, Table 4. An ordinarily skilled formulator would have been particularly motivated by the IDP-118 Study to investigate the vehicles of both formulations as a vehicle for a 0.045% tazarotene composition. Further, as I explained previously, formulators would have been particularly motivated to investigate Formula 4A as a vehicle for a 0.045% tazarotene composition because Formula 4A does not contain propylene glycol, an ingredient that was known to cause irritation and dryness. *Supra* § IX.A.2. Formula 4A also contains a relatively high concentration of moisturizing ingredients, such as diethyl sebacate, light mineral oil, and sorbitol, providing further motivation to use it as a vehicle for formulating tazarotene. *See* Ex. 1012 ('824 publication) at Table 4.

189. Persons of ordinary skill in the art 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 in view of the teachings of Anderson, Kircik, or Chim for the same reasons I explained in Grounds 1-3. *Supra* § VII.

190. My opinions regarding Anderson, Kircik, and Chim and the motivations of a person of ordinary skill in the art are further confirmed by the expert declaration submitted by Dr. Schwartz, an expert in the field of treating acne. I have read Dr. Schwartz's declaration, and I understand that Dr. Schwartz opines that Anderson, Kircik, and Chim all would have motivated a person of ordinary skill in the art to use the 0.045% tazarotene lotion disclosed in the IDP-118 Study to treat acne with a reasonable expectation of success. Ex. 1003 (Schwartz Decl.) at ¶¶ 174-175. I agree with Dr. Schwartz's analysis of those references.

3. Oil-in-Water Emulsion Lotion

191. Claim 1 next recites "wherein the composition is an oil-in-water emulsion lotion comprising an oil phase and an aqueous phase." The '824 publication discloses this limitation for the reasons I explained in Ground 5. *Supra* § IX.A.2. An ordinarily skilled formulator would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion lotion vehicles disclosed in the '824 publication, particularly Formula 4A, for the reasons I explained previously. *Supra* § XI.A.2.

4. Oil Phase

192. Claim 1 next recites “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.” The ’824 publication discloses this limitation for the reasons I explained in Ground 5. *Supra* § IX.A.2. An ordinarily skilled formulator would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion lotion vehicles disclosed in the ’824 publication, particularly Formula 4A, for the reasons I explained previously. *Id.*

5. Aqueous Phase

193. Claim 1 next recites “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.” The ’824 publication discloses this limitation for the reasons I explained in Ground 5. *Supra* § IX.A.2. An ordinarily skilled formulator would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion lotion vehicles disclosed in the ’824 publication, particularly Formula 4A, for the reasons I explained previously. *Id.*

6. Polymeric Emulsifier

194. Lastly, claim 1 recites “wherein the composition further comprises a polymeric emulsifier at a concentration of 0.3-0.5 percent by weight of the composition.” The ’824 publication discloses this limitation for the reasons I

explained in Ground 5. *Supra* IX.A.2. An ordinarily skilled formulator would have been motivated to formulate 0.045% tazarotene in the oil-in-water emulsion lotion vehicles disclosed in the '824 publication, particularly Formula 4A, for the reasons I explained previously. *Id.*

B. Claim 2

195. Claim 2 recites “[t]he method of claim 1, wherein the dicarboxylic acid ester in the oil phase is diethyl sebacate.” The '824 publication discloses the limitations of claim 2 for the reasons explained in claim 1 of Ground 5. *Supra* § IX.A.2. Therefore, it is my opinion that claim 2 of the '482 patent would have been obvious over the '824 publication in combination with the IDP-118 Study and Anderson, Kircik, or Chim.

C. Claim 3

196. Claim 3 recites “[t]he method of claim 1, wherein the oil phase comprises diethyl sebacate and light mineral oil.” The '824 publication discloses the limitations of claim 3 for the reasons explained in claim 1 of Ground 1. *Supra* § IX.A.2. Therefore, it is my opinion that claim 3 of the '482 patent would have been obvious over the '824 publication in combination with the IDP-118 Study and Anderson, Kircik, or Chim.

D. Claim 4-6

197. 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). Persons of ordinary skill in the art would have been motivated to use the 0.045% tazarotene lotion disclosed in the IDP-118 Study to treat acne for the reasons I explained in claim 1. *Supra* § XI.A.1. Persons of ordinary skill in the art would have been motivated to carry out that treatment for at least 12-weeks in view of Anderson, Kircik, or Chim for the reasons I explained in Grounds 1-3. *Supra* § VII.D. Therefore, the '824 publication and the IDP-118 study in combination with Anderson, Kircik, or Chim renders claims 4-6 obvious.

E. Claim 7

198. Claim 7 recites “wherein the tazarotene is in solution in the oil phase of the oil-in-water emulsion lotion.” The '824 publication discloses this limitation or renders it obvious for the reasons I explained in claim 1 of Ground 5. *Supra* § IX.A.2. Therefore, it is my opinion that claim 7 of the '482 patent would have been obvious over the '824 publication in combination with the IDP-118 Study and Anderson, Kircik, or Chim.

F. Claim 8

199. Claim 8 recites “wherein the composition has a pH of about 4 to about 6.” The '824 publication discloses the limitations of claim 8 for the reasons I

explained in claim 1 of Ground 5. *Supra* § IX.A.2. Therefore, it is my opinion that claim 8 of the '482 patent would have been obvious over the '824 publication in combination with the IDP-118 Study and Anderson, Kircik, or Chim.

G. Claims 9-10

200. 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%.”

201. The '824 publication disclosed each of the limitations recited in claims 9 and 10 except for 0.045% tazarotene for the reasons I explained in claim 1 of Ground 5. *Supra* § IX.A.2.

202. Because the clinical limitations (the usage of 0.045% to treat acne) of claims 9 and 10 would have been obvious in view of the '824 publication and the IDP-118 Study as explained in claim 1 and as expounded on by Dr. Schwartz, it is my opinion that claims 9 and 10 of the '482 patent would have been obvious over the '824 publication in combination with the Tazorac® Label. *See supra* § XI.A.1-2; Ex. 1003 (Schwartz Decl.) at ¶¶ 195-197.

H. Claim 11

203. Claim 11 is an independent claim that recites “[a] method of treating acne vulgaris, the method comprising topically applying a pharmaceutical composition to an affected area of a body of a subject suffering from acne vulgaris; wherein the composition 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%.”

204. The preamble of claim 11 is rendered obvious over the Tazorac® Label as discussed previously in claim 1 and as expounded on further in Dr. Schwartz’s declaration. *See supra* § XI.A.1.-2.; Ex. 1003 (Schwartz Decl.) at ¶ 199.

205. Formula 4A of the '824 publication disclosed each of the formulation limitations recited in claim 11 except for 0.045% tazarotene for the reasons I explained in Ground 5. *Supra* § IX.A.2.

206. The use of 0.045% tazarotene is rendered obvious over the combination of the '824 publication and the IDP-118 study in view of Anderson, Kircik, or Chim as discussed previously in Claim 1 and as expounded on further in Dr. Schwartz's declaration. *See supra* § XI.A.1.-2.; Ex. 1003 (Schwartz Decl.) at ¶¶ 199-201.

207. Therefore, it is my opinion that claim 11 of the '482 patent would have been obvious over the combination of the '824 publication and the IDP-118 study in view of Anderson, Kircik, or Chim.

XII. SECONDARY CONSIDERATIONS

208. I am aware that the Applicants argued during prosecution that the results of the clinical trials disclosed in the '482 patent demonstrated unexpected results that are indicative of non-obviousness because the Composition A allegedly provided similar efficacy and less irritation than the commercial 0.1% Tazorac® product. *See* Ex. 1002 ('482 patent prosecution history) at 81-84, 167-170, 205-206. In my opinion, an ordinarily skilled formulator in May 2017 would not have found the results relied upon by Applicants to be unexpected. As I explained above, it was well known in the prior art that reducing the concentration of tazarotene in a topical formulation would lead to a decrease in observed irritation. *See supra* ¶¶ 31-33.

Thus, it would have been entirely expected for a composition comprising 0.045% tazarotene (Composition A) to produce less irritation than a composition comprising 0.1% tazarotene (Tazorac® 0.1%). Additionally, as I explained above, an ordinarily skilled formulator in May 2017 would have known that the concentration of the active ingredient in a topical composition could be significantly reduced without reducing the efficacy of the composition through routine formulation techniques. *Supra* § III. Indeed, the prior art I discussed above provided exemplary lotion vehicles that were able to do just that. Therefore, it is my opinion that an ordinarily skilled formulator in May 2017 would not have been surprised that Composition A resulted in numerically similar efficacy as Tazorac® 0.1% in one of the clinical studies disclosed in the '482 patent. Additionally, I note that the clinical study the Applicants relied on does not compare Composition A to a formulation with 0.05% tazarotene, which would have been a more appropriate comparison for Composition A, particularly given that those formulations were used to treat acne, as evidenced by the prior art I discussed above.

209. Further, given that the formulations claimed in the '482 patent are not new, and were invented and publicly disclosed before May 2017, I am not aware of any long-felt need in the industry, skepticism of the invention, or teaching away from the invention. I am also not aware of any praise for the alleged inventions or copying of the alleged inventions. If Patent Owner identifies any alleged evidence of

secondary considerations in the future, I reserve the right to respond to that information.

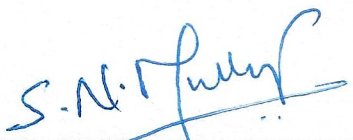
XIII. CONCLUSION

210. For the foregoing reasons, it is my opinion that the formulation limitations of claims 1-11 of the '482 patent are rendered obvious by the prior art discussed above in view of the knowledge of one of ordinary skill in the art at the time of the alleged invention.

211. I reserve the right to supplement my opinions in the future to address or respond to any arguments that Patent Owner may raise, as well as new information, including, but not limited to, any claim constructions advanced by Patent Owner or adopted by the Board in the Institution Decision, and respond to any alleged secondary considerations as they become available to me.

212. I declare that the foregoing is true and correct, and further that the foregoing statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: June 21, 2023.



Dr. Narasimha Murthy