Paper No. __

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ENCUBE ETHICALS PVT. LTD.
Petitioner

v.

DERMAVANT SCIENCES GMBH
Patent Owner

IPR2024-00834

U.S. Patent No. 11,590,088

PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 11,590,088

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EXHIBIT LIST[1]

Exhibit No.	Exhibit Description
1001	U.S. Patent No. 11,590,088 ("the '088 patent")
1002	File History of U.S. Patent No. 11,590,088
1003	Declaration of Wieke H. Liem, M.D.
1004	*Curriculum Vitae* of Wieke H. Liem, M.D.
1005	U.S. Patent Application Pub. No. 2016/0338973 ("Sonti")
1006	Dogra, et al., Psoriasis: Epidemiology, Clinical Features, Co-morbidities, and Clinical Scoring, Indian Dermatology Online Journal 7(6):471-480 (2016)
1007	Spuls, et al., How Good Are Clinical Severity and Outcome Measures for Psoriasis?: Quantitative Evaluation in a Systematic Review, Journal of Investigative Dermatology 130:933-943 (2010)
1008	Bissonnette, et al., Efficacy and Safety of Topical WBI-1001 in Patients With Mild to Moderate Psoriasis: Results From a Randomized Double-Blind Placebo-Controlled, Phase II Trial, Journal of the European Academy of Dermatology & Venereology 26:1516-1521 (2012) ("Bissonnette")
1009	Bolkote, et al., An Analysis of Psoriasis Skin Images, International Journal of Inventive Engineering and Sciences 2(12):17-22 (2014)

[1] All citations in this Petition are to the branded numbers added by the Petitioner in the bottom right corner of the exhibits, except citations to patents and published applications, which are cited by column and line or paragraph number.

1010	Cappelleri, et al., Psychometric Validation of the Physician Global Assessment Scale For Assessing Severity of Psoriasis Disease Activity, Quality of Life Research 22:2489-2499 (2013)
1011	Patel, et al., Evaluating Psoriasis: A Review of the Assessments Most Commonly Used in Clinical Trials, Psoriasis Forum 17(4):259-266 (2011)
1012	WO 2001/042231
1013	U.S. Patent No. 7,868,047 ("Chen")
1014	Valerie J. Paul, Sally Frautschy, William Fenical, and Kenneth H. Nealson, Antibiotics in Microbial Ecology, Isolation and Structure Assignment of Several New Antibacterial Compounds from the Insect-Symbiotic Bacteria Xenorhabdus spp., Journal of Chemical Ecology 7(3):589-597 (1981)
1015	Smriti K. Raychaudhuri, Emanual Maverakis, & Siba P. Raychaudhuri, Diagnosis and Classification of Psoriasis, 13 Autoimmunity Reviews 490 (2014)
1016	Chinese Clinical Trial Register Registration Number ChiCTR-TRC-10000995, Pharmacokinetics and Tolerability of Topically Applied Benvitimod Cream in Patients with Psoriasis
1017	Chinese Clinical Trial Register Registration Number ChiCTR-TRC-11001391, Multicentre, Randomised, Double-Blind, Placebo Controlled Trial on Topically Applied Benvitimod Cream in Patients With Psoriasis
1018	Chinese Clinical Trial Register Registration Number ChiCTR-TRC-13003259, Multi-centre, Randomised, Double-Blind, Placebo- and Comparator-Controlled Trial on Topically Applied Benvitimod Cream in Patients With Psoriasis
1019	Mark S. Butler, Avril A. B. Robertson, Matthew Cooper, Natural product and natural product derived drugs in clinical trials, Natural Product Reports (2014)
1020	USAP Dictionary of USAN and International Drug Names, 42nd ed., p. 212 (2006)
1021	Precision FDA, U.S. Food & Drug Administration, UNII Search, entry for UNII: L0Q8IK9E08 ("Steareth-20")

1022	Precision FDA, U.S. Food & Drug Administration, UNII Search, entry for UNII: V56DFE46J5 (“Steareth-2”)
1023	Global Ingredient Archival System, GSRS database (https://gsrs.ncats.nih.gov/ginas/app/beta/browse-substance), entry for Steareth-2
1024	Global Ingredient Archival System, GSRS database (https://gsrs.ncats.nih.gov/ginas/app/beta/browse-substance), entry for Steareth-20
1025	FDA Prescribing Information, VTAMA® (tapinarof) topical cream, 1%
1026	Clinical Trials website (https://clinicaltrials.gov/), clinical trials for plaque psoriasis treatments prior to November 2018
1027	U.S. Patent Publication No. 2003/0171429 (“Chen 1”)
1028	U.S. Patent Publication No. 2010/0094041 (“Chen 2”)
1029	U.S. Patent Publication No. 2008/0255245 (“Chen 3”)
1030	McMullen et al., Emulsions and their Characterization by Texture Profile Analysis, Handbook of Formulating Dermal Applications, Section II, Chapter 6, 131-151 (2017)
1031	Excerpts from Handbook of Pharmaceutical Excipients , 8th Edition
1032	Declaration of Paul T. Sudhakar, MS, MBA
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1034	Declaration of Sylvia D. Hall-Ellis, Ph.D.

I. INTRODUCTION

The ’088 patent is directed to a method of treating plaque psoriasis by topically administering a composition containing about 1% tapinarof to affected areas once a day. The specification contends that it was “surprisingly” found that once daily application was just as effective as twice daily. However, during prosecution the examiner cited a set of prior art by Chen et al.[2] disclosing treating plaque psoriasis by topically applying a composition containing 1% tapinarof once a day. The applicant did not dispute this. Instead, the applicant argued that Chen did not teach treating specifically “plaque” psoriasis and did not disclose efficacy specifically measured according to the Physician’s Global Assessment (“PGA”) scale.

This Petition identifies two alternative references, Sonti and Bissonnette, that each disclose what the applicant contended was missing. Sonti (Grounds 1-3) discloses treating plaque psoriasis by topically administering tapinarof (including

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[2] There are five related “Chen” references—three discussed during prosecution (Ex-1027, Ex-1028, Ex-1029) and two others cited in the Sonti reference (Ex-1012, Ex-1013).

1% tapinarof once a day) and achieving the claimed PGA score improvement by doing so. Bissonnette (Ground 4) also discloses treating plaque psoriasis by topically applying 1% tapinarof and achieving the claimed PGA score improvement by doing so. While Bissonnette discloses twice daily administration, once daily was already known to be a highly effective (as taught by each of Sonti and Chen) and would have been an obvious treatment modification.

By November 2018, there was nothing novel or non-obvious about topically administering a 1% tapinarof composition once a day to effectively treat plaque psoriasis as claimed. Petitioner respectfully requests that the Board institute *inter partes* review and cancel the challenged claims.

II. STANDING

Petitioner certifies that IPR is available for the '088 patent. Petitioner is not barred or estopped.

III. IDENTIFICATION OF THE CHALLENGE

A. Prior Art

The '088 patent was filed on July 22, 2022, with an earliest possible effective filing date of Nov. 13, 2018. The prior art relied upon includes:

- U.S. Patent Application Pub. No. 2016/0338973 **("Sonti"; "Ex-1005")**, published Nov. 24, 2016.

- Bissonnette, et al., *Efficacy and Safety of Topical WBI-1001 in Patients With Mild to Moderate Psoriasis: Results From a Randomized Double-Blind Placebo-Controlled, Phase II Trial*, Journal of the European Academy of Dermatology & Venereology 26:1516-1521 (2012) **("Bissonnette"; "Ex-1008")**, published and publicly available by 2013. Ex-1034, ¶¶60-67.
- U.S. Patent No. 7,868,047 **("Chen"; "Ex-1013")**, issued Jan. 11, 2011.

Each is prior art to the '088 patent under at least AIA §102(a)(1).

B. Grounds

Petitioner requests cancellation of claims 1-4, 6-10, 16, 18, 21-22 of the '088 patent ("Challenged Claims"). In support, this Petition includes the declarations of Dr. Wieke Liem, M.D., F.A.A.D. (Ex-1003) and Mr. Paul Sudhakar, M.S., M.B.A. (Ex-1032).

	Claims	Basis for Unpatentability
Ground 1	1-4, 6, 8-9, 16, 18, and 22	Anticipated by Sonti (Ex-1005)
Ground 2	1-4, 6-10, 16, 18, and 21-22	Obvious in view of Sonti (Ex-1005)
Ground 3	7, 9-10, 21	Obvious in view of either Ground 1 or Ground 2, further in view of Bissonnette (Ex-1008)
Ground 4	1-4, 6-10, 16, 18, 21-22	Obvious in view of Bissonnette (Ex-1008), further in view of Sonti (Ex-1005) and/or Chen (Ex-1013)

IV. THE '088 PATENT

A. Overview

The '088 patent relates to using tapinarof in a topical composition to treat atopic dermatitis or plaque psoriasis. Ex-1001, Abstract. The '088 patent contends that it was "surprisingly and unexpectedly found" that a 1% tapinarof cream applied once daily was just as effective as twice daily. Ex-1001, 6:46-68. However, as the Sonti and Chen references discussed below show, it was already known that once daily application of 1% tapinarof was highly effective in treating plaque psoriasis. *See also* Ex-1003, ¶¶56, 77-87, 95-104.

The '088 patent also describes using the Physician Global Assessment scale ("PGA") and percent body surface area affected ("BSA") to assess severity of and treatment response for plaque psoriasis. *E.g.,* Ex-1001, 21:9-36, 22:22-49, 23:24-46. The PGA and BSA were well-known assessment metrics for plaque psoriasis long before the priority date. *E.g.,* Ex-1003, ¶¶40-53; Ex-1005, Ex-1006; Ex-1007, Ex-1008; Ex-1010; Ex-1011.

B. Prosecution History

The Examiner first rejected the claims as anticipated by each of three Chen publications: "Chen 1" (Ex-1027), "Chen 2" (Ex-1028), and "Chen 3" (Ex-1029). Ex-1002, 234-37.

In response, the applicant argued that each of the Chen references "[did] not mention treating *plaque* psoriasis specifically with the compounds described therein" (emphasis added). Ex-1002, 284-87. However, the Chen references did disclose treating specifically plaque psoriasis. Ex-1003, ¶¶63-65; *see also, e.g.,* Ex-1027 ("Chen 1"), [0091]-[0102] ("Volunteer 2… with plaques on her back").

The applicant also argued that the Chen references did not disclose (i) "how to demonstrate that effective treatment of said plaque psoriasis can be done via numerous measurements," or (ii) "what is a measure of effective treatment of said plaque psoriasis." Ex-1002, 284-87. Specifically, the applicant argued that the references did not discuss using psoriasis scoring metrics such as PGA, BSA, or PASI. *Id.* But again, such metrics were commonplace by November 2018. Ex-1003, ¶¶66, 40-53.

The Examiner then rejected the claims as anticipated by Rubenstein.Ex-1002, 290-92. The Applicant asserted that Rubenstein was unavailable as prior art; the Examiner allowed the claims. *Id.*, 307-09.

V. LEVEL OF ORDINARY SKILL IN THE ART

A person of ordinary skill in the art ("POSA") is presumed to have known the relevant art at the time of the invention. MPEP §2141.03. A POSA has ordinary creativity, is not an automaton, and is capable of combining the teachings of the prior art. *E.g.*, *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420–21 (2007).

For the ’088 patent, the relevant art is methods of treating skin diseases with topical compositions, and formulations thereof. The relevant POSA would have been a medical doctor with an M.D. degree and a specialization in dermatology (such as a dermatologist), with at least two years’ experience as a clinician diagnosing and treating patients afflicted with skin conditions that include plaque psoriasis. Ex-1003, ¶¶23-24. A POSA would have had access to and would have consulted with a collaborative team of ordinarily skilled artisans, including drug formulators having a bachelor of pharmacy (B.Pharm) with at least 5 years of experience, or a masters in pharmacy (M.Pharm) with at least two years of experience, in the pharmaceutical sciences that included developing topical compositions for treating skin conditions. *Id.*

VI. CLAIM CONSTRUCTION

Claim terms are typically given their ordinary and customary meanings as would have been understood by a POSA at the time of the invention, having taken into consideration the language of the claims, the specification, and the prosecution history. 37 CFR §42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005).

This Petition applies the ordinary and customary meaning. At this time, Petitioner does not believe it necessary for the Board to expressly construe any term for the purpose of this IPR proceeding.[3]

VII. OVERVIEW OF THE PRIOR ART

A. Background

Plaque psoriasis is the most common type of psoriasis, affecting 80%-90% of psoriatic patients. Ex-1015, §4.1; Ex-1009, 2; Ex-1006, Abstract. Plaque psoriasis manifests as raised scaly patches on the skin, known as "plaques." Ex-1003, ¶¶38-39.

By November 2018 there were several well-known metrics for assessing plaque psoriasis severity and treatment response. These included the PGA and BSA. *E.g.*, Ex-1003, ¶¶40-46. Such metrics were commonly used because there are not biomarkers available for assessing plaque psoriasis. *E.g.,* Ex-1007, 1 ("as

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[3] Petitioner reserves all rights to raise claim construction arguments in any litigation concerning the '088 patent. Petitioner also reserves all rights to raise invalidity defenses not available in *inter partes* reviews, such failure to satisfy 35 U.S.C. §112. Petitioner has endeavored to apply the prior art to the claims but in doing so does not admit that the claims satisfy Section 112.

there are no biomarkers available.. clinical measures are used…"); Ex-1011, 1 (same); Ex-1003, ¶42.

As one example, prior to the alleged date of invention there were at least 36 studies of plaque psoriasis treatments using PGA score improvement as an "outcome measure," and at least 48 using BSA. Ex-1003, ¶¶47-51; Ex-1026. As another example, a series of clinical trials in China in the early 2010s treated plaque psoriasis patients with a topical 1% tapinarof composition and also used PGA score as a "primary outcome." Ex-1016, Ex-1017, Ex-1018; Ex-1003, ¶¶52-53.

B. Overview of References

1. Sonti (Ex-1005)

Sonti discloses topical emulsion compositions having a therapeutically effective amount of tapinarof[4], along with methods of treating atopic dermatitis and plaque psoriasis using the same. Ex-1005, Abstract, [0008]-[0010], [0273]-[0300]; Ex-1003, ¶¶77-87.

[4] Sonti uses the chemical name "3,5-Dihydroxy-4-isopropyl-trans-stilbene," which is tapinarof. Ex-1032, ¶¶58-63, 42-43; Ex-1003, ¶77; Ex-1001, 7:4-20.

Sonti explains that tapinarof was already known to effectively treat psoriasis: "[Tapinarof] is… suitable for the treatment of… psoriasis and inflammation." Ex-1005, [0010]. In support, Sonti cites two of the Chen references that specifically disclose a "1% cream" of tapinarof topically applied "once per day" to effectively treat plaque psoriasis. Ex-1005, [0010] (citing Ex-1013 (US 7,868,047) (*see* 32:10-66) and Ex-1012 (WO 2001/042231) (*see* 20:28-21:25)).

Sonti then teaches various formulations for topical emulsions that contain tapinarof. Sonti also teaches using the formluations to effectively treat "moderate to severe plaque psoriasis." *E.g.,* Ex-1005, [0286]-[0288].

Sonti teaches that the topical emulsions can contain several different amounts of tapinarof, including "1%... by weight." *E.g.,* Ex-1005, [055], [0196]. Sonti also discloses that the topical emulsions can be applied to the affected area with several different frequencies, including "once daily." Ex-1005, [0387].

Sonti also specifically teaches treating plaque psoriasis with the tapinarof compositions such that a PGA score is improved to 0 or 1 or improved by two grades, for example:

[0287] The PGA scale in its typical use, is a 7-point scale ranging from clear to severe.

Severe	Very marked plaque elevation, scaling, and/or erythema
Moderate to Severe	Marked plaque elevation, scaling, and/or erythema
Moderate	Moderate plaque elevation, scaling, and/or erythema
Mild to moderate	Intermediate between moderate and mild
Mild	Slight plaque elevation, scaling, and/or erythema
Almost clear	Intermediate between mild and clear
Clear	No signs of psoriasis

[0288] One embodiment of the invention is a percent of patients achieving a 50% or a 75% reduction in PASI score (PASI 50 or PASI 75) achieved by using a topical emulsion composition as described herein. This may be a standalone clinical endpoint, or may be used in combination with the patient also reaching a PGA score of 0 or 1 (clear or almost clear) at a defined time point, such as at 8, 12 weeks, 16 weeks, 20, or 24 weeks, or greater than 24 weeks of treatment. As a degree of measurement of severity, the patient will most likely have started with a PGA score of ≥4 at baseline for purposes herein, e.g. one with moderate to severe plaque psoriasis.

Ex-1005, [0287]-[0288].

2. Bissonnette (Ex-1008)

Bissonnette discloses treating patients with mild to severe plaque psoriasis with topical "1.0% WBI-1001" (tapinarof)[5] applied twice daily, using both PGA and BSA to show treatment efficacy. Ex-1008, Abstract, 1-2; Ex-1003, ¶¶88-94.

Bissonnette describes sixty-one patients having 1–10% BSA covered with plaque psoriasis and a PGA score of "two (mild) to four (severe)" at baseline. Ex-1008, 1, Abstract and 2. Forty were given 1% WBI-1001 (tapinarof) in a topical cream formulation twice daily for 12 weeks. Ex-1008, 1.

Efficacy was then evaluated using PGA, BSA, and PASI. Ex-1008, 1, Abstract. After 12 weeks, twenty-seven of the forty treated patients "achieved a PGA score of clear (0) or almost clear (1)." Ex-1008, 3. BSA affected had also decreased an average of 79.1%, compared to an increase for the placebo group. *Id*. The twice-daily administration regimen did result in adverse events at the site of application for about 80% of the subjects, though nearly all were "mild." Ex-1008,

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[5] "WBI-1001" is tapinarof. Ex-1032, ¶¶64-67; Ex-1003, ¶89; Ex-1019, 22; Ex-1001, 7:7-20. Also, a POSA would have understood "1% WBI-1001" cream to indicate 1% tapinarof by weight. Ex-1032, ¶¶74-75, 79-80.

4, Table 4. Bissonnette concluded that "topical WBI-1001 [tapinarof] at 1% is effective for the treatment of mild to moderate plaque psoriasis." Ex-1008, 4.

3. Chen (Ex-1013)

Chen discloses treating psoriasis by topically applying a "1% cream of 3,5-dihydroxy-4-isopropylstilbene" (tapinarof)[6] to affected areas "once per day." Ex-1013, Abstract, 32:10-33:4; Ex-1003, ¶¶95-104.

"[V]olunteers, each with a long psoriasis history, were recruited for the tests." Ex-1013, 32:26-29. Volunteer 1 had "scalp psoriasis for more than 15 years" and Volunteer 2 had "plaques on her back." Ex-1013, 32:30-37. A POSA would have understood that Chen was describing plaque psoriasis. Ex-1003, ¶¶98-101; Ex-1013, 2:56-3:4 and 32:25-37.

The "once per day" administration of 1% tapinarof "showed great efficacy" and was "active in reducing or eliminating symptoms of psoriasis." Ex-1013, 32:51-65, 32:15-18; *see also id.* 2:56-3:4, Claim 1. After seven days of treatment,

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[6] "*3,5-dihydroxy-4-isopropylstilbene*" is tapinarof. Ex-1032, ¶¶68-70; Ex-1003, ¶96; Ex-1001, 7:4-20. Also, a POSA would have understood the "1% cream" to indicate 1% tapinarof by weight. Ex-1032, ¶¶74-75, 78, 80.

Volunteer 1 showed "complete[] clearance" and Volunteer 2 showed "significant improvement." Ex-1013, 32:51-62.

VIII. GROUND 1: SONTI ANTICIPATES CLAIMS 1-4, 6, 8-9, 16, AND 22

A. Independent Claim 1

1. [1.pre] "A method for treating mild to severe plaque psoriasis in a subject…"

Sonti discloses the preamble. Ex-1003, ¶¶109-116. For example,

> One embodiment of the invention is a percent of patients achieving [a percentage PASI score reduction] by using a topical emulsion composition as described herein…in combination with the patient also reaching a PGA score of 0 or 1 (clear or almost clear) at a defined time point…of treatment… [T]he patient will most likely have started with a PGA score of ≥4 at baseline for purposes herein, e.g. one with **moderate to severe plaque psoriasis**.

Ex-1005, [0288] (emphasis added); *see also id.* [0285]-[0294], [0298]-[0300]. This disclosure anticipates. *See, e.g., Genentech, Inc. v. Hospira, Inc*., 946 F.3d 1333, 1338 (Fed. Cir. 2020) (Even "[a] prior art reference that discloses an overlapping but different range than the claimed range can be anticipatory, even where the prior art range only partially or slightly overlaps with the claimed range.").

Alternatively, Sonti's teaching also necessarily discloses treating mild plaque psoriasis. A POSA would have known that Sonti's disclosure of treating moderate to severe psoriasis is inherently also a method of treating mild psoriasis. Ex-1003, ¶116.

2. [1.a] "comprising topically administering a topical composition containing about 1.0% tapinarof"

Sonti discloses this element. Ex-1003, ¶¶117-124.

The "topical" compositions that are administered "to the skin," i.e., topically. Ex-1005, Title, Abstract; Ex-1003, ¶118. The compositions contain "therapeutically effective amounts" of "3,5-dihydroxy-4-isopropyl-trans-stilbene," which is tapinarof. Ex-1032, ¶¶58-63, 56-57; Ex-1005, Abstract, [0008]. The compositions can also contain about 1% tapinarof:

> **In all of the compositions described herein**, the amount of [tapinarof]… may range from about 0.25% to about 2% by weight of composition. In one embodiment, the amount may be… **1.0%**… by weight...

Ex-1005, [0196] (emphasis added); *see also id., e.g.*, [055], [0323] (formulation 1(a), "1.00 %w/w" of tapinarof), [0327], [0355], [0367], [0370] (Table 9, formulations 30-33, "1.00 % w/w" of tapinarof); Ex-1003, ¶¶120-122; Ex-1032, ¶¶49-50.

Even if Sonti did not expressly state, with respect to each embodiment disclosed as containing 1% tapinarof, that the particular composition is used as a method for treating mild to severe plaque psoriasis, a POSA would understand that is what Sonti discloses. Ex-1003, ¶¶123-124. For example, Sonti teaches "using a topical emulsion composition as described herein" to treat a patient with "moderate to severe plaque psoriasis." Ex-1005, [0288].

In addition, Sonti focuses on treating a limited number of diseases (atopic dermatitis and plaque psoriasis, Ex-1005, [273]-[0284], [0285]-[0295]), using a limited number of potential amounts of tapinarof (including 1%, as explained above). Even if Sonti did not expressly spell out the combination (it does), a POSA would at once envisage the option of treating plaque psoriasis with a 1% tapinarof composition as claimed. Ex-1003, ¶124; *see Kennametal, Inc. v. Ingersoll Cutting Tool Co*., 780 F.3d 1376, 1381 (Fed. Cir. 2015).

3. [1.b] "to affected areas of the subject"

Sonti discloses this element. Ex-1003, ¶¶125-127. The compositions "are generally applied in topical manner to the affected area, i.e. localized application to the skin region where the clinical abnormality is manifest." Ex-1005, [0301]; *see also id.*, Title, Abstract (tapinarof compositions administered "to the skin of the patient"), [0136], [0272], [0301], [0387].

4. [1.c] "once a day"

Sonti discloses this element. Ex-1003, ¶¶128-132; Ex-1005, [0387] ("Application of **a composition of the present invention** may be applied to affected areas… **once daily**… with the dose represented by **any of the embodiments herein**.") (emphasis added).

In describing the frequency, Sonti refers to "a composition of the present invention," "any of the embodiments herein," and "a formulation such as described above." Ex-1005, [0387]. A POSA would understand Sonti to be disclosing that its formulations (including the 1% tapinarof formulations) can be applied "once daily." Ex-1003, ¶¶129-131.

In addition, Sonti focuses specifically on treating a limited number of diseases (atopic dermatitis and plaque psoriasis), tapinarof strengths (including "1%"), and application frequencies (including "once daily"). Even if Sonti did not expressly spell out the combination (it does), a POSA would at once envisage the option of treating plaque psoriasis with a 1% tapinarof composition administered once a day. Ex-1003, ¶132; *see Kennametal*, 780 F.3d at 1381.

5. [1.d] "wherein after topically administering the topical composition a Physician Global Assessment (PGA) score[7] is improved by 2 grades or has improved to a score of 0 or 1."

Sonti discloses this element. Ex-1003, ¶¶133-146.

Sonti discloses that "an embodiment of the invention is" a percent of patients "**reaching a PGA score of 0 or 1** (clear or almost clear) at a defined time point, such as 8, 12 weeks… of treatment" (in combination with the patient also achieving a specified reduction in PASI score), "achieved by using a topical emulsion composition as described herein." Ex-1005, [0288] (emphasis added); *see also id.* [0285]-[295].

A POSA would understand "using a topical emulsion composition as described herein" includes topically administering the composition containing about 1% tapinarof once a day, as explained with respect to elements [1.pre], [1.a]-[1.c] above. Ex-1003, ¶141. Thus Sonti discloses that after topically administering

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[7] The '088 patent specification notes that in "embodiments described herein," a 5-point PGA scale is used. Ex-1001, 22:22-29. However, the claims do not identify a particular PGA scale, and in any event 0 or 1 meant the same thing under any PGA scale—"clear" and "almost clear." Ex-1003, ¶¶138, 352; Ex-1005), [0287]; Ex-1008, 3; *see also* Ex-1001, 22:30-33.

the topical composition a PGA score "*has improved to a score of 0 or 1*" as claimed.

Sonti also discloses the alternative PGA improvement—a score "improved by two grades." The patient "will most likely have started with a PGA score of [greater than or equal to] 4." Ex-1005, [0288]. A patient who starts with a PGA score of greater or equal to 4 and then reaches a PGA score of 0 or 1, has also had their PGA score improve by 2 grades (in fact by more than two grades). Ex-1003, ¶142. Sonti has additional disclosure of the claimed PGA score improvements. Ex-1003, ¶¶143-145; *see also, e.g.,* Ex-1005, [0289], [0290], [0293].

In addition, Sonti discloses a limited number of metrics for plaque psoriasis treatment response—the recited "PASI" and "PGA" scales. Ex-1005, [0285]-[0294]. Even if Sonti did not expressly spell out the combination (it does), a POSA would at once envisage the option of administering the tapinarof composition as claimed that results in the claimed PGA score improvement. Ex-1003, ¶¶146; *see Kennametal*, 780 F.3d at 1381.

B. Dependent Claim 2: "the method of claim 1, wherein the topical composition is an oil-in-water emulsion"

Sonti discloses this claim. Ex-1003, ¶¶147-148; Ex-1032, ¶¶92-94. Sonti discloses that suitable formulations include "emulsion[s]" and "oil-in-water emulsion[s]." Ex-1005, Abstract. And Sonti teaches that "'emulsion' and 'oil-in-water emulsion'" are the same thing. Ex-1005, [0054]; *see also id.,* [0101]. Sonti

also discloses this element elsewhere. *E.g.,* Ex-1005, Figures 1-2, [0021]-[0040], [0042]-[0044], [0048], [0050]-[0053], [0055] ("emulsions") and [0049], [0054]) [0100], claims 18, 20 ("oil-in-water emulsion").

C. Dependent Claim 3: "the method of claim 2, wherein the oil phase of the oil-in-water emulsion is comprised of medium chain triglycerides, propylene glycol, non-ionic emulsifying wax, diethylene glycol monoethyl ether, polyoxyl stearyl ether-2, polysorbate 80, polyoxyl stearyl ether-20, benzoic acid, and butylated hydroxytoluene"

Sonti discloses this claim. Ex-1003, ¶149; Ex-1032, ¶¶95-106.

Claim 3 recites a list of common ingredients for the oil phase of an oil-in-water emulsion. Ex-1032, ¶96. Sonti discloses these. The '088 patent itself actually incorporates the formulations of Sonti by reference. Ex-1001, 8:60-63.

A POSA would read Sonti for all that it discloses, and a POSA would not have understood Sonti to be teaching only a series of separate embodiments. Rather, a POSA would have understood Sonti as teaching menus of options and would have at once envisaged using the options for oil phase ingredients in any disclosed formulation. Ex-1032, ¶¶88-91, 45-50.

Sonti discloses medium chain triglycerides ("MCT") in the oil phase. Ex-1032, ¶97; Ex-1005, [0061], [0071]; *see also id.* [0370] (Table 9, "MCT" in the oil phase, including formulations 30-33 having 1% tapinarof).

Sonti discloses propylene glycol. Ex-1032, ¶98; Ex-1005, [0122]-[0123] (penetration enhancer may include "diols"), [0130] ("exemplary diols

include…propylene glycol"). Sonti indicates that the penetration enhancer can be part of the oil phase. Ex-1032, ¶98; Ex-1005, [0122], [0117]; *see also* Ex-1005, [0354], [0355], [0370] (Tables 8 and 9, showing "propylene glycol" in the oil phase, including formulations 21 and 30-33 having 1% tapinarof).

Sonti also discloses a surfactant such as a non-ionic surfactant (Ex-1005, [0074], [0077]), that includes emulsifying waxes (Ex-1005, [0078]). *See also id.* [0087], claims 16-17. The emulsifying wax can be a non-ionic emulsifying wax and can be part of the oil phase. Ex-1032, ¶99; Ex-1005, [0323], [0325], [0327] (*e.g.,* Tables 1, 3 listing "non-ionic emulsifying wax" in oil phase, including formulations 1a, 13 having 1% tapinarof).

Sonti discloses that the oil phase can include a co-solvent, such as diethylene glycol monoethyl ether. Ex-1032, ¶100; Ex-1005, [0119], [0120], [129], [0194], [0198], [0205], [0213], [0215], [0224], [0239], [0255], [0351] (Table 7, formulations 15-20), [0357] (Example 8, including formulation 21 having 1% tapinarof). The co-solvent can be "an oil miscible co-solvent" to help "solubilize the active ingredient in the oil phase." Ex-1005, [0117]; *see also id.* [0122], [0123], [129]; Ex-1032, ¶100.

Sonti also discloses a non-ionic surfactant that includes an ethoxylated fatty alcohol ether (Ex-1005, [0074], [0077], [0078]), such as "steareth-2" (Ex-1005, [0079]), in the oil phase. *See also* Ex-1005, Tables 1-4 and 7-9 ("steareth-2" in the

oil phase, including formulations 1a, 13, 21, 30-33 having 1% tapinarof). "Steareth-2" corresponds to polyoxyl stearyl ether-2. Ex-1032, ¶101; Ex-1022; Ex-1025.

Sonti also discloses the oil phase including a non-ionic including a sorbitan derivative (Ex-1005, [0074], [0077], [0078]), such as polysorbate 80 (Ex-1005, [0085]). Ex-1032, ¶102; *see also* Ex-1005, [0089], [0091]-[0092]. Specific examples also disclose this. Ex-1005, [0351], [0355], [0357], [0370], claims 13, 15, and 17 (Tables 8, 9, "polysorbate 80" in the oil phase, including formulations 21 and 30-33 having 1% tapinarof).

Sonti also discloses a non-ionic surfactant that includes an ethoxylated fatty alcohol ether (Ex-1005, [0074], [0077], [0078]), such as "steareth-20" (Ex-1005, [0079]). Ex-1032, ¶103; *see also* Ex-1005, Tables 1-4, 7-9 ("steareth-20" in the oil phase, including formulations 1a, 13, 21, and 30-33 having 1% tapinarof). "Steareth-20" corresponds to polyoxyl stearyl ether-20. Ex-1032, ¶103; Ex-1021; Ex-1024.

Sonti also discloses a pH adjusting agent that is an acid, such as benzoic acid in the oil phase. Ex-1032, ¶104; Ex-1005, [0103], [0104]. *See also* Ex-1005, [112], [0113]-[0115], [0191]-[0192], [0194], [0241], [0254], [0257]. Specific examples also disclose this. Ex-1005, [0327], [0351], [0355], [0357], [0370]

(Tables 3-4, 7-9 with "benzoic acid" in the oil phase, including formulations 13, 21, 30-33 having 1% tapinarof).

Sonti also discloses compositions that include an antioxidant, such as butylated hydroxytoluene (known as "BHT"). Ex-1032, ¶105; Ex-1005, [0093]-[0095], [0187]-[0188], [0191]-[0192], [0194], [0214], [0226], [0238], [0253], claim 5. Specific examples also disclose this. Ex-1005, [327], [0351]-[0374] (Tables 4, 7-9 with "BHT" in the oil phase, including formulations 13, 21 and 30-33 having 1% tapinarof).

D. Dependent Claim 4: "the method of claim 2, wherein the water phase of the oil-in-water emulsion is comprised of sodium citrate, edetate disodium, citric acid monohydrate, and water"

Sonti discloses this claim. Ex-1003, ¶150; Ex-1032, ¶¶107-113.

Sonti discloses a water phase comprising sodium citrate, edetate disodium, citric acid monohydrate, and water, including in formulations that have 1% tapinarof. Ex-1032, ¶¶109-109. For example, Formulation 13:

TABLE 4

Formulation Number Ingredient	10 % w/w	11 % w/w	12 (tergus) % w/w	13 % w/w	14 % w/w
	Active Phase				
Active ingredient	0.00	0.10	0.50	1.00	2.00
Polysorbate 80	1.50	1.50	1.50	1.50	1.50
Propylene glycol	10.00	10.00	10.00	10.00	10.00
Diethylene glycol monoethyl ether	2.00	2.00	2.00	2.00	2.00
	Water Phase				
Purified water	53.18	53.08	52.68	52.18	51.18
Sodium citrate	0.19	0.19	0.19	0.19	0.19
Citric acid	0.08	0.08	0.08	0.08	0.08
Disodium EDTA	0.10	0.10	0.10	0.10	0.10
	Oil Phase				
BHT	0.10	0.10	0.10	0.10	0.10
Benzoic Acid	0.25	0.25	0.25	0.25	0.25
Non-ionic emulsifying wax	7.20	7.20	7.20	7.20	7.20
Petrolatum white	16.50	16.50	16.50	16.50	16.50
Light mineral oil	6.00	6.00	6.00	6.00	6.00
Steareth 2	1.80	1.80	1.80	1.80	1.80
Steareth 20	1.10	1.10	1.10	1.10	1.10
	100.00	100.00	100.00	100.00	100.00

Ex-1005, [0327]; *see also id.*, [0355] (Example 8), [0370] (Example 9).

A POSA would have known that "disodium EDTA" is edetate disodium. Ex-1032, ¶110; Ex-1031, 23-24. A POSA also would have known that "citric acid" is "citric acid monohydrate," or at a minimum, includes "citric acid monohydrate." Ex-1032, ¶111.

Each of the Example 4, 8, and 9 formulations were also a "cream" comprising a "water phase" and an "oil phase" blended into an "emulsion." Ex-1032, ¶112.

Sonti also teaches the ingredients of the water phase recited by claim 4 in its overview of the formulations. Ex-1032, ¶113.

E. Dependent Claim 6: "the method of claim 1, wherein the topically administering includes application to the affected area of the skin selected from the group consisting of body, arms, legs, back, chest, buttocks, neck, scalp, fingernails, toenails, and combination thereof"

Sonti discloses this element. Ex-1003, ¶¶151-155.

Sonti discloses "topical" compositions and administering the "present compositions to the skin of the patient." Ex-1005, Abstract, [0021]. A POSA would understand this to disclose applying the topical compositions to an affected area of the skin on the "body." Ex-1003, ¶153. Sonti also discloses that the "PASI" scale analysis for diagnosing the severity of "plaque psoriasis" examines "four **body** regions," including "the hands and **arms**," "**chest**, abdomen, and **back**," "head and **neck**," and "**buttocks**, thighs and **legs**," to determine how much of that region is "affected by psoriasis." Ex-1005, [0286] (emphasis added). The compositions are then "generally applied in topical manner to the affected area...." Ex-1005, [0301]; *see also id.* [0136]. Thus a POSA would understand Sonti to disclose applying the topical compositions to an affected area of the skin selected

from one of the group of listed body parts commonly affected by plaque psoriasis. Ex-1003, ¶¶154-155.

F. Dependent Claims 8, 22: "the method of claim 1, wherein the subject has been diagnosed with mild to [severe/moderate] plaque psoriasis having a Physician Global Assessment (PGA) score of greater than or equal to 2"

Sonti discloses these claims. Ex-1003, ¶¶156-162. "As a degree of measurement of severity, the patient will most likely have started with a **PGA score of ≥4 at baseline** for purposes herein, e.g. **one with moderate to severe plaque psoriasis**." Ex-1005, [0288] (emphasis added); *see also* Ex-1005, [0287], [0289]-[0294].

A POSA would have understood that treating a "patient" having "moderate to severe plaque psoriasis" "at baseline" discloses treating a subject who has been "*diagnosed*" with moderate to severe plaque psoriasis. Ex-1003, ¶160. This also necessarily discloses a subject diagnosed with "*mild to severe*" (claim 8) and "*mild to moderate*" (claim 22) plaque psoriasis. Ex-1003, ¶¶160-161; *see also Genentech*, 946 F.3d at 1338. Sonti also teaches treating patients with a PGA score of "≥4 at baseline." Ex-1005, [0288]. This discloses a subject having a PGA score of "*greater than or equal to 2*" (claims 8, 22). Ex-1003, ¶162.

G. Dependent Claim 9: "The method of claim 1, further comprising after topically administering the topical composition an improvement of one or more symptom of mild to severe plaque psoriasis as measured according to an assessment selected from the group consisting of Physician Global Assessment (PGA) score, Psoriasis Area and Severity Index (PAST)[8], target lesion grading, Itch/Pruritus numeric rating scale, percent body surface area (BSA) affected, Psoriasis Symptom Diary (PSD), Dermatology Quality of Life Index (DLQI), or 36 Item Short Form Survey (SF-36)"

Sonti discloses this claim. Ex-1003, ¶¶163-170.

Sonti discloses that "one embodiment of the invention is a percent of patients achieving a **50% or a 75% reduction in PASI score**" which "may be used in combination with a patient also **reaching a PGA score of 0 or 1**…at a defined time point…, such as at 8, 12 weeks… of treatment." Ex-1005, [0288]; *see also* Ex-1005, [0285]-[0294], [0308]. Prior to treatment, the patient "will most likely have started with a PGA score of "≥4… e.g., one with moderate to severe plaque psoriasis." Ex-1005, [0288].

The improvement in PASI and PGA scores were "achieved by using a topical emulsion composition as described herein." Ex-1005, [0288]. A POSA

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[8] Claim 9 abbreviates "Psoriasis Area and Severity Index" as "PAST," but the abbreviation was also commonly abbreviated "PASI."

would have understood this to include a 1% tapinarof composition administered once daily, as explained above with respect to claim 1. Ex-1003, ¶170.

Sonti's teaching discloses the "*improvement of one or more symptom of mild to severe plaque psoriasis*" following topical administration of the topical composition, as recited by claim 9, as the reductions in PASI and PGA scores disclosed by Sonti mean that one or more symptoms of the plaque psoriasis had improved. Ex-1003, ¶¶167, 169; *see also* Ex-1005, [0308]. This teaching also discloses the improvement as measured according to the PASI (50% or a 75% reduction in PASI score) and PGA (patient "also reaching a PGA score of 0 or 1" from a baseline of "≥ 4") metrics. Ex-1003, ¶¶166, 168.

H. Dependent Claim 16: "the method of claim 9, wherein the one or more symptom is improved after about 2 weeks, about 4 weeks, or about 8 weeks of administering the topical composition"

Dependent Claim 18: "the method of claim 1, wherein the PGA score is improved after about 2 weeks, about 4 weeks, or about 8 weeks of administering the topical composition"

Sonti discloses these claims. Ex-1003, ¶¶171-174. "One embodiment of the invention is a percent of patients [having plaque psoriasis] achieving a 50% or a 75% reduction in PASI score . . . achieved by using a topical emulsion composition as described herein . . . in combination with the patient also reaching a PGA score of 0 or 1 (clear or almost clear) at a defined time point, such as at **8,** 12 **weeks**… of treatment." Ex-1005, [0288] (emphasis added); *see also id.* [0308]. Sonti further

states that "the patient will most likely have started with a PGA score of ≥4 at baseline." Ex-1005, [0288].

Thus, Sonti teaches that the "*PGA score is improved*" after about 8 weeks of administering the topical tapinarof composition, as recited by Claim 18. Ex-1003, ¶¶171-172. Sonti also at the same time teaches that "*one or more symptom is improved*" after about 8 weeks of administering the topical composition, as recited by Claim 16. A POSA would understand that improving a PGA or PASI score means that one or more symptom has been improved. Ex-1003, ¶173.

Sonti also discloses claims 16 and 18 in other places. *E.g.*, Ex-1005, [0290], [0294]; Ex-1003, ¶174.

IX. GROUND 2: CLAIMS 1-4, 6-10, 16, 18, AND 21-22 ARE OBVIOUS OVER SONTI AND THE KNOWLEDGE OF A POSA

As discussed above in Ground 1, Sonti anticipated each of the Challenged Claims, except claims 7, 10, and 21. All of the Challenged Claims (including claims 7, 10, and 21) are also obvious in view of Sonti's teachings. A POSA would have read Sonti as a whole and for all that it discloses, and in doing so a POSA would have had good reason to apply its teachings, with a reasonable expectation of success, in the manner recited the claims. Ex-1003, ¶¶175-177.

A. Independent Claim 1

1. [1.pre]

Sonti discloses [1.pre] for the reasons explained in Ground 1. Alternatively, it would have been obvious to treat mild to severe plaque psoriasis by topically administering the tapinarof compositions disclosed by Sonti as claimed. Ex-1003, ¶¶179-184.

Sonti teaches various topical compositions of tapinarof for "treating a dermatological condition or disorder in a patient by administering the present compositions to the skin of the patient." Ex-1005, Abstract. Sonti also teaches effectively treating "moderate to severe plaque psoriasis" using "a topical emulsion composition as described herein." Ex-1005, [0288]. Plaque psoriasis was known to manifest in severities ranging from mild to severe. A POSA would have expected a treatment taught as effective for moderate to severe plaque psoriasis to also be effective for lower-grade manifestations, e.g., mild psoriasis. Ex-1003, ¶182. Therefore, a POSA would have been motivated, with a reasonable expectation of success, to apply to mild psoriasis a method of treatment that Sonti expressly teaches is effective for moderate to severe psoriasis. Ex-1003, ¶¶182-183.

Treating mild plaque psoriasis with Sonti's disclosed tapinarof compositions would also have been obvious to try. *See KSR*, 550 U.S. at 417. There was market

(and professional) pressure to provide effective treatment; there were a finite number of plaque psoriasis severities to treat (mild, moderate, severe); and a POSA would have expected the treatment known to work for moderate to severe to also work for mild. Ex-1003, ¶184.

2. [1.a]-[1.c]

Sonti discloses [1.a]-[1.c] for the reasons explained in Ground 1. Even if it did not, [1.a]-[1.c] would have been obvious in view of the teachings of Sonti and the knowledge of a POSA. Ex-1003, ¶¶185-203.

Sonti teaches using the disclosed tapinarof amounts (including claimed 1%) and disclosed application frequencies (including the claimed once daily) with each of its compositions. Sonti teaches that "in all of the compositions described herein, the amount of [tapinarof] which may be present… may be… 1%". Ex-1005, [0196]; *see also id.* [0055]. Sonti also teaches that "a composition of the present invention may be applied to affected areas… once daily… with the dose represented by any of the embodiments herein." Ex-1005, [0387]. In view of Sonti's interoperability teachings, a POSA would have been motivated, with a reasonable expectation of success, to administer a topical composition containing 1% tapinarof (as taught by Sonti) once a day (as also taught by Sonti). Ex-1003, ¶¶187-188.

There were also other known reasons for using a method of treatment recited by claim 1, with a reasonable expectation of success, in view of Sonti's teachings.

First, it was known that 1% tapinarof, administered topically once daily, effectively treated plaque psoriasis. Ex-1003, ¶¶190-193. Sonti teaches this, as explained in Ground 1. *See supra* §VIII.A. Sonti *also* cites two Chen references as showing that tapinarof was "suitable for the treatment of… psoriasis." Ex-1005, [0010] (citing Ex-1012, Ex-1013). And the Chen references specifically taught that a topical cream of "1% 3,5-dihydroxy-4-isopropylstilbene" (which is tapinarof, Ex-1032, ¶¶68-70) applied "once per day" "showed great efficacy" in treating plaque psoriasis. *E.g.,* Ex-1013, 32:10-63; Ex-1003, ¶¶99-104. Moreover, even if the Chen references Sonti cites did not expressly disclose treating *plaque* psoriasis (they do), a POSA still would have been motivated to use the 1%/once daily method to treat plaque psoriasis specifically and would have expected it to work, given the impressive efficacy in treating psoriasis (including "plaques"). Ex-1003, ¶¶192-193; Ex-1013, 2:56-3:4, 32:35-63. In view of these teachings, a POSA would have reasonably expected administering a composition containing 1% tapinarof once a day to affected areas of plaque psoriasis to be effective and therefore would have been motivated to do so. Ex-1003, ¶193.

Second, there were known reasons to use a lower strength and/or lower application frequency of topical pharmaceutical, such as: (i) reducing risk of side

effects by minimizing the body's systemic exposure to the active ingredient, (ii) improving patient compliance with treatment recommendations, and (iii) reducing treatment cost. Ex-1003, ¶¶194-199; Ex-1032, ¶¶81-87. For these reasons also, a POSA would have been motivated to use the "1%" strength and "once daily" application frequency disclosed by Sonti and known to be effective. Ex-1003, ¶199.

The claimed method would also have been obvious to try. Ex-1003, ¶¶200-202. There was a recognized need. *E.g.,* Ex-1008, Abstract ("There is a need for the development of novel non-steroidal topical drugs for the treatment of psoriasis."); *see also* Ex-1011, Abstract. There were also a finite number of known potential tapinarof strengths and application frequencies to use when topically treating plaque psoriasis. Ex-1005, [0055], [0196] (strengths) and [0387] (frequencies); Ex-1008, Abstract (1% tapinarof, administered twice daily); Ex-1013, 32:25-27 and 32:41-43 (1% tapinarof, administered once daily). And as explained above, a POSA would have had a reasonable expectation of success in pursuing the options, in view of Sonti and Chen's teachings that the options worked. Ex-1003, ¶¶202, 190-193; *see also* Ex-1005, [0285]-[0293] (Sonti); Ex-1013, 32:10-66 (Chen).

3. [1.d]

The claimed PGA score improvements were also well-known and there was good reason to expect them. Therefore, this element also would have been obvious. Ex-1003, ¶¶204-216.

A POSA would have been motivated, for at least two reasons. **First**, Sonti itself teaches that the tapinarof compositions it discloses may be used in the method of treating plaque psoriasis that results in the PGA score improvements. Ex-1005, [0288] (PGA score reduction "achieved by using a topical emulsion composition as described herein"). A POSA would understand "a topical emulsion composition as described herein" to refer to the tapinarof compositions Sonti discloses (including 1% tapinarof administered once a day). Ex-1003, ¶207.

Second, the benchmarks of a PGA "improved by two grades" or "improved to a score of 0 or 1" after treatment were already well-known and frequently used by November 2018, and a POSA would have been motivated to use them to measure treatment response. Ex-1003, ¶¶208-210; Ex-1011, 1 ("Because no psoriasis biomarkers are available…. Clinical measures [such as PGA score] are used"); Ex-1026 (plaque psoriasis treatment clinical trials, many specifically identifying PGA improvement of 2 grades or to score of 0 or 1 as an "outcome measure"); Ex-1016, Ex-1017, Ex-1018 (ChiCTR trials that included PGA as an "outcome measure").

A POSA also would have had a reasonable expectation that the claimed PGA score improvements would follow from the method of claim 1. Ex-1003, ¶¶211-216. Sonti specifically teaches this result after "using a topical emulsion composition as described herein" (Ex-1005, [0288]), which as explained above includes applying a 1% tapinarof composition to affected areas once a day. Further, the Chen references (which Sonti cites, Ex-1005, [0010]) disclose that treating subjects by administering a 1% tapinarof composition once daily to areas affected by psoriasis "showed great efficacy," including "complete clearance." *E.g.,* Ex-1013, 32:51-65. In fact, a POSA would have understood "complete clearance" taught by Chen indicated a PGA score improvement to 0 or 1, as claimed. Ex-1003, ¶¶213-215; *see also, e.g.,* Ex-1001, 22:30 (PGA "[s]core of 0 represents clear skin"); Ex-1005, [0288] (PGA score of 0 means "clear").

It would also have been obvious to try the claimed method of treating where the PGA score was improved as claimed. Ex-1003, ¶¶217-221. There was a recognized need for effective plaque psoriasis treatments and a recognized need for clinical scales (such as the PGA) to measure treatment response. Ex-1003, ¶218; *see also, e.g.,* Ex-1008, Abstract, Ex-1011, 1. Also, improvement in PGA score (improvement to 0 or 1 or improvement of two grades) was one of a finite number of known options for measuring plaque psoriasis treatment response. Ex-1003, ¶219; *see also, e.g.,* Ex-1005, [0288]-[0290], [0293]; Ex-1008, 1518 and Table 2.

And, there would have been good reasons to reasonably expect the claimed PGA score improvements. As explained above, it was already known that the option of once-daily topical application of 1% tapinarof improved PGA grades by the specific scores claimed. *E.g.,* Ex-1005, [0288]; Ex-1013, 32:51-65; Ex-1003, ¶220.

B. Dependent Claims 2-4

Sonti discloses claims 2-4 as explained in Ground 1. To the extent Patent Owner argues that the ingredients of a claim are not all taught in a single embodiment, the claims still would have been obvious. Ex-1003, ¶¶222-224; Ex-1032, ¶¶114-127. A POSA also would have been motivated to combine the formulation teachings of Sonti into a single embodiment in order to provide a standard oil-in-water emulsion, with a reasonable expectation of success.

First, a POSA would have been motivated to consider all of Sonti's teachings. Ex-1032, ¶118. Sonti itself explains that "the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention." Ex-1005, [0322]; *see also id.* [0136]. Also, oil-in-water emulsions (as recited by claims 2-4) were known to permit an active ingredient that could not be sufficiently dissolved in water to be uniformly dispersed in a spreadable form suitable for use on skin. Ex-1032, ¶118; Ex-1030, 10.

Second, the oil-phase ingredients recited by claim 3 were known, and had predictable functions in the formulation art. Ex-1032, ¶120; Ex-1031 at, e.g., 14, 20, 26, 30, 40; Ex-1005, [0074], [0088]-[0089], [0091]-[0092]. The same is true of the water-phase ingredients of claim 4. Ex-1032, ¶121. Thus a formulator would have expected to use them when creating an oil-in-water emulsion and would have expected to be able to do so using only routine skill. Ex-1032, ¶122.

Third, Sonti discloses ingredients recited by claim 3 by listing them as options for various parts of a formulation. *E.g.,* Ex-1005, [0094] ("exemplary chelating agents include…"), [0107] ("exemplary co-solvents include…"), [0119] ("exemplary penetration enhancers include…"). This indicated to a POSA that the ingredients had known functions and were intended to be used predictably in many different embodiments (and would reasonably be expected to work). Ex-1032, ¶123.

Fourth, Sonti itself teaches that its formulation ingredients can be used in various combinations with each other. Ex-1032, ¶124; *see also* Ex-1005, [0088], [0089], [0091], [0110], [0120].

Fifth, to a POSA there was nothing about the formulations recited by claims 2-4 would have been unusual or unexpected to a formulator tasked with creating a topical oil-in-water emulsion. Ex-1032, ¶125.

Sixth, the ’088 patent specification confirms that a POSA would have expected to combine known teachings according to routine practices when formulating oil-in-water emulsions, noting that a POSA could refer to pharmacologic references such as Banker & Rhodes and Goodman & Gilman’s. Ex-1001, 8:23-29; Ex-1032, ¶126.

For any and all of these reasons, the formulations of claims 2-4 would have been obvious in view of the teachings of Sonti. The ingredients of claims 3 and 4 were standard for topical oil-in-water emulsions, and a POSA would have expected to be able to combine the teachings of Sonti using only routine skill. Ex-1032, ¶127.

C. Dependent Claim 6

Sonti discloses claim 6, for the reasons explained in Ground 1. Further, claim 6 would have been both obvious and obvious to try. Ex-1003, ¶¶225-228. Claim 6 just lists body parts, including the body itself, that are commonly affected by plaque psoriasis. Ex-1003, ¶227; Ex-1015, 3; Ex-1006, 2. A POSA would have been motivated, with a reasonable expectation of success, to use the method of treatment of claim 1 on body part(s) that are commonly affected by plaque psoriasis. Ex-1003, ¶¶227-228.

D. Dependent Claims 8, 22

Sonti discloses claims 8 and 22 as explained in Ground 1. These claims also would have been obvious. Ex-1003, ¶¶229-237.

In view of Sonti's teaching of treating a patient having moderate to severe plaque psoriasis at "baseline" (as explained in [1.pre]), it would have been an obvious, common-sense step to use that method on subject who had been "diagnosed" with moderate to severe plaque psoriasis. Ex-1003, ¶231. A subject diagnosed with moderate to severe plaque psoriasis is also one with a diagnosis falling within the "mild to severe" (claim 8) and "mild to moderate" (claim 22) ranges. Moreover, given Sonti's teaching of treating a subject diagnosed with moderate to severe plaque psoriasis, it also would have been obvious to treat a subject diagnosed with *mild* plaque psoriasis, for the same reasons explained with respect to [1.pre] in this Ground 2. Ex-1003, ¶232.

Treating a plaque psoriasis subject who had a PGA score of greater than or equal to two at baseline would also have been obvious, as doing so was well-known and common by November 2018. *E.g.,* Ex-1005 [0287]-[0288] (treating subjects with baseline PGA ≥4); Ex-1008, 1 (treating subjects with baseline PGA of 2-4). Ex-1003, ¶¶233-235. The method of claim 1 was also known to be *effective* for treating mild to severe plaque psoriasis where the subject had a PGA score of greater than or equal to 2, providing a reasonable expectation of success.

Ex-1003, ¶236; *see also, e.g.,* Ex-1005, [0288] (treatment of "moderate to severe plaque psoriasis" was effective as indicated by improvement in PGA score from ≥4 to a 0 or 1); Ex-1013, 32:25-62 (treatment of plaque psoriasis with 1% tapinarof composition applied once daily "showed great efficacy").

Using the method of claim 1 with a subject diagnosed with mild to severe plaque psoriasis and having a PGA score of greater than or equal to 2 as claimed would have been merely a matter of common sense. Ex-1003, ¶237. A POSA would have been motivated, with a reasonable expectation of success, to treat a subject diagnosed with plaque psoriasis as claimed and having a PGA score indicating symptoms (PGA greater than or equal to 2) with a method known to be effective.

E. Dependent Claim 9

Sonti discloses claim 9, for the reasons explained in Ground 1.

Claim 9 also would have been obvious and obvious to try, for at least three reasons. Ex-1003, ¶¶239-246. First, as explained in Ground 1 for element [1.d] and claim 9, Sonti teaches an improvement in PGA score following the method of treatment recited in claim 1. A POSA would have known and reasonably expected that an improvement in PGA score would correspond to one or more symptom of the mild to severe plaque psoriasis improving, as the PGA scale is based on observed symptoms. Ex-1003, ¶240; *see also* Ex-1005, [0287]; Ex-1011, Fig. 2.

Second, the claimed symptom improvement as measured according to an assessment from the group including PGA, BSA, and PASI, would have been just the reasonably expected and common-sense result of the method of treating recited by claim 1, which was already known to be effective. Ex-1003, ¶¶241-244. Third, a POSA also would have been motivated to use known psoriasis assessment scales such as the PGA, BSA, or PASI because there were "no psoriasis biomarkers [available]" for assessing treatment response. Ex-1011, 1; Ex-1003, ¶244.

F. Dependent Claims 7, 21: "the method of claim 1, wherein the subject has been diagnosed with mild to [severe/moderate] plaque psoriasis having a percent body surface area (BSA) affected of about 3% to about 20%"

Claims 7 and 21 are obvious in view of the teachings of Sonti and the knowledge of a POSA. Ex-1003, ¶¶247-264.

Sonti discloses, and also makes obvious, treating a subject "diagnosed" with "mild to severe" (claim 7) and "mild to moderate" (claim 21) plaque psoriasis as claimed for the same reasons explained with respect to claims 8, 22, and [1.pre] in this Ground 2.

To the extent that Sonti does not expressly teach treating a subject having the claimed percent BSA affected by *plaque psoriasis* specifically, a POSA would be motivated to do so, with a reasonable expectation of success, for several reasons.

First, Sonti teaches applying tapinarof compositions where "the amount of

body surface area (BSA) for which the drug is applied to is… less than 30%" and/or ">10%." Ex-1005, [0268]; *see also id.*, [0267]. Thus, Sonti teaches applying the compositions to a skin surface area within the claimed BSA affected of "about 3% to about 20%." Sonti's teaching of *applying* the tapinarof composition to a BSA within the claimed range would have plainly suggested, as a matter of common sense and logic, treating a subject having a BSA was *affected* by plaque psoriasis in the same range. Ex-1003, ¶¶250-251. A POSA also would have understood that a subject having the specified BSA *affected* by plaque psoriasis also would have been *diagnosed* with plaque psoriasis as claimed. Ex-1003, ¶252.

Second, a POSA would have been motivated to use a clinical measure such as the well-known BSA to assess plaque psoriasis, because there were not biomarkers available. Ex-1003, ¶253; Ex-1007, 2-3; Ex-1011, 1-2. Treating subjects with BSA in the specific percentage range claimed was also known and common. Ex-1003, ¶¶254-255; *see also* Ex-1008, Abstract, 2 (subjects diagnosed with plaque psoriasis having BSA affected of 1%-10%); Ex-1026, 485 ("plaque psoriasis covering 2% to 20% of total body surface area (BSA)"). It would have been common sense to apply the method of claim 1 to subjects diagnosed with plaque psoriasis and having the common BSA affected range of claims 7 and 21. Ex-1003, ¶¶253-256.

Third, as explained above a POSA already knew that the method of claim 1 was effective to treat plaque psoriasis. *E.g.,* Ex-1003, ¶257; Ex-1005, [0285]-[0294]; Ex-1013, 2:56-3:4, 32:10-62. Therefore there was a good reason to apply it to subjects diagnosed with plaque psoriasis and having a BSA affected as claimed, and to expect the treatment to be successful.

Fourth, Sonti also teaches treating a subject having a BSA affected with atopic dermatitis that is in the claimed range. Ex-1005, [0272] ("1-10% BSA" and "15-35% BSA"). Anti-inflammatory topical treatments for atopic dermatitis were commonly used (and expected to work) as topical treatments for plaque psoriasis, as both diseases were known to be inflammatory skin diseases. Ex-1003, ¶¶258-263; *see also* Ex-1005, [0272]-[0284] and [0285]-[0295]; Ex-1013, 2:56-3:17 and 32:8-3:4. Thus, a POSA would have been motivated to treat subjects with BSA affected by *plaque psoriasis* in the same range, and would have reasonably expected the treatment to work. Ex-1003, ¶263.

The method of claim 10 also would have been obvious to try. Ex-1003, ¶264. There was a known need for effective plaque psoriasis treatments and for clinical assessments of severity. *E.g.,* Ex-1008, Abstract; Ex-1011, 1. The BSA metric (including a BSA affected within the claimed range) was one of a finite number of known options for clinical assessments. *E.g.,* Ex-1008, Abstract, 2; Ex-1006, 3; Ex-1011, 2; Ex-1026. A POSA also would have expected the method of

claim 1 to effectively treat plaque psoriasis, as explained above. Therefore, a POSA would have had good reason to try claim 1's method of treatment with a subject having a BSA affected by plaque psoriasis of about 3% to about 20% as claimed.

G. Dependent Claim 10: "The method of claim 9, wherein the percent body surface area (BSA) affected is decreased to less than 20% after topically administering the topical composition"

Sonti does not disclose the decrease in BSA affected recited in Claim 10 with respect to treating plaque psoriasis specifically. But Sonti does disclose it with respect to treating atopic dermatitis, another inflammatory skin disease. Claim 10 would have been obvious in view of Sonti's teachings and the knowledge of a POSA. Ex-1003, ¶¶265-276.

Sonti teaches a "method of improving the % body surface area (BSA) of a person affected with atopic dermatitis" by administering a topical composition having an "effective amount" of tapinarof, where the method includes "% BSA improvement" after treatment of between 10% and 100%. Ex-1005, [0280]. Sonti also teaches treating atopic dermatitis in subjects who started with a baseline BSA affected of 1-10% and 15-35%, with average BSA improvements of 52% and 77% respectively. Ex-1005, [0272]. This teaches average BSA reductions from approximately 10% to 5% and from approximately 35% to 8% for the top-end of the BSA affected range, respectively. Ex-1003, ¶¶270-271. This discloses the

"percent surface area (BSA) affected [that] is decreased to less than 20%" after the treatment, as recited by claim 10. *Id.*

A POSA would have been motivated to also measure *plaque psoriasis* treatment response using the same common BSA metric, and to reasonably expect a similar reduction in BSA affected. Ex-1003, ¶¶272-276.

Reduction in BSA affected was a common, known measure of treatment response not only for atopic dermatitis but also for plaque psoriasis. Ex-1008, Abstract, 2; Ex-1007, 2; Ex-1006, 3 (Table 2); Ex-1011, 1-2; Ex-1026 (generally). Given the BSA's known utility as a treatment response metric for plaque psoriasis, a POSA would have been motivated to use it. Ex-1003, ¶273.

A POSA also would have reasonably expected a similar reduction in BSA affected. One, anti-inflammatory topical treatments for atopic dermatitis were commonly used with and expected to work for plaque psoriasis, as explained with respect to claims 7, 21 in this Ground 2. Ex-1003, ¶274. And two, Sonti itself taught that treatment of plaque psoriasis with the method of claim 1 (1% tapinarof once daily) was highly effective, as explained with respect to Claim 1. Ex-1003, ¶275; Ex-1005, [0288], *see also id.* [0055], [0196], [0285]-[0294], [0301], [0308], [0387]. Sonti also cites the two Chen references that similarly teach 1% tapinarof administered once daily is highly effective to treat plaque psoriasis. Ex-1005, [0010]; *see also* Ex-1013, 32:10-66, Ex-1012, 20:28-21:25.

The claimed decrease in percent BSA affected recited by claims 9-10, following topical administration of a 1% tapinarof composition as recited by claim 1, would have been a reasonably expected and obvious outcome to a POSA.

H. Dependent Claims 16, 18

Sonti discloses claims 16 and 18, for the reasons explained in Ground 1.

The improvement timelines recited by claims 16 and 18 would also have been obvious in view of the teachings of Sonti. Ex-1003, ¶¶277-283.

As explained above, it was known that the method of claim 1 was effective to treat plaque psoriasis. *E.g.,* Ex-1005, [0288]; Ex-1013, 32:25-62. It was also known—as taught by the Chen references—that the method of claim 1 improved plaque psoriasis in only one week. Ex-1013, 32:51-63. Therefore it would have been predictable and expected that the method of claim 1 would also improve symptoms after 2, 4, and 8 weeks of treatment. Ex-1003, ¶¶279-281. Also, for a plaque psoriasis treatment known to be effective, it was common and reasonably expected to see improvement of a symptom (and also as measured by an improvement in PGA score) after 2, 4, and 8 weeks. Ex-1003, ¶¶279, 282; Ex-1008, 2.

In view of these teachings and the knowledge of a POSA, the improvement timeline recited by claims 16 and 18 (improvement after about 2, 4, or 8 weeks of

administering the topical composition) would have been obvious and expected to a POSA.

X. GROUND 3: DEPENDENT CLAIMS 7, 21 AND 9-10 ARE OBVIOUS FOR THE REASONS EXPLAINED IN GROUND 1 AND/OR GROUND 2, FURTHER IN VIEW OF BISSONNETTE

Claims 7, 21, and 9-10 recite use of percent BSA affected: claims 7, 21 for assessing severity and claims 9-10 for assessing treatment response. Sonti discloses and/or renders obvious these claims for the reasons explained in Grounds 1 and 2. Alternatively, these claims are obvious for those same reasons, further in view of the teachings of Bissonnette. Ex-1003, ¶¶284-291. Bissonnette teaches treating a subject having the claimed BSA affected (claims 7, 21) and the claimed BSA improvement following treatment (claims 9-10), and it does so regarding treatment of plaque psoriasis with topical 1% tapinarof. *E.g.*, Ex-1008, Abstract, 2, 3-4, Tables 1, 3.

A. Dependent Claims 7, 21

Claims 7 and 21 depend from independent claim 1. Sonti anticipates and renders obvious claim 1 for the reasons explained in Ground 1 and 2.

Sonti also teaches and suggests treating a subject diagnosed with "*mild to severe*" and "*mild to moderate*" plaque psoriasis, as explained with respect to claims [1.pre], 8, 22 in Grounds 1 and 2. Ex-1003, ¶293.

Bissonnette likewise discloses these elements. Ex-1008, Abstract and 1-2 (treating patients "diagnosed" with "mild to moderate plaque psoriasis" and having a PGA of "two (mild) to four (severe) at Day 0"). Ex-1003, ¶¶294-296.

Claims 7 and 21 further recite that the subject has a "*body surface area (BSA) affected [by plaque psoriasis] of about 3% to about 20%*." Bissonnette also teaches this. Ex-1003, ¶¶297-299; Ex-1008, 1 (treating forty patients with "1% and 10% body surface area (BSA)" affected by plaque psoriasis), Abstract, 2-3, Table 1. Treating patients with 1-10% BSA affected includes treating subjects having BSA affected of "*about 3% to about 20%*" as claimed. Ex-1003, ¶299.

There would have been good reason to combine the teachings of Sonti and Bissonnette. Each is in the same field of art. In fact each teaches treating the *same* condition (plaque psoriasis) with the *same* amount of the *same* active compound (1% tapinarof). *Compare* Ex-1005 (Sonti), Abstract, [0008], [0288], [0196], [0055] *with* Ex-1008 (Bissonnette), Abstract, 2-5; *see also* Ex-1003, ¶300 and ¶¶78-82, 109-124 (Sonti), ¶¶88-91, 288-289, 294-296 (Bissonnette). A POSA therefore would have been motivated, with a reasonable expectation of success, to perform the method of claim 1 (as taught by Sonti) with a subject diagnosed with mild to moderate/severe plaque psoriasis having a BSA affected within the range of about 3% to 20%, (as taught by Bissonnette). Ex-1003, ¶300.

There were also other good reasons to combine the teachings of Sonti and Bissonnette and to reasonably expect success. Ex-1003, ¶¶301-306.

First, BSA was known as a useful tool to assess plaque psoriasis severity. Ex-1003, ¶302; Ex-1011, 1-2 (clinical measures such as BSA were used "because no psoriasis biomarkers are available"); Ex-1006, 7 and Table 5. The claimed BSA range (about 3% to about 20%) was also common for plaque psoriasis patients seeking treatment. Ex-1003, ¶302; Ex-1008, Abstract, 2; Ex-1011, 2; Ex-1026, *e.g*. p.485. Combining Sonti's teaching of treating plaque psoriasis with Bissonnette's teachings of treating subjects with BSA affected by plaque psoriasis in the claimed range would have been just the predictable application of a known method to subjects having a common severity of plaque psoriasis as measured by a known metric (the BSA) Ex-1003, ¶303; *see KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 415-16 (2007).

Second, as explained above in Ground 2 with respect to claims 7, 21, Sonti itself also teaches applying the tapinarof compositions to subjects with a percent BSA affected in the claimed range, both generally and specifically with respect to atopic dermatitis. *See supra* §IX.F. This also would have motivated a POSA to administer the tapinarof compositions to subjects having a BSA affected by plaque psoriasis in the same range, and to reasonably expect it to work. Ex-1003, ¶304.

Third, as explained above in Grounds 1 and 2 it was already known that the method of claim 1 was effective for treating plaque psoriasis, providing additional motivation to treat subjects diagnosed with plaque psoriasis as claimed, with a reasonable expectation of success. Ex-1003, ¶305; *see also, e.g.,* Ex-1005, [0285]-[0295], [0055], [0196], [0387]; Ex-1013, 2:56-3:4, 32:10-62; Ex-1012.

For any one of these reasons, performing the method of claim 1 with a subject having a percent BSA affected within the range recited by claims 7 and 21, as suggested by Bissonnette, would have been no more than the predictable and common-sense extension of what Sonti already teaches. Ex-1003, ¶306.

B. Dependent Claims 9, 10

Claim 9 depends from claim 1. Sonti anticipates and renders obvious claim 1 for the reasons explained in Grounds 1 and 2. Claim 10 depends from claim 9 and adds that the BSA affected "is decreased to less than 20%." Claims 9 and 10 are obvious in view of Sonti for the reasons explained in Ground 2; alternatively they also would have been obvious in view of the teachings of Sonti and Bissonnette. Ex-1003, ¶¶307-318.

Bissonnette teaches the BSA improvement recited by claims 9 and 10 (though the 1% tapinarof was administered twice daily rather than once daily). Bissonette discloses that after 12 weeks of treatment, the percent BSA affected by plaque psoriasis had decreased an average of 79.1%, from a mean of 3.3% BSA to

a mean of 0.7% BSA. Ex-1003, ¶309; Ex-1008, 3-4, Tables 1, 3. The large decrease following treatment discloses "*an improvement of one or more symptom of mild to severe plaque psoriasis as measured according to . . . percent body surface area (BSA) affected*" (claim 9) and also that the BSA affected "*has decreased to less than 20% after topically administering the topical composition*" (claim 10). A decrease in percent BSA affected of 79.1%, to a mean of 0.7% BSA affected, is a decrease to "*less than 20%*" BSA affected. Ex-1003, ¶¶310-311.

The claimed decrease in BSA would have been obvious in view of the teachings of Sonti and Bissonnette.

First, decrease in percent BSA affected was known to be a useful measure of treatment response for plaque psoriasis treatments, and a POSA would have been motivated to use it for that purpose. Ex-1003, ¶¶313, 51, 45; *see also* Ex-1008, Abstract, 2; Ex-1007, 2; Ex-1006, 3 (Table 2); Ex-1011, 1-2; Ex-1026 (generally).

Second, while Bissonnette teaches twice daily application of the 1% tapinarof composition, it was *also* already known that *once daily* application was highly effective to treat mild to severe plaque psoriasis, as both Sonti and the Chen references teach. Ex-1003, ¶314; *see also* Ex-1003, ¶¶190-193, 211-216, 242. This included "complete[] clearance" of the psoriasis in one of the volunteers, which a POSA would have understood as indicating that the percent BSA affected had

decreased to 0%. Ex-1003, ¶314; Ex-1013, 32:53-62. Thus a POSA would have reasonably expected the method of claim 1 to result in a percent BSA affected improvement as recited by claims 9 and 10. Ex-1003, ¶¶314-315.

Third, as explained above with respect to claim 10 in Ground 2, Sonti itself teaches the specific reduction in BSA affected recited by claims 9-10, in the context of topical treatment of atopic dermatitis, another inflammatory skin disease. *See supra* §IX.G. A POSA also would have reasonably expected a topical treatment that is effective for atopic dermatitis to be effective as a topical treatment for plaque psoriasis, as explained above. *Id.*; Ex-1003, ¶¶316, 274-275; *see also* Ex-1003, ¶¶258-263 (same).

In view of the teachings of Sonti and Bissonnette, a POSA would have been motivated to use BSA to measure treatment response when applying the treatment method of claim 1, and a POSA would have reasonably expected the improvement in BSA affected recited by claims 9 and 10 when doing so.

Claims 9 and 10 also would have been obvious to try. There was a known need for effective topical plaque psoriasis treatments. Ex-1003, ¶¶318, 200; *see also* Ex-1008, Abstract; Ex-1011, 1; Ex-1013, 2:31-33, 2:56. There were only a finite number of options for treating plaque psoriasis with topical tapinarof that were known to be effective. Ex-1003, ¶318; *see also* Ex-1013, 32:41-65; Ex-1005, [0387] (1% once daily); Ex-1008, 1 (1% twice daily); *see supra* IX.A.2-IX.A.3.

There were also only a finite number of known options for measuring treatment response (including BSA, PGA, and PASI). *E.g.*, Ex-1013, 32:10-65; Ex-1005 Abstract, [0287]-[293], [0387], [0196], [301]; Ex-1008, Abstract. Thus a POSA would have had good reason to try the method of claim 1 along with BSA as the treatment response metric, and to reasonably expect the BSA improvement recited by claims 9 and 10. Ex-1003, ¶318.

XI. GROUND 4: CLAIMS 1-4, 6-10, 16, 18, AND 21-22 ARE OBVIOUS OVER BISSONNETTE FURTHER IN VIEW OF THE TEACHINGS OF SONTI AND/OR CHEN

Bissonnette discloses treating subjects suffering from plaque psoriasis with a topical composition of 1% tapinarof and discloses that the treatment improved plaque psoriasis symptoms as measured by both PGA score and percent body surface area (BSA) affected. In doing so, it discloses nearly every element of the Challenged Claims. The only element Bissonnette does not disclose is once daily administration (Bissonnette discloses twice daily).

Sonti and Chen each disclose once-daily administration of a topical composition containing 1% tapinarof to treat plaque psoriasis. A POSA would have been motivated to combine Bissonnette with the teachings of Sonti and/or Chen, with a reasonable expectation of success, as each taught that topical application of the *same* active ingredient (tapinarof) at the *same* strength (1%) to treat the *same* condition (plaque psoriasis). Ex-1003, ¶¶320-321, 322-323. Each of

Sonti and Chen also taught that the once-daily administration was highly effective. *E.g.,* Ex-1005, [0285]-[295]; Ex-1013, 2:56-3:4 and 32:10-63. Moreover, as discussed in further detail below, there was strong motivation and market pressure to decrease the frequency of application from twice daily to once daily, including to reduce side effect risk by reducing the body's exposure to the active compound, to improve patient compliance with treatment recommendations, and to reduce cost of treatment. Ex-1003, ¶¶332-346; Ex-1032, ¶¶81-87.

By November 2018, the Challenged Claims would have been both obvious and obvious to try in view of Bissonette and the teachings of Sonti and/or Chen.

A. Independent Claim 1

1. [1.pre]

Bissonnette discloses the preamble. Ex-1003, ¶¶324-325. Bissonnette describes a study of sixty-one patients having "1–10% body surface area (BSA) covered with plaque psoriasis" and a physician's global assessment score (PGA) of "two (mild) to four (severe)" at day 0 of the study. Ex-1008, Abstract, 2. This discloses treatment of "mild" to "severe" plaque psoriasis. Bissonnette's further discussion of "treatment of mild to moderate" plaque psoriasis (Ex-1008, Abstract, 5) also discloses treatment of mild to severe plaque psoriasis as claimed, as "mild to moderate" plaque psoriasis is within the claimed range. *See, e.g., Genentech*, 946 F.3d at 133.

2. [1.a]

Bissonnette discloses this element. Ex-1003, ¶326. Forty of the study participants administered a topical composition comprising 1% "WBI-1001" to areas of the skin affected by plaque psoriasis. Ex-1008, Abstract, 1-2 ("1% WBI-1001 in a cream formulation"). WBI-1001 is tapinarof. Ex-1032, ¶¶64-67. A POSA would have understood a "1% WBI-1001 cream" to refer to 1% tapinarof by weight. Ex-1032, ¶¶74-77, 79; *see also* Ex-1008, Abstract, 2, 4. Also, the tapinarof in an amount equal to 1% by weight would have been the expected, obvious approach. Ex-1032, ¶80.

3. [1.b]

Bissonnette discloses this element. Ex-1003, ¶327. Bissonnette discloses that the forty test subjects given the 1% tapinarof cream "appl[ied]" the cream to the areas of skin affected by the plaque psoriasis. Ex-1008, Abstract, 2.

4. [1.c]

Bissonnette does not disclose this—it discloses twice daily administration. However, each of Sonti and Chen teaches topically administering 1% tapinarof *once a day* as claimed. Ex-1003, ¶¶328-349.

Sonti teaches administering the tapinarof compositions (including 1% tapinarof compositions) to treat plaque psoriasis "**once daily**," as explained with

respect to elements [1.pre], [1.a], and [1.c] in Grounds 1 and 2 above. *See also* Ex-1003, ¶329.

Chen also discloses administering a 1% tapinarof cream[9] "**once per day**":

> The volunteers were treated once per day by applying the creams once per day on top of the affected area with the basic cream as the control (except for volunteer 3). Two comparable body areas were chosen, and one was treated with the control and the other with the cream containing the compound of the invention. The cream of the invention contained 1% 3,5-dihydroxy-4-isopropylstilbene. The control cream was identical except that it contained no 3,5-dihydroxy-4-isopropylstilbene. Each cream was rubbed into the skin in the area to be treated until no more could be rubbed in.

Ex-1013, 32:41-50. A POSA would have understood Chen was describing the treatment of plaque psoriasis specifically. Ex-1003, ¶¶330-331 and Ex-1013, 2:56-3:4, 32:25-37; *see also* Ex-1003, ¶¶99-101, 191-192.

A POSA would have been motivated to perform the method of treating disclosed in Bissonnette with a once-daily application of the tapinarof cream as taught by Sonti and/or Chen, rather than twice daily, with a reasonable expectation of success, for any one or combination of the below reasons. Ex-1003, ¶¶322-323, 332-349.

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[9] The cream was "1% cream of 3,5-dihydroxy-4-isopropylstilbene." Ex-1013, 32:25-27. This is tapinarof. Ex-1032, ¶¶68-70, 56-61; *see also* Ex-1001, 7:4-20.

First, Bissonnette, Sonti, and Chen are each directed to not only the same technological subject matter, but also to treating the very same skin condition (plaque psoriasis) with the very same composition (a topical 1% tapinarof cream). *E.g.,* Ex-1008, Abstract, 1-2 (Bissonnette); Ex-1005, [0285]-[295], [0055], [0196], [0387] (Sonti); Ex-1013, 32:10-63 (Chen); Ex-1003, ¶333. Given the nearly complete overlap in teachings, a POSA would be motivated to look to the teachings of Sonti and Chen and expect to combine them with the teachings of Bissonnette with a reasonable expectation of success. Ex-1003, ¶333.

Second, a POSA would have been motivated to use the once-daily application frequency rather than twice-daily to minimize risk of side effects. Ex-1003, ¶¶334-336; Ex-1032, ¶¶82-85. A POSA would have expected lower application frequency to reduce systemic exposure to the active ingredient. Ex-1005, [0387] (the embodiments "can provide lower systemic exposure of the active ingredient"). And it was known that reducing systemic exposure to the active ingredient was desirable, when it could be done while still maintaining efficacy, because it reduced risk of side effects. Ex-1003, ¶334; Ex-1032, ¶¶81-85. Bissonnette itself taught that there were some adverse effects with the twice daily application regimen. Ex-1008, Abstract and 4, Table 4. While most were mild (Ex-1008, 4), a POSA still would have been motivated to decrease the application frequency from twice to once daily to minimize the risk of such adverse events,

given that the once-daily administration would have been expected to still be highly effective (as explained below). Ex-1003, ¶¶335-336; Ex-1005, [0387] (recognizing motivation to "provide lower systemic exposure of the active ingredient to the patient").

Third, a POSA would have been motivated to use once-daily application rather than twice daily to improve patient compliance with the treatment regimen. Ex-1003, ¶337; Ex-1032, ¶87. It was commonly known (and also common-sense) that patients were more likely to follow the recommended treatment regimen when the application frequency was once daily, rather than twice daily. *Id.*

Fourth, a POSA would have been motivated to use once-daily application to lower treatment cost. Less frequent application uses less volume of the topical composition, resulting in lower overall treatment cost. Ex-1003, ¶338; Ex-1032, ¶86.

Finally, a POSA would have reasonably expected the once-daily application to be successful. Ex-1003, ¶¶340-346. Each of Sonti and Chen already taught that a 1% tapinarof topical composition was highly effective to treat plaque psoriasis when applied *once daily*. Sonti taught this, as explained above in Grounds 1 and 2, with respect to Claim 1 (for example, [1.d]). Ex-1003, ¶341; Ex-1005, [0285]-[0295]. Chen similarly taught that once daily application of 1% tapinarof "showed

great efficacy" in treating plaque psoriasis, with Volunteer 1 achieving "complete[] clearance" and Volunteer 2 showing "significant improvement":

> The volunteers were treated once per day by applying the creams once per day on top of the affected area with the basic cream as the control (except for volunteer 3). Two comparable body areas were chosen, and one was treated with the control and the other with the cream containing the compound of the invention. The cream of the invention contained 1% 3,5-dihydroxy-4-isopropylstilbene. The control cream was identical except that it contained no 3,5-dihydroxy-4-isopropylstilbene. Each cream was rubbed into the skin in the area to be treated until no more could be rubbed in.
>
> Results: the inventive compound showed great efficacy on the volunteers treated in comparison with the untreated areas and before and after treatment. In the case of volunteer 1, the area applied with the inventive compound started showing improvement in the inflammation and a decrease in proliferative cells three days after the treatment and completely clearance in 7 days. No change occurred in the condition of the area treated with the control cream. In the case of volunteer 2, there was visible improvement in inflammation and in clearance of the proliferative cells three days after the treatment and significant improvement of the psoriasis were observed within seven days of treatment. In the case of volunteer 3, the

Ex-1013, 32:25-62; *see also id.* Abstract, 3:3-4, Claim 1; Ex-1003, ¶¶342-344. Also, even if Chen did not expressly disclose treating *plaque* psoriasis (it does), a POSA still would have been motivated to use the method with plaque psoriasis specifically and would reasonably expect it to be successful, given the impressive efficacy Chen's method showed in treating psoriasis (including "plaques" of psoriasis). Ex-1003, ¶345; Ex-1013, 2:56-3:4, 32:10-62.

For any and all of these reasons, a POSA would have been motivated to look to the teachings of Sonti and/or Chen, and to reasonably expect success in applying

the method of treatment taught by Bissonnette with a once-daily application frequency rather than twice-daily.

5. [1.d]

Bissonnette discloses this element. Ex-1003, ¶¶350-363. Bissonnette discloses that each of the forty patients treated with the 1% tapinarof composition began with a PGA score of "two (mild) to four (severe)." Ex-1008, Abstract and 2. After the 12 weeks, 67.5% of the treated patients "achieved a PGA score of clear (0) or almost clear (1)." Ex-1008, 3, Table 2:

Table 2 Proportion of patients with PGA 0 or 1 at each visit

	1% WBI-1001 (*N* = 40) *n* (%)	Placebo (*N* = 21) *n* (%)
Day 0	0 (0)	0 (0)
Day 14	5 (12.5)	0 (0)
Day 28	11 (27.5)	0 (0)
Day 42	23 (57.5)	0 (0)
Day 56	22 (55.0)	1 (4.8)
Day 84	27 (67.5)	1 (4.8)

PGA, physician's global assessment.

Thus, Bissonnette discloses that a PGA score "*has improved to a score of 0 or 1*" as recited by element [1.d]. Ex-1003, ¶¶350, 352.

Bissonnette also discloses the alternative PGA metric recited by [1.d]. Bissonnette explains that the test subjects started with a mean PGA score of 3.2 and that following treatment the mean PGA score had improved by 62.5% and

62.8%, which is a PGA score "*improved by 2 grades*" as claimed. Ex-1003, ¶¶351-352; Ex-1008, 3, Table 1:

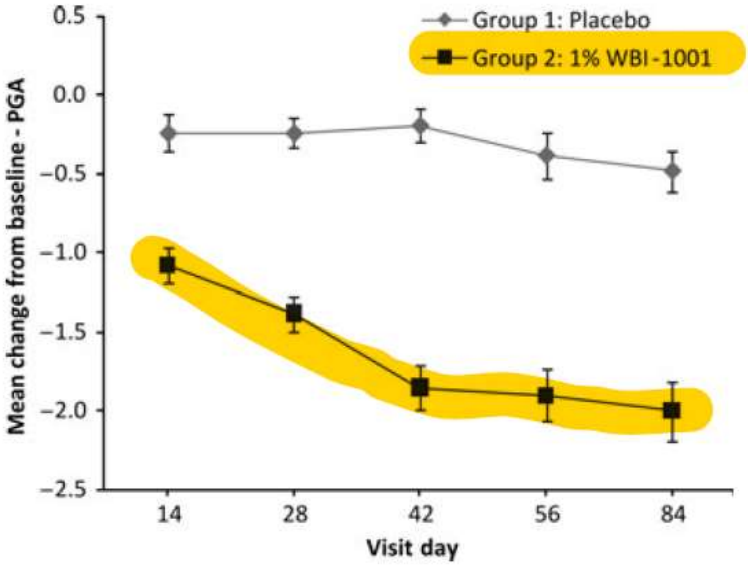


Figure 2 Change from baseline in PGA at each visit; ITT population (mean ± SEM).

Sonti also teaches the claimed PGA score improvement as explained above with respect to Claim 1 in in Grounds 1 and 2, resulting from application of a 1% tapinarof composition to affected areas once a day. Ex-1003, ¶352; *see also supra* §VIII.A.5, §IX.A.3; Ex-1005, [0288] ("patient also reaching a PGA score of 0 or 1").

Chen also would have disclosed the claimed PGA score improvement to a POSA, as a result of treatment consisting of once-daily topical application of a 1% tapinarof to areas affected by plaque psoriasis. *See* Ex-1013, 32:51-65; Ex-1003, ¶¶354-357. Volunteer 1 achieved "complete clearance" after seven days of

treatment. Ex-1013, 32:51-57. A POSA would understand the "complete clearance" necessarily means that a PGA score has improved to 0. Ex-1003, ¶355; *see also, e.g.,* Ex-1001, 22:30 (PGA "[s]core of 0 represents clear skin"). Volunteer 2 also achieved "significant improvement" after seven days of treatment. Ex-1008, 32:57-64. A POSA would understand "significant improvement" to indicate an improvement of at least two PGA grades. Ex-1003, ¶¶356-357.

Given that Bissonnette discloses the claimed PGA score improvements for twice daily application of a 1% tapinarof composition and Sonti and Chen teach a POSA to expect the same claimed PGA score improvements for ***once daily*** application of a 1% tapinarof composition, it would have been predictable to and reasonably expected by a POSA that modifying Bissonnette from twice daily to once daily application would still result in one or both of the claimed PGA score improvements. Ex-1003, ¶358.

A POSA also would have had additional reasons to combine Bissonnette with the teachings of Sonti and/or Chen, with a reasonable expectation of success. Ex-1003, ¶¶359-363. **First**, as explained above each of Bissonnette, Sonti, and Chen taught topical application of the same active ingredient (tapinarof) at the same concentration (1%) to effectively treat the same condition (plaque psoriasis). Ex-1003, ¶¶360, 333. Given this near-complete overlap in teachings, POSA would be motivated to, and would expect to easily and successfully be able to, combine

their teachings. *Id.* **Second**, as explained above each of Bissonnette and Sonti disclosed using the PGA metric to assess treatment response. Further, each of Bissonnette, Sonti, and Chen taught that treatment would have been expected to result in the claimed PGA score improvements, whether the 1% tapinarof topical was administered twice daily (Bissonnette) or once daily (Sonti and Chen). Ex-1003, ¶361; *see also id.* ¶¶350-358. There was nothing unpredictable about the combination, and a POSA would reasonably have expected once-daily treatment to result in the same PGA score reductions that Bissonnette discloses and [1.d] recites. *Id.* **Third**, the claimed PGA improvement metric was widely used at the time, and would have been an obvious choice to measure treatment response.Ex-1003, ¶362; *supra* §IX.A.3.

In view of this prior art and the knowledge of a POSA, the claimed improvement in PGA score was obvious in that it was just the recitation of predictable outcomes according to a well-known and common metric.

6. Claim 1 Would Have Been Obvious to Try in View of the Teachings of Bissonnette, Further in View of Sonti and/or Chen

It would also have been obvious to try the method recited by claim 1, where the application frequency is once daily rather than twice daily. Ex-1003, ¶¶347-349, 364-368; *see, e.g., Yeda Research & Dev. Co. v. Mylan Pharms., Inc.,* 906 F.3d 1031, 1043-46 (Fed. Cir. 2018) (less frequent dosing regimen obvious to try).

There was a known need in the art for (i) effective, safe plaque psoriasis treatments and (ii) clinical metrics to measure treatment response *E.g.,* Ex-1003, ¶347, Ex-1008, Abstract and Ex-1013, 2:31-33, 2:56 (need for effective treatment); Ex-1003, ¶¶365-366, Ex-1011, 1 and Ex-1007, 1 (need for clinical metrics). Once-daily application of 1% tapinarof was one of a finite number of options for treating plaque psoriasis known to be effective. Ex-1003, ¶348; *see also* Ex-1013, 32:41-65 (once daily); Ex-1008, Abstract (twice daily); Ex-1005 Abstract, [0387], [0288] (once daily). There were also a finite number of generally accepted ways to assess treatment response, including the PGA score improvements recited by [1.d]. Ex-1003, ¶¶366 and 43-44, 46-53. And, there would have been good reason to expect one or both of the PGA score improvements recited by claim [1.d]—Sonti and Chen each already taught that once-daily topical application of 1% tapinarof resulted in those improvements. Ex-1003, ¶¶367, 353-358.

B. Dependent Claims 2-4

Bissonnette does not disclose the precise formulation of the topical 1% tapinarof composition used. However, the formulations recited by dependent claims 2, 3, and 4 are disclosed by and obvious in view of Sonti for the reasons explained above in Grounds 1 and 2. And for the reasons explained with respect to claim 1 in this Ground 4, it would have been obvious to modify Bissonnette in view of the teachings of Sonti. Ex-1003, ¶¶369-71; Ex-1032, ¶¶128-133.

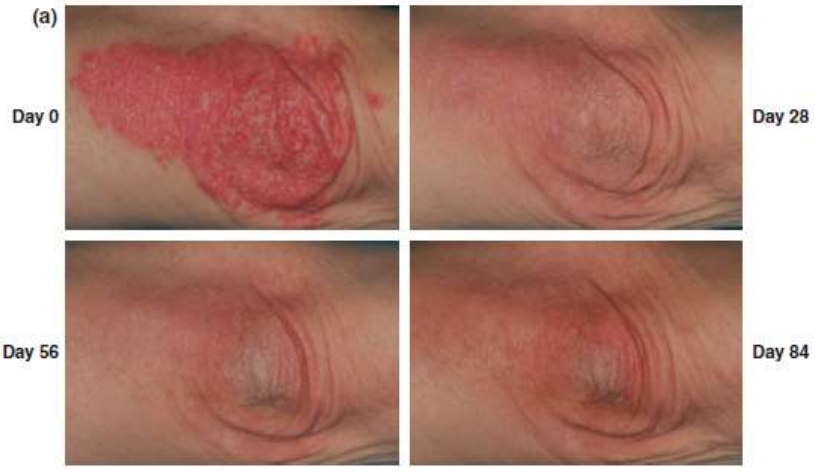
The formulations taught by Sonti and recited by claims 2-4 were merely standard formulations for topical emulsions at the time of purported invention. *E.g.* Ex-1032, ¶¶120-122. It would have been predictable and common sense for a POSA to use the teachings of Sonti to create the topical 1% tapinarof cream that Bissonnette refers to. Ex-1032, ¶¶128-130. Sonti—like Bissonnette—teaches topical *cream* formulations for the *same* active ingredient (tapinarof), the *same* use (treating plaque psoriasis), and the *same* strength (1%). Ex-1032, ¶131; Ex-1008, Abstract; Ex-1005, Abstract, [0285]-[0296], [0100]-[0101] (tapinarof "formulated as a cream"), [0055] and [0196] ("1%... by weight" of tapinarof), [0008]-[0010]. A POSA would have reasonably expected to be able to do so using only ordinary skill in the art—Sonti already taught tapinarof "cream" formulations for treating plaque psoriasis. Ex-1032, ¶132. This is confirmed by the fact that Bissonnette did not see it necessary to describe exactly how the 1% tapinarof cream was formulated, indicating that creating the cream formulation was routine in the art by that time. Ex-1032, ¶133. For at least these reasons, a POSA would have been motivated to use the formulation recited by claims 2-4 and taught by Sonti when creating the 1% tapinarof cream of Bissonnette, with a reasonable expectation of success.

C. Dependent Claim 6

Bissonnette discloses this claim. Ex-1003, ¶¶372-375.

Bissonnette discloses subjects having "between 1% and 10% of body surface area (BSA) covered with psoriasis (excluding the face, groin, scalp and genital regions)." Ex-1008, Abstract, 2. Thus the subjects had plaque psoriasis at least on their "body." Forty of the subjects "appl[ied]" 1% tapinarof cream. Ex-1008, Abstract, 2. A POSA would understand this to mean that the subjects applied the 1% tapinarof cream topically to the affected area of the skin at least on the "body." Ex-1003, ¶373.

Bissonnette also discloses a subject who applied the tapinarof cream to an elbow, which is part of the "arm" as claimed (Ex-1003, ¶374).



Ex-1008, 5, Fig. 3.

The method of claim 6 also would have been an obvious way to treat plaque psoriasis, as the body, arms, legs, back, chest, buttocks, neck, scalp, fingernails, toenails are all areas of the body commonly affected by plaque psoriasis. Claim 6 simply recites applying the tapinarof to these commonly affected body parts. A

POSA would have been motivated, with a reasonable expectation of success, to apply the tapinarof to body parts commonly affected by psoriasis, as recited by claim 6. Ex-1003, ¶375.

D. Dependent Claims 7, 21

Bissonnette discloses these claims. Ex-1003, ¶¶376-378.

Bissonnette discloses treating a subject who has been diagnosed with mild to severe (claim 7) and mild to moderate (claim 21) plaque psoriasis. Ex-1008, Abstract, 2 (treating patients "diagnosed with stable, mild to moderate plaque psoriasis" and having a PGA score of "two (mild) to four (severe)"); Ex-1003, ¶377.

Bissonnette also discloses treating a subject having a BSA affected of "about 3% to about 20%" as claimed. Bissonnette discloses treating a study cohort of forty patients who have been "diagnosed" with "plaque psoriasis," having "between 1% and 10% body surface area (BSA) covered with psoriasis". Ex-1008, 1, Abstract, 2-3, Table 1. This disclosure includes treating subjects with 3% to 10% BSA affected, which is in the claimed BSA affected range. Ex-1003, ¶378.

E. Dependent Claims 8, 22

Bissonnette discloses these claims. Ex-1003, ¶¶379-381.

Bissonnette discloses treating a subject diagnosed with mild to severe (claim 8) and mild to moderate (claim 22) plaque psoriasis, as explained above with respect to claims 7 and 21.

Bissonnette also discloses treating a subject "having a Physician Global Assessment (PGA) score of greater than or equal to 2" as recited by claims 8 and 22. Bissonnette discloses that the study subjects each had a "Physician's Global Assessment (PGA) of two (mild) to four (severe) at Day 0." Ex-1008, 2; *see also id.* Abstract. This is disclosure of treating a subject having a PGA score of "greater than or equal to 2," as claimed.

F. Dependent Claim 9

Bissonnette discloses this claim. Ex-1003, ¶¶382-385.

Bissonnette discloses an improvement in one or more symptom of mild to severe plaque psoriasis as measured according to "*Physician Global Assessment (PGA) score*," after topically administering the 1% tapinarof cream, for the reasons explained with respect to [1.d] above. A POSA would understand that a patient who started with a PGA score of 2 to 4 and improves to a PGA score of 0 or 1 following the topical administration the 1% tapinarof cream will have achieved the "*improvement of one or more symptom of mild to severe plaque psoriasis*" as claim 9 states. Ex-1003, ¶383.

Bissonnette also discloses an improvement in one or more symptom of mild to severe plaque psoriasis as measured according to BSA affected, for the reasons explained in Ground 3 with respect to claim 9. Following twelve weeks of treatment, the BSA affected had decreased an average of 79.1%. Ex-1008, 3-4, Tables 1, 3. This is "*an improvement of one or more symptom of mild to severe plaque psoriasis as measured according to . . . percent body surface area (BSA) affected*," as recited by claim 9. Ex-1003, ¶384.

A POSA also would have reasonably expected the claimed improvement, because each of Sonti and Chen already taught once-daily administration was highly effective, as explained above in this Ground 4 with respect to elements [1.c], [1.d]. Ex-1003, ¶385.

G. Dependent Claim 10

Bissonnette discloses this claim. Ex-1003, ¶¶386-390.

Bissonnette discloses that the forty subjects treated with the 1% tapinarof topical composition showed a change in mean body surface area (BSA) affected of "-2.6%" following twelve weeks of treatment. Ex-1008, Table 3. The mean BSA when the study began was 3.3%. Ex-1008, Table 1. Thus Bissonnette discloses that the mean BSA decreased to 0.7% following the treatment. A BSA that has decreased to 0.7% has also decreased to "less than 20%" as recited by claim 10, as 0.7% is (far) less than 20%. Ex-1003, ¶¶387-389.

A POSA also would have reasonably expected the claimed BSA improvement, because each of Sonti and Chen already taught once-daily administration was highly effective, as explained above in this Ground 4 with respect to elements [1.c], [1.d]. Ex-1003, ¶390.

H. Dependent Claims 16, 18

Bissonnette discloses these claims. Ex-1003, ¶¶391-400.

Bissonnette discloses that a PGA score is improved after about 8 weeks (and also after about 2 weeks and after about 4 weeks) of administering the 1% tapinarof cream:

Table 2 Proportion of patients with PGA 0 or 1 at each visit

	1% WBI-1001 (*N* = 40) *n* (%)	Placebo (*N* = 21) *n* (%)
Day 0	0 (0)	0 (0)
Day 14	5 (12.5)	0 (0)
Day 28	11 (27.5)	0 (0)
Day 42	23 (57.5)	0 (0)
Day 56	22 (55.0)	1 (4.8)
Day 84	27 (67.5)	1 (4.8)

PGA, physician's global assessment.

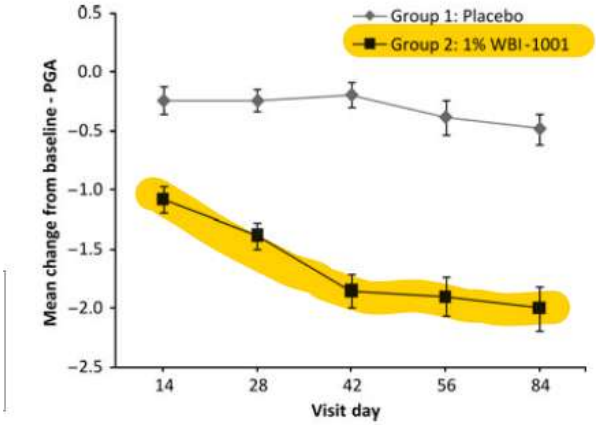


Figure 2 Change from baseline in PGA at each visit; ITT population (mean ± SEM).

Ex-1008, Table 2, Figure 2, p.3 (annotated).

This disclosure shows that the "PGA score is improved" after 8 weeks (and also after two and four weeks) of administering the topical tapinarof composition, as recited by claim 18. Ex-1003, ¶¶393, 395. It also indicates to a POSA that "one or more symptom is improved" after about 8 weeks of administering the topical composition, as recited by claim 16. Ex-1003, ¶394.

Bissonnette also alternatively discloses claim 16—that "one or more symptom is improved" after about 8 weeks (also two and four weeks) of treatment—via its teaching regarding improvement in BSA affected. Ex-1003, ¶¶396-397. Bissonnette discloses that percent BSA affected was decreased by 71.6% after eight weeks of treatment. Ex-1008, Table 3.

A POSA also would have reasonably expected the claimed symptom and PGA score improvement on the timeline recited, because each of Sonti and Chen

already taught once-daily administration was highly effective, as explained above in this Ground 4 with respect to elements [1.c], [1.d]. Ex-1003, ¶¶398-400*; see also* Ex-1005, [0288] (PGA score improved by two grades after 8 weeks treatment); Ex-1013, 2:53-3:4, 32:10-63 ("great efficacy" after only one week treatment).

XII. THE BOARD SHOULD NOT DENY THIS PETITION ON DISCRETIONARY GROUNDS

In evaluating §325(d), the Board uses a two-part framework: (1) whether the same or substantially the same art or arguments were previously presented to the Office; and (2) if either condition is satisfied, whether the petitioner has demonstrated that the Office erred materially. *Advanced Bionics*, IPR2019-01469, Paper 6 at 8 (PTAB Feb. 13, 2020) (precedential); *see also Becton,* IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017) (precedential in part).

The first condition is not satisfied. Bissonnette (Ground 4, raised against all Challenged Claims) was not before the Office during prosecution and has never been considered.

Sonti (Grounds 1-3) is cited in the ’088 patent, but for a different purpose.[10] The ’088 patent incorporates Sonti’s “formulations” of tapinarof topicals. Ex-1001, 8:60-63. However, to the extent the examiner considered Sonti, the examiner evidently overlooked that Sonti is not just about formulations. Sonti *also* teaches *treating* plaque psoriasis using the tapinarof formulations, including using PGA score to evaluate severity and treatment response (an element the Applicant argued was missing from the prior art). There is no indication Sonti’s teachings regarding *methods of treating* were ever presented to the Office; if they were, then the examiner materially erred by overlooking them. *See, e.g., Samsung Bioepis Co., Ltd. v. Alexion Pharms, Inc*., IPR2023-00998, Paper 9 (PTAB Dec. 8, 2023).

Chen (Ex-1013) does contain disclosures similar to the Chen references that were before the examiner (Ex-1027–Ex-1029), but this is not a reason to discretionarily deny. First, Chen is a secondary reference; the Bissonnette/Chen combination was not previously before the Office. Second, the Examiner also evidently erred or overlooked material disclosures in Chen. One, contrary to what the applicant argued, Chen did disclose treating specifically “*plaque*” psoriasis.

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[10] The patent that issued from the Sonti publication—U.S. 10,195,160—is also cited on the face of the ’088 patent, but was never discussed by the examiner.

Ex-1003, ¶¶64-65; Ex-1027 [0095]-[0102] ("Volunteer 2… with ***plaques*** on her back") (emphasis added). Two, a POSA would have understood that while Chen did not specifically refer to PGA scores, it did disclose improvements that a POSA would have understood to be the PGA score improvements claimed. Ex-1003, ¶66; Ex-1027, [0100]-[0102] (compound showed "great efficacy," resulted in "complete clearance" after treatment).

XIII. MANDATORY NOTICES UNDER 37 C.F.R. §42.8(B)

A. Real Party-in-Interest

Encube Ethicals Pvt. Ltd. is the real party-in-interest.

B. Related Matters

As of the filing date of this Petition and to the best knowledge of Petitioner, the '088 patent has not been involved in any other judicial or administrative matters.

C. Lead and Back-Up Counsel

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D. Service Information

Please address all correspondence to lead and back-up counsel at the addresses shown above. Petitioner consents to electronic service by e-mail.

E. Fees

Petitioner electronically submits the required fees for this Petition. The Board is authorized to charge Carlson, Caspers, Vandenburgh & Lindquist, PA.'s deposit account, No. 50-2880, for any fee deficiency.

XIV. CONCLUSION

For the reasons stated above, Petitioner respectfully requests that the Board institute this IPR and cancel each Challenged Claim.

Dated: April 23, 2024

Respectfully submitted,

/Gary J. Speier/

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Lead Counsel for Petitioner

APPENDIX A: CLAIMS LISTING

U.S. Patent No. 11,590,088
Claims 1-4, 6-10, 16, 18, and 21-22

Designation	Claim 1
[1.pre]	1. A method for treating mild to severe plaque psoriasis in a subject
[1.a]	comprising topically administering a topical composition containing about 1.0% tapinarof
[1.b]	to affected areas of the subject
[1.c]	once a day,
[1.d]	wherein after topically administering the topical composition a Physician Global Assessment (PGA) score is improved by 2 grades or has improved to a score of 0 or 1.
Claim 2	2. The method of claim 1, wherein the topical composition is an oil-in-water emulsion.
Claim 3	3. The method of claim 2, wherein the oil phase of the oil-in-water emulsion is comprised of medium chain triglycerides, propylene glycol, non-ionic emulsifying wax, diethylene glycol monoethyl ether, polyoxyl stearyl ether-2, polysorbate 80, polyoxyl stearyl ether-20, benzoic acid, and butylated hydroxytoluene.
Claim 4	4. The method of claim 2, wherein the water phase of the oil-in-water emulsion is comprised of sodium citrate, edetate disodium, citric acid monohydrate, and water.
Claim 6	6. The method of claim 1, wherein the topically administering includes application to the affected area of the skin selected from the group consisting of body, arms, legs, back, chest, buttocks, neck, scalp, fingernails, toenails, and combination thereof.

Claim 7	7. The method of claim 1, wherein the subject has been diagnosed with mild to severe plaque psoriasis having a percent body surface area (BSA) affected of about 3% to about 20%.
Claim 8	8. The method of claim 1, wherein the subject has been diagnosed with mild to severe plaque psoriasis having a Physician Global Assessment (PGA) score of greater than or equal to 2.
Claim 9	9. The method of claim 1, further comprising after topically administering the topical composition an improvement of one or more symptom of mild to severe plaque psoriasis as measured according to an assessment selected from the group consisting of Physician Global Assessment (PGA) score, Psoriasis Area and Severity Index (PAST), target lesion grading, Itch/Pruritus numeric rating scale, percent body surface area (BSA) affected, Psoriasis Symptom Diary (PSD), Dermatology Quality of Life Index (DLQI), or 36 Item Short Form Survey (SF-36).
Claim 10	10. The method of claim 9, wherein the percent body surface area (BSA) affected is decreased to less than 20% after topically administering the topical composition.
Claim 16	16. The method of claim 9, wherein the one or more symptom is improved after about 2 weeks, about 4 weeks, or about 8 weeks of administering the topical composition.
Claim 18	18. The method of claim 1, wherein the PGA score is improved after about 2 weeks, about 4 weeks, or about 8 weeks of administering the topical composition.
Claim 21	21. The method of claim 1, wherein the subject has been diagnosed with mild to moderate plaque psoriasis having a percent body surface area (BSA) affected of about 3% to about 20%.
Claim 22	22. The method of claim 1, wherein the subject has been diagnosed with mild to moderate plaque psoriasis having a Physician Global Assessment (PGA) score of greater than or equal to 2.

CERTIFICATE OF COMPLIANCE

The undersigned hereby certifies that the foregoing Petition for *Inter Partes* Review contains 13,996 words, excluding those portions identified in 37 C.F.R. §42.24(a), as measured by the word-processing system used to prepare this paper.

/Gary J. Speier/_____
Gary J. Speier

CERTIFICATE OF SERVICE

I certify that on April 23, 2024, I caused a true and correct copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 11,590,088 and supporting exhibits to be served via overnight delivery on the Patent Owner at the following correspondence address of record as listed on PAIR:

DLA Piper LLP (US)/Roivant
1650 Market Street, Suite 5000
Philadelphia, PA 19103
United States

/Gary J. Speier/_____
Gary J. Speier