

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

DECLARATION OF WIEKE H. LIEM, M.D., F.A.A.D.

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EXHIBIT LIST

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	<i>Curriculum Vitae</i> 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)
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 <i>Xenorhabdus</i> spp., <i>Journal of Chemical Ecology</i> 7(3):589-597 (1981)
1015	Smriti K. Raychaudhuri, Emanuel Maverakis, & Siba P. Raychaudhuri, <i>Diagnosis and Classification of Psoriasis</i> , 13 <i>Autoimmunity Reviews</i> 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, <i>Natural product and natural product derived drugs in clinical trials</i> , <i>Natural Product Reports</i> (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 , 8 th Edition
1032	Declaration of Paul T. Sudhakar, MS, MBA
1033	<i>Curriculum Vitae</i> of Paul T. Sudhakar
1034	Declaration of Sylvia D. Hall-Ellis, Ph.D.

I, Wieke Liem, declare as follows:

I. INTRODUCTION

1. I have been retained by Encube Ethicals Pvt. Ltd (“Petitioner”) as an independent expert consultant in this proceeding before the United States Patent and Trademark Office.

2. I am being compensated at a rate of \$800/hour for my time spent on this proceeding, which is my regular and customary rate for consulting work. I am being separately reimbursed for any out-of-pocket expenses. I am not receiving any other compensation.

3. My compensation is not contingent on the nature of my findings, the presentation of my findings in testimony or this declaration, or the outcome of this or any other proceeding. I also have no other interest in this proceeding.

4. I have been asked to consider whether certain references disclose and/or suggest the features recited in certain claims of U.S. Patent No. 11,590,088 (“the ’088 patent”) (Ex-1001), including considering what the prior art would disclose and/or teach and suggest to a person of ordinary skill in the art (“POSA”) at the time of the purported invention.

5. My opinions, their factual support, and the related discussion of background technology presented herein are true to the best of my knowledge. I am over 18 years of age and I am competent to testify as to the matters set forth

herein.

6. My analysis of the relevant materials is ongoing, and I will continue to review any new material as it is provided. This declaration represents only those opinions that I have formed to date. I reserve the right to revise, supplement, or amend my opinions below based on new information and on my continuing analysis of the materials already provided, and to respond to any testimony or other information provided by or on behalf of the owner of the patent at issue in this proceeding.

7. In this declaration I also add emphasis to various quotations and citations, and I add highlighting to various excerpts. Unless I note otherwise, the emphasis added (for example bolding or italics) and highlighting is mine.

8. My opinions are set forth below.

II. QUALIFICATIONS AND BACKGROUND

9. I am an independent consultant for this matter. All of the opinions I provide in this declaration are based on my own personal knowledge, experience, and professional judgment as a practicing medical doctor specializing in dermatology. In forming these opinions, I have relied on my years of education, research and experience in the field, as well as my review of the materials identified below and throughout this report.

10. I set forth my education, experience, and qualifications in my resume,

provided as Exhibit 1003. I also provide a summary below.

11. In 1985, I earned a bachelor's degree in biological sciences from Stanford University. In 1989, I earned my M.D. degree from the University of California, Irvine M.D. College of Medicine.

12. Thereafter, I completed an internship in Internal Medicine at the Oregon Health Sciences University. Following my internship, I completed my residency in Dermatology at the University of California, Irvine. I concluded my dermatology residency in 1993, and I have been a practicing dermatologist since that time.

13. I am currently a dermatologist at Enhanced Dermatology of Orange County in Tustin, California, as well as a dermatology associate at Silverberg Surgical Medical Group in Newport Beach, California. I am also affiliated with the St. Joseph Hospital in Orange, California.

14. Throughout my career as a practicing M.D. dermatologist, I have also held various academic positions. From 1994-1998, I was a Clinical Instructor in Dermatology, at the University of California-LA (UCLA). From 1994-1997, I was the Vice Chairman of the Department of Medicine, at Verdugo Hills Hospital in Glendale, California. From 2001-2006, I was an Assistant Clinical Professor in the Department of Dermatology, at the University of California-Irvine.

15. I have also authored and co-authored medical journal articles,

including multiple articles regarding psoriasis treatments.

III. MATERIALS REVIEWED AND SUMMARY OF OPINIONS

16. My opinions contained in this Declaration are based on my knowledge and experience gained from my education as a medical doctor with a specialization in dermatology, as well as my experience as a practicing clinical dermatologist for the last 30+ years, and the specific references, documents, and other materials I discuss in this Declaration.

17. In forming my opinions, I also reviewed and considered the declaration of Paul Sudhakar, along with Mr. Sudhakar's CV. Ex-1032, Ex-1033.

18. In forming my opinions, I also reviewed the following, along with any other materials I discuss in my Declaration¹:

- The '088 Patent (Ex-1001).
- The prosecution history of the '088 Patent (Ex-1002), and the references discussed therein (*e.g.*, Ex-1027, Ex-1028, Ex-1029).
- U.S. Patent Application Pub. No. 2016/0338973 ("Sonti"; "Ex-1005"), published Nov. 24, 2016.

¹ All of my citations to various documents are to the branded numbers added by the Petitioner in this matter in the bottom right corner of the exhibits, except citations to patents and published applications, which I cite by column/line number or paragraph number.

- Dogra, et al., Psoriasis: Epidemiology, Clinical Features, Co-morbidities, and Clinical Scoring, Indian Dermatology Online Journal 7(6):471-480 (2016) (“Dogra 2016”; “Ex-1006”), published Nov.-Dec. 2016.
- 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) (“Spuls 2010”; “Ex-1007”), published Dec. 31, 2009.
- 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 Nov. 12, 2011.
- Bolkote, et al., An Analysis of Psoriasis Skin Images, International Journal of Inventive Engineering and Sciences 2(12):17-22 (2014) (“Bolkote 2014”; “Ex-1009”), published Nov. 2014.
- 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) (“Cappelleri”; “Ex-1010”), published Mar. 9, 2013
- Patel, et al., Evaluating Psoriasis: A Review of the Assessments Most Commonly Used in Clinical Trials, Psoriasis Forum, Vol. 17, No. 4, published Winter 2011 (“Patel”, “Ex-1011”).
- WO 2001/042231 (“Ex-1012”), published Jun. 14, 2001.
- U.S. Patent No. 7,868,047 (“Chen”; “Ex-1013”), issued Jan. 11, 2011.
- Smriti K. Raychaudhuri, Emanuel Maverakis, & Siba P. Raychaudhuri, Diagnosis and Classification of Psoriasis, 13 Autoimmunity Reviews 490 (2014) (“Raychaudhuri 2014”; “Ex-1015”), published Jan. 13, 2014.
- ChiCTR studies (Ex-1016, Ex-1017, Ex-1018)
- Mark S. Butler, Avril A. B. Robertson, Matthew Cooper, Natural product and natural product derived drugs in clinical trials, Natural Product Reports (2014) (“Butler 2014”; “Ex-1019”).

- Clinical Trials website (<https://clinicaltrials.gov/>) (“ClinicalTrials.gov”; “Ex-1026”).

19. I have been asked to form the opinions discussed in this Declaration by placing myself in the position of a person of ordinary skill prior to November 13, 2018. I have done so. I note that it was easy to place myself in that frame of mind, as I was a person of ordinary skill in the art at that time. My opinions would not change if the relevant timeframe was slightly earlier or slightly later.

20. I am also guided by my understanding of how a person having ordinary skill in the art would have understood the claims and the specification of the '088 patent at the time of the alleged invention. My opinions reflect how a POSA would have understood the '088 patent, the prior art to the patent, and the state of the art at the time of the alleged invention.

21. In my opinions below, I also discuss some reasons that a POSA would be motivated to combine teachings of references, and would reasonably expect to be successful when doing so. While I often provide multiple reasons, in view of the state of the prior art and the knowledge a POSA would have, I believe that any one of the reasons I list would have been sufficient.

22. Based on my experience, it is my opinion that certain references I discuss below disclose and/or suggest all the features recited in claims 1-4, 6-10, 16, 18, and 21-22 of the '088 patent, as I explain in more detail in the following

sections.

IV. LEVEL OF ORDINARY SKILL IN THE ART

23. I understand that, in the context of an invalidity analysis, a person having ordinary skill in the art is a hypothetical person who would be aware of the prior art at the time of the invention. I also understand that to determine the appropriate level of skill in the art, the following factors may be considered: (a) the types of problems encountered by those working in the field and prior art solutions thereto; (b) the sophistication of the technology in question and the rapidity with which inventions occur in the field; (c) the education level of active workers in the field; and (d) the education level of the inventor.

24. Applying these considerations, it is my opinion that the relevant POSA for the '088 patent 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. A POSA would have had access to and would have consulted with a collaborative team of ordinarily skilled artisans, including drug formulators. I understand that a drug formulator with the ordinary level of skill at the relevant time would have had a technical degree in the relevant field (B. Pharm.) and five years of experience in the pharmaceutical sciences developing topical compositions for treating skin conditions, or an advanced

degree (M. Pharm.), and two years of experience in the pharmaceutical sciences that included developing topical compositions for treating skin conditions.

25. Based on my qualifications and experience, I met the qualifications of a POSA, by November 13, 2018 and well before then. I have also reviewed and relied on the opinions of Mr. Paul Sudhakar where relevant. Mr. Sudhakar is a drug formulator who meets the level of ordinary skill for a drug formulator at the time.

26. All my opinions in this declaration are from the perspective of one of ordinary skill in the art as I have defined it here during the relevant timeframe, which I understand is before November 13, 2018. This is true even if I do not expressly state or restate the specific timeframe when providing my opinions below. My opinions in this declaration would not change if the level of skill in the art was slightly higher or lower.

V. LEGAL PRINCIPLES

27. I am not an attorney and I do not offer any legal opinions in this Declaration. For the purposes of this declaration, I have been informed about certain aspects of the law that are relevant to forming my opinions. I summarize my understanding of the law below.

28. I have been informed that a patent claim is invalid as anticipated under 35 U.S.C. § 102 if each and every element of a claim, as properly construed,

is found either expressly or inherently in a single prior art reference. Under what is known as inherency, I understand that if the prior art necessarily functions in accordance with, or includes the claimed limitations, it anticipates. I also understand that I may examine evidence that is outside of the prior art reference in determining whether a feature, while not expressly discussed in the reference, is necessarily present in that reference.

29. I have been informed that a reference can anticipate a claim even if it does not expressly spell out all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would “at once envisage” the claimed arrangement or combination.

30. I also understand that a patent claim is only valid if it is nonobvious. I understand that a patent claim can be considered to be obvious even if all of the requirements of a claim are not found in a single prior art reference, if the differences between the subject matter in the prior art and the subject matter in the claim would have been obvious to a person having ordinary skill in the art at the time of the invention.

31. I have been informed that the Supreme Court considered the legal standard for obviousness in its decision in *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398 (2007). I understand that a patent claim is invalid as obvious under 35 U.S.C. § 103 if the subject matter would have been obvious to a POSA at the time the

alleged invention was made. I understand that the analysis of obviousness requires consideration of three factors: (1) a determination of the scope and content of the prior art; (2) the level of ordinary skill in the art; and (3) the differences between the prior art and the asserted claims. I also understand that, when evidence is presented, certain objective considerations are to be considered as part of the obviousness analysis.

32. I have been informed that, under KSR, claims directed to a combination of familiar elements according to known methods may be invalid as obvious when the combination does no more than yield predictable results.

33. I have been informed that a claim may be obvious in light of a single prior art reference or in light of the combination of multiple prior art references. To be obvious in light of a single prior art reference or multiple prior art references, I understand there must be a reason to modify the single prior art reference, or combine two or more references, with a reasonable expectation of success, in order to achieve the claimed invention. This reason may come from a teaching, suggestion, or motivation to combine. However, I understand that a specific teaching, suggestion, or motivation to combine elements in the prior art to achieve the claimed combination is not required for obviousness. Instead, I understand that a combination of known elements may be obvious in light of the interrelated teachings of the prior art, the effects of demands in the market, the background

knowledge possessed by a POSA, and inferences and creative steps that a POSA would employ.

34. I also understand that a combination of known elements may be obvious when there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions known to a person of ordinary skill, such that the combination would have been obvious to try.

35. I also understand that in considering obviousness, obviousness may not be determined using the benefit of hindsight, including hindsight derived from the patent being considered.

36. I also understand that what is known as evidence of secondary considerations or objective evidence of non-obviousness, such as commercial success of an embodiment of the invention, solving a long-felt need, or industry praise, is relevant to obviousness. I am not currently aware of such evidence or purported evidence regarding the claims of the '088 patent. If I do become aware of such evidence, I may offer opinions regarding that evidence.

VI. TECHNICAL BACKGROUND

37. In this section, I provide some background on the diagnosis and treatment of skin disorders, including plaque psoriasis. I focus the discussion on some aspects I view as relevant to this declaration regarding the subject matter of the '088 patent.

A. Psoriasis

38. Psoriasis is a common inflammatory skin disorder, with a worldwide prevalence of around 2-5%. Ex-1008, 1; Ex-1015, 1. Plaque-type psoriasis is the most common type, representing 80-90% of psoriatic patients. Ex-1015, §4.1; Ex-1009 at 2; Ex-1006 at Abstract. Plaque psoriasis is a common disorder among the patients I have treated throughout my career as a practicing dermatologist. In any given year, I see approximately 150-200 patients having plaque psoriasis, totaling over 600 patient visits per year.

39. Plaque psoriasis manifests as raised scaly patches on the skin, known as “plaques.” *E.g.*, Ex-1009, 2 (plaque psoriasis is “characterized by thick red patches of skin, often with a silver or white layer of scale”); Ex-1015, §4.1 (plaque psoriasis characterized “by dry, sharply demarcated round/oval plaques with loosely adherent silvery white scales”); Ex-1006, 2 (plaque-type psoriasis “manifests as circumscribed well-demarcated erythematous plaques” and the scaling “varies from the typical silvery-white scales to waxy yellow or orange-brown scales”); Ex-1005, [0287] (“plaque elevation, scaling , and/or erythema”); Ex-1013, 2:59-62 (“inflamed swollen skin lesions covered with silvery white scaling patches and raised, inflamed, thickened and scaly lesions”). The plaques can appear pink, red, or purple in color, and may be associated with itching or pain. The cause is understood to be an autoimmune dysfunction, where the

immune cells (e.g., T-cells) are stimulated to produce hyperproliferation and inflammation in the skin, and less commonly in the nails and joints.

B. Physician Global Assessment (“PGA”), Body Surface Area (“BSA”), and other Common, Known Metrics for Evaluating Psoriasis

40. By November 2018, there were several different known and commonly used metrics in the field of dermatology for diagnosing and assessing plaque psoriasis. These included Physician Global Assessment (“PGA”), Body Surface Area (“BSA”), Psoriasis Area and Severity Index (“PASI”), Psoriasis Symptom Diary (“PSD”), Dermatology Quality of Life Index (“DLQI”), and 36 Item Short Form Survey (“SF-36”). For example, the Dogra article from 2016 explained that “[a] variety of scoring systems have been used to assess the severity of plaque-type psoriasis. These include the clinical severity scores and quality of life scores, which are enumerated in Table 5.” Ex-1006, 5. I reproduce Table 5 below (highlighting added):

Table 5: Various clinical severity scores and quality of life impairment scores employed in assessing psoriasis severity

Assessing clinical severity	Assessing quality of life
Psoriasis area severity index (PASI)	Short form 36 (SF36)
Psoriasis log based area and severity index (PLASI)	World organization quality of life (WHOQOL)
Body surface area (BSA)	Euro Qol 5D5 (EQ5D)
Physician global assessment (PGA)	Dermatology life quality index (DLQI)
Lattice system Physician global assessment (LS-PGA)	Skindex 29, Skindex 17
Self-assessment Psoriasis area severity index (SAPASI)	Dermatology quality of life scale (DQOLS)
Salford psoriasis index (SPI)	Psoriasis disability index (PDI)
Response to treatment score (RT)	Impact of psoriasis questionnaire (IPSO)
Dermatology index of disease severity (DIDS)	Psoriasis index of quality of life (PSORIQOL)
Copenhagen psoriasis severity index (CoPSI)	Psoriasis quality of life questionnaire (PQLQ)
Beer-Sheva psoriasis severity index (BPSS)	Impact of chronic skin disease on daily life (ISDL)
National psoriasis foundation psoriasis score index (NPF-PS)	Salford psoriasis index (SPI)
	Psoriasis life stress inventory (PLSI)
	Family dermatology life quality index (FDLQI)
	Illness perception questionnaire (IPQ)
	Patients global psoriasis assessment (PGA)
	Psoriasis symptom assessment (PSA)
	Itching visual analog scale (IVA)

A 2010 journal article (Ex-1007) similarly identifies PASI, BSA, and PGA as commonly used metrics for measuring plaque psoriasis, at Tables 1 and 2 (excerpted below):

Table 1. All retrieved clinical outcome measures re-grouped in 11 main clinical severity and outcome measures for analysis

1. **Psoriasis Area and Severity Index (PASI)**
 - Psoriasis Area and Severity Index (PASI)
 - Extend Score of the Salford Psoriasis Index (SPI)
2. **Body surface area (BSA)**
 - Body surface area (BSA)
 - Total Body Surface Involvement
 - Area Index (AI)
 - Rule of Nines
3. **Physician's/Psoriasis Global Assessment (PGA)**

Static assessment:

 - Physician's Global Assessment (PGA)
 - Psoriasis Global Assessment (PGA)
 - Investigator's Global Assessment of Plaque Severity
 - Investigator's Global Severity Assessment of Psoriasis
 - Investigator's Global Assessment of Disease Severity
 - Physicians' Overall Assessment of the Extent of Psoriatic Involvement
 - Investigator's Global Assessment of Overall Severity
 - Overall Lesion Severity Scale (OLS)
 - Physician Static Global Assessment

Table 2. Overview of the 11 main clinical psoriasis measures that were analyzed

Instrument	Description
BSA	Estimation of involved body surface area, several scores are used
Signs	Evaluation of the plaque characteristics erythema, scaling, and induration. Erythema and scaling are easily influenced by external factors
PASI	The affected area and lesion characteristics are entered in a formula that results in a score from 0 to 72. The PASI is most often used in clinical trials
PGA	The PGA is a 5, 6, or 7-point ordinal rating ranging from "clear" to "very severe psoriasis"

Ex-1007, 2-3.

41. These metrics are assessed by a medical professional, and PGA, BSA, and PASI had been approved by the U.S. FDA for use in clinical trials well before 2018. Ex-1006, 7.

42. Because no psoriasis biomarkers are available to assess disease severity, clinical measures (such as PGA and BSA) were used in daily practice and in research to measure both severity and treatment response. Ex-1011, 1-2; Ex-1007, 1 ("As there are no biomarkers available to assess disease severity, clinical measures are used in clinical trials and daily practice to measure severity and treatment response.").

43. The **PGA specifically** was a known metric, generally a 5, 6, or 7 point scale ranging from “clear” to “severe” psoriasis. *E.g.*, Ex-1011, 5; Ex-1007, Table 2, 6. The PGA was (and is) commonly used in psoriasis clinical trials. *E.g.*, Ex-1011, 2 (“The PGA is the most commonly used scoring method in [psoriasis] clinical trials after the PASI”). A 2013 article by Cappelleri et al. (Ex-1010) explains that “[t]he Physician Global Assessment (PGA) is a key measure of psoriasis severity frequently used in clinical trials as an efficacy endpoint.” Cappelleri provides an example having a five-point scale (scores of 0 to 4):

Fig. 1 a Physician's Global Assessment (PGA). b Patient's Global Assessment (PtGA)

(a) PGA

Erythema, induration and scaling are rated separately across all psoriatic lesions. Severity rating scores are summed and the average taken, with the average rounded to the nearest integer to determine the PGA score.

ERYTHEMA (E)
Determine erythema (averaged over the whole body)
☐ 0 = no evidence of erythema (post-inflammatory hyperpigmentation and/or hypopigmentation may be present)
☐ 1 = light pink
☐ 2 = light red
☐ 3 = red
☐ 4 = dark, deep red

INDURATION (I)
Determine induration (averaged over the whole body)
☐ 0 = no evidence of plaque elevation
☐ 1 = barely palpable
☐ 2 = slight but definite elevation, indistinct edge
☐ 3 = elevated with distinct edges
☐ 4 = marked plaque elevation, hard/sharp borders

SCALING (S)
Determine scaling (averaged over the whole body)
☐ 0 = no evidence of scaling
☐ 1 = occasional fine scale
☐ 2 = fine scale predominates
☐ 3 = coarse scale predominates
☐ 4 = thick, coarse scale predominates

Add E + I + S = / 3 = (Total Average)

PHYSICIAN GLOBAL ASSESSMENT - based upon above Total Average
☐ 0 = Clear - cleared, except for any residual discoloration
☐ 1 = Almost clear - majority of lesions have individual scores for E + I + S / 3 that average 1
☐ 2 = Mild - majority of lesions have individual scores for E + I + S / 3 that average 2
☐ 3 = Moderate - majority of lesions have individual scores for E + I + S / 3 that average 3
☐ 4 = Severe - majority of lesions have individual scores for E + I + S / 3 that average 4

Note: Total average is rounded to the nearest whole number score, eg if total ≈ 2.49 , score = 2; if total ≥ 2.50 , score = 3

Ex-1010, 3.

44. Other examples of the known PGA metric include:

- Ex-1005, [0287] (“The PGA scale in its typical use, is a 7-point scale ranging from clear to severe”); *see also id.*, [0288]-[0293];
- Ex-1008, 2 (“PGA score corresponding to the degree of overall lesion severity using a 5-point scale ranging from 0 to 5 (clear to very

severe) was performed for the entire body excluding face, scalp, groin, and genitals”);

- Ex-1011, 5 (“Typically, the PGA is a 5-, 6-, or 7-point ordinal rating ranging from “clear” to ‘very severe psoriasis.’”).

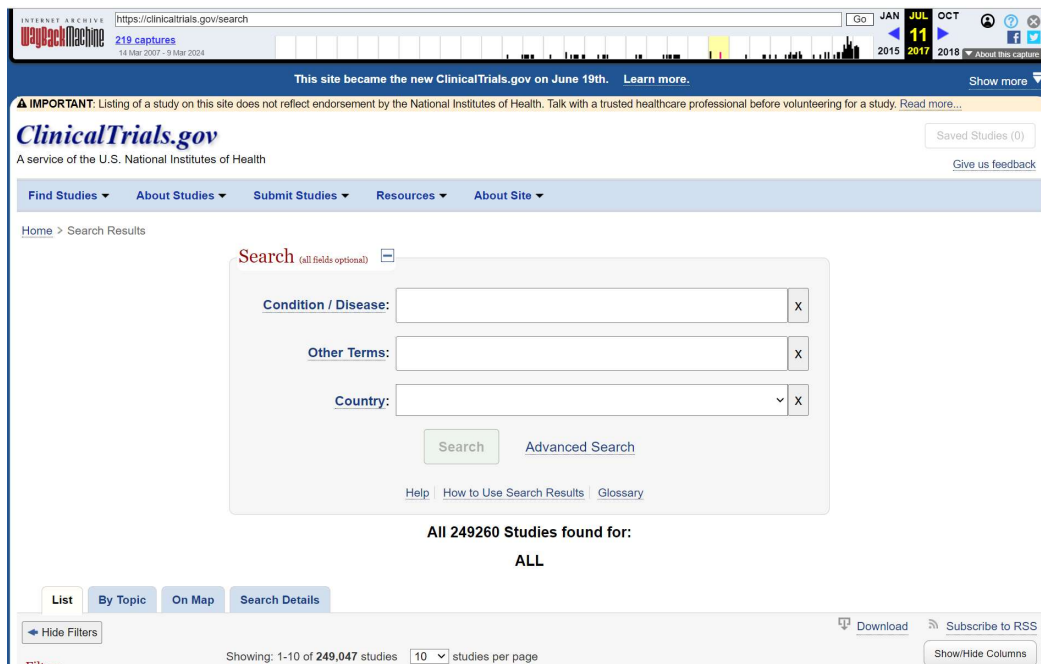
45. The **BSA specifically** was also a known metric used to assess severity of plaque psoriasis by well before 2018. One percent BSA is approximately equivalent to psoriasis plaque covering a body area equivalent to a patient’s open palm. *E.g.*, Ex-1007, 2 (“BSA can also be estimated by the number of patients’ hand areas affected, assuming that one ‘handprint’ reflects approximately 1% of BSA”); Ex-1006, 3 (Table 2); Ex-1011, 2. Psoriasis affecting over 10% of a patient’s body area (so a BSA of greater than 10%) was usually considered “severe.” *E.g.*, Ex-1006, 3 (Table 2); Ex-1011, 2 (“BSA involvement greater than 10% or a PASI score greater than 12 is frequently used as a criterion for severe disease”).

46. Both in my experience, and as the references above confirm, the PGA and BSA metrics were commonly used long before 2018, both to evaluate plaque psoriasis severity at baseline and to assess response to treatments of or for plaque psoriasis.

47. To provide additional examples of PGA and BSA use with respect to plaque psoriasis prior to November 13, 2018, I used a resource provided by the

U.S. National Library of Medicine and provide the results as Ex-1026. This resource is available at: <https://clinicaltrials.gov/search>.

48. This U.S. National Library of Medicine database allows users to search for and find information about privately and publicly funded clinical studies conducted around the world, including those supported by the U.S. government. This database is a resource that a POSA like myself would have and could have used prior to 2018. *See also* Ex-1032, ¶¶134-138. I recall using this database prior to 2018. Additionally, the WayBack Machine internet archive website shows that the database was publicly searchable and accessible prior to 2018, for example in July of 2017:



<https://web.archive.org/web/20170711212053/https://clinicaltrials.gov/search>

49. I accessed this database on March 21, 2024 and April 5, 2024. I

provided the following inputs, which retrieved 148 studies.

Search Field (Filter)	Input
Condition or disease	Plaque Psoriasis
Study Status	All studies
Sex	All
Age	Selected ranges: Child (birth – 17), Adult (18 – 64), and older adult (65+)
Study Results	With results
Date Range: Study start	To: 11/12/2018
Date Range: Primary completion	To: 11/12/2018
Date Range: First posted	To: 11/12/2018
Date Range: Results first posted	To: 11/12/2018
Date Range: Last update posted	To: 11/12/2018
Date Range: Study completion	To: 11/12/2018

Based on the inputs, a POSA would know that the information retrieved was publicly available as of November 12, 2018. *See also* Ex-1032, ¶¶134-138.

50. The 148 studies were downloaded with the following fields: NCT Number, Study Title, Study URL, Study Status, Brief Summary, Study Results, Conditions, Interventions, Primary Outcome Measures, Secondary Outcome Measures, Other Outcome Measures, Phases, Enrollment, Study Type, Start Date, Primary Completion Date, First Posted, Results First Posted, and Last Update Posted. The 148 studies are shown in Ex-1026.

51. Within the 148 studies above, 36 studies were obtained when the

search was further focused to include the below inputs for PGA and 48 studies when focused to include the below inputs for BSA.

Search Field (Filter)	Input	Number of studies (from the original 148)
Outcome measure	“Physician Global Assessment” and PGA	36 of 148
Outcome measure	“Body Surface Area” and BSA	48 of 148

The **36 studies using PGA** are shown at pages 53-62, 115-139, 197-206, 222-239, 349-361, 362-372, 373-384, 418-429, 449-461, 686-700, 725-735, 736-746, 780-803, 824-836, 837-856, 945-954, 955-978, 1031-1041, 1066-1073, 1166-1190, 1266-1274, 1296-1301, 1426-1441, 1442-1451, 1464-1479, 1480-1488, 1489-1498, 1499-1514, 1515-1525, 1549-1559, 1560-1572, 1573-1588, 1624-1632, 1643-1654, 1745-1756, and 1757-1769 in Ex-1026, and the **48 studies using BSA** are shown at pages 1-10, 63-66, 115-139, 140-149, 222-239, 362-372, 397-408, 440-448, 462-481, 482-495, 496-504, 529-540, 570-578, 601-616, 627-637, 638-649, 669-685, 686-700, 701-712, 736-746, 758-767, 780-803, 804-812, 813-823, 824-836, 837-856, 857-867, 898-907, 932-944, 955-978, 1013-1018, 1031-1041, 1074-1081, 1093-1111, 1166-1190, 1210-1218, 1219-1227, 1357-1371, 1372-1382, 1384-1414, 1426-1441, 1442-1451, 1573-1588, 1643-1654, 1666-1676, 1700-1713, 1736-1744, and 1757-1769 Ex-1026. This means that at the relevant time, approximately 24% of plaque psoriasis studies indicated Physician Global

Assessment (PGA) as an outcome measure, and 32% referenced Body Surface Area (BSA) in an outcome measure.

52. In the early 2010s, there was also a series of clinical trials conducted in China that consisted of topically applying tapinarof compositions (including 1% tapinarof compositions) to areas of the body affected by plaque psoriasis. Ex-1016, Ex-1017, Ex-1018. I refer to these as the “ChiCTR” trials. These trials consisted of topically applying “benvitimod cream” to treat plaque psoriasis. Ex-1016, 1; Ex-1017, 1; Ex-1018, 1. “Benvitimod” is another name for a cream containing tapinarof as the active ingredient. Ex-1032, ¶¶71-73; *see also* <https://pubchem.ncbi.nlm.nih.gov/compound/6439522#section=MeSH-Entry-Terms>; <https://en.wikipedia.org/wiki/Tapinarof> (“tapinarof, also known as benvitimod”).

53. The subjects included in the ChiCTR trials had been diagnosed with “plaque psoriasis,” having a 2-10% BSA coverage (excluding the face, groin, scalp, and genital regions) (Ex-1016, 3), less than or equal to 10% BSA coverage (Ex-1017, 3), and a baseline PGA greater than or equal to 2, in addition to a maximum of 10% BSA coverage (excluding the face, groin, scalp, and genital regions) (Ex-1018, 3). Each identified “PGA” score as a “primary indicator” of outcome. Ex-1016, 4; Ex-1017, 5; Ex-1018, 6. Each also included a group receiving a cream comprising 1% tapinarof. Ex-1016, 4 (Group 2 receiving “1.0%

Benvitimod cream”); Ex-1017, 4 (Groups B and C receiving “1.0% Benvitimod cream”); Ex-1018, 4 (Group A receiving “1.0% Benvitimod cream”).

VII. THE '088 PATENT

A. '088 Patent Overview

54. The '088 patent relates to using tapinarof in a topical composition to treat atopic dermatitis or plaque psoriasis. Ex-1001, Abstract. The '088 patent states that atopic dermatitis and psoriasis are each a “chronic[,] relapsing[,] inflammatory skin disease.” Ex-1001, 5:34-36 (atopic dermatitis) and 5:66-67 (psoriasis).

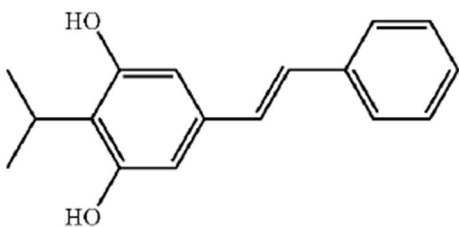
55. The '088 patent states that clinical studies of up to 12 weeks treatment of atopic dermatitis and psoriasis with 1% tapinarof cream were conducted, and that it was “surprisingly and unexpectedly found” that a 1% tapinarof cream applied once daily was just as effective as the same applied twice daily. Ex-1001, 6:46-68.

56. However, as I explain in more detail below, it was already known that 1% tapinarof applied topically once a day effectively treated plaque psoriasis. *E.g.*, Ex-1005; Ex-1012; Ex-1013.

57. In various embodiments, the '088 patent also describes using the body surface area (“BSA”) and Physician Global Assessment (“PGA”) metrics I discussed above to assess severity of and treatment response for psoriasis. *E.g.*,

Ex-1001, 21:9-36, 22:23-49, 23:24-46. As I explained above, PGA and BSA were well-known and common metrics used in conjunction with psoriasis long before the priority date of the '088 patent. *E.g.*, Ex-1005; Ex-1006; Ex-1007; Ex-1008; Ex-1010; Ex-1011.

58. The '088 patent also explains that “tapinarof” refers to “3,5-Dihydroxy-4-isopropyl-transstilbene or a pharmaceutically acceptable salt thereof.” Ex-1001, 7:4-20. Tapinarof is also known as “(E)-2-isopropyl-5-styrylbenzene-1,3” and has an empirical formula of $C_{17}H_{18}O_2$. *Id.* The '088 patent also provides a drawing of the molecular structure of tapinarof:



Id.; see also Ex-1032, ¶¶56-57.

B. Prosecution History

59. I have reviewed the file history of the '088 patent. Below I provide a brief summary of my review.

60. During prosecution, the Patent Office examiner rejected the claims as being anticipated by each of Chen et al. (US Pub. 20030171429) (“Chen 1”, Ex-1027), Chen et al. (US Pub. 20100094041) (“Chen 2”, Ex-1028), and Chen et al.

(US Pub. 20080255245) (“Chen 3”, Ex-1029). *See* Ex-1002, 236-237.

61. The Applicant responded by arguing that “Chen 1 does not mention treating plaque psoriasis specifically with the compounds described therein” and noted that there are other types of psoriasis. Ex-1002, 284.

62. The Applicant also argued that Chen 1 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.” *Id.*, 284. The Applicant added that:

Chen 1 makes no mention of how to demonstrate that treatment of said plaque psoriasis is effective, the presently pending claims are directed to using the Physician Global Assessment (PGA) score, Psoriasis Area and Severity Index (PASI), 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)(see claims 8-15) to determine whether treatment is effective. Accordingly, a generic disclosure to simply treat plaque psoriasis but which does not teach how to do so cannot destroy the novelty of a claim. Finally, Chen 1 makes no mention of what is a measure of effective treatment of said plaque psoriasis, whereas the presently pending claims are directed to improving a subject's PGA score by 2 grades

or to a score of 0 or 1, as well as improvement in other measurements, such as BSA decreased to less than 20% (claim 10), 3 point improvement in Itch/Pruritus rating (claim 12), 75% improvement in PASI (claim 11), and improvement in patient reported outcomes (claim 13).

Id. The Applicant made similar arguments regarding the Chen 2 and Chen 3 references. *Id.*, 285-286. The Applicant did not amend the claims.

63. I note that the Applicant did not dispute that the Chen references disclosed treating mild to severe² psoriasis with a 1% tapinarof topical composition once a day.

64. And I note that the Chen references do disclose treating specifically “plaque” psoriasis with the 1% tapinarof cream administered once a day, contrary to what the Applicant argued.

65. For example, Chen 1 discloses treating “Volunteer 2, Female, 24 years old with *plaques* on her back” and explains that the treatment resulted in “significant improvement of the psoriasis” on Volunteer 2. Ex-1027, [0098], [0100]-[0102] (emphasis added). A POSA would understand the reference to

² The Applicant contended that Chen 3 did not disclose “the severity” of the plaque psoriasis, but the Applicant did not dispute that Chen 1 and Chen 2 did so. Ex-1002, 286.

treating a patient with “plaques” on her back to be a reference to treating *plaque* psoriasis specifically. In clinical practice, when a dermatologist such as myself talks about treating “plaques” on a patient’s back with respect to psoriasis, that is a reference to treating plaque psoriasis (and not other forms of psoriasis such as guttate psoriasis or pustular psoriasis).

66. I further note that, also contrary to the Applicant’s arguments, the Chen references would disclose the claimed PGA score improvement to POSA, such as improvement “to a score of 0 or 1”. For example, Chen 1 teaches that Volunteer 1 achieved “complete[] clearance” of the psoriasis after seven days of once-daily treatment with the 1% tapinarof composition. Ex-1027, [0101]. A POSA would have understood that “complete clearance” means that the psoriasis is “clear,” and “clear” equated to a PGA score of 0. *E.g.*, Ex-1001, 22:30 (PGA “[s]core of 0 represents clear skin”); Ex-1005, [0288] (equating PGA score of 0 with “clear”); Ex-1008, 2 (“clear” is a PGA score of 0); Ex-1007, 6 (equating the start of the PGA scale (0) with “clear”); Ex-1026, 6 (in the PGA scale “0 = clear”), 119 (same); Ex-1010, 2.

67. The examiner then rejected the claims under 35 U.S.C. 102(a)(1) as being anticipated by Rubenstein et al. (Amer. Acad. of Dermatology 2019) (“Rubenstein”). Ex-1002, 292-293. In response, Applicant asserted that Rubenstein was not available as prior art. Ex-1002, 302-303. Again, the Applicant did not

amend the claims.

68. In response, the U.S. Patent Office issued a Notice of Allowance on January 20, 2023. The Reasons for Allowance states, “The following is an examiner's statement of reasons for allowance: the methods were not found to be obvious or anticipated by the prior art of record. The prior art does not teach or suggest the methods encompassing compounds substituted in the manner claimed by the Applicant.” Ex-1002, 311-312.

C. Claims

69. The '088 patent contains one independent claim, reproduced below.

1. A method for treating mild to severe plaque psoriasis in a subject comprising topically administering a topical composition containing about 1.0% tapinarof to affected areas of the subject once a day, 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.

70. Dependent claims 2-4 recite standard formulations of topical compositions.³

71. Dependent claim 6 recites topically administering the 1% tapinarof of claim 1 to an affected area of the body selected from a group of areas commonly affected by plaque psoriasis.

³ For some claims, such as claims 2-4, I also rely on the opinions of Mr. Sudhakar.

72. Dependent claims 7-10, 16, 18 and 21-22 merely recite common, known ways of assessing the plaque psoriasis severity or improvement following treatment.

73. I discuss each of these limitations in more detail in my detailed claim analysis that follows. I also provide an appendix listing the claim elements, for reference, at Appendix A.

VIII. CLAIM CONSTRUCTION

74. I have been advised that the claims terms of the '088 patent are to be given their plain and ordinary meaning, *i.e.*, the meaning that the terms would have had to a POSA at the time of the claimed invention, which I am informed is approximately early November 2018.

75. The '088 patent appears to provide some discussion of certain terms and phrases at columns 3 and 4. Ex-1001, cols. 3, 4. I provide my opinions in this declaration consistent with the understanding provided at those columns.

76. For the claims I discuss below, I have given the claim terms their plain and ordinary meaning, as would have been understood by a person having ordinary skill in the art at the time of the alleged invention, having considered the language of the claims, the specification, and the prosecution history of record.

IX. OVERVIEW OF THE PRIOR ART

A. Sonti (Ex-1005)

77. Sonti discloses, in a U.S. patent application published on November 24, 2016, a set of topical formulations for the active ingredient “3,5-dihydroxy-4-isopropyl-trans-stilbene” (which is tapinarof)⁴ along with methods of treating both atopic dermatitis and plaque psoriasis using the same. Ex-1005, Abstract, [0273]-[0300].

78. Sonti explains that it was already known that 3,5-dihydroxy-4-isopropyl-*trans*-stilbene (i.e., tapinarof) was “suitable for the treatment of various key dermatological conditions, including psoriasis and inflammation.” Ex-1005, [0010]. In support, Sonti cites WO 2001/042231 (Welichem Biotech Inc.) and U.S. Pat. No. 7,868,047. *Id.* The cited ’047 patent (Ex-1013) specifically teaches that a “1% cream” of tapinarof cream topically applied “once per day” effectively treated plaque psoriasis. Ex-1013, 32:19-66. A POSA reading Sonti would understand Sonti to teach that it was already known that 1% tapinarof cream administered

⁴ The compound “3,5-dihydroxy-4-isopropyl-trans-stilbene” disclosed by Sonti (for example, Ex-1005 at [0008]) is tapinarof. The ’088 patent explains that “3,5-Dihydroxy-4-isopropyl-trans-stilbene is referred to as tapinarof.” Ex-1001, 7:4-20; Ex-1032, ¶¶43, 58-63.

once a day effectively treats plaque psoriasis.

79. Therefore, Sonti stated that its embodiments were intended to provide topical compositions of tapinarof (“3,5-dihydroxy-4-isopropyl-trans-stilbene”) that is “both chemically and physically stable, which delivers the active ingredient [tapinarof] to the desired site . . . and which does not irritate the skin.” Ex-1005, [0011]. A POSA would understand Sonti as providing various specific formulations of tapinarof—all of which were already understood to be effective—that were also stable and did not irritate the skin.

80. Sonti discloses using a “topical pharmaceutical emulsion” formulation of tapinarof to effectively treat plaque psoriasis, including to treat patients diagnosed with “moderate to severe plaque psoriasis.” *E.g.*, Ex-1005, [0286]-[0288]; *see also* Ex-1005, Abstract, [0285]-[0295]. As an example, Sonti explains that one embodiment of the invention is a percent of patients achieving a certain reduction in PASI score “in combination with the patient also reaching a PGA score of 0 or 1” and that “as a degree of measurement of severity, the patient will most likely have started . . . with moderate to severe plaque psoriasis.” Ex-1005, [0286]-[0288]; *see also* Ex-1005, Abstract, [0285]-[0295].

81. Sonti explains that using an “effective amount” of the topical tapinarof formulations means “the amount which will cause an improvement or change in the condition for which it is applied when applied to the affective area

repeatedly over a period of time.” Ex-1005, [0301]. Sonti also explains that the appropriate amounts are “readily apparent” to a POSA or “capable of determination by routine experimentation.” Ex-1005, [0301]. Sonti further explains that the tapinarof 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].

82. Sonti also discloses applying a topical composition that includes 1% tapinarof by weight to the affected area. *E.g.*, Ex-1005, [0196] (“the amount of 3,5-Dihydroxy-4-isopropyl-*trans*-stilbene or a pharmaceutically acceptable salt thereof which may be present in a composition may range from about 0.25% to about 2% by weight of composition. In one embodiment, the amount may be ... 1.0% ... by weight, based on the total weight of the composition. ... In another embodiment, the amount is about 1.0% by weight, based on the total weight of the composition”); *see also* Ex-1005, [0055], [0323], [0327], [0355], [0367], [0370].

83. Sonti also discloses applying a 1% tapinarof composition topically to the affected area “once daily.” Ex-1005, [0387]. Sonti also teaches the “use of a formulation such as described above which can provide lower systemic exposure of the active ingredient to the patient during use” and that “the dosing frequency to the affected area(s) may be now be dosed less frequently than previously envisioned.” Ex-1005, [0387].

84. Finally, Sonti discloses using known metrics to assess severity and treatment response of skin conditions such as plaque psoriasis and atopic dermatitis, including the Physician Global Assessment (PGA), PASI, and Body Surface Area (BSA)⁵ scores. *E.g.*, Ex-1005, [0285], [0272].

85. Sonti specifically discloses using the PGA and PASI scores to show effectively treating plaque psoriasis using the tapinarof topical emulsion compositions described therein. Ex-1005, [0285]-[0293]. For example, Sonti discloses that: “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, [0288] (emphasis added).

86. A POSA would understand Sonti’s reference to “using a topical

⁵ Sonti’s discussion of BSA is in the context of effectively treating atopic dermatitis (“AD”).

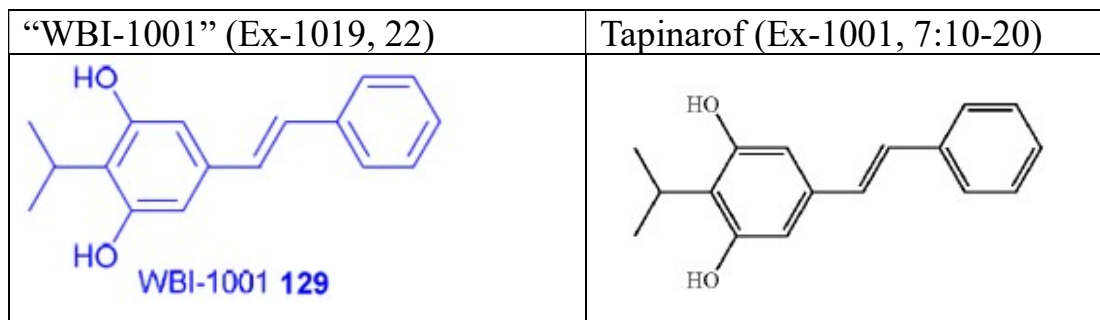
emulsion composition as described herein” to include administering any of the compositions Sonti describes, at any of the dosing frequencies Sonti discloses.

87. Sonti also discloses a method for reducing the time to achieve “a >50% improvement in PGA scores of clear or almost clear or a 2-point reduction in PGA score in a patient with psoriasis in need thereof,” that comprising administering a topical emulsion comprising an effective amount of tapinarof (e.g., one of the 1% tapinarof compositions disclosed in Sonti). Ex-1005, [0290]; *see also* Ex-1005, [0289]-[0294].

B. Bissonnette (Ex-1008)

88. The article by Bissonnette, et al. is a 2012 journal article that discloses treating patients with mild to severe plaque psoriasis with topical 1.0% WBI-1001 and concludes that topical WBI-1001 induces rapid and significant improvement in patients with plaque psoriasis, using both the PGA and BSA metrics to assess treatment efficacy. EX-1008, 1; *see also id.*, 2 (“The objectives of the current study were to evaluate the safety and efficacy of topical WBI-1001 at 1% in a cream formulation for the treatment of psoriasis” and “Patients had to have between 1% and 10% of body surface area (BSA) covered with psoriasis . . . [and a PGA of] two (mild) to four (severe) at Day 0” of the study). The study specifically concludes that “WBI-1001 is effective for the treatment of mild to moderate psoriasis.” Ex-1008, 5.

89. WBI-1001 is tapinarof. Ex-1032, ¶¶64-67. For example, a 2014 review article in the journal *Natural Product Reports* explains that WBI-1001 (also known as “benvitimod”) completed a phase II trial for the treatment of psoriasis and provides the chemical structure (Ex-1019, 22), which is the same as the chemical structure for tapinarof provided by the ’088 patent:



Bissonnette also provides the chemical name of WBI-1001 as “2-isopropyl-5-[(E)-2-phenylethenyl]benzene-1,3-diol,” which the ’088 patent notes is an alternative nomenclature for tapinarof. Ex-1008, 1; Ex-1001, 7:7-10; Ex-1032, ¶66; *see also* <https://en.wikipedia.org/wiki/Tapinarof> (“tapinarof, also known as benvitimod”).

90. A POSA would have understood Bissonnette’s descriptions of a “1% WBI-1001 in a cream formulation” and “1% WBI-1001 cream” refer to 1% tapinarof *by weight*. Ex-1032, ¶79, *see also id.* ¶¶74-77, 80; Ex-1008, 1, 2, 4.

91. Bissonnette describes a 61-patient study on patients with “**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, 1 (Abstract), 2 (“Study population”) (emphasis added). The intent-to-treat (ITT) patients (40 of the 61 participants) received 1% WBI-1001 (tapinarof) in a cream formulation twice daily for 12 weeks. Ex-1008, 1. The remainder received placebo cream. Ex-1008, 1 (Abstract), 2, (“Study design”). Efficacy was then evaluated using both PGA and BSA, as well as PASI. Ex-1008, 1 (Abstract). The primary efficacy parameter was “change from baseline in PGA at day 84.” Ex-1008, 2 (“Efficacy evaluations”). Secondary endpoints included “the proportion of patients who achieved a PGA of 0 (clear) or 1 (almost clear) at Day 84,” and “the change from baseline in BSA.” *Id.*

92. For PGA, “[a] PGA score corresponding to the degree of overall lesion severity using a 5-point scale ranging from 0 to 5 (clear to very severe) was performed for the entire body excluding face, scalp, groin, and genitals.” Ex-1008, 2 (“Efficacy evaluations”). This was done at each of 7 visits, from day 0 to day 84. Ex-1008, 2 (“Study design”). For the primary efficacy parameter (change from baseline PGA): PGA decreased by an average of ~62% for the patients treated with WBI-1001 (compared with ~14% for placebo). Ex-1008, 3. For the secondary efficacy parameter (proportion of patients achieving PGA of 0 or 1 by Day 84): twenty-seven (67.5%) of the 40 patients achieved a PGA score of clear (0) or almost clear (1), compared with one patient (4.8%) for the placebo group. *Id.*

93. The body surface area (BSA) affected by psoriasis was also evaluated

at each visit throughout the 12-week trial. Ex-1008, 2 (“Study Design” and “Efficacy evaluations”). Bissonnette discloses a decrease of 79.1% in BSA at Day 84 for patients treated with WBI-1001 (compared with an increase of 9.4% for patients randomized to placebo). Ex-1008, 3.

94. Based on the study results, Bissonnette discloses that “topical WBI-1001 [tapinarof] at 1% is effective for the treatment of mild to moderate plaque psoriasis,” as measured by metrics that included both PGA and BSA (as well as PASI). Ex-1008, 4.

C. Chen (Ex-1013)

95. Chen discloses “methods of treating psoriasis.” Ex-1013, Abstract. Chen specifically teaches effectively treating plaque psoriasis with a topical composition containing 1% tapinarof, topically applied once a day to affected areas of the skin. Ex-1013, Abstract, 32:12-33:4.

96. Chen discloses that “[a] 1% cream of 3,5-dihydroxy-4-isopropylstilbene was prepared for tests on volunteers” Ex-1013, 32:25-27. 3,5-dihydroxy-4-isopropylstilbene is tapinarof. Ex-1001, 7:4-20; Ex-1032, ¶¶68-70.

97. A POSA also would have understood Chen’s descriptions of a “1% cream” to refer to 1% tapinarof *by weight*. Ex-1032, ¶78, *see also id.* ¶¶74-77, 80; Ex-1013, 32:25-26. Preparing the tapinarof cream with 1% tapinarof *by weight* also would have been an obvious, predictable approach. Ex-1032, ¶80.

98. Volunteers, “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. Volunteer 1 had tried “various conventional drugs and treatments, includ[ing], steroids, phototherapy and other medicine during the course of his illness” but all had “no or very limited effect on this psoriasis.” Ex-1013, 32:31-34. Volunteer 2 had used hydrocortisone previously, but she stopped “because of side effects.” Ex-1013, 32:35-38. Neither volunteer was on any medication a month before the test began. Ex-1013, 32:27-29.

99. A POSA would have understood this as describing patients suffering from plaque psoriasis.

100. Volunteer 1 was described as having had “scalp psoriasis for more than 15 years,” and he had “used various conventional drugs and treatments, include, steroids, phototherapy and other medicine during the course of his illness.” Ex-1013, 32:30-34. In my experience (and as a POSA would have known), scalp psoriasis is nearly always plaque-type psoriasis. *E.g.*, Ex-1015, 3 (under the heading “plaque psoriasis,” explaining that “scalp may be the most common site of involvement”); Ex-1006, 2 (“Chronic plaque-type psoriasis is the most common morphologic variety which manifests as circumscribed, well-demarcated, erythematous plaques involving particularly the extensor aspects

of elbows and knees, buttocks, scalp, and lower back.”) And the treatments that Volunteer 1 had tried were commonly known treatments for plaque psoriasis. Further, when Chen discusses “psoriasis” in the Background section, it actually describes *plaque* psoriasis specifically. Ex-1013, 2:56-3:4 (“Psoriasis is a common, chronic inflammatory skin disease, characterized by rapid multiplication and turnover of the epithelial cells with a consequent thickening of the epidermis, as well as inflamed swollen **skin lesions covered with silvery white scaling patches and raised, inflamed, thickened and scaly lesions**”) (emphasis added). This also would have indicated to a POSA that Chen’s discussion of treating scalp psoriasis was referring to treating plaque psoriasis. For at least these reasons, a POSA would understand that Volunteer 1, as described by Chen, was being treated for plaque psoriasis.

101. Volunteer 2 was described as having psoriasis with “plaques” on her back. Ex-1013, 32:35-37. As I explained above, a POSA would have understood the reference to treating a patient with “plaques” on her back to be a reference to treating *plaque* psoriasis specifically. In clinical practice, when a dermatologist such as myself talks about treating “plaques” on a patient’s back with respect to psoriasis, that is a reference to treating plaque psoriasis (and not other forms of psoriasis such as guttate psoriasis or pustular psoriasis).

102. The volunteers were “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).” *Id.*, 32:41-50.

103. Chen discloses that the treatment with 1% tapinarof cream “showed great efficacy on the volunteers treated in comparison with the untreated areas and before and after treatment.” Ex-1013, 32:51-65; *see also id.*, 32:15-18 (representative compound of the invention [tapinarof] “is active in reducing or eliminating symptoms of psoriasis”), 2:56-3:4 (“The compounds of the invention possess specific activity against psoriasis.”), Claim 1 (“a method of treating psoriasis comprising administering to a patient a pharmaceutical composition comprising 3,5 dihydroxy-4-isopropylstilbene.”).

104. For example, with Volunteer 1 there was “complete[] clearance” in 7 days. Ex-1013, 32:53-57. In addition, “[n]o change occurred in the condition of the area treated with the control cream.” *Id.*, 32:57-58. With Volunteer 2 (who had plaque psoriasis on her back), “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.” Ex-1013, 32:58-63.

X. THE PRIOR ART DISCLOSES OR SUGGESTS ALL OF THE FEATURES OF THE CHALLENGED CLAIMS

105. Based on my experience, knowledge, and expertise, it is my opinion

that certain references disclose and/or suggest all the features recited in each of claims 1-4, 6-10, 16, 18, and 21-22 of the '088 patent.⁶

106. Below, I explain my opinions regarding several different grounds that show this. These grounds are:

<i>Ground</i>	<i>Claims</i>	<i>References</i>
Ground 1	1-4, 6, 8-9, 16, 18, and 22	Anticipated by Sonti
Ground 2	1-4, 6-10, 16, 18, and 21-22	Obvious in view of Sonti
Ground 3	7, 9-10, 21	Obvious in view of either Ground 1 or Ground 2, and Bissonnette
Ground 4	1-4, 6-10, 16, 18, 21-22	Obvious in view of Bissonnette, and Sonti and/or Chen

A. GROUND 1: Sonti Anticipates Claims 1-4, 6, 8-9, 16, 18, and 22

107. Based on my review of the '088 patent, its claims and prosecution history, and the Sonti reference, Sonti discloses every element of claims 1-4, 6, 8-9, 16, 18, and 22. Therefore it is my opinion that Sonti anticipates those claims.

1. Independent Claim 1

108. In my opinion, Sonti discloses all of the elements of claim 1 and therefore anticipates that claim.

⁶ For some of the claims, such as dependent claims 2-4, I also rely on the opinion of Paul Sudhakar, a formulation expert.

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

109. In my opinion, Sonti discloses the preamble of claim 1.

110. For example, Sonti expressly discloses a method for treating “moderate to severe plaque psoriasis”:

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 [. . .] in combination with the patient also reaching a PGA score of 0 or 1 (clear or almost clear) at a defined time point . . . 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].

111. Sonti also has additional disclosure of a method for treating mild to severe plaque psoriasis. Sonti discloses that 3,5-dihydroxy-4-isopropyl-*trans*-stilbene was known in the art as being suitable for treatment of psoriasis, citing WO 2001/042231 (Welichem Biotech Inc.) and in U.S. Pat. No. 7,868,047. Ex-1005, [0010]. U.S. Pat. No. 7,868,047 is the Chen reference (Ex-1013). As I explained above, Chen also discloses a method of treating plaque psoriasis.

112. As another example, Sonti describes methods for “reducing the time

to achieving a >50% improvement in PGA scores of clear or almost clear or a 2-point reduction in PGA score in a patient with psoriasis” by administering an “effective amount” of 3,5-Dihydroxy-4-isopropyl-trans-stilbene (tapinarof). Ex-1005, [0290], [0293]; *see also id.*, [0285]-[0294],], [0298]-[0300].

113. A POSA would have understood that Sonti’s discussion of achieving the recited reduction in PGA score “by using a topical emulsion composition as described herein” and administering an “effective amount” of tapinarof to a patient with psoriasis to reduce the amount of time to achieve a particular reduction in PGA score is disclosure of a method of “treating” psoriasis. In the field of dermatology, administering a pharmaceutical to a patient with a condition, in order to improve that condition, is “treating” that condition.

114. Further, Sonti itself explains that administering an “effective amount” means treating:

The phrase "therapeutically effective amount" or "effective amount" is used herein to refer to an amount of the active ingredient sufficient to have a therapeutic effect upon administration, e.g. that amount which will cause an improvement or change in the condition for which it is applied when applied to the affected area repeatedly over a period of time. Effective amounts will vary with the particular condition being treated, the severity of the condition the duration of the treatment, the

stage of advancement of the condition, the body surface area affected with the clinical condition, and the specific components of the composition. An effective amount of the active ingredient for treatment of a condition or disorder can be determined by standard clinical techniques. Appropriate amounts in any given instance will be readily apparent to those skilled in the art or capable of determination by routine experimentation. 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].

115. A POSA would also understand that, in the context of the Sonti reference, the discussion of administering tapinarof to patients “with psoriasis” to achieve specific reductions in “PGA” scores includes treating *plaque* psoriasis. Doing the analysis required by the PGA scoring system requires evaluation of “plaques” on patients. Ex-1005, [0287]. The ’088 patent also explains that the PGA analysis includes assessments of “plaque thickness.” Ex-1001, 22:22-43; *see also* Ex-1011, Fig. 2 (PGA metric requiring analysis of “plaque elevation” and “scaling”). The analysis of “plaques” and “scaling” indicates “plaque psoriasis,” rather than other (far less common) psoriatic variants.

116. A POSA also would have understood that Sonti’s specific disclosure of treating “moderate to severe plaque psoriasis” (Ex-1005, [0288]) necessarily

discloses treating mild plaque psoriasis. Because the treatment taught by Sonti was effective to treat moderate or severe plaque psoriasis, a POSA would know that the same treatment would also necessarily effectively treat mild psoriasis. A clinician such as myself would know that if a topical treatment is effective for moderate to severe plaque psoriasis (the more severe end of the spectrum), it necessarily follows, as a matter of experience and common sense, that it will also be effective to topically treat mild plaque psoriasis. I also know this from my personal experience in 30+ years of practice as a dermatologist, having treated well over 1,000 patients with mild to severe plaque psoriasis.

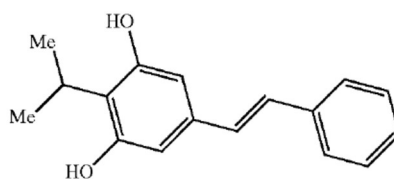
b. [1.a] “comprising topically administering a topical composition containing about 1.0% tapinarof”

117. In my opinion, Sonti discloses this element.

118. The patent publication by Sonti et al. is titled “Topical Pharmaceutical Compositions.” Ex-1005. The Abstract explains that “the present invention relates to topical pharmaceutical emulsion compositions” and “methods of treating a dermatological condition or disorder in a patient by administering the present compositions to the skin of the patient.” To a POSA, administering a “topical” composition to the skin of a patient is “topically administering a topical composition.”

119. I understand that Sonti discloses tapinarof as the active ingredient in its compositions. Sonti states that the compositions contain “3,5-dihydroxy-4-

isopropyl-*trans*-stilbene,” a compound that has following structural formula:



Ex-1005, Abstract, [0008]. This is the same chemical name and structure as what the '088 patent calls “tapinarof.” Ex-1001, 7:4-20 (“3,5-Dihydroxy-4-isopropyl-*trans*-stilbene is referred to as tapinarof”); Ex-1032, ¶¶56-57, 58-63. Therefore, I understand Sonti’s teaching of 3,5-dihydroxy-4-isopropyl-*trans*-stilbene to be tapinarof. Ex-1032, ¶¶58-63.

120. Sonti also discloses that the topical compositions used in its methods of treating dermatologic conditions (including treating plaque psoriasis) can have about 1% tapinarof. For example, Sonti discloses that:

In all of the compositions described herein, the amount of 3,5-Dihydroxy-4-isopropyl-*trans*-stilbene or a pharmaceutically acceptable salt thereof which may be present in a composition may range from about 0.25% to about 2% by weight of composition. In one embodiment, the amount may be ... **1.0%** ... by weight, based on the total weight of the composition. ... In another embodiment, the amount is about **1.0%** by weight, based on the total weight of the composition.

Ex-1005, [0196].

121. Sonti discloses other examples of compositions containing about 1%

tapinarof. At paragraph [0055], Sonti states that “in an embodiment, the 3,5-dihydroxy-4-isopropyl-trans-stilbene or a pharmaceutically acceptable salt thereof is present in an amount of about . . . 1% . . .”). Sonti provides additional examples, including at [0323] (Table 1, formulation 1(a), 1.00 % w/w “active ingredient”), [0327] (Table 4, formulation 13, 1.00 % w/w “active ingredient”), [0355] (Table 8, formulation 21, 1.00 % w/w “active ingredient”), [0367] (Table 9, formulations 30-33, 1.00 % w/w “active ingredient”), and [0370] (Example 9, 1.0% w/w 3,5-Dihydroxy-4-isopropyl-*trans*-stilbene). Sonti explains that in each of these formulations, the “active ingredient” is 3,5-dihydroxy-4-isopropyl-*trans*-stilbene. *Id.*; see also Ex-1005, Abstract (“present invention relates to topical pharmaceutical emulsion compositions comprising a therapeutically effective amount of 3,5-dihydroxy-4-isopropyl-trans-stilbene”). As I explained above in paragraph 119, this is tapinarof.

122. A POSA would understand Sonti’s references to a composition that has “1% w/w” of a compound to mean that the composition comprises 1% of that compound by weight. “w/w” was understood in the art to mean “weight by weight”—in other words, the percentage of the total mass of the substance that is comprised by the mass of the particular compound. *See, e.g.*, <https://www.chemicals.co.uk/blog/what-do-vv-ww-wv-mean>; Ex-1032, ¶¶76-77.

123. I also note that even if the Sonti publication did not expressly say that

each embodiment disclosed as containing 1% tapinarof was for treating mild to severe plaque psoriasis, a POSA would understand that is what the Sonti publication teaches. Sonti tells a POSA that an embodiment of the invention is “using a topical emulsion composition as described herein” to treat a patient with “moderate to severe plaque psoriasis.” Ex-1005, [0288]. Referring to “a topical emulsion composition as described herein” directs a POSA to all the compositions disclosed in Sonti, including those with 1% tapinarof. Sonti also specifically explains that “[i]n all of the compositions described herein,” the amount of tapinarof may be “1%.” Ex-1005, [0196]. A POSA would understand the reference to “all of the compositions described herein” to refer to all of the various formulations Sonti teaches.

124. Even if Sonti did not expressly spell out the combination, from Sonti’s disclosure a POSA would immediately recognize the option of treating plaque psoriasis with a 1% tapinarof composition. The Sonti patent application focuses specifically only on two skin conditions—atopic dermatitis and plaque psoriasis. Ex-1005, [273]-[0284], [0285]-[0295]). I note that Sonti does mention treating other similar skin conditions, but it focuses specifically on atopic dermatitis and plaque psoriasis. Sonti also identifies a small number of options for the amount of tapinarof included in the compositions it teaches (including the claimed 1%), as I explained above. Ex-1005, [0196], *see also* [0055], [0327], [0355], [0367], [0370].

Therefore, a POSA reading Sonti would immediately understand that Sonti is disclosing treating plaque psoriasis with a composition including 1% tapinarof.

c. [1.b] “to affected areas of the subject”

125. In my opinion, Sonti discloses this element.

126. Under the definition of “therapeutically effective amount,” Sonti references “the body surface **area affected with the clinical condition**” and states “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].

127. Sonti teaches that 3,5-dihydroxy-4-isopropyl-*trans*-stilbene can be applied to a patient in a “dermatologically acceptable formulation,” for the treatment of a dermatological disease or disorder, applied topically and which will permit “even spreading of the active ingredient **over the affected area**, rapid drying, and/or increased penetration.” Ex-1005, [0136]; *see also id.*, Title (“Topical Pharmaceutical Compositions”), Abstract (“administering the present compositions to the skin of the patient”), [0272], [0301], [0387] (“dosing frequency **to the affected area(s)** may now be dosed less frequently than previously envisioned”).

d. [1.c] “once a day”

128. In my opinion, Sonti discloses this element.

129. At paragraph [0387], Sonti explains that an embodiment of the invention is use of “a formulation such as described above which can provide lower systemic exposure of the active ingredient to the patient during use” and “another embodiment [where] the dosing frequency to the affected area(s) may now be dosed less frequently than previously envisioned”. Ex-1005, [0387].

130. Sonti explains that “[a]pplication of a composition of the present invention may be applied to affected areas twice daily, **once daily**, once every other day; twice weekly; three times weekly, or once weekly, with the dose represented by any of the embodiments herein.” Ex-1005, [0387].

131. Sonti’s teaching refers to “a formulation such as described above” and “a composition of the present invention.” Ex-1005 [0387]. Therefore, a POSA would understand Sonti to be disclosing that any of the tapinarof compositions taught by Sonti, including the 1% tapinarof compositions for treating plaque psoriasis, can be applied “once daily.”

132. Even if Sonti did not expressly spell out the combination, from Sonti’s disclosure a POSA would immediately recognize the option of treating plaque psoriasis with a 1% tapinarof composition applied once a day. As I explained with respect to element [1.a] above, Sonti focuses specifically treating atopic dermatitis and plaque psoriasis and also teaches a limited number options for the amount of tapinarof in the compositions (including 1%, as explained above). Sonti also

discloses only a limited number of application frequencies. Ex-1005, [0387]. In view of this, a POSA reading Sonti would immediately understand that Sonti is disclosing treating plaque psoriasis with a composition including 1% tapinarof that is applied once a day.

e. [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.”

133. In my opinion, Sonti discloses this element.

134. Sonti first discloses that psoriasis can be assessed using tools that are “currently available” including the Psoriasis Area and Severity Index (PAST) and Physician Global Assessment (PGA)”. Ex-1005, [285] (“psoriasis can be assessed. Of the many psoriasis assessment tools currently available, the Psoriasis Area and Severity Index (PAST) and Physician Global Assessment (PGA) tools are most used.”); *see also id.*, [0286]-[295]. As I explained above, I am familiar with both metrics, though I have more often seen the Psoriasis Area and Severity Index referred to as the “PASI” index.

135. Sonti then provides an example of a “typical” PGA scale, ranging from “clear” to “severe” psoriasis:

[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

Ex-1005, [0287]. A POSA would understand that PGA scale shown by Sonti is a 7-point scale, where “clear” means a score of “0,” “1” means “almost clear, and on up to “severe,” which equates to a score of “6.”

136. This scale is similar to PGA scales with which I am familiar. While the number of points in the PGA scale can vary slightly, PGA scales start with “clear” as a score of “0,” and the highest number on the scale equates to “severe” or “very severe” plaque psoriasis. *E.g.*, Ex-1008, 2 (“5 point scale,” from “clear” to “very severe”); Ex-1010, 3 (5 point scale, from “clear” to “severe”); Ex-1011, 3 (Table 2) (7 point scale, from “clear” to “severe”); Ex-1007, 6 (“the PGA is a 5, 6, or 7 point ordinal rating ranging from ‘clear’ to ‘very severe psoriasis’”); *see also* Ex-1001, 22:22-42 (5-point scale, from “clear” to “severe”).

137. I do not see that claim 1 of the ’088 patent specifies using any particular or specific PGA scale.

138. I also note that it was common knowledge in the field that a PGA score of 0 or 1 meant the same thing under any PGA scale, whether it was a 5-point, 6-point, or 7-point scale. This is evident in the various prior art reference I discuss. For example: Ex-1005 (Sonti), [0287] (0 = “clear”; 1 = “almost clear”); Ex-1008 (Bissonnette), 3 (“PGA score of 0 (clear) or 1 (almost clear)”; Ex-1011, 3 (PGA score of 0=“clear” and 1=“almost clear”). The ’088 patent specification similarly states that in the PGA scale used with embodiments it described, a PGA “score of 0 represents clear” and “1 represents almost clear”. Ex-1001, 22:30-33.

139. Sonti specifically discloses each of the alternative PGA score metrics for measuring efficacy that are recited by claim element [1.d]—that after topical administration of the topical composition, the PGA score is “improved by 2 grades” or “has improved to a score of 0 or 1.”

140. For example, at paragraph [0288] Sonti discloses that after topical administration of “a topical composition as described herein” (meaning, the compositions Sonti teaches that include 1% tapinarof cream applied once daily), the PGA score “has improved to a score of 0 or 1,” as recited by claim element [1.d]. Paragraph [0288] is below:

[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.

141. Here, Sonti teaches 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), which is “achieved by using a topical emulsion composition as described herein.” Ex-1005, [0288]. A POSA would understand Sonti’s reference to “using a topical emulsion composition as described herein” to include administering the composition containing about 1% tapinarof, as I explained previously with respect to elements [1.pre], [1.a], [1.b], and [1.c]. Sonti also explains, in the same “embodiment,” that the patient “will most likely have started with a PGA score of [greater than or equal to] 4.” Ex-1005, [0288]. Thus, in my opinion Sonti discloses that after topically administering the topical composition a PGA score “has improved to a score of 0 or 1” as claimed.

142. Sonti also discloses that the PGA score has been “improved by two

grades,” which is the alternative metric recited by claim 1. Sonti explains that 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 after treatment, has had a PGA score “improved by two grades” as claimed. The patient has actually had the PGA score improved by three or four grades, but a patient who improves by 3 or 4 PGA grades following treatment has necessarily also had a PGA score “improved by two grades” at some point during the treatment (and therefore after topical administration of the composition).

143. Sonti also discloses claim element [1.d] in other places. For example:

[0290] Another embodiment of the invention is a method for reducing the time to achieving a >50% improvement in PGA scores of clear or almost clear or a 2-point reduction in PGA score in a patient with psoriasis in need thereof, the method comprising administering to said patient a topical pharmaceutical emulsion composition comprising an effective amount of 3,5-Dihydroxy-4-isopropyl-trans-stilbene or a pharmaceutically acceptable salt thereof, an oil phase, a water phase, a surfactant, and an antioxidant, and wherein the emulsion composition is homogenous. In one embodiment, the time to achievement of the 50% reduction is at 12 weeks. In another embodiment, the time to achievement of the 50% reduction is at 8 weeks. In one embodiment, the reduction of time may be compared to administration of a suitable comparator such as formulation 1/1a or 12 (of comparable % w/w active).

Here, Sonti discloses that an “embodiment of the invention” is a method for reducing the time to achieving “a **2-point reduction in PGA score** in a patient

with psoriasis in need thereof,” comprising administering a “topical pharmaceutical emulsion composition” that has an “effective amount” of tapinarof, an oil phase, a water phase, a surfactant, and an antioxidant, and is homogenous.” Ex-1005 at [0290]. In my opinion, this discloses a method where after topically administering the topical composition a PGA score “is improved by 2 grades” as claimed (i.e. there has been a 2-point reduction in PGA score).

144. A POSA would also understand the “effective amount” of the tapinarof composition recited in paragraph [0290] to include the tapinarof compositions I discussed with respect to claim elements [1.pre], [1.a], [1.b], and [1.c]. For example, Sonti’s Abstract tells a POSA that all of Sonti’s embodiments use “therapeutically effective amounts” of tapinarof (meaning that the disclosed 1% tapinarof compositions are therapeutically effective). Ex-1005, Abstract. Sonti also teaches that any of its compositions may be effectively administered once daily. Ex-1005, [0387] (“application of a composition of the present invention may be applied to affected areas . . . once daily”)

145. Sonti also contains additional, similar disclosures, for example: Ex-1005 at [0293] (“a method for reducing the time to achieving a >50% improvement in scores of **clear or almost clear** or a **2 point reduction in PGA score** . . . in a patient with psoriasis in need thereof, comprising administering to said patient a topical pharmaceutical emulsion composition comprising an effective amount of

[tapinarof], an oil phase, a water phase, a surfactant, and an antioxidant [and wherein the emulsion composition] is homogeneous . . . In another embodiment, the patient achieves a **PGA score of clear or almost clear**”), [0289] (“method of obtaining optimal dosing for the treatment of psoriasis . . . wherein the dosing continues until the patient achieves a **PGA score of clear or almost clear**”).

146. Even if Sonti did not expressly spell out the combination, from Sonti’s disclosure a POSA would immediately recognize the option of treating plaque psoriasis with a 1% tapinarof composition applied once a day where the PGA score is improved to 0 or 1 or by two grades. As I explained with respect to elements [1.a] and [1.c] above, Sonti focuses specifically on treating two skin diseases, and teaches only a limited number of potential amounts of tapinarof in those compositions (including 1%), and a limited number of application frequencies. Sonti also only discloses a limited number of metrics to assess treatment efficacy—the “PASI” and “PGA” scoring systems. Ex-1005, [0285]-[0294]. In view of this, a POSA reading Sonti would immediately understand that Sonti is disclosing treating plaque psoriasis with a composition including 1% tapinarof that is applied once a day, where the PGA score is improved as Sonti discloses in paragraph [0288].

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

147. In my opinion, Sonti discloses the elements of claim 2. *See also* Ex-

1032, ¶¶88-91, 92-94.

148. Sonti explains that the “terms ‘emulsion’ and ‘oil-in-water emulsion’” should be understood to refer to the same thing. Ex-1005, [0054]. Sonti discloses that suitable formulations of its tapinarof compositions include “emulsion[s]” and “oil-in-water emulsion[s]”. Ex-1005, Abstract, Figs. 1-2, [0021]-[0040], [0042]-[0044], [0048], [0050]-[0053], [0055] (“emulsions”); *id.*, [0049], [0054]) [0100], claims 18, 20 (“oil-in-water emulsion”); *id.*, [0101] (“Suitably, the emulsion may be formulated as a cream. The cream may be an oil-in-water cream . . .”); *see also* Ex-1032, ¶¶93-94.

3. **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”**

149. I understand from Mr. Sudhakar that Sonti discloses this claim. Ex-1032, ¶¶88-91, 95-106.

4. **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”**

150. I understand from Mr. Sudhakar that Sonti discloses this claim. Ex-1032, ¶¶88-91, 107-113.

5. **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”**

151. Sonti discloses this claim.

152. Claim 6 recites the common areas of the body that plaque psoriasis manifests, and then also generically recites “the body.” Applying a topical medication to the “affected area,” meaning the area affected by the psoriasis, is nothing more than the method every plaque psoriasis patient does when receiving a topical medication (and has done for as long as I have been practicing, and likely long before that).

153. Sonti also plainly discloses this routine method. Sonti teaches “topical” compositions, and also administering the “present compositions to the skin of the patient.” Ex-1005, Abstract, [0021]. A POSA would understand that description to disclose the way that topicals were used at the time (and still are)—applying the topical composition to an affected area of the skin on the “body.”

154. Sonti also explains 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**.” Ex-1005, [0286] (emphasis added). It was common at the relevant time (before November 2018) for a clinical dermatologist to examine these regions

when diagnosing and treating plaque psoriasis, as they are regions more commonly affected by plaque psoriasis.

155. Sonti also explains that the compositions it discloses “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.*, [0136] (“even spreading of the active ingredient over the affected area”). A POSA would understand this also to be disclosing applying the topical compositions disclosed by Sonti to an affected area of the skin of one or more of the group including arms, chest, back, neck, buttocks, and legs, as required by dependent claim 6.

- 6. 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”**

156. Claims 8 and 22 are nearly the same, with the only difference being that claim 8 recites a subject diagnosed with “mild to severe” plaque psoriasis, while claim 22 recites a subject diagnosed with “mild to moderate” plaque psoriasis. Sonti discloses these limitations.

157. Sonti shows an exemplary 7-point PGA scale that ranges from “clear” at the bottom end to “severe” at the top end.

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

Ex-1005, [0287]. A POSA would understand that the exemplary PGA scale provided by Sonti is a 7-point scale, with “clear” equating with a score of “0” and “severe” equating to a score of “6.” Sonti therefore teaches that “mild” equates to a PGA score of “2,” and “moderate” equates to a score of “4.”

158. This scale is similar to PGA scales with which I am familiar. While the number of points in the PGA scale can vary slightly, PGA scales start with “clear” as a score of “0,” and the highest number on the scale equates to “severe” plaque psoriasis. *E.g.*, Ex-1008 at 2 (“5-point scale,” from “clear” to “very severe,” with “mild” equating to a PGA score of 2); Ex-1010, 3 (5 point scale, from “clear” to “severe”, with “mild” equating to a PGA score of 2); Ex-1011, 3 (Table 2) (7 point scale, from “clear” to “severe”, with “mild” equating to a PGA score of 2); Ex-1007, 6 (“the PGA is a 5, 6, or 7 point ordinal rating ranging from ‘clear’ to ‘very severe psoriasis’”); *see also* Ex-1001, 22:22-42 (5-point scale, from “clear” to “severe,” with “score of 2 represent[ing] mild psoriasis”).

159. First, Sonti discloses that the subject has been diagnosed with “mild to

severe” plaque psoriasis (claim 8) and with “mild to moderate” plaque psoriasis (claim 21). Sonti explains that “[a]s 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, [0289]-[0294].

160. A POSA would understand Sonti’s teaching of treating a “patient” who “started with” moderate to severe plaque psoriasis “at baseline” disclosure of treating a subject who has been “diagnosed” with plaque psoriasis having a severity level of moderate to severe. The term “at baseline,” to a POSA such as myself, means the starting point—in other words, the diagnosis that the patient has at the beginning of the trial. A POSA would not have treated someone for plaque psoriasis without first “diagnosing” them with plaque psoriasis.

161. A patient diagnosed with “moderate” plaque psoriasis (as Sonti teaches) is necessarily one who has been diagnosed with “mild to severe” plaque psoriasis (claim 8) and also “mild to moderate” plaque psoriasis (claim 22). “Moderate” plaque psoriasis is within both of the claimed ranges.

162. Second, Sonti also discloses that a subject has been diagnosed with mild to moderate/severe plaque psoriasis having a PGA score of “greater than or equal to 2” (claims 8, 22). A patient who starts with a PGA score of “ ≥ 4 at baseline” is a subject who has been diagnosed with plaque psoriasis having a PGA

score of “greater than or equal to 2.” A PGA score of 4 or above is greater than or equal than 2.

7. **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), 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)”**

163. Sonti discloses claim 9.

164. Sonti discloses that after topical application of the topical emulsion compositions it describes, there is an improvement of one or more symptom of mild to severe plaque psoriasis, as measured by each of the “Psoriasis Area and Severity Index”⁷ and “Physician Global Assessment score” metrics recited by claim 9.

⁷ Dependent claim 9 recites the abbreviation of “Psoriasis Area and Severity Index” as “PAST.” However, in my experience the abbreviation was more commonly written “PASI.” This abbreviation (“PASI,” rather than “PAST”), is the one Sonti uses and it is also the one that matches the initials of the full name of the index—**Psoriasis Area and Severity Index**. In any event, PAST and PASI are the same thing.

165. Sonti discloses the following:

[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, [0288]; *see also* Ex-1005, [0285]-[0287]. Sonti also explains that “[o]f the many psoriasis assessment tools currently available, the Psoriasis Area and Severity Index (PASI) and Physician Global Assessment (PGA) tools are most used.” Ex-1005, [0285]. In doing so, it expressly discloses the PASI and PGA metrics of claim 9.

166. First, Sonti discloses an improvement of one or more symptom of mild to severe plaque psoriasis as measured according to an assessment using the Psoriasis Area and Severity Index score. Sonti discloses that “one embodiment of the invention is a percent of patients achieving a 50% or a 75% reduction in PASI score...achieved by using a topical emulsion composition as described herein.” Ex-1005, [0288]. Sonti also explains that “a PASI score is used to measure the severity and extent of psoriasis.” Ex-1005, [0285]-[0286]. The severity score includes scores for “redness, thickness and scale” of the skin affected by plaque psoriasis.

Id.

167. A POSA would understand that a patient who achieves a 50% or 75% reduction in PASI score has achieved an improvement of one or more symptom of mild to severe plaque psoriasis. For example, a 50% or 75% reduction in PASI score is a significant reduction, that would necessarily include improvement of one or more symptoms—e.g., reduction in redness, thickness, scale, or body coverage of the psoriasis plaques.

168. Second, Sonti also discloses an improvement of one or more symptom of mild to severe plaque psoriasis as measured according to an assessment using the Physician Global Assessment (PGA) score. Sonti explains that the percent of patients achieving the reduction in PASI score “may be used in combination with the patient also reaching a PGA score of 0 or 1 (clear or almost clear) at a defined timepoint, such as 8, 12 weeks...of treatment.” Ex-1005, [0288]. Sonti discloses that 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]; *id.*, [0289]-[0294].

169. A POSA would understand the disclosed improvement in PGA score (from “ ≥ 4 ...e.g., one with moderate to severe plaque psoriasis” to “0 or 1 (clear or almost clear)”) following weeks of “treatment” to be an improvement of one or more symptom of mild to severe plaque psoriasis. For example, if a patient starts

at a PGA score of greater than or equal to 4, they will have some plaque elevation, scaling, and/or erythema. *See* Ex-1005, [0287]. After improving to a PGA score of 0 or 1, one or more of those symptoms (e.g., moderate plaque elevation, scaling and/or erythema) will have improved to slight to no plaque elevation, scaling or erythema. Sonti also discloses that the terms “treatment” or “treating” a dermatological condition “encompasses alleviation of at least one symptom thereof”. Ex-1005, [0308]. Therefore, Sonti’s teaching of an improvement in PGA score following (for example) 8 or 12 weeks of “treatment” (Ex-1005, [0288]) also means that one or more symptoms of the moderate to severe plaque psoriasis improved. *See also* Ex-1005, [0289]-[0294].

170. Sonti also discloses that the improvement in PASI and PGA scores came “after topically administering the topical composition [of claim 1],” as recited by claim 9. Sonti discloses that the improvements in PASI and PGA scores were “achieved by using a topical emulsion composition as described herein...” Ex-1005, [0288]. A POSA would have understood Sonti’s reference to “a topical emulsion composition as described herein” to include the 1% tapinarof topical compositions administered once daily that Sonti teaches, as I explained above with respect to Claim 1.

8. **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”

171. Sonti discloses these claims. Sonti explains that:

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**, 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, [0288] (emphasis added); *see also* Ex-1005, [290] (time to achieve 50% reduction in PGA score is “8 weeks”), [0294] (time to reach a “PASI 50” score is “at 8 weeks”), [0308] (teaching “treatment” or “treating” a dermatological condition “encompasses alleviation of at least one symptom thereof”).

172. In disclosing this, Sonti discloses that the “PGA score is improved” after about 8 weeks of administering the topical tapinarof composition, as recited

by Claim 18. Going from a PGA score of greater than or equal to 4, to a PGA score of “0 or 1” means that the PGA score “is improved.”

173. With this same disclosure, Sonti also teaches that “one or more symptom is improved” after about 8 weeks of administering the topical composition, as recited by Claim 16. This is because a POSA would understand that improving a PGA score or a PASI score means that one or more symptom has been improved. I explained this above with respect to Claim 9. For example—looking at the exemplary PGA scale provided by Sonti at paragraph [0287]—if a patient starts at a PGA score of greater than or equal to 4, they will have some plaque elevation, scaling, and/or erythema, but after improving to a PGA score of 0 or 1, one or more of those symptoms (e.g., moderate plaque elevation, scaling and/or erythema) will have improved to slight to no plaque elevation, scaling or erythema.

174. Sonti also has additional disclosure of the limitations of claims 16 and 18. *E.g.*, Ex-1005, [0290] (“the invention is a method for reducing the time to achieving a **>50% improvement in PGA scores** of clear or almost clear or a 2-point reduction in PGA score in a patient with psoriasis in need thereof ... the time to achievement of the 50% reduction is at 12 weeks ... is at **8 weeks**”); *id.*, [0294] (“a method of improving the time to reaching a PASI 50 or PASI 75 score in a person affected in a person with psoriasis ... the **time to reach a PASI 50** is at 16

weeks, or 12 weeks, or **at 8 weeks** ... the time to reach a PASI 70 is at 16 weeks, or 12 weeks, or at 8 weeks.”). A POSA would understand an improvement in PASI score is an improvement in one or more symptom, as recited in claim 16.

B. GROUND 2: Claims 1-4, 6-10, 16, 18, and 21-22 Would Have Been Obvious in View of Sonti and the Knowledge of a POSA

175. As I explained above, Sonti discloses all elements of the claims identified in Ground 1.

176. However, even if one viewed the elements as being taught in different embodiments (though I do not think they are) or viewed Sonti as only suggesting an element, a POSA also would have had good reasons to perform the method recited by the claims in view of Sonti’s teachings, with a reasonable expectation of success. A POSA would not have read portions of Sonti in isolation without considering Sonti’s teaching as a whole. Rather, a POSA would have looked to all of Sonti’s teachings (and all of its embodiments) when implementing a method of treating plaque psoriasis.

177. And, a POSA would have had a reasonable expectation of success in implementing the teachings of Sonti, even if not all from the same “embodiment” or even if an element was only suggested. For example, Sonti itself teaches that its embodiments (and in particular the embodiments disclosing the elements of the claims of the ’088 patent) can be implemented in combination with any of the other embodiments discussed in the Sonti patent. In addition, Chen (which Sonti

cites, Ex-1005, [0010]) already taught that the specific application of a 1% tapinarof topical composition once a day was highly effective. Ex-1013, 32:10-62. So to a POSA, such as a practicing dermatologist like myself, combining embodiments in Sonti's patent would be no more than combining known features in a routine and common-sense manner to yield a predictable result.

1. Independent Claim 1

178. In my opinion, a POSA would have been motivated to arrive at the method of treating recited by claim 1, with a reasonable expectation of success, given the teachings of Sonti as a whole along with the background knowledge of a POSA.

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

179. In my opinion, Sonti discloses [1.pre], as I explained above.

180. However, even if Sonti did not disclose this element, this method would have been obvious from the teachings of Sonti as a whole. In particular, a POSA reading Sonti would have been motivated, with a reasonable expectation of success, to treat mild to severe plaque psoriasis by topically applying the tapinarof compositions disclosed by Sonti.

181. Sonti explains to a POSA 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 then

specifically describes effectively treating “moderate to severe plaque psoriasis” using “a topical emulsion composition as described herein.” Ex-1005, [0288].

182. A POSA would have known that plaque psoriasis presents in various severities, ranging from mild to severe. A POSA would have reasonably expected that a method of topical treatment known to be effective for moderate to severe plaque psoriasis would also be effective for lower-grade manifestations of the disease—for example, mild psoriasis. To a practicing dermatologist, this is a matter of common sense. Also, mild to moderate plaque psoriasis was generally treated with topicals (while severe plaque psoriasis was more often treated with systemic pharmaceuticals). So if a topical treatment was known to be effective for severe plaque psoriasis, there would be even more reason to use it to treat mild to moderate plaque psoriasis, which were the severity grades most commonly treated with topicals.

183. In view of this, a POSA would have been motivated, with a reasonable expectation of success, to apply to *mild* psoriasis the method of treatment Sonti expressly teaches is effective for moderate to severe plaque psoriasis. I also note that the literature taught that the adverse effects for tapinarof used to treat plaque psoriasis were mostly mild, even when applied twice a day. *See* Ex-1008, 4, Table 4 (most adverse effects observed were “mild,” only two were “moderate,” and none were severe—“[a]ll dermatological adverse events observed in patients

randomized to WBI-1001 [which is tapinarof] were either mild (34) or moderate (two) in intensity”). In view of this, a POSA would have been comfortable using the method to treat mild psoriasis.

184. Applying the method of treating moderate to severe plaque psoriasis that Sonti teaches to treat mild psoriasis would also have been an obvious thing to try. Based on my experience as a practicing dermatologist who frequently treats plaque psoriasis, there was (and always is) both market and professional pressure to prescribe effective treatments to all grades of plaque psoriasis (including mild psoriasis). Many of my patients see me for treatment of mild psoriasis. And there were (and are) only a finite number of plaque psoriasis severities—generally mild, moderate, and severe. *E.g.*, Ex-1011, 1 (“In the clinic, psoriasis may be graded by the dermatologist as mild to severe”); Ex-1006, 1 (“psoriasis may be classified as mild psoriasis, moderate psoriasis, and severe psoriasis”). If a topical treatment is effective for psoriasis in the moderate to severe range, it would be a matter of common sense to a POSA to try that same topical treatment for mild psoriasis, for any one (or more) of the reasons I explained above. Also, a POSA would reasonably expect that topical treatment to be successful for mild psoriasis, given that (as I also explained above), Sonti (and the Chen references Sonti cites, Ex-1012 and Ex-1013) already teaches that it was successful for treating moderate to severe plaque psoriasis.

- b. [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”

185. In my opinion, Sonti discloses elements [1.a], [1.b], and [1.c] for the reasons I explained above in Ground 1.

186. However, even if Sonti did not disclose these elements as part of a single discrete embodiment, this method would have been no more than a routine, predictable, and common-sense combination in view of the teachings of Sonti as a whole and the knowledge of a POSA.

187. The first reason is that Sonti expressly teaches using the disclosed tapinarof amounts (including claimed 1%) and disclosed application frequencies (including the claimed once daily) in combination with each of its disclosed compositions:

- **“in all of the compositions described herein**, the amount of [tapinarof] which may be present... may be... 1%”. Ex-1005, [0196] (emphasis added); *see also id.*, [0055] (generally describing the compositions)
- “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] (emphasis added)

188. A POSA would understand this teaching to indicate that in each of Sonti’s formulations, the composition may include 1% tapinarof, and that each of

Sonti's disclosed formulations ("any of the embodiments") may also effectively be applied once daily. This means that even if Sonti did not teach the elements of claim 1 as part of the same embodiment (though I think it does), a POSA would have been motivated, with a reasonable expectation of success, to apply a topical composition containing 1% tapinarof once a day.

189. There were additional known reasons for using the claimed method of treating, with a reasonable expectation of success.

190. **One**, it was already known in the art that a 1% tapinarof composition, applied topically once a day, was highly effective to treat plaque psoriasis. The Sonti reference explains that the compound "3,5-Dihydroxy-4-isopropyl-trans-stilbene"⁸ was known to be "suitable for the treatment of various key dermatological conditions including psoriasis." Ex-1005, [0008]-[0010]. Sonti also teaches effectively treating plaque psoriasis with 1% tapinarof, including administered once a day and as measured by PGA score improvement, as I explained above with respect to Claims 1 and 9 in Ground 1. *See supra* ¶¶85-87, 110-116, 118-122, 129-146; *see also* Ex-1005, [0285]-[0295].

191. Sonti also cites two of the Chen references teaching this: Ex-1013 (US

⁸ As I explained in my overview of Sonti and in Ground 1 above, "3,5-Dihydroxy-4-isopropyl-trans-stilbene" is tapinarof. *See also* Ex-1032, ¶¶58-63.

7,868,047) and Ex-1012 (WO 2001/042231). *Id.* These Chen references teach that a “1%” tapinarof cream,⁹ applied topically “**once per day**,” showed “great efficacy” in treating plaque psoriasis. Ex-1013, 32:19-66; *see also* Ex-1012, 20:28-21:25; *see also* §IX.C. For example, Exhibit 1013 explained that:

- “The compounds of the invention possess specific activity against psoriasis.” Ex-1013, 2:54-3:4.
- “In these tests, representative compound of this invention, i.e., 3,5-dihydroxy-4-isopropylstilbene¹⁰ **is active in reducing or eliminating symptoms of psoriasis** and eczema.” Ex-1013, 32:15-18.
- “[T]he inventive compound showed **great efficacy** on the Volunteers treated in comparison with the untreated areas and before and after treatment.” Ex-1013, 32:51-53.
- For Volunteer 1, “the inventive compound started showing

⁹ As I explained at paragraph 97 above, a POSA also would have understood Chen’s descriptions of a “1% cream” to refer to 1% tapinarof by weight, and even if not, providing the tapinarof as 1% by weight would have been the most common, predictable way to formulate the cream. Ex-1032, ¶¶74-80.

¹⁰ “3,5-dihydroxy-4-isopropylstilbene” is tapinarof, as Mr. Sudhakar explains. Ex-1032, ¶¶68-70.

improvement in the inflammation and a decrease in proliferative cells three days after the treatment and **complete[] clearance** in 7 days” Ex-1013, 32:53-57.

- For 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.” Ex-1013, 32:58-62.

192. I note that even if the Chen references did not expressly teach treating *plaque* psoriasis (and in my opinion they do, as I explained above in my discussion of Chen at paragraphs 99-101), a POSA would still be motivated by Chen’s teachings to use the 1% tapinarof composition, applied once a day, to treat *plaque* psoriasis specifically and would have reasonably expected it to work. Chen expressly teaches that this method of treatment was highly effective for treating “plaques” on Volunteer 2’s back, so a POSA would expect it to work on plaque psoriasis. Ex-1013, 32:35-63. Also, Chen disclosed that the treatment was highly effective in treating Volunteer 1’s scalp psoriasis, which I explained above would have almost certainly been understood to be plaque psoriasis. Ex-1013, 32:30-63. And, a POSA would understand Chen’s discussion of treating psoriasis to be referring to treating plaque psoriasis specifically, as Chen’s description of psoriasis is actually a description of *plaque* psoriasis. *E.g.*, Ex-1013, 2:56-3:4 (“Psoriasis is a common, chronic inflammatory skin disease, characterized by rapid

multiplication and turnover of the epithelial cells with a consequent thickening of the epidermis, as well as inflamed swollen **skin lesions covered with silvery white scaling patches** and **raised, inflamed, thickened and scaly lesions**”) (emphasis added). In any event, Chen’s teaching would have motivated a POSA to use the method of treating on *plaque* psoriasis (which very commonly manifests on the scalp) and to expect it to work, just like it worked for Volunteer 1’s scalp psoriasis and Volunteer 2’s “plaques.”

193. In view of these teachings, a POSA would have reasonably expected that treatment of plaque psoriasis via the steps recited by [1.a]-[1.c] would be effective and therefore would have been motivated to use that method.

194. **Two**, it was also known in the art that if a treatment containing a lower amount of active ingredient and/or administered less frequently was still effective, there were good reasons to use that lower amount and/or that lower frequency. *See also* Ex-1032, ¶¶81-87.

195. One known reason to do this was to reduce the body’s systemic exposure to the active ingredient, which would predictably reduce risk of side effects. For example, the Bissonnette clinical study teaches that there were some adverse events observed in patients treated with a 1% tapinarof composition applied topically twice a day, and that the adverse events were higher for those treated with the tapinarof cream than those treated with placebo. Ex-1008, 1, 4;

see also id., 4 (Table 4). Bissonnette stated that about 80% of the patients treated with the 1% tapinarof cream twice daily experienced at least one adverse event, while only about 52% of the patients treated with placebo experienced adverse events. Ex-1008, 4 (Table 4). While most of the adverse events within the cohort treated with the 1% tapinarof cream were “mild” in severity (and two were “moderate”), a POSA still would have been motivated to minimize the risk of these side effects. A known way to minimize risk of side effects was to lower the body’s systemic exposure to the active ingredient, and a known (predictable) way to do that was to decrease application frequency. *See also* Ex-1032, ¶¶84-85.

196. Consistent with this, Sonti also teaches using a lower dosing frequency: “the dosing frequency to the affected area(s) may now be dosed less frequently than previously envisioned.” Ex-1005, [0387]. Sonti further explains (in the same paragraph) that an embodiment of the invention is the use of a formulation such as described in Sonti that “can provide lower systemic exposure of the active ingredient to the patient during use.” *Id.*

197. Another known reason in my field to use a lower application frequency to improve patient compliance. In my experience, patients are generally more likely to be compliant with treatment recommendations when the application frequency is once a day, rather than more frequent applications. *See also* Ex-1032, ¶87. From my interactions with my colleagues at the clinics I worked at prior to

November 2018, and also from other professional interactions over my career such as at medical conferences, I know that my colleagues had similar experiences and views.

198. A third known reason was to reduce cost of the treatment. Generally, it was known that if a topical treatment can be applied less frequently, the patient would need less of the topical, which would reduce the overall cost of the treatment. *See also* Ex-1032, ¶86.

199. In view of these teachings and knowledge in the art, a POSA would have been motivated, with a reasonable expectation of success, to use the “1%” strength and “once daily” application frequency disclosed by Sonti. This is particularly true given that, as I explained above, the 1% tapinarof compositions topically applied once a day were already known to be highly effective in treating plaque psoriasis.

200. I also note that the claimed method of treating plaque psoriasis where the composition contained 1% tapinarof and was applied once daily would have been an obvious thing to try. There was a recognized need in the art for effective methods of treating plaque psoriasis. *E.g.*, Ex-1008, 1 (“There is a need for the development of novel non-steroidal topical drugs for the treatment of psoriasis”); Ex-1011, 1 (“Psoriasis is a chronic autoimmune inflammatory skin disease that affects 1% to 3% of the global population [and has a] substantial impact on quality

of life”); Ex-1015, 3 (“Plaque psoriasis...is the commonest form of psoriasis, representing almost 90% of psoriatic patients”).

201. As I explained above, there were a finite number of known potential tapinarof concentrations to use to treat plaque psoriasis. Ex-1005, [0055], [0196] (0.25%, 0.3%, 0.4%, 0.5%, 0.75%, 1.0%, 1.25%, 1.5%, 1.75%, and 2% by weight); Ex-1008, 1 (1% by weight); Ex-1013, 32:25-27 (1% by weight). As I also explained above, there were likewise a finite number of known potential application frequencies to use when treating plaque psoriasis with tapinarof. Ex-1005, [0387] (twice daily, once daily, once every other day, twice weekly, three times weekly, or once weekly); Ex-1008, 1 (twice daily); Ex-1013, 32:41-43 (once daily). Applying a composition containing 1% tapinarof once daily to skin areas affected by plaque psoriasis was one of these finite number of known options.

202. A POSA also would have reasonably expected success in trying the known options. As I explained above with respect to Claim 1 in Ground 1, Sonti teaches that its tapinarof compositions effectively treat plaque psoriasis. *See also supra* ¶¶190-191; Ex-1005, [0285]-[0293]. Sonti also cites the Chen references as showing that tapinarof is “suitable” for treating psoriasis, and the Chen references it cites specifically teach that 1% tapinarof applied once daily effectively treats plaque psoriasis. Ex-1005, [0010] (citing Ex-1013 (US 7,868,047, *see* 32:19-66) and Ex-1012 (WO 2001/042231, *see* 20:28-21:25)).

203. For any one (or more) of these reasons, a POSA would have had good reason to try treating plaque psoriasis with 1% tapinarof administered once daily.

c. [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.”**

204. In my opinion, Sonti discloses element [1.d] for the reasons I explained above.

205. The claimed method would also have been no more than a routine, predictable, and common-sense combination in view of the teachings of Sonti as a whole and the knowledge of a POSA.

206. The claimed PGA score improvements were well-known and there was good reason to expect them with all of Sonti’s disclosed tapinarof compositions.

207. **First**, Sonti teaches a POSA that all of its tapinarof compositions may be used in the method of treating plaque psoriasis that results in the PGA score improvements disclosed by Sonti. Ex-1005, [0288]. Sonti explains that an embodiment of the invention is treatment of “mild to moderate plaque psoriasis” such that the patient “reach[es] a PGA score of 0 or 1...at a defined time point such as at 8, 12 weeks...of treatment,” that is **“achieved by using a topical emulsion composition as described herein.”** Ex-1005, [0288] (emphasis added). A POSA would understand “a topical emulsion composition as described herein” to refer to

the topical tapinarof compositions Sonti discloses, including a 1% tapinarof emulsion administered once daily.

208. **Second**, to a practicing dermatologist like myself at the relevant time, a PGA score “improved by two grades” or “improved to a score of 0 or 1” after topical treatment of plaque psoriasis were well-known and frequently used treatment response metrics. For example, as I explained above, a search of the U.S. National Library of Medicine database shows at least thirty-six studies for plaque psoriasis treatment published prior to November 12, 2018 that used PGA as an outcome measure. Ex-1026. Many of these specifically use a PGA improvement of 2 grades or achieving a PGA of 0 or 1 as an “outcome measure.” *E.g.*, Ex-1026, 6-7, 27, 58-59, 119-125, 157-158, 202-203, 475-476, 609-610, 880-881, 1709-1710, 1715, 1722-1724, 1752-1753.

209. There also was a series of Chinese clinical trials that disclosed using PGA as an outcome measure in trials that included application of a 1% “Benvitimod” (which I understand is tapinarof¹¹) composition to treat plaque psoriasis. Ex-1016, Ex-1017, Ex-1018.

210. Given that the specific PGA score improvements recited by claim 1 were known and commonly used in conjunction with measuring outcomes of

¹¹ Ex-1032, ¶¶71-73 (“Benvitimod” is “tapinarof”).

plaque psoriasis treatment, a POSA would have been motivated to use either of the PGA score improvements recited by Claim 1 in conjunction with treating plaque psoriasis.

211. A POSA would also have reasonably expected that the claimed PGA score improvements would be the result of performing the method of treating recited by claim 1, for at least two reasons.

212. One, Sonti specifically teaches the claimed PGA score improvements following treatment with the topical compositions it describes, as I explained with respect to [1.d] in Ground 1 above. Ex-1005, [0288]. As I also explained above, a POSA would understand that this teaching includes (and certainly also suggests) applying a 1% tapinarof composition to affected areas once a day. Ex-1005, [0288].

213. Two, Sonti also cites the Chen references as showing that tapinarof is “suitable” for treatment of psoriasis. Ex-1005, [0010] (citing Ex-1012 and Ex-1013). In fact, the Chen references disclose more than that. They explain that treating subjects with a 1% tapinarof composition applied to areas affected by plaque psoriasis once daily “showed great efficacy,” with Volunteer 1 achieving “complete[] clearance” following treatment and Volunteer 2 achieving “significant improvement.” Ex-1013, 32:51-65, 32:15-17; *see also* ¶¶95-104, 191-192, *supra*.

214. A POSA would understand the “complete clearance” of plaque

psoriasis disclosed by Chen means that a PGA score has improved to 0 (as claimed). Ex-1001, 22:30 (PGA “[s]core of 0 represents clear skin”); Ex-1005, [0288] (equating PGA score of 0 with “clear”); Ex-1008, 2 (“clear” is a PGA score of 0); Ex-1007, 6 (equating the start of the PGA scale (0) with “clear”); Ex-1026, 6 (in the PGA scale “0 = clear”) and 119 (same); Ex-1010, 2.

215. A POSA would also understand the “significant improvement” for Volunteer 2 taught by Chen includes improvement by at least two PGA grades (which would include the claimed improvement “by 2 grades”). *See* Ex-1013, 32:51-65. A PGA improvement of only 1 grade would not generally be considered to be a “significant improvement” by a POSA. This is reinforced by Chen, which differentiates between the “visible improvement in inflammation and in clearance of the proliferative cells three days after treatment” of Volunteer 2, and the “significant improvement of the psoriasis” (meaning substantially more improvement) that was observed within seven days of treatment. Ex-1013, 32:58-62.

216. These teachings—those in Sonti itself and also in the Chen references Sonti cites—confirm that a POSA would reasonably expect to achieve one or both of the recited PGA score improvements following treatment as claimed.

217. I also note that the claimed method of treating plaque psoriasis, where the PGA score is improved as claimed, would have been a common sense,

predictable thing to try for a POSA at the relevant time.

218. There was a recognized need for effective plaque psoriasis treatments, and also a recognized need for clinical metrics such as the PGA to measure plaque psoriasis severity and treatment response. *E.g.*, Ex-1008, 1 (Abstract); Ex-1011, 1 (“Because no psoriasis biomarkers are available to assess disease severity, clinical measures are used in daily practice and in research to measure both severity and treatment response.”).

219. The PGA metric generally, and also the two alternative specific PGA score improvements recited by claim 1 specifically (PGA score improving to 0 or 1; PGA score improving by 2 grades), were part of a finite number of known ways to assess plaque psoriasis treatment response. *E.g.*, Ex-1005, [0288]-[0290], [0293] (disclosing PGA score reaching “0 or 1 (clear or almost clear)” and “2-point reduction in PGA score” as benchmarks for treatment response for plaque psoriasis treatment); Ex-1008, 1518, Table 2 (using “proportion of patients with a PGA of 0 or 1 at each visit” as a metric for treatment response); specifically *e.g.*, Ex-1026, 6-7, 27, 58-59, 119-125, 157-158, 202-203, 475-476, 609-610, 880-881, 1709-1710, 1715, 1722-1724, 1752-1753 (using a PGA improvement of 2 grades or improvement to 0 or 1 as an “outcome measure” for plaque psoriasis clinical trials); *see also* Ex-1007, Table 2 (PGA listed as one of eleven “main clinical psoriasis measures that were analyzed”), Ex-1011, 1 (focusing on “three global

scoring methods,” the PASI, PGA, and LS-PGA); Ex-1006, 7 (Table 5) (noting that the “PASI, BSA, and PGA” metrics have been approved by the FDA for use in clinical trials for psoriasis). A POSA would understand the various teachings of using a PGA score improvement to “clear or almost clear” when assessing treatment response to be the equivalent of using a PGA score improvement to “0 or 1.” *See, e.g.*, Ex-1005, [0287] (PGA score of 0 = “clear”; PGA score of 1 = “almost clear”); Ex-1008, 3 (“PGA score of 0 (clear) or 1 (almost clear)”; Ex-1001, 22:30-33 (“score of 0 represents clear” and “score of 1 represents almost clear”).

220. A POSA also would have had good reasons to reasonably expect either of the PGA score improvements recited by claim 1 in conjunction, when trying the method of claim 1 using PGA scores to assess treatment response. As I explained above and with respect to [1.d] in Ground 1, Sonti specifically teaches the claimed PGA score improvements following treatment with the topical compositions it describes. Ex-1005, [0288]. As I also explained above, the Chen references Sonti cites also disclose that treating subjects with a 1% tapinarof composition applied to affected areas of the skin once daily “showed great efficacy,” with Volunteer 1 achieving “complete[] clearance” following treatment and Volunteer 2 achieving “significant improvement.” Ex-1013, 32:51-65; *see also* Ex-1013, 32:15-17.. As I explained above, a POSA also would understand this to

teach the specific PGA score improvements recited by claim 1.

221. In view of all of this teaching, a POSA certainly would have had a reasonable expectation of seeing at least one of the PGA score improvements recited by claim 1, when trying the method of treatment the claim recites.

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

222. Sonti discloses claim 2, as I explained above in Ground 1. Further, I understand from Mr. Sudhakar that this also would have been an obvious composition. Ex-1032, ¶¶114-127.

3. 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”

223. I understand from Mr. Sudhakar that this claim would have been obvious in view of Sonti and the knowledge of a POSA. Ex-1032, ¶¶114-127.

4. 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”

224. I understand from Mr. Sudhakar that this claim would have been obvious in view of Sonti and the knowledge of a POSA. Ex-1032, ¶¶114-127.

5. Dependent Claim 6: “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”

225. Sonti discloses this claim, as I explained above in Ground 1.

226. Even if Sonti did not, this would have been a common-sense, predictable method of treating plaque psoriasis.

227. From my 30+ years as a practicing dermatologist, and from having treated over 1,000 patients with mild to severe plaque psoriasis, I know the body, arms, legs, back, chest, buttocks, neck, scalp, fingernails, toenails are all areas of the body commonly afflicted with plaque psoriasis. For example, in patients I see it is most common to have plaque psoriasis on trunk, elbows (of the arms), knees (of the legs), and scalp. *See also, e.g.,* Ex-1015, 3 (under the heading “plaque psoriasis,” explaining that “scalp may be the most common site of involvement”); Ex-1006, 2 (“Chronic plaque-type psoriasis is the most common morphologic variety which manifests as circumscribed, well-demarcated, erythematous plaques involving particularly the extensor aspects of elbows and knees, buttocks, scalp, and lower back.”) And I also know, from my experience, that it is common for a patient suffering from plaque psoriasis to have more than one of these body parts afflicted. Claim 6 simply lists these commonly-afflicted body parts. A POSA also would have known this.

228. Given this knowledge, a POSA would have been motivated, with a reasonable expectation of success, to apply the topical method of treatment of claim 1 to a body part or parts that were known to be commonly affected by psoriasis, including those listed by claim 6.

6. 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”

229. Sonti discloses the elements of claims 8 and 22, as I explained above in Ground 1.

230. Even if Sonti did not disclose, this would have been an obvious application of the method of claim 1.

231. One, Sonti already teaches a method of treating moderate to severe plaque psoriasis, as I explained with respect to element [1.pre]. In view of this, it would have been common sense and straightforward for a POSA to apply that method to a subject who has been “diagnosed” with moderate to severe plaque psoriasis. In fact, as I explained earlier, a POSA at the time would not have treated a subject for plaque psoriasis without first having “diagnosed” the subject as having plaque psoriasis.

232. Two, given Sonti’s teaching and suggestion of treating a subject diagnosed with “moderate to severe plaque psoriasis” at “baseline,” a POSA also

would have been motivated to treat a subject diagnosed with *mild* plaque psoriasis, and would have reasonably expected to be successful, for the same reasons explained in this Ground 2 with respect to element [1.pre].

233. Three, using PGA as the metric for assessing severity when diagnosing mild to severe/mild to moderate plaque psoriasis was well-known by the relevant time. *E.g.*, Ex-1005, [0287]-[0288] (explaining that “The PGA scale in its typical use, is a 7-point scale ranging from clear to severe” and further disclosing treating patients “who most likely will have started with a PGA score of ≥ 4 ”); Ex-1008, 1 (clinical study of patients with baseline PGA of 2 to 4); Ex-1006, 5; Ex-1007, 2-3 (Table 2) (providing the “main clinical psoriasis measures” and explaining that “The PGA is a 5, 6, or 7 point ordinal rating ranging from “clear” to “very severe psoriasis”); Ex-1011, 2 (explaining that “clinical measures are used in daily practice and in research to measure both severity and treatment response,” and further explaining that “[t]he PGA is the most commonly used scoring method in clinical trials after the PASI”); Ex-1010, 2-3.

234. Four, treating a subject diagnosed with plaque psoriasis and having a PGA score of greater than or equal to two was also known. *E.g.*, Ex-1005 [0287]-[0288] (treating subjects who “started with a PGA score of ≥ 4 at baseline”); Ex-1008, 1 (clinical trial of patients having a “physician’s global assessment score (PGA) of 2-4” at the start of trial). PGA scales at the relevant time (*e.g.*, prior to

November 2018) generally used five, six, or seven point scales, that started with zero and increased to one, two, three, etc. *E.g.*, Ex-1005, [0287]; Ex-1007, 2-3 (Table 2); Ex-1010, 3.

235. In my clinical experience prior to November 2018, I also commonly treated patients diagnosed with plaque psoriasis who would have had PGA scores of greater than or equal to two. Those having a PGA score of greater than or equal to 2 had symptoms including plaques, scaling, and/or erythema, and a POSA therefore would have been motivated to treat them. *See* Ex-1005, [0287].

236. Five, the prior art I've discussed, including Sonti and Chen, shows that method of claim 1 was also already 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. *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" and resulted in "complete clearance" for one subject and "significant improvement" for the other).

237. In view of all of this, using the method of claim 1 to treat a subject diagnosed with plaque psoriasis as claimed and having a PGA score greater than or equal to 2 would have been a straightforward, common-sense course of action for a POSA at the relevant time. The claimed PGA metric was known (as a common

metric for assessing severity of plaque psoriasis at baseline); the method of claim 1 was also known to be effective for treating plaque psoriasis with a severity equivalent to a PGA score of 2 or greater. Therefore, a POSA would have been motivated, with a reasonable expectation of success, to use the treatment method of claim 1 to treat a subject diagnosed with plaque psoriasis as claimed and having a PGA score “*greater than or equal to 2.*” To a POSA, this would have been merely common sense: treating a subject diagnosed with plaque psoriasis having a common severity level measured by a known metric (PGA greater than or equal to 2) with a method known to be effective.

- 7. 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 (PASI), 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)”**

238. Sonti discloses claim 9, as I explained above in Ground 1.

239. Even if Sonti did not, an improvement of one or more symptom as measured by one of the metrics recited in claim 9 would have been just a common sense, expected extension of claim 1.

240. One, as I explained with respect to claim element [1.d] and claim 9 in Ground 1 above, Sonti teaches an improvement in PGA score following the

treatment recited in claim 1. *See supra* ¶¶133-146, 168-170. Given this, a POSA would have reasonably expected that the disclosed improvement in PGA score would come with an improvement of one or more symptom of mild to severe plaque psoriasis, as claim 9 recites. This is because, as a POSA would have known, an improvement in PGA score *means* that one or more symptom of the plaque psoriasis has improved. This is evident from PGA scales. For example, the PGA scale Sonti provides shows that as PGA score improves (meaning becomes lower), the symptoms of plaque psoriasis improve. Ex-1005, [0287]; *see also, e.g.*, Ex-1011, Fig. 2 (same). As one example, going from “moderate,” which would be a PGA score of 4 in Sonti, to “almost clear” or “clear,” which would be a PGA score of 1 or 0, means that symptoms of “moderate plaque elevation, scaling, and/or erythema” have improved or disappeared completely. Ex-1005, [0287].

241. Two, even if Sonti somehow did not disclose the claimed improvement of one or more symptom, as measured according to one of the recited metrics, such an improvement would have been a common sense and expected result of the method of treatment recited by claim 1.

242. As I’ve previously explained with respect to claim element [1.d] in Grounds 1 and 2 above, a POSA already knew that the method for treating plaque psoriasis recited by claim 1 was effective, given the teachings of references such as Sonti and Chen. *E.g.*, Ex-1005, [0288] (treatment of “moderate to severe plaque

psoriasis” improved PGA score from ≥ 4 to a 0 or 1, following a defined duration of “treatment”), [0308] (“treatment” of a dermatological condition encompasses “alleviation of at least one symptom thereof, a reduction in the severity thereof, or the delay, prevention, or inhibition of the progression thereof”), *see also* [0289]-[0294]; Ex-1013, 32:10-62 (treatment of plaque psoriasis with 1% tapinarof composition applied once daily “showed great efficacy” and resulted in “complete clearance” for one subject and “significant improvement” for the other). A POSA would have understood the teaching in Sonti of improvement in PGA score following treatment, and the “complete clearance” and “significant improvement” reported by Chen, to indicate that one or more symptom of plaque psoriasis had improved following the treatment.

243. As I’ve also previously explained, the metrics for measuring improvement of one or more symptom[s] of plaque psoriasis following treatment that claim 9 recites were also already well-known and commonly used by the relevant time. *E.g.*, Ex-1005, [0285]-[0293] (PGA and PASI); Ex-1008, 1 (PGA and BSA); Ex-1006, 5 (PASI, BSA, PGA, SF-36, DQLI); Ex-1007, 2-3 (PASI, BSA, PGA); Ex-1011, 2-3 (PGA, BSA, PASI); Ex-1008, 1 (PGA, BSA); Ex-1026 *generally*.

244. This means that a POSA (1) would have known that the method of claim 1 was effective to improve one or more symptom of plaque psoriasis, and (2)

would have been aware of the known assessments, such as PASI, PGA, and BSA, for measuring improvement in symptoms following treatment. In view of this knowledge, what is recited by claim 9—that after administering the topical composition there is “an improvement of one or more symptom of mild to severe plaque psoriasis as measured according to an assessment” selected from one of a group including PASI, PGA, and BSA—would have just been the common-sense, expected result of the method of claim 1.

245. A POSA would also have been motivated, with a reasonable expectation of success, to measure an improvement in one or more symptom using one of these well-known assessments, because the art taught that there were “no psoriasis biomarkers [available]” and therefore assessments such as the PGA, BSA, and PASI were needed to assess treatment response. Ex-1011, 1 (“Because no psoriasis biomarkers are available to assess disease severity, clinical measures are used in daily practice and in research to measure both severity and treatment response.”).

246. In my opinion, the method of claim 9 also would have been a common sense and predictable option to try. There was a known need for effective plaque psoriasis treatments (Ex-1008, 1), and there was a known need for clinical assessments (such as PGA, BSA, and PASI) to assess psoriasis “treatment response” (Ex-1011, 1). The clinical assessments recited by claim 9 (e.g., PASI,

BSA, PGA) were a finite set of known options for measuring the improvement of symptom[s] of plaque psoriasis after topical treatment. *E.g.*, Ex-1005, [0287]-[0293]; Ex-1006, 5; Ex-1007, 2-3; Ex-1011, 2-3; Ex-1008, 1; Ex-1026. And as I explained above, a POSA would have had good reasons to expect the treatment method of claim 1 to improve one or more symptom of plaque psoriasis. So, a POSA like myself would have had good reason to try the method of treatment where one or more symptom was improved as measured with an assessment according one of the known metrics, such as PGA, BSA, or PASI.

8. 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%”

247. As with claims 8 and 22, the only difference between claims 7 and 21 is that claim 7 recites a subject diagnosed with “mild to severe” plaque psoriasis, while claim 21 recites a subject diagnosed with “mild to moderate” plaque psoriasis. Given this, I discuss these claims together.

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

249. In my opinion, treating a subject having the BSA affected recited by claims 7 and 21 would have been a straightforward, common-sense extension of the method of claim 1, in view of the teachings of Sonti as a whole and the

knowledge of a POSA. A POSA would have been motivated to do this, with a reasonable expectation of success, for at least four reasons.

250. **One**, Sonti also discloses applying tapinarof compositions where “the amount of body surface area (BSA) for which the drug is applied to is” within the claimed BSA affected range. For example, Sonti teaches that the BSA for which the disclosed tapinarof compositions are applied is “...less than 30%” and/or “>10%.” Ex-1005, [0268]. Sonti also teaches “administration [of tapinarof compositions] to the skin in an amount not exceeding 35%...BSA... [or] the amount is not exceeding 30% BSA”. Ex-1005, [0267]. “[L]ess than 30%” to a POSA means about 1% to about 29% BSA. This includes the entire claimed “about 3% to about 20%” range. “> 10%” to a POSA includes an about 11%-20% range. This teaches over half of the claimed “about 3% to about 20%” range. Thus, Sonti teaches and suggests at least applying the tapinarof compositions to “about 3% to about 20%” of the body surface area of a subject.

251. A POSA would understand Sonti’s disclosure of *applying* the tapinarof compositions to skin (body) surface areas within the claimed range to suggest that such treated areas are *affected* by the skin diseases Sonti discloses treating (specifically, atopic dermatitis and plaque psoriasis). *See, e.g.*, Ex-1005, [273]-[0284] (treating atopic dermatitis), [0285]-[0295] (treating “moderate to severe plaque psoriasis”).

252. A POSA would also understand that a subject having body surface area *affected* by plaque psoriasis would also have been “diagnosed” with such disease. In my field, concluding that someone has areas of skin affected by plaque psoriasis is a diagnosis of plaque psoriasis.

253. **Two**, a POSA would have been motivated to use a clinical measure such as the common, known BSA metric to assess plaque psoriasis severity, because there were no biomarkers available for psoriasis. *E.g.*, Ex-1011, 1-2 (“because no psoriasis biomarkers are available to assess disease severity, clinical measures [such as BSA] are used in daily practice and in research to measure both severity and treatment response”); *see also* Ex-1007, 2-3 (providing the “main clinical psoriasis measures” and explaining that the BSA is an “estimation of involved body surface area”); Ex-1006, 3 (Table 2); Ex-1008, 1.

254. Subjects having a BSA affected within the claimed range (“about 3% to about 20%”) was known and common. *E.g.*, Ex-1008, 1 (clinical study of patients diagnosed with plaque psoriasis affecting a BSA of 1-10%); Ex-1006, 3 (Table 2); Ex-2011, 2 (“BSA involvement greater than 10% or a PASI score greater than 12 is frequently used as a criterion for severe disease”); Ex-1026, 200 (“subject has involved BSA $\geq$ 10%... at baseline”), 186 (same), 293 (same), 304, 342, 485 (“At Baseline, have plaque psoriasis covering 2% to 20% of total body surface area (BSA)”); 631 (“involvement of 10-15% of their BSA”), 1326

(“Coverage of the body surface area (BSA) of 10% or more with plaques”).

255. BSA was also the metric I used most commonly to assess severity and treatment efficacy for plaque psoriasis, prior to November 2018 and also to this day. In plaque psoriasis patients I see, having a BSA within the about 3% to 20% BSA range recited by claims 7 and 21 is quite common. This range (3% to 20% BSA) spans what was generally considered mild, moderate, and severe plaque psoriasis.

256. In view of this, it would have been common sense to use the method of claim 1 with subjects diagnosed with plaque psoriasis having a severity measured according to the well-known BSA metric, including those with about 3% to about 20% BSA.

257. **Three**, I explained above that a POSA already knew that the method of claim 1 was effective to treat plaque psoriasis. *See supra* ¶¶190-193, 211-216, 242; *see also* Ex-1005, [0285]-[0294]; Ex-1013, 2:56-3:4, 32:10-62. Given this knowledge, there was a good reason to apply the method of claim 1 to subjects diagnosed with mild to severe plaque psoriasis having a body surface area (BSA) affected of about 3% to about 20%, and also good reason to expect the treatment to be successful.

258. **Four**, Sonti further teaches effectively treating a subject having a BSA affected by atopic dermatitis (though not expressly plaque psoriasis) that is in the

range recited by claims 7 and 21. Ex-1005, [0272] (treating groups of subjects with “1-10% BSA” and “15-35% BSA” affected by AD (atopic dermatitis)). It was known that anti-inflammatory treatments for atopic dermatitis were often used with and could be expected to work for plaque psoriasis.

259. This is because both atopic dermatitis and plaque psoriasis were known to be inflammatory skin diseases. Ex-1013, 3:5-8 (“Eczema is a chronic inflammatory skin disorder, also known by terms used to describe the disorder as atopic dermatitis...”); Ex-1011, 1 (“Psoriasis is a chronic autoimmune inflammatory skin disease”); Ex-1005, [0029] (“the inflammatory dermatological condition or disorder is atopic dermatitis and/or psoriasis and/or acne”); Ex-1001, 5:34-36 and 5:66-67 (atopic dermatitis and psoriasis are each a “chronic[,] relapsing[,] inflammatory skin disease.”)

260. Consistent with this, publications discussing topical treatment for plaque psoriasis often discuss using the same topical treatment for atopic dermatitis. *E.g.*, Ex-1005, [0272]-[0284] (treating atopic dermatitis with tapinarof) and [0285]-[0295] (treating plaque psoriasis with tapinarof); Ex-1013, 2:56-3:17, 32:8-3:4 (treating eczema¹² and plaque psoriasis with tapinarof). Also consistent

¹² Eczema was also known as atopic dermatitis. Ex-1013, 3:5-9 (“Eczema is a chronic inflammatory skin disorder, also known by terms used to describe the

with this, in my clinical practice prior to November 2018 and still today, many of the topical treatments I prescribe for atopic dermatitis I also prescribe for plaque psoriasis.

261. Tapinarof was known to be a topical anti-inflammatory, and thus would have been expected to effectively treat plaque psoriasis, in addition to atopic dermatitis. *See, e.g.*, Ex-1008, 1 (“WBI-1001...is a non-steroidal, anti-inflammatory”). “WBI-1001” is tapinarof. Ex-1032, ¶¶64-67. *See also* Ex-1005, [0320] (the tapinarof compositions of Sonti “offer patients a novel therapeutic treatment options for various inflammatory skin conditions”).

262. Plaque psoriasis and atopic dermatitis do have some differences. They are different in that their inflammatory mediators or triggers are different interleukins or messengers and their skin manifestations differ. Psoriasis presents with hyperproliferation and inflammation whereas atopic dermatitis is eczematous and inflamed. However, topical therapies that reduce inflammation (like tapinarof) would have been expected to treat both conditions well (while topical therapies that address the hyperproliferation component would be more likely to be effective

disorder as atopic dermatitis, neurodermatitis, disseminated lichen simplex chronicus, or atopic eczema.”); Ex-1001, 5:33-35 (“Atopic dermatitis (AD) (also called atopic eczema)...”).

in psoriasis rather than atopic dermatitis).

263. Because of this knowledge in the art, a POSA reading Sonti's disclosure of treating atopic dermatitis in subjects having a BSA affected within the claimed "about 3% to about 20%" range would have been motivated to apply that teaching to the treatment of plaque psoriasis in subjects diagnosed with mild to severe plaque psoriasis having a BSA affected in the same range, and would have reasonably expected the treatment to work.

264. In my opinion, the method of claims 7 and 21 also would have been an obvious thing to try. There was a known need in my field for effective plaque psoriasis treatments and also a known need for clinical assessments to measure severity. *E.g.*, Ex-1008, 1; Ex-1011, 1. The BSA assessment, as well as the specific "about 3% to about 20%" BSA affected that claims 7 and 21 recite, was part of a finite number of known options for clinical assessments of plaque psoriasis severity. *E.g.*, Ex-1008, 1, 2 (BSA affected of 1-10%); Ex-1006, 3 (Table 2); Ex-1011, 2; *e.g.*, Ex-1026, 485 ("2% to 20%" BSA affected). A POSA also would have expected the method of treating of claim 1 to effectively treat plaque psoriasis, as I explained in detail above. Because of this, a POSA would have had good reason to try the method of treatment with a subject having a percent body surface area (BSA) affected by plaque psoriasis of about 3% to about 20%, and to reasonably expect it to work. Doing so would have been straightforward and

common-sense to POSA at the time. This is particularly true given that the method of claim 1 was known to be effective for treating plaque psoriasis, as I explained above.

9. 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”

265. In my opinion, the BSA decrease recited by Claim 10 would have been an obvious extension of claim 1 and claim 9.

266. Sonti does not disclose the improvement in BSA affected recited by claim 10 in the context of treating *plaque psoriasis* specifically. It does disclose it, however, in the context of treating the closely related skin disease of atopic dermatitis.

267. 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 a “% BSA improvement” after treatment of between 10% and 100%. Ex-1005, [0280]. This means that the percentage of the body surface area affected by the disease (atopic dermatitis in Sonti’s example) has decreased (i.e. improved) by between 10% and 100%. Sonti teaches that an “effective amount” of tapinarof can be 1%. *E.g.*, Ex-1005, [0196]; *see also id.* [0301].

268. Sonti also teaches treating subjects with a BSA affected of 1-10% and

15-35% with 1% tapinarof formulations, twice daily (“BID”). Ex-1005, [0272].

Sonti further teaches that those subjects treated with the 1% tapinarof (the “1% BID cohort data only” table) resulted in an average of 52% (21% -100% range) reduction in BSA for the 1-10% BSA-affected group, and 77% (56%-94% range) reduction in BSA for the 15-35% BSA-affected group. Ex-1005, [0272] (“1% BID cohort data only” table). Sonti provides tables showing this at paragraph [0272]:

Study		
Formulation	Formulation 1a	Formulation 21
Age	18-65 y	18-65 y
Disease duration	≥6 months diagnosis of AD	≥6 months diagnosis of AD
Affected area	1-10% BSA, excluding face, groin, scalp, genitals	15-35% BSA, excluding scalp
IGA (0-5)	2-3 (mild-moderate)	≥3 (moderate-severe)
Average % BSA treated	2.7% (1-7%)	19.8% (15-33%)
Study duration	28 day	21 day
Study treatment	Vehicle, 0.5%, 1% BID	1%, 2% BID (no vehicle control)
Subject numbers	N = 12/10/12 (completed)	N = 6/2 (completed)
PK sampling scheme	Pre-dose, 1, 2, 4, 6, 8 h post-dose	Pre-dose, 1, 2, 4, 8, 10, 12, 24 h post-dose
LLOQ	0.1 ng/mL + 100 pg/mL	40 pg/mL

1% BID cohort data only		
N	12	6
Day 1 Cmax (ng/mL)	0.46 (0-3.32)	1.23 (0.2-3.96)
Day 1 AUC(0-8) (ng.h/mL)	1.22 (0-8.61)	5.56 (1.05-15.14)
IGA score change from baseline at Day 21	42% (0%-100%)	55% (33%-75%)
BSA affected change from baseline at Day 21	52% (-21%-100%)	77% (56%-94%)

269. In view of these teachings, a POSA would understand Sonti to teach improvement of one or more symptoms of a skin disease such as atopic dermatitis as measured according to BSA affected, and specifically where the BSA affected is “decreased to less than 20%” as claimed, after topical administration of the 1% tapinarof composition.

270. For example, the average reduction of 77% for a subject in the group starting with a BSA affected of 15-35% (see second group, “1% BID cohort data only” table) would also result in a BSA reduced to ~8%, in a subject starting with 35% BSA affected. This discloses the claimed “percent surface area (BSA) affected [that] is decreased to less than 20%,” as recited by claim 10.

271. As another example, the average reduction of 52% for a subject in the group starting with a BSA affected of 1-10% (see first group, “1% BID cohort data only” table) would result in a BSA reduced to ~5% BSA, in a subject starting with ~10% BSA affected. This is also within the claimed “percent surface area (BSA) affected [that] is decreased to less than 20%,” as recited by claim 10.

272. In view of the teachings of Sonti and the general knowledge in the art, a POSA would have been motivated to also measure treatment response for *plaque psoriasis* using the BSA metric, and would have reasonably expected a similar reduction in BSA following the treatment method recited by Claim 1. This is true for several reasons.

273. First, a POSA would have been motivated to measure treatment response for plaque psoriasis specifically using the BSA metric, because the BSA metric was known as a useful tool for measuring plaque psoriasis treatment response. *E.g.*, Ex-1008, 1, 2 (using percent BSA affected to measure efficacy of plaque psoriasis treatment); Ex-1007, 2; Ex-1006, 3 (Table 2); Ex-1011, 2; Ex-

1026 generally. In my clinical practice prior to November 2018, I routinely used BSA affected as the metric to measure treatment response for both atopic dermatitis and plaque psoriasis, and I still do today.

274. Second, a POSA would have reasonably expected the treatment recited by claim 1 to result in a BSA reduction similar to what Sonti taught for topically treating atopic dermatitis with tapinarof. A POSA at the time knew that anti-inflammatory treatments for atopic dermatitis were also used with and reasonably expected to work for plaque psoriasis, as I explained above with respect to Claims 7 and 21. See my discussion above at ¶¶258-263.

275. In addition, it was already known that the method of claim 1 was highly effective in treating plaque psoriasis. See, for example, my discussion previously at ¶¶190-193, 211-216, and 247. As I explained with respect to claim 1 in Ground 1 above, Sonti teaches that topical application of the 1% tapinarof compositions is effective to treat plaque psoriasis, including once a day application as recited by claim 1. *See also, e.g.*, Ex-1005, [0288], *see also id.*, [0055], [0196], [0285]-[0294], [0301], [0308], [0387]. Sonti also cites two other references that teach topical application of a 1% tapinarof composition once daily is effective to treat plaque psoriasis. Ex-1005, [0010] (citing Ex-1012 and Ex-1013); *see also* Ex-1013, 32:10-66; Ex-1012, 20:28-21:25. Thus, while the specific example Sonti provides at [0272] of treating atopic dermatitis with 1% tapinarof administered the

composition twice daily (“BID”), it was already known that 1% tapinarof administered once daily was highly effective for treating plaque psoriasis.

276. Given these teachings, and viewing the teaching of Sonti as a whole, to a POSA the claimed decrease in BSA affected recited by claims 9-10, following topical administration of a 1% tapinarof composition as recited by claim 1 to treat plaque psoriasis, would have been a reasonably expected and obvious outcome to a POSA.

10. 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”

277. Sonti discloses claims 16 and 18, as I explained above in Ground 1.

278. Even if Sonti did not, in my opinion these claims would have been an obvious result of the treatment of claims 9 and 1.

279. As I explained above, it was known that the method of claim 1 was effective to treat plaque psoriasis, including as measured by PGA score. *E.g.*, Ex-1005, [0288]; Ex-1013, 32:25-62; *see also supra* ¶¶190-193, 211-216, 242. From my clinical experience, I know that for a treatment of plaque psoriasis known to be effective, it was common and expected to see improvement of a symptom after several weeks treatment, such as the recited 2, 4, or 8 weeks.

280. Sonti also teaches this common, known timeline for improvement following treatment. Ex-1005, [0288] (“patient also reaching a PGA score of 0 or 1... at a defined time point, such as at 8, 12 weeks... of treatment [for plaque psoriasis]”); *see also id.*, [290] (time to achieve 50% reduction in PGA score is “8 weeks”); [0294] (time to reach a “PASI 50” score is “at 8 weeks”). It was also common and expected that improvement in plaque psoriasis symptoms could and would be measured as an improvement in PGA score. *E.g.*, Ex-1005, [0288]; Ex-1008, 1, 2; Ex-1026 *generally*; Ex-1016; Ex-1017; Ex-1018. As I explained above, an improvement in PGA score was understood to indicate an improvement in one or more symptoms of plaque psoriasis, as that is how the PGA scale is set up. *See supra* ¶¶168-169.

281. Chen (which Sonti cites at [0010]) also teaches that symptoms of plaque psoriasis were significantly improved after only one week (“seven days”) of treatment with a 1% tapinarof composition, applied topically once daily. Ex-1013, 32:51-63; *see supra* ¶¶103-104. This shows that a POSA would reasonably expect the claimed symptom and PGA score improvement after an even longer time of treatment, such as the 2, 4 or 8 weeks recited by Claims 16 and 18. A POSA would know that if a treatment is effective in improving symptoms after one week, it also will have improved symptoms after 2 weeks (and after 4 and after 8).

282. In addition, measuring improvement at the recited 2, 4, or 8 week

increments was also common for efficacy studies, including one specifically using 1% tapinarof to treat plaque psoriasis. Ex-1008, 2 (patients assessed at 2, 4, 6, 8, and 12 weeks).

283. In view of these teachings, the improvement timeline recited by claims 16 and 18, as well as the improvement in PGA score recited by claim 18, would have been routine and reasonably expected by a POSA.

C. GROUND 3: Dependent Claims 7, 9-10, and 21 Would Have Been Obvious for the Reasons Explained in Grounds 1 or 2, Additionally in View of the Teachings of Bissonnette and the Knowledge of a POSA

284. Dependent claims 7, 10, and 21 each adds a requirement that uses the percent body surface area (“BSA”) metric to assess plaque psoriasis severity or treatment response.

285. By November 2018, using percent BSA affected to assess plaque psoriasis severity and treatment response was well-known. *E.g.*, Ex-1007, 2-3 (providing the “main clinical psoriasis measures” and explaining that the BSA is an “estimation of involved body surface area”); Ex-1006, 3 (Table 2), 7-8 (Table 5, Table 6); Ex-1011, 1-2 (“Because no psoriasis biomarkers are available...clinical measures are used in daily practice...”); Ex-1026 *generally*. As I explained above, before November 2018 I commonly used the BSA metric with my plaque psoriasis patients to assess severity of the plaque psoriasis and also to assess treatment response.

286. Sonti also already teaches using the BSA metric, as I explained above in Ground 2, as part of my discussion of claims 7 and 21, and claim 10.

287. Bissonnette teaches using percent BSA affected both to assess baseline severity and to measure treatment response, for plaque psoriasis specifically. *E.g.*, Ex-1008, 1, 2-3, Tables 1, 3.

288. Specifically, Bissonnette discloses a clinical study of patients who began with a baseline plaque psoriasis diagnosis that included “1-10% body surface area (BSA) covered with plaque psoriasis.” Ex-1008, 1, 2 (defining “study population”):

Study population

To be eligible, patients had to be between 18 and 65 years of age, diagnosed with stable, mild to moderate plaque psoriasis for at least 6 months. Patients had to have between 1% and 10% of body surface area (BSA) covered with psoriasis (excluding the face, groin, scalp and genital regions) and a Physician’s Global Assessment (PGA) of two (mild) to four (severe) at Day 0. Patients were excluded if they had pustular, erythrodermic or other non-plaque forms of psoriasis.

Ex-1008, 1.

289. Bissonnette teaches applying a “1% WBI-1001 in a cream formulation” to the plaque psoriasis, twice daily. Ex-1008, 1. I understand that WBI-1001 is tapinarof. Ex-1032, ¶¶64-67.

290. Bissonnette reported that the average percent BSA affected at week 12

of treatment decreased by 79.1%, compared to a 9.4% *increase* for the placebo group. Ex-1008 1, 2-3, Table 3:

Table 3 Change from baseline in PASI and BSA at each visit

	1% WBI-1001 (N = 40) n (%)	Placebo (N = 21) n (%)	P-value
PASI			
Day 14	-1.9 (-31.9)	-0.8 (-12.4)	0.0010
Day 28	-2.8 (-47.5)	-0.8 (-13.1)	<0.0001
Day 42	-3.6 (-60.7)	-0.8 (-12.7)	<0.0001
Day 56	-3.9 (-65.9)	-0.8 (-12.4)	<0.0001
Day 84	-4.2 (-71.0)	-0.7 (-11.1)	<0.0001
BSA			
Day 14	-0.5 (-16.3)	-0.1 (-2.7)	0.0273
Day 28	-1.3 (-40.8)	0.1 (+2.4)	0.0004
Day 42	-2.1 (-63.4)	0.01 (+0.3)	<0.0001
Day 56	-2.4 (-71.6)	0.3 (+9.4)	<0.0001
Day 84	-2.6 (-79.1)	0.3 (+9.4)	<0.0001

PASI, Psoriasis Area Severity Index; BSA, body surface area.

291. In my opinion, using the known BSA metric as recited by dependent claims 7, 21 and 9-10 would have been obvious in view of the teachings of Sonti, Bissonnette, and the knowledge of a POSA.

- 1. 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%”**

292. As I explained above with respect to Grounds 1 and 2, Sonti discloses (and makes obvious) the elements of claim 1.

293. Sonti further discloses and suggests treating a subject diagnosed with mild to severe/moderate plaque psoriasis, as I explained above in Grounds 1 and 2

with respect to dependent claims 8 and 22, and also with respect to claim element [1.pre].

294. Bissonnette also teaches treating subjects who have been diagnosed with mild to severe and mild to moderate plaque psoriasis, by administering a topical composition of 1.0% tapinarof (though applied twice daily, rather than once daily as claim 1 recites). Ex-1008, 1, 2 (“Study population” consisted of patients having PGA score of “two (mild) to four (severe)”) (“Study population” had patients “diagnosed” with “mild to moderate plaque psoriasis”). A POSA would understand Bissonnette’s disclosure of treating subjects starting with a baseline of plaque psoriasis of between “mild” and “severe” to include treating subjects “diagnosed” with “mild to severe” plaque psoriasis (claim 7) and “mild to moderate” plaque psoriasis (claim 21).

295. For example, Bissonnette’s disclosure of subjects diagnosed with “mild to moderate plaque psoriasis” is a disclosure of a subject diagnosed with “mild to severe” plaque psoriasis as well as a subject diagnosed with “mild to moderate” plaque psoriasis. This is because “mild to moderate” falls within the range of “mild to severe” recited by claim 7.

296. As another example, Bissonnette teaches that patients in the study cohort had all been “diagnosed” with plaque psoriasis, and patients “were excluded” if they had “non-plaque forms of psoriasis.” Ex-1008, 2 (“Study

Population”). Bissonnette additionally discloses that patients at the top end of the study cohort (those with the most severe plaque psoriasis) had a PGA score of “four (severe) at Day 0.” Ex-1008, 2. A POSA would understand this to indicate that at least some patients in the study cohort had been “*diagnosed*” with severe plaque psoriasis, under the PGA severity scale Bissonnette was using.

297. Claims 7 and 21 additionally state that the subject has been diagnosed with plaque psoriasis “*having a percent body surface area (BSA) affected of about 3% to about 20%.*” Bissonnette also discloses this.

298. Bissonnette discloses treating a study cohort of 40 patients who have been “diagnosed” with “plaque psoriasis” and having “between 1% and 10% body surface area (BSA) covered with psoriasis”:

Study population

To be eligible, patients had to be between 18 and 65 years of age, diagnosed with stable, mild to moderate plaque psoriasis for at least 6 months. Patients had to have between 1% and 10% of body surface area (BSA) covered with psoriasis (excluding the face, groin, scalp and genital regions) and a Physician’s Global Assessment (PGA) of two (mild) to four (severe) at Day 0. Patients were excluded if they had pustular, erythrodermic or other non-plaque forms of psoriasis.

Ex-1008, 1; *see also id.* (“A total of 61 patients with 1-10% body surface area (BSA) covered with plaque psoriasis”), 2-3, Table 1. The total number of patients in the study cohort was 61, but 40 of those were treated with the 1% tapinarof cream, while the remaining 20 were given placebo. Ex-1008, 1, 2-3, Table 1.

299. Treating a set of 40 subjects with BSA affected of between 1% and 10% is a disclosure of a subject having a BSA affected of about 3% to 20%, as the study cohort included patients with BSA affected of between about 3% and 10%, which is within the claimed range of “about 3% to about 20%.” Bissonnette also teaches that the mean BSA affected of the 40 study subjects receiving the treatment was 3.3%, placing the mean BSA also within the claimed range of “about 3% to about 20%.” *See* Ex-1008, Table 1.

300. In my opinion, a POSA would have been motivated to perform the method of claim 1 on a subject diagnosed with mild to moderate and mild to severe plaque psoriasis having a BSA in the claimed range, with a reasonable expectation of success, in view of the teachings of Sonti, Bissonnette and the knowledge of a POSA. Sonti and Bissonnette are in exactly the same field of art. Even more than that, each reference specifically teaches topically treating the same condition (plaque psoriasis) with the same active ingredient at the same strength (1% tapinarof composition that is topically applied). *Compare* Ex-1005, Abstract, [0008], [0288], [0196], [0055] *with* Ex-1008, 1 (Abstract), 2-5; *see also supra* ¶¶78-82, 109-124 (Sonti) and ¶¶88-91, 288-289, 294-296 (Bissonnette). In view of these teachings, a POSA would have been motivated, with a reasonable expectation of success, to perform the method of claim 1 with a subject diagnosed with mild to moderate and mild to severe plaque psoriasis having a BSA affected in the range of

about 3% to 20%, as suggested by Bissonnette.

301. A POSA also would have been motivated, with a reasonable expectation of success, to perform the method of claim 1 on a subject diagnosed with a BSA affected in the claimed range for other reasons.

302. **One**, the BSA metric was a common assessment tool for plaque psoriasis, known to be useful in assessing both baseline severity and treatment response. For example, Ex-1011 explains that “[b]ecause no psoriasis biomarkers are available to assess disease severity, clinical measures [such as BSA] are used in daily practice and in research to measure both severity and treatment response.” *See also id.*, 2 (identifying the BSA metric as a “commonly incorporated” clinical measure); Ex-1006, 7 and Table 5. It was also very common to treat patients having a BSA affected at baseline that was within the claimed “about 3% to about 20%” BSA range. *E.g.*, Ex-1008, 1 (clinical study of treatment for patients diagnosed with plaque psoriasis affecting a BSA of 1-10%); Ex-1011 at 2 (“BSA involvement greater than 10% or a PASI score greater than 12 is frequently used as a criterion for severe disease”); Ex-1026, 200 (“subject has involved BSA $\geq$ 10%... at baseline”), 186 (same), 293 (same), 304, 342, 485 (study treating subjects who “[a]t Baseline, have plaque psoriasis covering 2% to 20% of total body surface area (BSA)”), 631 (“involvement of 10-15% of their BSA”), 1326 (“Coverage of the body surface area (BSA) of 10% or more with plaques”). In my clinical

practice, I frequently used the BSA metric to assess plaque psoriasis severity at baseline, and I frequently treated patients having a percent BSA affected within the claimed “about 3% to about 20%” range. This is true of my practice both prior to November 2018 and today.

303. In view of this, performing the method of treating plaque psoriasis recited by claim 1 on a subject diagnosed with plaque psoriasis as claimed and having a BSA affected within the claimed “about 3% to about 20%”, as suggested by Bissonnette, would have been common sense to a POSA. It would have been just using a known method to treat plaque psoriasis patients who had a percent BSA affected within a range commonly treated.

304. **Two**, as I explained above in Ground 2 with respect to claims 7 and 21, Sonti already teaches treating a subject having BSA affected within the claimed range (about 3% to about 20%). Sonti teaches this generally and also with respect to atopic dermatitis specifically. *See supra* ¶¶250-251, 258-263; *see also* Ex-1005, [0267]-[0268], [0272], [0280]. This teaching would have motivated a POSA to also apply the tapinarof compositions to plaque psoriasis patients having a BSA affected in the same range, and a POSA would have expected it to work. As I also explained above, in my field it was understood that plaque psoriasis and atopic dermatitis were both inflammatory skin diseases, and topical anti-inflammatory treatments for one disease were used and expected to work for the other disease.

See supra ¶¶258-263.

305. **Three**, as I explained above in Grounds 1 and 2, a POSA already knew that the method of claim 1 was effective to treat plaque psoriasis. *E.g.*, Ex-1005, [0285]-[0295], [0055], [0196], [0387]; Ex-1013 (one of the Chen references), 32:25-62 (teaching that 1% tapinarof composition applied once daily to skin affected by plaque psoriasis showed “great efficacy” on the volunteers treated); *see also* Ex-1005, [0010] (citing the Chen references (Ex-1012, Ex-1013) that show efficacy of 1% tapinaorf composition applied topically to plaque psoriasis once daily). Given this knowledge, there was a good reason to apply the method of claim 1 to subjects diagnosed with plaque psoriasis having a percent BSA affected within the common, known range recited by claims 7 and 21, and also good reason to expect the treatment to be successful.

306. For any one (or more) of these reasons, performing the method of claim 1 with a subject diagnosed with plaque psoriasis as claimed and having a BSA affected recited by claims 7 and 21 would have been a predictable, common-sense application of what Sonti already teaches.

**2. Dependent Claim 9 (stated above) and 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”**

307. As I explained above with respect to Grounds 1 and 2, Sonti discloses (and makes obvious) the elements of claim 1 and 9, and also makes claim 10

obvious.

308. In my opinion, claims 9 and 10 also would have been an obvious extension of claim 1 in view of the teachings of Sonti and Bissonnette along with the knowledge of a POSA.

309. Bissonnette teaches the improvement in percent BSA affected that is recited by claims 9 and 10, following treatment of plaque psoriasis with a topical composition containing 1% tapinarof that was applied twice daily. Bissonnette reports a study of 61 patients having 1–10% BSA covered with plaque psoriasis at the inception of the study. Ex-1008, 1, 2. Forty of the study participants applied a topical composition of 1% tapinarof to affected areas twice daily for 12 weeks. Ex-1008, 1. Following twelve weeks of treatment, the BSA affected by plaque psoriasis for those subjects had decreased an average of 79.1%. Ex-1008, 3-4, Tables 1, 3. The study showed a change in mean body surface area (BSA) affected of “-2.6%” following treatment. Ex-1008, Table 3. Bissonnette teaches that the mean BSA at baseline (at the study start) was 3.3% (Ex-1008, Table 1), so a mean decrease of 2.6% means that the **mean BSA decreased to 0.7% following the treatment** ($3.3\% - 2.6\% = 0.7\%$). Bissonnette’s Table 1 and Table 2 are shown below:

Table 1 Demographics and baseline values of efficacy assessments

Characteristic	1% WBI-1001 (N = 40)	placebo (N = 21)	All (N = 61)
Age mean ± SD	50.4 ± 8.8	51.1 ± 13.0	50.6 ± 10.3
Male N (%)	33 (82.5)	18 (85.7)	51 (83.6)
Mean PGA ± SD	3.2 ± 0.6	3.4 ± 0.5	3.3 ± 0.6
Mean PASI ± SD	5.9 ± 2.7	6.2 ± 2.0	6 ± 2.5
Mean BSA ± SD	3.3 ± 2.1	3 ± 1.6	3.2 ± 2.0

BSA, body surface area; PASI, Psoriasis Area and Severity Index; PGA, physician's global assessment.

Table 3 Change from baseline in PASI and BSA at each visit

	1% WBI-1001 (N = 40) n (%)	Placebo (N = 21) n (%)	P-value
PASI			
Day 14	-1.9 (-31.9)	-0.8 (-12.4)	0.0010
Day 28	-2.8 (-47.5)	-0.8 (-13.1)	<0.0001
Day 42	-3.6 (-60.7)	-0.8 (-12.7)	<0.0001
Day 56	-3.9 (-65.9)	-0.8 (-12.4)	<0.0001
Day 84	-4.2 (-71.0)	-0.7 (-11.1)	<0.0001
BSA			
Day 14	-0.5 (-16.3)	-0.1 (-2.7)	0.0273
Day 28	-1.3 (-40.8)	0.1 (+2.4)	0.0004
Day 42	-2.1 (-63.4)	0.01 (+0.3)	<0.0001
Day 56	-2.4 (-71.6)	0.3 (+9.4)	<0.0001
Day 84	-2.6 (-79.1)	0.3 (+9.4)	<0.0001

PASI, Psoriasis Area Severity Index; BSA, body surface area.

310. The nearly 80% decrease in BSA affected that Bissonnette discloses following topical treatment with the 1% tapinarof composition discloses “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. A POSA would understand such a significant decrease in BSA affected to indicate “improvement” of one or more symptoms of plaque psoriasis. Such symptoms included plaques on the skin that had been reduced or eliminated by the treatment.

311. Bissonnette’s disclosure that the average BSA affected decreased to 0.7% following treatment also discloses that the BSA affected “*is decreased to less than 20% after topically administering the topical composition,*” which is the BSA metric recited by claim 10. A BSA that has decreased to 0.7% is a BSA that has decreased to “less than 20%,” as 0.7% is (far) less than 20%.

312. A BSA affected that has decreased to less than 20% would have been a predictable, common-sense, and expected result following application of the treatment method of claim 1 to a subject diagnosed with plaque psoriasis, in view of the teachings of Sonti, Bissonnette, and the knowledge in the art. This is true for several reasons.

313. **One**, decrease in BSA affected was a common measure of efficacy for plaque psoriasis treatment. *E.g.*, Ex-1008, 1, 2; Ex-1007, 2; Ex-1006, 3(Table 2); Ex-1011, 2. See also my discussion of the widespread use of percent BSA affected as a clinical metric in the studies I discuss with respect to Ex-1026. *See supra* ¶¶51, 45. It was known that “because no psoriasis biomarkers are available to

assess disease severity clinical measures [such as BSA] are used in daily practice and in research to measure...treatment response.” Ex-1011, 1. Consistent with this, I commonly used decrease in percent BSA affected as a metric for plaque psoriasis treatment response in my clinical practice, both before and after November 2018. A POSA would have been motivated to use this common, known metric for assessing plaque psoriasis treatment response.

314. **Two**, though the Bissonnette study applied the 1% tapinarof cream twice daily rather than the once daily recited by claim 1, it was also already known in the art that treatment of mild to severe plaque psoriasis with a 1% tapinarof composition applied *once* daily was highly effective. *E.g.*, Ex-1005 [0387], [0288], [0055], [0196]; Ex-1005, [0010] (citing Ex-1012 and Ex-1013, the “Chen” references); *see also* Ex-1013, 2:56-3:4 and 32:10-66; Ex-1012, 20:28-21:25; *see also supra* ¶¶190-193, 211-216, 242. Chen, for example, taught that the once-daily treatment resulted in “complete[] clearance” of the plaque psoriasis in one of the volunteers and “significant improvement” in the other. Ex-1013, 32:53-62. A POSA would have considered this an impressive result, as Volunteer 1 had suffered from scalp psoriasis for more than 15 years and had unsuccessfully tried many other treatments, and Volunteer 2 had also unsuccessfully tried other treatment. Ex-1013, 32:30-37. In the case of Volunteer 1, a POSA would have understood the “complete clearance” observed to indicate that the percent BSA affected had

decreased to 0%, following treatment.

315. Given that it was already known that once daily treatment was highly effective (including to reduce a percent BSA affected to zero), a POSA would have reasonably expected the method of claim 1 (the once daily application) to result in a percent BSA affected improvement similar to that taught in Bissonnette and recited by claims 9 and 10.

316. **Three**, as I explained above in Ground 2 with respect to Claim 10, Sonti itself already teaches the specific reduction in BSA affected recited by claims 9-10, in the context of treatment of the closely related inflammatory skin disorder atopic dermatitis. *See supra* ¶275. Topical anti-inflammatory treatments for atopic dermatitis were also often applied topically to treat plaque psoriasis, and were reasonably expected to work, for the reasons I explained with respect to claims 7, 21 in Ground 2. Ex-1003, ¶¶258-263 (topical anti-inflammatory treatment for atopic dermatitis (such as tapinarof) expected to work for plaque psoriasis because atopic dermatitis and plaque psoriasis were known as inflammatory skin diseases). In view of this, a POSA would be motivated to apply teaching of effective anti-inflammatory treatments for atopic dermatitis to plaque psoriasis and would have reasonably expected the treatment to be successful.

317. For any of these reasons, it is my opinion that a POSA would have been motivated to use the BSA metric as a measure of treatment response and

would have reasonably expected the improvement in percent BSA affected in the range recited by claims 9 and 10.

318. In my opinion, it also would have been obvious to try administering the 1% tapinarof composition once daily (as recited by claim 1) rather than twice daily, with the improvement in percent BSA affected following treatment that is stated by claims 9 and 10. As I have previously explained, there was a known need for effective, safe topical plaque psoriasis treatments. *E.g.*, Ex-1008, 1; Ex-1013, 2:31-33, 2:56, 32:11-15, 32:30-37. There were also only a finite number of known options for treating plaque psoriasis with topical tapinarof that were known to be effective—including once daily or twice daily application of 1% tapinarof. *E.g.*, Ex-1013, 32:41-65 (disclosing effectively treating with once daily application); Ex-1008, 1 (Abstract) (disclosing twice daily); Ex-1005, Abstract, [0288]-[293], [0387], [0196], [301] (effectively treating plaque psoriasis, including with once-daily application of 1% tapinarof cream); *see also supra* ¶¶190-193, 211-216, 242. There were also only a finite number of known options for measuring treatment response (including the BSA, PGA, and PASI metrics). *E.g.*, Ex-1005, Abstract, [0287]-[293] (disclosing using PGA and PASI to measure plaque psoriasis treatment response); Ex-1008, 1 (Abstract) (disclosing using BSA and PGA metrics to assess treatment response). In view of these teachings, a POSA would have been motivated to try the method of claim 1 using the BSA metric to measure

treatment response, and a POSA also would have reasonably expected the percent BSA affected to decrease “*to less than 20%*” after administering the 1% tapinarof, as recited by claim 10.

D. GROUND 4: Claims 1-4, 6-10, 16, 18, and 21-22 Would Have Been Obvious in View of Bissonnette, and the teachings of Sonti and/or Chen, along with the Knowledge of a POSA

319. Based on my review of the '088 patent, its claims and prosecution history and the Bissonnette reference (Ex-1008), Bissonnette discloses nearly every element of claims 1-4, 6-10, 16, 18, and 21-22, except the “once a day” application frequency. Sonti and Chen each disclose the once a day application frequency.

320. In my opinion, a POSA would have been motivated to combine the teachings of Bissonnette with the teachings of Sonti and/or Chen, with a reasonable expectation of success. This is because each of Bissonnette, Sonti and Chen were not only in the same field of art, they each also taught application of the *same* active ingredient (tapinarof) at the *same* strength (1%) to treat the *same* condition (plaque psoriasis). *Compare* Ex-1008, 1 (Abstract), 2-5 *with* Ex-1005, Abstract, [0008], [0288], [0196], [0055] *and* Ex-1013, 31:10-63; *see also supra* ¶¶88-91, 288-289, 294-296 (Bissonnette), ¶¶78-82, 109-124 (Sonti) and ¶¶95-102 (Chen). Sonti and Chen also each taught that a once-daily administration was highly effective, further showing that a POSA would have had a reasonable expectation of

success in combining the teachings. *E.g.*, Ex-1005, [0285]-[295] (for example, reduction in PGA scores of greater than or equal to 4 at baseline to 0 or 1 (clear or almost clear) after treatment); Ex-1013, 32:10-63 (treatment showed “great efficacy” in comparison with untreated areas, including “complete[] clearance” for Volunteer 1), 2:56-3:4 (“The compounds of the invention possess specific activity against psoriasis”). Also, as I explain in more detail below, by November 2018 there would have been strong reasons to decrease the frequency of application from two times to once daily, such as: to reduce the body’s systemic exposure to the active compound (thus lowering risk of side effects), improve patient compliance with treatment recommendations, and reduce cost of treatment.

321. Because there was a good reason (in fact, multiple good reasons) to combine the teachings of Bissonnette with those of Sonti and/or Chen, and a reasonable expectation of success in doing so, it is my opinion that claims 1-4, 6-10, 16, 18, and 21-22 would have been obvious to a POSA by November 2018.

1. Independent Claim 1

322. Based on my review of Bissonnette, Bissonnette discloses each of the elements of claim 1, except the “once a day” application frequency. However, each of Sonti and Chen taught a once daily application frequency, using the 1% strength tapinarof composition, and each of Sonti and Chen also disclosed that treatment regimen was effective.

323. A POSA would have had good reason to look to combine Bissonnette with the teachings of Sonti and/or Chen, with a reasonable expectation of success, as I explain in more detail below. Each of Sonti and Chen taught topical application of the same active ingredient (tapinarof) as Bissonnette, applied at the same strength (1%) as Bissonnette, and that the treatment was effective to treat the same condition (plaque psoriasis), again just like Bissonnette. Also, at the time of purported invention there would have been strong motivation and market pressure to decrease the frequency of application from two times to once daily, including to reduce the body's exposure to the active compound, to improve patient compliance with treatment recommendations, and to reduce cost.

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

324. Bissonnette discloses this element. Bissonnette discloses a clinical study of 61 patients, each 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, 1, 2. With this teaching, Bissonnette discloses treating “*mild to severe plaque psoriasis*” as claimed, as the subjects had between “mild” and “severe” plaque psoriasis as measured by PGA score on Day 0. *Id.*

325. Bissonnette also discloses “treatment of mild to moderate psoriasis,” where the study concerned patients diagnosed with “plaque psoriasis.” Ex-1008, 5;

see also id., 1. This disclosure of a method of treating “mild to moderate” plaque psoriasis” is a disclosure of a method of treating “mild to severe plaque psoriasis,” as “mild to moderate” plaque psoriasis is within the claimed range.

b. [1.a] “comprising topically administering a topical composition containing about 1.0% tapinarof”

326. Bissonnette discloses this element. Forty of the study participants received a topical composition containing 1% “WBI-1001” to areas of the skin affected by plaque psoriasis. Ex-1008, 1, 2 (“1% WBI-1001 in a cream formulation”). WBI-1001 is tapinarof. Ex-1032, ¶¶64-67; Ex-1019, 22; Ex-1001, 7:10-20. As I explained above, a POSA would have understood Bissonnette’s descriptions of a “1% WBI-1001 cream” to refer to a composition containing 1% tapinarof by weight. Ex-1032, ¶79; *see also* Ex-1008, 1, 2, 4. Also, I understand that providing the tapinarof in an amount equal to 1% by weight of the composition would have been the expected, common-sense thing to do. Ex-1032, ¶¶74-75, 80.

c. [1.b] “to affected areas of the subject”

327. Bissonnette discloses this element. The forty test subjects receiving the 1% tapinarof cream “appl[ied]” the cream to the areas of skin affected by the plaque psoriasis. Ex-1008, 1, 2. Also, a POSA would understand that a “phase II trial” of human subjects to “evaluate the safety and efficacy of topical WBI-1001 at 1% in a cream formulation” necessarily involves applying the cream to the affected

areas of the subject. Ex-1008, 2.

d. [1.c] “once a day”

328. This is the only element of Claim 1 that Bissonnette does not disclose. Bissonnette states that the 1% tapinarof cream was applied “twice daily.” Ex-1008, 1. However, each of Sonti and Chen teaches this element.

329. Sonti teaches administering the tapinarof compositions (including the 1% tapinarof compositions) with a “once daily” application frequency to treat plaque psoriasis, for the reasons I explained in Grounds 1 and 2 above with respect to elements [1.pre], [1.a], and [1.c]. *See supra* ¶¶109-116 (treating plaque psoriasis), 118-124 (1% tapinarof), 128-132 (once daily), 186-202; Ex-1005, [0387].

330. Chen also teaches topically administering a “1%” tapinarof composition (a cream) with a “**once per day**” frequency:

25 A 1% cream of 3,5-dihydroxy-4-isopropylstilbene was prepared for tests on volunteers. Three volunteers, each with a long psoriasis history, were recruited for the tests. Neither of them was on any medication a month before the initiation of the test.

30 Volunteer 1, Male, 48 years old with scalp psoriasis for more than 15 years. He had used various conventional drugs and treatments, include, steroids, phototherapy and other medicine during the course of his illness. All of these treatments had no or very limited effect on this psoriasis.

35 Volunteer 2, Female, 24 years old with plaques on her back. She had used hydrocortisone before and stopped using it because of side effects.

Volunteer 3, Male, 35 years old, had an unspecific type of eczema with 3,000 cm² affected area on the trunk and
40 extremities.

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
45 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
50 treated until no more could be rubbed in.

Ex-1013, 32:25-50. Chen explains that the cream used was a “1% cream of 3,5-dihydroxy-4-isopropylstilbene.” Ex-1013, 32:25-27. I understand that “3,5-dihydroxy-4-isopropylstilbene” is tapinarof. Ex-1032, ¶¶53, 68-70; *see also* Ex-1001, 7:4-20. I also understand that even if Chen did not specifically disclose that the 1% tapinarof cream was 1% tapinarof “by weight”, that would have been the obvious, common way to measure the strength of the tapinarof in a cream like that Chen refers to. Ex-1032, ¶80.

331. Chen also teaches topically administering the 1% tapinarof cream “once per day” to treat *plaque* psoriasis specifically. A POSA would understand

that Volunteers 1 and 2 described in Chen had *plaque* psoriasis, as I explained above. *See supra* ¶¶99-101, 191-192; *see also* Ex-1013, 2:56-3:4 and 32:25-37. And even if not, as I explained above in paragraph 192, a POSA would have still been motivated to use the method of treating psoriasis disclosed by Chen (1% tapinarof cream, topically applied once daily) to treat plaque psoriasis specifically, with a reasonable expectation of success, given that the treatment was shown to be so successful in treating the scalp psoriasis and “plaques” on the volunteers Chen discusses.

332. In my opinion, a POSA would have been motivated, with a reasonable expectation of success, to treat plaque psoriasis patients with a 1% tapinarof composition as taught by Bissonnette, using a once-daily application as taught by Sonti and/or Chen, for any one (or more) of the reasons I identify below.

333. **One**, Bissonnette, Sonti, and Chen are all directed to the same technological subject matter. In fact, each reference discloses treating the same skin condition (plaque psoriasis) with the very same composition (a topical 1% tapinarof cream). *E.g.*, Ex-1008, Abstract, 1-2 and *supra* ¶¶88-92 (Bissonnette); Ex-1005, [0285]-[295], [0055], [0196], [0387] and *supra* ¶¶77-83 (Sonti); Ex-1013, 32:10-63 and *supra* ¶¶95-102, (Chen). Because of the almost completely overlapping teachings, a POSA would be motivated to look to the teachings of Sonti and Chen and expect to be able to combine them with the teachings of

Bissonnette with a reasonable expectation of success.

334. **Two**, a POSA would have known that if treatment could be administered less frequently and remain effective (as Sonti and Chen taught), there would have been a strong motivation to use the less frequent application option. This is because doing so would have been expected to minimize risk of side effects. I explained this above with respect to [1.c] in Ground 2. In particular, a reduced application frequency (such as from the twice daily application disclosed by Bissonnette to the once daily application disclosed by Sonti and Chen) would have been expected to reduce the body's systemic exposure to the active ingredient in a pharmaceutical. A POSA would have been motivated to do this. This is because most pharmaceuticals were known to carry with them a risk of adverse side effects. And it was known that decreasing the body's systemic exposure to such pharmaceuticals would predictably lower the risk for those adverse events. *See also* Ex-1032, ¶¶81-85. (This was also common-sense). So if it was known that a treatment could be administered less frequently but still be effective, there would have been a good reason to use the lower application frequency.

335. This is confirmed by the literature. Bissonnette teaches that there were some adverse events observed when treating patients twice daily with a 1% tapinarof topical composition (and that those adverse events were significantly higher than what was observed in the placebo group). Ex-1008, 1, 4; *see also id.*,

Table 4 (80% of the patients treated twice-daily with 1% tapinarof cream twice daily had at least one adverse event, compared with only 52% of placebo patients). Though most of the adverse events were “mild” in severity, a POSA still would have been motivated to minimize the risk of a patient having these side effects. And a known way of doing that was to reduce the body’s systemic exposure to the active ingredient, by reducing the application frequency.

336. Sonti teaches that it was desirable to use a lower dosing frequency: “the dosing frequency to the affected area(s) may now be dosed less frequently than previously envisioned.” Ex-1005, [0387]. Sonti also explains (in the same paragraph) that an embodiment of the invention is the use of a formulation such as described in Sonti that “can provide lower systemic exposure of the active ingredient to the patient during use.” *Id.* Thus Sonti states what was common knowledge to a POSA—that there were good reasons to provide a lower systemic exposure of the active ingredient, when it was possible to do so, by dosing “less frequently.”

337. **Three**, in my field there was also a general motivation to use a lower application frequency to improve patient compliance. Patients were (and still are) generally more likely to follow treatment recommendation correctly when the application frequency is once a day, rather than twice a day. This is due to both common sense and human nature. If the treatment recommendation is ‘apply the

topical composition to the plaque psoriasis once daily,” instead of twice daily, that is generally easier for the patient to remember and more practical and convenient to do. And that means that the patient is more likely to follow the treatment recommendation, which predictably leads to better overall outcomes for the treatment. It has also been my experience that a lower application frequency (for example once a day instead of twice a day) also improves patient satisfaction and quality of life, as the lower application frequency is less intrusive and burdensome for the patient. *See also* Ex-1032, ¶87.

338. **Four**, a POSA also would have expected a reduced application frequency (twice daily to once daily) to reduce treatment cost. A POSA was always motivated to lower cost, if it could be done while still maintaining treatment safety and efficacy. As a matter of common sense less frequent application uses less volume of the topical composition, and going from twice daily to once daily would be expected to reduce usage by about 50%. That would have been expected to significantly reduce the cost of treatment, which as a matter of common sense would have been a desirable thing. Ex-1032, ¶86. I also know from my personal experience if I can reduce the amount of cream a patient needs to use, such as by prescribing a once-daily application instead of twice-daily, that would have been expected to help the patient ultimately save money. The patient would be expected to need significantly less of the cream over the course of the

treatment.

339. Any one of these known benefits would have motivated a POSA to look to the teachings of Sonti and/or Chen, and to apply the method of treating plaque psoriasis taught by Bissonnette using a once-daily application rather than twice daily.

340. **Lastly**, a POSA such as myself would have reasonably expected the once-daily application of 1% tapinarof to be successful. This is because Sonti and Chen *already taught* that a 1% tapinarof cream was effective to treat plaque psoriasis when applied once daily, rather than twice daily.

341. Sonti teaches that once daily application of a 1% tapinarof composition is effective to treat plaque psoriasis, for the reasons I explained above in Grounds 1 and 2, for Claim 1. *See supra* ¶¶108-146, 178-221. As I previously explained, Sonti teaches that “using a topical emulsion as described herein” resulted in the patient reaching a PGA score of 0 or 1 after a defined time-period of treatment (Ex-1005, [0288]). *See also* Ex-1005, [0285]-[0295]. Sonti also explained that “a composition of the present invention may be applied...once daily” and that in “all of the compositions described [by Sonti],” the amount of tapinarof present may be “1%”. Ex-1005, [0387], [0196].

342. Chen also teaches that application of a 1% tapinarof composition once a day was effective to treat plaque psoriasis. Chen specifically discloses that

treatment of plaque psoriasis with 1% tapinarof composition applied once daily “showed great efficacy” and resulted in “complete[] clearance” for one subject and “significant improvement” for the other:

25 A 1% cream of 3,5-dihydroxy-4-isopropylstilbene was prepared for tests on volunteers. Three volunteers, each with a long psoriasis history, were recruited for the tests. Neither of them was on any medication a month before the initiation of the test.

30 Volunteer 1, Male, 48 years old with scalp psoriasis for more than 15 years. He had used various conventional drugs and treatments, include, steroids, phototherapy and other medicine during the course of his illness. All of these treatments had no or very limited effect on this psoriasis.

35 Volunteer 2, Female, 24 years old with plaques on her back. She had used hydrocortisone before and stopped using it because of side effects.

Volunteer 3, Male, 35 years old, had an unspecific type of eczema with 3,000 cm² affected area on the trunk and
40 extremities.

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
45 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
50 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
55 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 clear-
60 ance 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, 32:10-62; *see also id.* Abstract, 3:3-4, Claim 1. As I explained above, a POSA would understand Chen’s descriptions of Volunteer 1 and Volunteer 2 to be describing *plaque* psoriasis specifically. *See supra* ¶¶99-101.

343. For Volunteer 1, for example, Chen explained that the volunteer had suffered from “scalp psoriasis for more than 15 years” and had “used various conventional drugs and treatments...during the course of his illness” and “[a]ll of these treatments had no or very limited effect on this psoriasis.” Ex-1013, 32:30-34. Chen explains that following application of the “inventive compound” (the 1% tapinarof cream) once daily, there was “complete clearance in 7 days” for the areas of skin that were treated, while “[n]o change occurred in the condition of the area treated with the control cream.” Ex-1013, 32:30-34, 32:51-58.

344. In the case of Volunteer 2, Chen explains that the volunteer suffered from “plaques on her back” and had tried using hydrocortisone to treat them but stopped because of side effects. Ex-1013, 32:35-37. After treatment with the 1% tapinarof cream, Volunteer 2 saw a “visible improvement in inflammation and in clearance of the proliferative cells three days after treatment and a significant improvement of the psoriasis...within seven days of treatment.” Ex-1013, 32:58-62. A POSA would have viewed this as significant and impressive efficacy for the 1% tapinarof cream, applied once daily.

345. In addition, as I explained above, even if the Chen references did not expressly teach treating *plaque* psoriasis (they do), a POSA would still be motivated by Chen’s teachings to treat *plaque* psoriasis specifically and to reasonably expect it to work. Chen expressly teaches the “once per day” method

of treatment was highly effective for treating “plaques” on Volunteer 2’s back, so a POSA would expect it to work on plaque psoriasis. Ex-1013, 32:35-63. Also, the treatment was highly effective in treating Volunteer 1’s scalp psoriasis (it resulted in “complete[] clearance”), which I explained above would have almost certainly been understood to be plaque psoriasis. Ex-1013, 32:30-63; *see also id.* 2:54-3:4 (Chen’s description of “psoriasis” is actually describing *plaque* psoriasis specifically—discussing “psoriasis” as characterized by “skin lesions covered with **silvery white scaling patches** and raised, inflamed, thickened, and **scaly lesions**”). In any event, that teaching would have motivated a POSA to use the method of treating on *plaque* psoriasis (which very commonly manifests on the scalp) and to expect it to work, just like it worked for Volunteer 1’s scalp psoriasis.

346. In view of the teachings in either Sonti or Chen, a POSA would reasonably expect that applying a tapinarof composition with the claimed strength (1% tapinarof) and application frequency (once daily) would be successful.

347. It is also my opinion that applying the method of treatment taught by Bissonnette, but with a once daily application of the tapinarof composition rather than twice daily, would have been an obvious thing to try. There was market pressure for safe and effective plaque psoriasis treatments. *See* Ex-1008, 1 (Abstract) (“There is a need for the development of novel non-steroidal topical drugs for the treatment of psoriasis”); Ex-1013, 2:31-33, 2:56 (“Inflammatory

diseases, whether of a chronic or acute nature, represent a substantial problem in the healthcare industry...Psoriasis is a common, chronic inflammatory skin disease”), 32:35-37 (Volunteer 2 had stopped using a plaque psoriasis treatment “because of side effects”); *see also* Ex-1026, Ex-1016, Ex-1017, Ex-1018 (describing various clinical studies focused on testing treatments for plaque psoriasis). There was also a known need for treatment regimens that required less-frequent applications, as I explained above. *See supra*, ¶¶334-339. Such less-frequent treatment regimens were known to reduce risk of side effects, improve patient compliance with treatment recommendations, and to decrease cost of treatment. *Id.*

348. Applying a 1% tapinarof composition once daily to treat plaque psoriasis was also one of a finite number of options for treating plaque psoriasis that were known to be effective. For example, *see* Chen (Ex-1013, 32:41-65 (volunteers with plaque psoriasis “were treated once per day by applying the creams once per day on top of the affected area,” which showed “great efficacy”)) and Sonti (Ex-1005, [0387] (disclosing treating plaque psoriasis and atopic dermatitis with tapinarof compositions that could be applied “twice daily, once daily, once every other day; twice weekly; three times weekly, or once weekly”)). And, as I explained above, it was already known that the once-daily application of 1% tapinarof was effective to treat plaque psoriasis. *See, e.g.* Ex-1005, 1, [0288]-

[293], [0387], [0196], [301]; Ex-1013, Abstract, 2:56-3:4, 32:10-65, Claim 1; *see also supra* ¶¶190-193, 211-216, 242.

349. In view of these teachings, a POSA would have been motivated to try the method of claim 1 with a once daily application rather than the twice daily application of Bissonnette, and also would have expected it to work.

e. [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.”

350. Bissonnette discloses this element. Bissonnette teaches that each of the 40 patients treated with the 1% tapinarof composition started the trial with a plaque psoriasis physician’s global assessment score (PGA) of “two (mild) to four (severe).” Ex-1008, 1, 2. After the 12 weeks, 67.5% of the treated patients “achieved a PGA score of clear (0) or almost clear (1).” Ex-1008, p.3 and 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.

With this teaching, Bissonnette discloses that a PGA score “*has improved to a score of 0 or 1*” after topically administering the topical composition, as recited by

element [1.d].

351. Bissonnette also indicates to a POSA that the PGA score was improved by at least “2 grades” for at least one patient. This is the alternative PGA score improvement recited by element [1.d]. The mean PGA score for the 40 subjects treated with tapinarof at the start of the study was 3.2. Ex-1008, Table 1. Following twelve weeks of treatment, the mean change from baseline PGA score was negative ~62.5%. Ex-1008, 4 (“mean change from baseline in PGA at Day 84 for the ITT and the PP population (Fig. 2) was -62.5% and -62.8%...”). This means that the mean PGA score had decreased by had decreased by exactly 2 grades ($3.2 \times 0.625 = 2$). This is also what Figure 2 of Bissonnette shows:

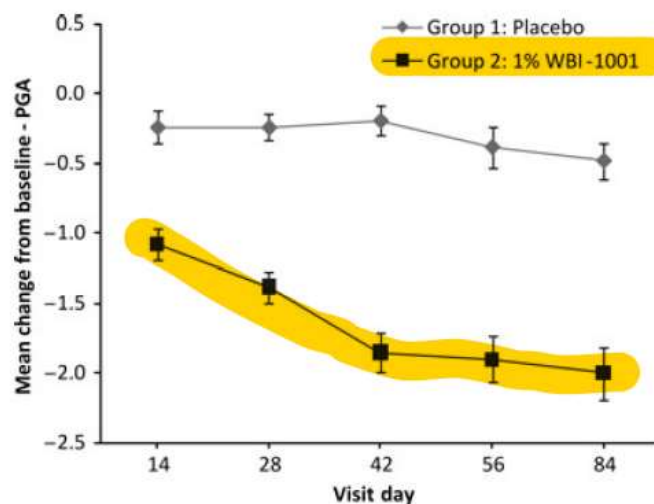


Figure 2 Change from baseline in PGA at each visit; ITT population (mean ± SEM).

352. As I stated above with respect to this element [1.d] in Ground 1, I do not see that Claim 1 specifies a particular PGA scale to use. Also, in the “0 to 5” point PGA scale used by Bissonnette, scores of 0 and 1 had the same meaning as

every other PGA scale. 0 meant “clear” and 1 “almost clear.” Ex-1008, 3 (following treatment 67.5% of patients “achieved a PGA score of clear (0) or almost clear (1)”).

353. Sonti similarly teaches and makes obvious the claimed PGA score improvement following topical application of tapinarof compositions as recited by claim 1, including for a once-daily application of 1% tapinarof. For example, see Ex-1005, [0288] (“patient also reaching a PGA score of 0 or 1”). I explained this above in Grounds 1 and 2, with respect to element [1.d].

354. Chen (which Sonti cites, Ex-1005, [0010]) also discloses the claimed PGA score improvement, following a once-daily topical application of a 1% tapinarof to areas affected by plaque psoriasis. Chen teaches that the once daily treatment “showed great efficacy.” Ex-1013, 32:51-65. Volunteer 1 achieved “complete[] clearance” following treatment and Volunteer 2 showed “significant improvement” of the plaque psoriasis. *Id.* Chen also disclosed that “No change occurred in the condition of the area treated with the control cream” for Volunteer 1. *Id.*, 32:57-58.

355. A POSA would understand the “complete clearance” following treatment for Volunteer 1 that was disclosed by Chen means that a PGA score has improved to 0 (as claimed) after topically administering the 1% tapinarof composition once daily to affected areas. *See, e.g.*, Ex-1001, 22:30 (PGA “[s]core

of 0 represents clear skin”); Ex-1005, [0288] (equating PGA score of 0 with “clear”); Ex-1008, 2 (“clear” is a PGA score of 0); Ex-1007 at 938 (equating the start of the PGA scale (0) with “clear”); Ex-1026, 6 (in the PGA scale “0 = clear”), 119 (same); Ex-1010, 2.

356. In addition, Chen explains that Volunteer 1 had suffered from “scalp psoriasis for more than 15 years” and had “used various conventional drugs and treatments...during the course of his illness” and “[a]ll of these treatments had no or very limited effect on this psoriasis.” Ex-1013, 32:30-34. This indicates to a POSA that prior to the treatment with the 1% tapinarof cream, Volunteer 1 was suffering from a significant plaque psoriasis affliction. Otherwise, Volunteer 1 would not have tried all of those treatments over the course of 15 years. It also indicates to a POSA that, prior to treatment, Volunteer 1 was necessarily suffering from plaque psoriasis with a score of greater than 0 (and almost certainly greater than 1), as the description indicates Volunteer 1 had suffered from significant psoriasis symptoms for an extended period of time that had affected his life significantly enough to try many different treatments. In my experience, a patient does not try multiple treatments over a 15-year period unless the plaque psoriasis symptoms are significant.

357. A POSA would also understand the “significant improvement” for Volunteer 2 taught by Chen includes improvement by at least two PGA grades. *See*

Ex-1013, 32:51-65. A PGA improvement of only 1 grade would not generally be considered to be a “significant improvement” by a POSA. This is reinforced by Chen, which differentiates between the “visible improvement in inflammation and in clearance of the proliferative cells three days after treatment” of Volunteer 2, and the “significant improvement of the psoriasis” (meaning substantially more improvement) that was observed within seven days of treatment. Ex-1013, 32:58-62.

358. To summarize, Bissonnette expressly discloses each of the alternative PGA grade improvements recited by claim [1.d], for twice daily application of a 1% tapinarof composition. Each of Sonti and Chen taught and suggested that *once daily* application of 1% tapinarof *also* effectively treated plaque psoriasis, as measured by the alternative claimed PGA score improvements recited by claim [1.d]. Given this teaching in the prior art, the claimed PGA score improvements following treatment with 1% tapinarof applied topically once a day would have been expected by and predictable to a POSA.

359. A POSA would have had additional good reasons to combine Bissonnette with the teachings of Sonti and/or Chen, with a reasonable expectation of success.

360. **One**, each of Bissonnette, Sonti, and Chen taught topical application of the same active ingredient (tapinarof) at the same concentration (1%) to the

same condition (plaque psoriasis), as I explained above. *See supra* ¶333; *see also* Ex-1008, Abstract, 1-2; Ex-1005, [0288]-[0293], [0055], [0196], [0387]; Ex-1013, 32:25-63. In view of this nearly complete overlap in teachings, a POSA would be motivated to, and would expect to easily and successfully be able to, combine their teachings.

361. **Two**, each of Bissonnette and Sonti expressly taught use of the well-known PGA metric to assess response to treatment, as I explained above. *See supra* ¶¶350-353. Each of Bissonnette and Sonti also taught that the treatment was effective, as measured by decrease in PGA grade (including the specific PGA grade decreases recited by [1.d]). *See supra* ¶¶350-353. And a POSA would have understood Chen to show the same decrease in PGA score, as I also explained. *See supra* ¶¶354-358. Because all three of these references (Bissonnette, Sonti, and Chen) taught the same reduction in PGA score following administration of 1% tapinarof to treat plaque psoriasis whether administered twice daily (Bissonnette) or once daily (Sonti and Chen), there would have been nothing unpredictable or unexpected about the combination. Given these teachings, a POSA would have reasonably expected the method of treatment of Bissonnette to still be successful when applied once daily rather than twice daily, including as measured by one or both of the specific PGA metrics that claim 1 recites.

362. **Three**, the claimed PGA improvement metric was an extremely well-

known and common measure of treatment efficacy by November 2018 (and well before), and a POSA would have been motivated to use it as a measure of treatment response. *E.g.*, Ex-1005, [0287]-[0288] (“The PGA scale in its typical use, is a 7-point scale ranging from clear to severe”); Ex-1008, 1 (clinical study of patients with baseline PGA of 2 to 4); Ex-1006, 5; Ex-1007, 2-3 (Table 2) (providing the “main clinical psoriasis measures” and explaining that “The PGA is a 5, 6, or 7 point ordinal rating ranging from “clear” to “very severe psoriasis”); Ex-1011, 2 (“The PGA is the most commonly used scoring method in clinical trials after the PASI”); Ex-1010, 2-4; Ex-1026, 6-7, 27, 58-59, 119-125, 157-158, 202-203, 475-476, 609-610, 880-881, 1709-1710, 1715, 1722-1724, 1752-1753 (studies for plaque psoriasis treatments using PGA as an outcome measure, including specifically a PGA improvement of two grades or improvement to a score of 0 or 1).

363. For any one of these reasons, it is my opinion that the improvement in PGA score recited by [1.d] is just the recitation of predictable (and in fact known) outcomes, using a well-known metric.

364. It is also my opinion that it would have been obvious to try the method of treating that is recited by claim elements [1.pre]-[1.c], where the PGA score was improved as stated by claim element [1.d].

365. In the art, there was a recognized need for an at least roughly

standardized way to measure plaque psoriasis treatment efficacy. For example, Ex-1011 explains that “[b]ecause no psoriasis biomarkers are available to assess disease severity, clinical measures are used in daily practice and in research to measure both severity and treatment response.” Ex-1011, 1; *see also* Ex-1007, 1 (“valid outcome and severity measures for psoriasis are a prerequisite for fully informative clinical research and evidence-based medicine”).

366. The PGA metric was one of a relatively small number of generally accepted, known ways to assess treatment response. Ex-1008, Abstract and 2; Ex-1005, [0285]-[0295]; Ex-1011, 2 (“The PGA is the most commonly used scoring method in clinical trials after the PASI.”); Ex-1005, [0287]; Ex-1007, 6, Table 2; Ex-1010, 2-3; Ex-1011, 3; *see also supra* ¶¶43-44, 46-53. Also, as I explained above the specific PGA improvements that are recited by element [1.d] were often used at the time as an “outcome measure.” *See supra* ¶¶47-51; *see generally* Ex-1026.

367. In my opinion there also would have been good reason to expect one or both of the specific PGA score improvements recited by element [1.d] when applying the method of treatment taught by Bissonnette, with a once daily application frequency rather than twice daily. As I explained in detail previously, Sonti and Chen each already show a POSA that once-daily topical application of a 1% tapinarof composition improved PGA scores, including by the specific scores

stated in claim element [1.d]. *See supra* ¶¶353-358; *see also* Ex-1005, [0288]; Ex-1013, Ex-1013, 32:10-65.

368. In view of these teachings in the art, a POSA would have been motivated to try the method of claim 1 using the PGA metric to measure the treatment response, and good reason to expect that the treatment would result in one or both of the PGA score improvements stated in element [1.d].

2. Dependent Claims 2, 3, and 4

369. As I explained above in Grounds 1 and 2, I understand from Mr. Sudhakar that these claims are disclosed by Sonti and also would have been obvious in view of the teachings of Sonti. I also understand from Mr. Sudhakar that the formulations stated in claims 2, 3, and 4 were just standard, common ways of formulating topical compositions by and before November 2018. Ex-1032, ¶¶33, 114-127.

370. I additionally understand from Mr. Sudhakar that a POSA would have been motivated to use these standard formulation methods when creating a topical composition for the tapinarof "cream" taught by Bissonnette, with a reasonable expectation that it would work. Ex-1032, ¶¶128-133.

371. I agree that a POSA would have been motivated to use a standard, known formulation as the vehicle to provide the 1% tapinarof "cream" that Bissonnette refers to. I also agree that a POSA would have reasonably expected to

be able to do this (and to expect that it could be done) using only routine skill in the art. This is reinforced by the fact that Bissonnette did not see a need to describe specifically how the 1% tapinarof cream was formulated, as this was already known in the art.

3. Dependent Claim 6: “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”

372. Bissonnette discloses this claim.

373. Bissonnette discloses that the participation criteria required subjects to have “between 1% and 10% of body surface area (BSA) covered with psoriasis (excluding the face, groin, scalp and genital regions).” Ex-1008, 1, 2. Thus, the subjects had plaque psoriasis at least on their “body.” Bissonnette discloses that 40 of the subjects “appl[ied]” 1% tapinarof cream. Ex-1008, 1,2. 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.”

374. Bissonnette also shows photos of a subject who applied the 1% tapinarof to an affected area of the skin on an arm:



Ex-1008, Fig. 3. These photos show plaque psoriasis on a subject's elbow improving from Day 0 to Day 84, following application of the 1% tapinarof to the elbow skin affected by plaque psoriasis. Thus, a POSA would understand Bissonnette to also teach that the application to the affected area of the skin of an “arm,” as the elbow is part of the arm.

375. The method of claim 6 also would have been an obvious method of treating plaque psoriasis, for the same reasons I explained above in Ground 2 with respect to claim 6. From my 30+ years as a practicing dermatologist, and from having treated over 1,000 patients with mild to severe plaque psoriasis, I know 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 lists these body parts that are often affected by plaque psoriasis. A POSA also would have known this. Given this, a POSA would have been motivated, with a reasonable expectation of success, to apply the topical method of treatment of

claim 1 to a body part or parts that is/are commonly affected by plaque psoriasis, including those listed by claim 6.

4. 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%”

376. Bissonnette discloses this.

377. Bissonnette discloses treating a subject who has been diagnosed with mild to severe and mild to moderate plaque psoriasis. Ex-1008, 1, 2 (“Study population” consisted of patients “diagnosed with stable, mild to moderate plaque psoriasis for at least 6 months” and having a PGA score of “two (mild) to four (severe)”; *id.*, 2 (“Study population” had patients “diagnosed” with “mild to moderate plaque psoriasis”). A POSA would understand Bissonnette’s disclosure of treating subjects starting with a baseline of plaque psoriasis of between “mild” and “severe” to include treating subjects diagnosed with “mild to severe” plaque psoriasis (claim 7) and “mild to moderate” plaque psoriasis (claim 21).

378. Bissonnette also discloses treating a subject who has a BSA affected of “about 3% to about 20%” as claimed. Bissonnette discloses treating a study cohort of 40 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. A set of 40 subjects with BSA affected of between 1% and 10% is a disclosure of a subject having a BSA affected of about 3% to 20%.

For example, Bissonnette's subjects include those with BSA affected of up to 10%, which is within the claimed "about 3% to about 20%" range. Bissonnette teaches that the mean BSA affected of the 40 study subjects receiving the treatment was 3.3%, which is also within the claimed range of "about 3% to about 20%." *See* Ex-1008, Table 1.

5. 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"

379. Bissonnette discloses this.

380. Bissonnette discloses treating a subject who has been diagnosed with mild to severe and mild to moderate plaque psoriasis, for the same reasons I explained above with respect to claims 7, 21 in this Ground 4.

381. Bissonnette also discloses a subject "having a Physician Global Assessment (PGA) score of greater than or equal to 2" at baseline. Bissonnette discloses that the inclusion criteria for the 61 study subjects required each to have a "Physician's Global Assessment (PGA) of two (mild) to four (severe) at Day 0." Ex-1008, 2; *see also id.* Abstract. This is a disclosure treating a subject having a PGA score of "greater than or equal to 2," as claimed.

6. **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 (PASI), 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)”**

382. Bissonnette discloses this claim. Bissonnette discloses an improvement of one or more symptoms of mild to severe plaque psoriasis after topically administering the 1% tapinarof composition, as measured according to both PGA score and percent BSA affected.

383. Bissonnette discloses an improvement in one or more symptoms of mild to severe plaque psoriasis as measured according to “*Physician Global Assessment (PGA) score*,” after topically administering the 1% tapinarof cream. This is true for the reasons I explained above with respect to [1.d] in in this Ground 4. *See supra* ¶¶350-352. As I explained there, Bissonnette discloses that the study subjects started the trial with a plaque psoriasis physician’s global assessment score (PGA) of “two (mild) to four (severe).” Ex-1008, 1 (Abstract), 2. After the 12 weeks, 67% of the treated patients achieved a PGA score of clear (0) or almost clear (1). Ex-1008, 3. In doing so, Bissonnette discloses improvement one or more symptoms of mild to severe plaque psoriasis as measured according to PGA score. 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.

384. Bissonnette also discloses an improvement in one or more symptom of mild to severe plaque psoriasis as measured according “*percent body surface area (BSA) affected,*” after topically administering the 1% tapinarof cream. This is true for the reasons I explained above in Ground 3 with respect to Claim 9. See *supra* ¶¶309-311. For example, Bissonnette reports a study of 61 patients having 1–10% BSA covered with plaque psoriasis at the inception of the study. Ex-1008, 1 (Abstract), 2. Forty of the study participants applied a topical composition of 1% tapinarof to affected areas twice daily for 12 weeks. Ex-1008, 1. Following twelve weeks of treatment, the BSA affected by plaque psoriasis for those subjects had decreased an average of 79.1%. Ex-1008, 3-4, Tables 1, 3. The nearly 80% decrease in BSA that Bissonnette discloses after topical treatment with the 1% tapinarof composition discloses “*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.

385. I also note that a POSA would have reasonably expected the improvement stated in claim 9. This is because, as I explained above with respect to elements [1.c] and [1.d], Sonti and Chen each taught a POSA that a once-daily

administration of a composition containing 1% tapinarof was very effective in improving plaque psoriasis symptoms. *See supra* ¶¶340-345; *see also* Ex-1005, [0285]-[295]; Ex-1013, 2:56-3:4 and 32:10-63; *see also supra* ¶¶190-193, 211-216, 242.

7. 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”

386. Bissonnette discloses this claim.

387. Bissonnette reports a study of 61 patients having 1–10% BSA covered with plaque psoriasis at the inception of the study. Ex-1008, 1 (Abstract), 2. Forty of the study participants applied a topical composition of 1% tapinarof to affected areas twice daily for 12 weeks. Ex-1008, 1. Following twelve weeks of treatment, the BSA affected by plaque psoriasis for those subjects had decreased an average of 79.1%. Ex-1008, 2-3, Tables 1, 3. The study showed a change in mean body surface area (BSA) affected of “-2.6%” following treatment. Ex-1008, Table 3. Bissonnette teaches that the mean BSA at baseline (at the study start) was 3.3% (Ex-1008, Table 1), so a mean decrease of 2.6% means that the **mean BSA decreased to 0.7% following the treatment** ($3.3\% - 2.6\% = 0.7\%$). Bissonnette’s Table 1 and Table 2 are shown below:

Table 1 Demographics and baseline values of efficacy assessments

Characteristic	1% WBI-1001 (N = 40)	placebo (N = 21)	All (N = 61)
Age mean $\pm$ SD	50.4 $\pm$ 8.8	51.1 $\pm$ 13.0	50.6 $\pm$ 10.3
Male N (%)	33 (82.5)	18 (85.7)	51 (83.6)
Mean PGA $\pm$ SD	3.2 $\pm$ 0.6	3.4 $\pm$ 0.5	3.3 $\pm$ 0.6
Mean PASI $\pm$ SD	5.9 $\pm$ 2.7	6.2 $\pm$ 2.0	6 $\pm$ 2.5
Mean BSA $\pm$ SD	3.3 $\pm$ 2.1	3 $\pm$ 1.6	3.2 $\pm$ 2.0

BSA, body surface area; PASI, Psoriasis Area and Severity Index; PGA, physician's global assessment.

Table 3 Change from baseline in PASI and BSA at each visit

	1% WBI-1001 (N = 40) n (%)	Placebo (N = 21) n (%)	P-value
PASI			
Day 14	-1.9 (-31.9)	-0.8 (-12.4)	0.0010
Day 28	-2.8 (-47.5)	-0.8 (-13.1)	<0.0001
Day 42	-3.6 (-60.7)	-0.8 (-12.7)	<0.0001
Day 56	-3.9 (-65.9)	-0.8 (-12.4)	<0.0001
Day 84	-4.2 (-71.0)	-0.7 (-11.1)	<0.0001
BSA			
Day 14	-0.5 (-16.3)	-0.1 (-2.7)	0.0273
Day 28	-1.3 (-40.8)	0.1 (+2.4)	0.0004
Day 42	-2.1 (-63.4)	0.01 (+0.3)	<0.0001
Day 56	-2.4 (-71.6)	0.3 (+9.4)	<0.0001
Day 84	-2.6 (-79.1)	0.3 (+9.4)	<0.0001

PASI, Psoriasis Area Severity Index; BSA, body surface area.

388. Bissonnette's disclosure that the average BSA affected decreased to 0.7% following treatment also discloses that the BSA affected "*has decreased to less than 20% after topically administering the topical composition,*" which is the

BSA metric recited by claim 10. A BSA that has decreased to 0.7% is a BSA that has decreased to “less than 20%,” as 0.7% is (far) less than 20%.

389. Further, the “mean” BSA affected values necessarily indicate (to a POSA) that at least some study subjects had an actual BSA affected that decreased to equal or less than the mean BSA affected value (which was 0.7% BSA following treatment). This is true due to the definition of a “mean” value. A POSA understood the “mean” BSA values connoted the average values. The actual baseline BSA value of each subject who was to receive treatment was added together, and then the sum divided by the total number of subjects receiving treatment, to get the mean BSA affected at baseline. Following treatment, the BSA affected of each of those subjects was again added, and the sum again divided by the total number who received treatment. Then this number was subtracted from the mean BSA at baseline to get the mean decrease in BSA of -2.6%. Given that the mean (average) decrease in BSA affected was -2.6%, to a mean BSA affected of 0.7%, at least some of the study participants receiving treatment must have achieved an actual decrease in BSA affected to 0.7% or lower, which is within the claimed decrease “to less than 20%.”

390. I also note, again, that a POSA would have reasonably expected the BSA improvement stated in claim 10, from performing the method of claim 1 and 9. This is because, as I explained above with respect to elements [1.c] and [1.d],

Sonti and Chen each taught a POSA that a once-daily administration of a composition containing 1% tapinarof was very effective in improving plaque psoriasis. *See supra* ¶¶340-345; *see also* Ex-1005, [0285]-[295]; Ex-1013, 2:56-3:4 and 32:10-63; *see also supra* ¶¶190-193, 211-216, 242.

8. **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”

391. Bissonnette discloses these claims.

392. Bissonnette discloses each of claim 16 and claim 18 via its disclosure that a PGA score is improved after about 8 weeks (“day 56”) of administering the 1% tapinarof cream. Ex-1008, 3, Table 2. Bissonnette explains that the portion of patients with a PGA of 0 or 1 at the start of the study was zero. After 8 weeks of treatment, the portion of patients with a PGA of 0 or 1 was 55% (over half of the 40 study subjects who were applying the 1% tapinarof cream). This is shown in the table below:

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.

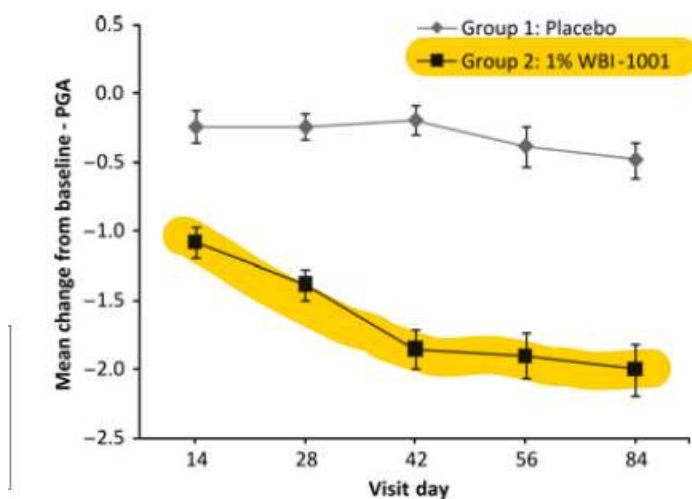


Figure 2 Change from baseline in PGA at each visit; ITT population (mean ± SEM).

Ex-1008, 3 (Table 2, Fig. 2).

393. A POSA would understand from this that Bissonnette discloses that the “PGA score is improved” after 8 weeks of administering the topical tapinarof composition, as recited by **Claim 18**. For example, Bissonnette’s disclosure that a larger proportion of patients had a PGA score of 0 or 1 after 8 weeks necessarily means that the PGA score “improved” following those 8 weeks of administering

the tapinarof composition for at least some study subjects.

394. With this same disclosure, Bissonnette also discloses that “*one or more symptom is improved*” after about 8 weeks of administering the topical composition, as recited by **Claim 16**. This is because a POSA would understand that improving a PGA score means that one or more symptoms has been improved. Assigning a PGA grade is based on analysis of plaque psoriasis symptom severity (e.g., plaque elevation, scaling and/or erythema). Changing a PGA score to a lower grade than the one previously assigned necessarily means that a symptom (or more than one symptom) of the plaque psoriasis has improved.

395. Bissonnette also discloses that a PGA score is improved after about 2 weeks (“day 14”) and about 4 weeks (“day 28”) (as recited by **claim 18**), for the same reasons. Ex-1008, Table 2 (proportion of patients with PGA of 0 or 1 improved from none to 12.5% after two weeks of treatment, and from none to 27.5% after four weeks of treatment):

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.

Ex-1008, Table 2; *see also* 3 (Fig. 2).

396. Bissonnette also discloses **claim 16** via its disclosure of improvement of BSA affected after 2, 4, and 8 weeks of administering the 1% tapinarof composition. Bissonnette discloses that the percent BSA affected had decreased 16.3% after 14 days (two weeks) of administering the 1% tapinarof cream, 40.8% after 28 days (four weeks) of administering the 1% tapinarof cream, and 71.6% after 56 days (eight weeks) of administering the 1% tapinarof cream:

Table 3 Change from baseline in PASI and BSA at each visit

	1% WBI-1001 (N = 40) n (%)	Placebo (N = 21) n (%)	P-value
PASI			
Day 14	-1.9 (-31.9)	-0.8 (-12.4)	0.0010
Day 28	-2.8 (-47.5)	-0.8 (-13.1)	<0.0001
Day 42	-3.6 (-60.7)	-0.8 (-12.7)	<0.0001
Day 56	-3.9 (-65.9)	-0.8 (-12.4)	<0.0001
Day 84	-4.2 (-71.0)	-0.7 (-11.1)	<0.0001
BSA			
Day 14	-0.5 (-16.3)	-0.1 (-2.7)	0.0273
Day 28	-1.3 (-40.8)	0.1 (+2.4)	0.0004
Day 42	-2.1 (-63.4)	0.01 (+0.3)	<0.0001
Day 56	-2.4 (-71.6)	0.3 (+9.4)	<0.0001
Day 84	-2.6 (-79.1)	0.3 (+9.4)	<0.0001

PASI, Psoriasis Area Severity Index; BSA, body surface area.

Ex-1008, Table 3.

397. A POSA would understand each of these decreases in percent BSA affected to disclose that “*one or more symptom is improved*”, as recited by Claim 16. Reduction in percent BSA affected necessarily means that the symptoms of

plaque psoriasis have improved, as there is less of the body area that is affected.

398. I also note that a POSA would have reasonably expected the improvement timeline recited by claims 16 and 18, with the method of treatment of claim 1. This is because, as I explained above with respect to elements [1.c] and [1.d], Sonti and Chen each taught a POSA that a once-daily administration was very effective in improving plaque psoriasis. *See supra* ¶¶340-345; *see also* Ex-1005, [0285]-[295]; Ex-1013, 2:56-3:4 and 32:10-63; *see also supra* ¶¶190-193, 211-216, 242.

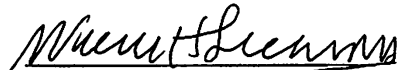
399. Sonti also specifically taught that the treatment improved the PGA score (as recited by claim 18) and did so after about 8 weeks of administering the treatment (as recited by claims 16 and 18). Ex-1005, [0288]. A POSA would also understand the PGA score improvement to indicate that one or more symptom has improved (claim 16). I explained Sonti's teaching in detail above in Grounds 1 and 2 with respect to claims 16 and 18.

400. Chen likewise taught that the once-daily treatment with 1% tapinarof showed "great efficacy" after only seven days of treatment. Ex-1013, 32:51-63. Volunteer 1 showed "complete clearance" of the psoriasis after seven days' treatment, and Volunteer 2 showed "visible improvement in inflammation and in clearance of the proliferative cells" after only three days of treatment. Ex-1013, 32:51-63. A POSA would understand these improvements to indicate that "one or

more symptom is improved” (claim 16) and that the PGA score had improved (claim 18). I also explained this above with respect to element [1.d]. Finally, Chen’s teaching of the significant improvement in symptoms (and therefore also PGA score) after only seven days of treatment certainly teaches that there were the claimed improvements after about 2, 4, and 8 weeks. The fact that there were the claimed improvements after 1 week indicates that there was necessarily the claimed improvement after 2, 4 or 8 weeks.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Dated: April 23, 2024


Wieke H. Liem, M.D.,
F.A.A.D.

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 (PASI), 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.