

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ENCUBE ETHICALS PVT. LTD.
Petitioner

v.

DERMAVANT SCIENCES GMBH
Patent Owner

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

DECLARATION OF PAUL T. SUDHAKAR, MS, MBA

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I, Paul Sudhakar, 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 (“PTO”).

2. I am being compensated at a rate of \$300/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 certain issues related to U.S. Patent No. 11,590,088 (“the ’088 patent”) (Ex-1001), including providing information regarding the background knowledge of a person of ordinary skill in the art (“POSA”) in the field of pharmaceutical formulations at the time of purported invention, and considering what the prior art would disclose and/or teach and suggest to a POSA at that time.

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. 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, add to, or change my opinions below based on new information and on my continuing analysis of the materials already provided, in addition to responding to any testimony or other information provided by or on behalf of the owner of the patent at issue in this proceeding.

7. My opinions are set forth below. I also add emphasis (highlighting, underlining, etc.) to statements in various of the references I discuss. Unless I note otherwise, the emphasis added is mine.

II. QUALIFICATIONS AND BACKGROUND

8. 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 pharmaceutical formulator and regulatory consultant. 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.

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

attached as Appendix B to this declaration. I also provide a summary below.

10. In 1982, I graduated from Kakatiya University earning a Bachelor of Pharmacy (B. Pharm.), Pharmaceutical Sciences. In 1984, I graduated from UDCT (which is now the Institute of Chemical Technology), Bombay earning a Masters of Pharmacy (M. Pharm.), Pharmaceutics and Drug Design. In 1986 I graduated from Kansas State University earning a Masters in Business Administration (MBA). From 1986 to 2003, I was the President & CEO of Martec Scientific and Martec Pharmaceutical, a full-fledged pharmaceutical company. From 2004 to present, I have been the founder and owner of PTS Consulting. I own and operate a 30,000 square foot facility, on 5 acres of land, in a suburb of Kansas City, MO. The facility is FDA-inspected and used for contract development and clinical manufacturing work of pharmaceutical drugs covering a range of dosage forms (e.g., solid orals, liquid orals, injectables, semisolid topicals, etc.). PTS Consulting has licensed numerous ANDAs, NDAs and other such FDA approvable products to various pharmaceutical firms. PTS can also manufacture some of these dosage forms on its own site and also with numerous partner CMOs.

11. Over my professional career, I worked to formulate numerous pharmaceutical products including topical creams for treating skin conditions. I also handled the quality and regulatory work for these products, to obtain FDA regulatory approval. These creams included active ingredients across a wide range

of therapeutic indications (i.e., skin diseases or disorders). The topical creams include over-the-counter (OTC), potential 505(b)(2) new drug applications (NDAs), and abbreviated new drug applications (ANDAs). During my professional career my work has also entailed other functions, including formulations advisor, pharmaceutical scientist, and manager.

III. MATERIALS REVIEWED AND SUMMARY OF OPINIONS

12. My opinions contained in this Declaration are based on my knowledge from my education and my experience as a pharmaceutical scientist and manager over the past 30 years. They are also based on the specific references, documents, and other materials I discuss in this Declaration.

13. 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).
- U.S. Patent Application Pub. No. 2016/0338973 (“Sonti”; “Ex-1005”), published Nov. 24, 2016.

¹ My citations to these (and any other documents I discuss) are to the branded numbers added by the Petitioner on the bottom right corner of the exhibits, except where I discuss patents and published applications, which I cite by column/line number or paragraph number.

- 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.
- WO 2001/042231 (“Ex-1012”), published Jun. 14, 2001.
- U.S. Patent No. 7,868,047 (“Chen”; “Ex-1013”), issued Jan. 11, 2011.
- 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”).
- GSRS Database Entries, Ex-1021, Ex-1022, Ex-1023, Ex-1024.
- VTAMA® (tapinarof) cream prescribing information from label, Ex-1025
- Clinical Trials website (<https://clinicaltrials.gov/>) (“ClinicalTrials.gov”; “Ex-1026”).
- U.S. Publication No. 2003/0171429 A1 (“Chen 1”; “Ex-1027”), published Sept. 11, 2003.
- U.S. Publication No. 2010/0094041 A1 (“Chen 2”; “Ex-1028”), published Apr. 15, 2010.
- U.S. Publication No. 2008/0255245 A1 (“Chen 3”; “Ex-1029”), published Oct. 16, 2008.
- Nava Dayan, Handbook of Formulating Dermal Applications (2016) (“Ex-1030”).
- Paul J. Shesky, et al., Handbook of Pharmaceutical Excipients (2017, 8th ed.) (“Ex-1031”).

14. 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 that. I also note that my opinions would not change if the relevant timeframe was slightly earlier or slightly later.

15. I also note that I was a person of ordinary skill in the art at that time. My opinions in this declaration 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, even if I use present tense.

IV. LEVEL OF ORDINARY SKILL IN THE ART

16. 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.

17. I have been informed 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, and that this POSA would have also had access to and would have

consulted with a collaborative team of ordinarily skilled artisans, including drug formulators. Applying the considerations of the previous paragraph, I believe that the relevant drug formulator having ordinary skill in the art prior to November 2018 would have had a technical degree in the relevant field (B. Pharm.) and five years of experience in the pharmaceutical sciences that included 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.

18. Based on my qualifications and experience, I met the qualifications of a drug formulator with the ordinary level of skill by November 13, 2018 and well before then.

19. All my opinions in this declaration are from the perspective of a drug formulator of ordinary skill in the art as I have defined it here during the relevant timeframe. My opinions in this declaration would not change if the level of skill in the art was slightly higher or lower.

V. LEGAL PRINCIPLES

20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

25. 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.

26. 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.

27. 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.

28. 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.

29. 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.

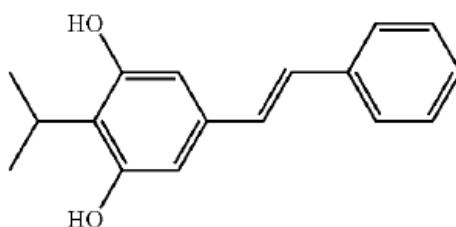
VI. OVERVIEW OF THE '088 PATENT

A. '088 Patent

30. The '088 patent relates to using tapinarof in a topical composition to

treat atopic dermatitis or plaque psoriasis. Ex-1001, Abstract.

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



Id.

32. The '088 patent discloses that the topical tapinarof composition can be an “oil-in-water emulsion.” Ex-1001, 7:23-36. Such oil-in-water emulsions were extremely common formulations for topical skin creams by 2018 (and well before).

33. The '088 patent continues to describe a series of standard, known options for formulating a topical oil-in-water emulsion. Ex-1001, 7:23-10:4.

34. For example, the '088 patent notes that the compositions may include “one or more pharmaceutical and/or cosmetically acceptable excipients selected from the group consisting of diluents, fillers, disintegrants, binders, lubricants, surfactants, hydrophobic vehicles, water soluble vehicles, emulsifiers, buffers,

humectants, moisturizers, solubilizers, preservatives, colorants, plasticizers, carriers, excipients, or combinations thereof.” Ex-1001, 8:15-23. The ’088 patent then refers to common, widely-used pharmacologic references at the time as an indication that the specific formulations were routine and well-known:

combinations thereof. The person of ordinary skill in the art can refer to various pharmacologic references such as, for example, Modern Pharmaceutics, Banker & Rhodes, Marcel Dekker, Inc. (1979) and Goodman & Gilman’s The Pharmaceutical Basis of Therapeutics, 6th Edition, MacMillan Publishing Co, New York (1980) for guidance in determining the amount of such components in the topical compositions and formulations of embodiments.

Ex-1001, 8:23-29.

35. The ’088 patent also explains that “the topical compositions may be formulated “in any formulation suitable for topical administration,” and specifically incorporates by reference the formulations of tapinarof compositions disclosed by the Sonti patent publication (Ex-1005, which is U.S. Patent Publication No. 2016/0338973). See the below:

In embodiments, the topical compositions may be formulated in any formulation suitable for topical administration, including, but not limited to, a solution, fluid, emulsion, suspension, solid, semi-solid, jelly, paste, gel, hydrogel, ointment, lotion, emulsion, cream, foam, mousse, liquid, spray, suspension, dispersion, powder, aerosol, or transdermal patch. Formulations described in U.S. Patent Publication Nos. 2016/0338973, 2018/0064656, and 2019/0144367 are incorporated herein by reference in their entirety.

Ex-1001, 8:54-63.

B. Prosecution History

36. I have reviewed the file history of the '088 patent.

37. Based on my review, the U.S. Patent Office rejections did not concern whether or not the prior art disclosed tapinarof. The rejections also did not concern whether or not the references disclosed specific formulations, such as those recited in dependent claims 2-4. *See generally* Ex-1002.

38. Instead, the Applicant made arguments about whether the prior art disclosed specifically using tapinarof to treat “plaque” psoriasis and whether the prior art taught the specific improvements according to a scale known as the Physician Global Assessment (“PGA”). *E.g.*, Ex-1002, 284.

C. Claims

39. The '088 patent contains one independent claim:

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.

40. The '088 patent also contains a series of dependent claims. Dependent claims 2 through 4 recite common, routine formulations for topical skin creams:

2. The method of claim 1, wherein the topical composition is an oil-in-water emulsion.

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.

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.

I discuss these claims in more detail below.

VII. CLAIM CONSTRUCTION

41. 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. For the claims I discuss below, I have used this meaning.

VIII. OVERVIEW OF THE REFERENCES

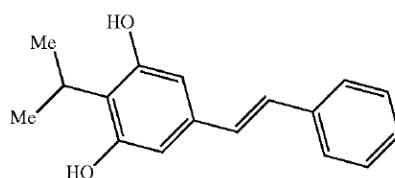
A. Sonti (Ex-1005)

1. Sonti Generally

42. Sonti (Ex-1005) discloses both formulations for compositions containing “3,5-dihydroxy-4-isopropyl-trans-stilbene” and methods of treating skin diseases with the disclosed formulations. *E.g.*, Ex-1005, Abstract.

43. Sonti provides for the following structural formula for the compound

3,5-dihydroxy-4-isopropyl-trans-stilbene:



Ex-1005, [0008]. Sonti states that compound is also known as 5-[(*E*)-2-phenylethenyl]-2-(propan-2-yl)benzene-1,3-diol or 2-(1-methylethyl)-5-[(1*E*)-2-phenylethenyl]-1,3-benzenediol. Ex-1005, [0009]. As I explain below, this is tapinarof.

44. Sonti teaches that *3,5-dihydroxy-4-isopropyl-trans-stilbene* is further described in WO 2001/042231 (Welichem Biotech Inc.) and in U.S. Pat. No. 7,868,047 and as being suitable for the treatment of various key dermatological conditions, including psoriasis and inflammation. Ex-1005, [0010].

2. Sonti's Formulations

45. As I explained above, the '088 patent specifically adopts the formulations for tapinarof emulsions described by Sonti: "Formulations described in [Sonti, which is US Patent Pub. No. 2016/0338973] are incorporated herein by reference in their entirety." Ex-1001, 8:60-63.

46. Sonti discloses "topical pharmaceutical emulsion compositions comprising a therapeutically effective amount of 3,5-dihydroxy-4-isopropyl-trans-stilbene [which is tapinarof, as I explain in this declaration] or a pharmaceutically

acceptable salt thereof, an oil phase, a water phase, a surfactant, and an antioxidant”. Ex-1005, Abstract. Sonti further teaches that the tapinarof compositions 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* Ex-1005, [0272], [0301], [0387].

47. Specific suitable formulations disclosed in Ex-1005 include an oil-in-water emulsion. *E.g.*, Ex-1005, Abstract, [0101] (“Suitably, the emulsion may be formulated as a cream. The cream may be an oil-in-water cream or a water-in-oil cream. In one particular embodiment, the cream is an oil-in-water cream”); *see also id.*, [0021]-[0023], [0049], [0054]) [0100], claim 18.

48. Sonti describes the tapinarof formulations it discloses in a manner that is common in the field. Specifically, Sonti identifies menus of acceptable options for each portion of the emulsion. *See generally*, Ex-1005, [0055]-[0258]. For example, Sonti teaches that “exemplary antioxidants include...” (Ex-1005, [0094]), “exemplary chelating agents include...” (Ex-1005, [0107]), “exemplary co-solvents include...” (Ex-1005, [0119]), “exemplary penetration enhancers include...” (Ex-1005, [0123]), et cetera.

49. Sonti also teaches that the amount of active ingredient (tapinarof) can

be 1.0 wt.%: “In all of the compositions described herein, the amount of 3,5-Dihydroxy-4-isopropyl-trans-stilbene or 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 another embodiment, the amount is about 1.0% by weight, based on the total weight of the composition.” Ex-1005, [0196]; *see also id.*, [0055].

50. Sonti then provides seven specific examples of formulations that a POSITA could use. *See generally*, Ex-1005, [0322]-[0374] (Examples 1-4, 7-9). Each of these is an oil-in-water emulsion. Most include specific formulation examples having 1% tapinarof (the “active ingredient”) by weight. *E.g. id.*, Example 1, Formulation 1(a) (Ex-1005, [323]); Example 4, Formulation 13 (Ex-1005, [0327]); Example 8, Formulation 21 (Ex-1005, [0355]); Example 9, Formulations 30-33 (Ex-1005, [0370]).

B. Bissonnette (Ex-1008)

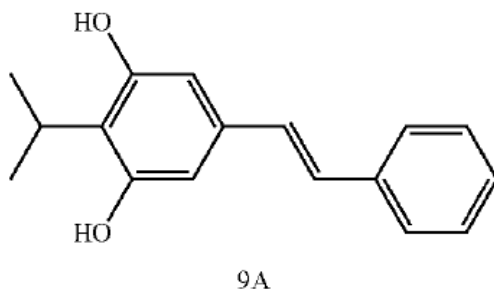
51. Bissonnette’s stated objective is to assess the efficacy and safety of topical 1.0 wt.% “WBI-1001” in patients with plaque psoriasis. Ex-1008, 1. Bissonnette also provides the chemical name of WBI-1001 as *2-isopropyl-5-[(E)-2-phenylethenyl]benzene-1,3-diol*. *Id.* As I explain below, this is tapinarof. With a topical cream, unless expressly stated otherwise, amount of ingredients provided in a formulation are generally understood by POSAs to be weight percent (wt.%). As

such, while Bisonette doesn't expressly state the percentage amount as weight percent, a POSA would understand it to be weight percent.

52. Bissonette teaches applying the 1 wt. % WBI-1001 composition "in a cream formulation." Ex-1008, 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"). Bissonette does not specifically describe the ingredients of the cream formulation.

C. Chen (Ex-1013)

53. Chen discloses the compound 3,5-dihydroxy-4-isopropyl-trans-stilbene. Chen teaches that "[a] particularly preferred compound is *3,5-dihydroxy-4-isopropylstilbene* (9A)." Ex-1013, 21:41. Chen provides the structural formula for compound (9A), shown below.



Ex-1013, 16:40-47 (Scheme 4). As I explain below, this is tapinarof.

54. Chen also discloses the preparation of compound (9A) (Ex-1013, 19:49-56), as well as the protein kinase inhibitory activity IC₅₀ (mM) (Ex-1013,

33:40-53), and asserts that compound (9A) is endowed with valuable properties of inhibiting protein kinases (Ex-1013, 33:54-56).

55. Chen teaches that a “1% cream of *3,5-dihydroxy-4-isopropylstilbene* was prepared for tests on volunteers,” including two with plaque psoriasis. Ex-1013, 32:25-37; *see also id.*, 32:46-47 (“The cream of the invention contained 1% *3,5-dihydroxy-4-isopropylstilbene*”).

IX. OPINIONS

A. Tapinarof: Its Chemical Formula and Its Various Nomenclatures

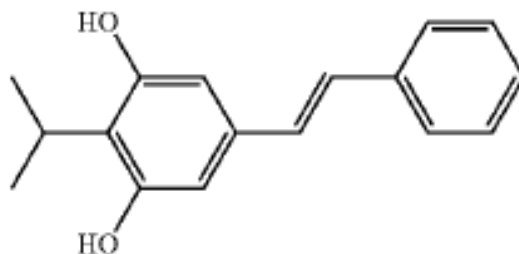
1. The '088 Patent's Description of “Tapinarof”

56. The '088 patent claims refer to administering a composition that contains 1% “tapinarof”. The '088 patent describes the chemical structure of “tapinarof” as follows:

- “*3,5-Dihydroxy-4-isopropyl-trans-stilbene* is referred to as tapinarof” (Ex-1001, 7:4-9)
- “[tapinarof] is also known as *(E)-2-isopropyl-5-styrylbenzene-1,3 diol*” (Ex-1001, 7:8-10)

57. The '088 patent also provides the chemical structure diagram for tapinarof:

Embodiments of the invention are directed to topical compositions comprising 3,5-Dihydroxy-4-isopropyl-*trans*-stilbene or a pharmaceutically acceptable salt thereof. Throughout this disclosure 3,5-Dihydroxy-4-isopropyl-*trans*-stilbene is referred to as tapinarof, and is also known as (E)-2-isopropyl-5-styrylbenzene-1,3 diol, with the empirical formula $C_{17}H_{18}O_2$, a molecular weight of 254.32, and the following structure:



Ex-1001, 7:4-21.

2. Sonti (Ex-1005) Discloses Methods of Treating Using Tapinarof

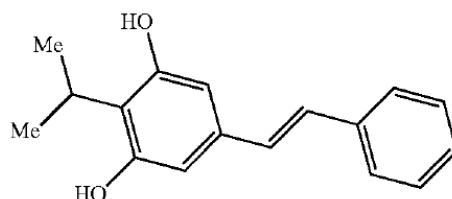
58. Sonti discloses various compositions that use tapinarof as the active ingredient.

59. Sonti explains that “The present invention relates to topical pharmaceutical emulsion compositions comprising a therapeutically 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 homogeneous and/or the active is solubilized in the oil phase.” Ex-1005, Abstract.

60. Sonti also explains that 3,5-dihydroxy-4-isopropyl-*trans*-stilbene is

the “active ingredient of interest” in its formulations, and provides a structure of the compound:

[0008] One active ingredient of interest to be formulated in a physically and chemically stable topical composition is 3,5-Dihydroxy-4-isopropyl-trans-stilbene which has the following formula:



[0009] This compound is also known as 5-[(E)-2-phenylethenyl]-2-(propan-2-yl)benzene-1,3-diol or 2-(1-Methylethyl)-5-[(1E)-2-phenylethenyl]-1,3-benzenediol

[0010] 3,5-Dihydroxy-4-isopropyl-trans-stilbene is believed to have been originally disclosed by Paul et al., *Journal of Chemical Ecology* 1981 7(3): 589-597 as an antibiotic. Li et al, *Applied and Environmental Microbiology* 1995 61(12): 4329-4333 also isolated the compound, but from a different bacterial strain and further demonstrated its fungicidal activity. The fungicidal activity of the compound was also described in WO 1995/003695 (Agro-Biotech Corporation). The compound is further described in WO 2001/042231 (Welichem Biotech Inc.) and in U.S. Pat. No. 7,868,047 and as being suitable for the treatment of various key dermatological conditions including psoriasis and inflammation. Example 3 of the U.S. Pat. No. 7,868,047

Ex-1005, Abstract , [0008]-[0010].

61. 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”); *see also id.*, 7:11-20 (showing chemical structure of tapinarof).

62. While in the Sonti drawing of the tapinarof compound the left side

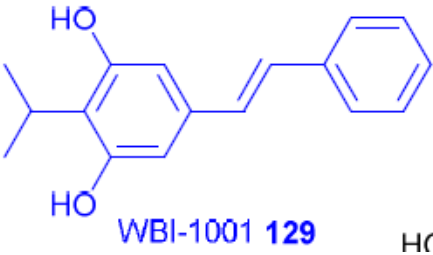
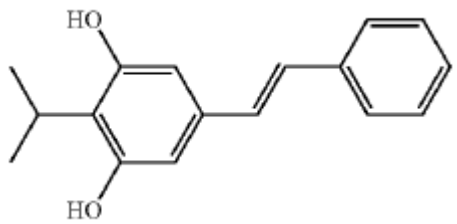
terminates with “Me” annotations, this is the same as the tapinarof compound structure shown in the '088 patent. Drawing every bond and every atom is tedious, so chemists have devised several shorthand ways for writing structures. In condensed structures, carbon–carbon single bonds often aren’t shown; instead, they’re understood. Specifically, a carbon atom is assumed to be at each intersection of two lines (bonds) and at the end of each line. Occasionally, a carbon atom might be indicated for emphasis or clarity. For example, at the end of a line can be drawn “Me” (as in the Sonti drawing) or be left blank (as in the '088 patent drawing). Both indicate a methyl group. *E.g.*, <https://openstax.org/books/organic-chemistry/pages/1-12-drawing-chemical-structures>.

63. The Prescribing Information for Vtama® cream provides the same chemical name. Ex-1025, 3 (“Chemically, tapinarof is 3, 5-dihydroxy-4-isopropyl-*trans*-stilbene, also known as (E)-2-isopropyl-5-styrylbenzene-1,3-diol”).

3. Bissonnette (Ex-1008) Discloses Methods of Treating Using Tapinarof

64. Bissonnette describes a study assessing the efficacy and safety of “topical 1.0% WBI-1001” to treat patients with plaque psoriasis. Ex-1008, 1. Bissonnette explains that “WBI-1001 (*2-isopropyl-5-[(E)-2-phenylethenyl]benzene-1,3-diol*) is a non-steroidal, anti-inflammatory, new chemical entity (NCE) that was originally derived from the metabolites of a group of bacterial symbionts of entomopathogenic nematodes.” Ex-1008, 1-2.

65. “WBI-1001” is tapinarof. First, a 2014 review article in the journal Natural Product Reports explains that WBI-1001 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:

“WBI-1001” (Ex-1019, 21)	Tapinarof (Ex-1001, 7:10-20)
 WBI-1001 129 Hr	

Ex-1019 also states that the structure of WBI-1001 was first published in 1981 by Scripps Institution of Oceanography and that the source of WBI-1001 is bacteria. Ex-1019 , 34 (Table 10).

66. Second, Bissonnette also provides the chemical name of WBI-1001 as “2-isopropyl-5-[(E)-2-phenylethenyl]benzene-1,3-diol.” Ex-1008, 1. The ’088 patent notes that this is the chemical name for tapinarof. Ex-1001, 7:7-10 (“tapinarof . . . is also known as (E)-2-isopropyl-5-styrylbenzene-1,3 diol”). These are the same thing. It was readily known and understood by POSAs that organic compounds are often referred to by multiple chemical names. With tapinarof, in addition to those mentioned above, these include (E)-3,5-dihydroxy-4-isopropyl-trans-stilbene and the IUPAC name, 5-[(E)-2-phenylethen-1-yl]-2-(propan-2-yl)benzene-1,3-diol. This occurs because there can be multiple ways in which an organic compound is named, following conventional nomenclature.

67. A compound used in medication can also have multiple common names. With tapinarof, in addition to those mentioned above, these include GSK-2894512 (the internal name at GSK while under development). At the relevant time, POSAs would have readily known that tapinarof would have been understood by reference to any of its multiple names.

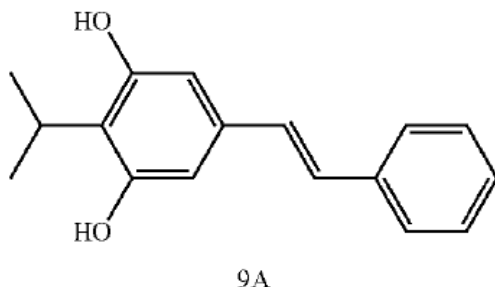
4. The Chen References (Ex-1012, Ex-1013, Ex-1027, Ex-1028, Ex-1029) Disclose Methods of Treating Using Tapinarof

68. The Chen references each teach that “[a] 1% cream of 3,5-dihydroxy-

4 -isopropylstilbene” was used to treat subjects with plaque psoriasis. Ex-1012, 20:27-30; Ex-1013, 32:11-29; Ex-1027, [0096]; Ex-1028, [0188]-[0190]; Ex-1029, [0169]-[0171].

69. “3,5-dihydroxy-4 -isopropylstilbene” is tapinarof. The ’088 patent explains this: “3,5-Dihydroxy-4-isopropyltrans-stilbene is referred to as tapinarof.” Ex-1001, 7:4-9.

70. Further, the Chen references provide an illustration of the chemical structure for “3,5-dihydroxy-4 -isopropylstilbene,” which is the compound (9A) in Ex-1013, shown below.



Ex-1013, 16:40-47 (Scheme 4). This is the same as the chemical structure for “tapinarof” that is illustrated in the ’088 patent. Ex-1001, 7:10-20.

5. “Benvitimod” Is Another Name for Tapinarof

71. Certain prior art refers to administration of “Benvitimod” or “Benvitimod cream” to treat plaque psoriasis. *E.g.*, Ex-1016, Ex-1017, Ex-1018.

72. “Benvitimod” was another name for tapinarof. For example, Ex-1019 notes that another name for “WBI-1001” is “benvitimod,” when describing a 2012

phase two trial for treating psoriasis. Ex-1019, 22. As I explained above, WBI-1001 is tapinarof.

73. Other sources also note that “tapinarof” is also known as “benvitimod.” *E.g.*,

<https://pubchem.ncbi.nlm.nih.gov/compound/6439522#section=MeSH-Entry-Terms>; <https://en.wikipedia.org/wiki/Tapinarof> (“tapinarof, also known as benvitimod”).

B. References to a “1% cream” or a “1% [active ingredient] in a cream formulation” Were Understood to Refer to Percent-by-Weight

74. In the field of formulation, and specifically in the field of formulations for topical compositions such as skin creams, the amount of active ingredient in a formulation was customarily referred to as a percentage *by weight*.

75. This is because it is much easier, and thus conventional, for a formulator to measure mass/weight (as opposed to volume) of each ingredient, as well as the resulting product.

76. Consistent with this practice, the Sonti publication refers to compositions having “1% w/w” of the active ingredient tapinarof. For examples, *see* Ex-1005, [0196] (describing the “amount” of tapinarof in a composition as percentages “by weight”); [0261] (describing the applied dose of active ingredient as a percentage “w/w”); [283], [290] (referring to a “% w/w/ active [ingredient]”).

77. Percent “by weight” and “w/w” of an active ingredient mean the same thing. They mean the percentage of the total mass of the substance that is comprised by the weight of the particular compound. *See, e.g.,* <https://www.chemicals.co.uk/blog/what-do-vv-ww-wv-mean>.

78. The Chen references refer to a “1% cream of 3,5-dihydroxy-4-isopropylstilbene[that] was prepared for tests on volunteers.” Ex-1013, 32:25-26; *see also* Ex-1012, Ex-1027, Ex-1028, Ex-1029. A POSA would have understood this as a reference to a cream having 1% *by weight* of the tapinarof compound. That is because those practicing in the field often used shorthand when describing the amount of active ingredient in topical skin formulations. But it was understood that “1% cream” of a particular active ingredient contained 1% *by weight* of that ingredient.

79. The Bissonnette reference also refers to “topical 1% WBI-1001 [tapinarof]” and “1% WBI-1001 in a cream formulation” (Ex-1008, Abstract), “1% WBI-1001 cream” (Ex-1008, 2), and “topical WBI-1001 at 1%” (Ex-1008, 4). A POSA also would have understood this as a reference to a cream having 1% *by weight* of the WBI-1001 (which is tapinarof) compound. As I explained in the previous paragraph with respect to the Chen references, this is because those practicing in the field often used shorthand when describing the amount of active ingredient in topical skin formulations. It was understood from this shorthand that

“1% cream” of a particular active ingredient contained 1% *by weight* of that ingredient.

80. I also note that it would have been common sense and obvious, in any event, to provide a composition containing 1% *by weight* of the active ingredient tapinarof, in view of references like Chen and Bissonnette describing a “1% cream” of tapinarof. To a formulator prior to November 2018, providing the active ingredient as 1% by weight of the composition (as opposed to 1% by volume for example), where the reference did not expressly say “by weight,” would have been the most common, expected way to formulate the topical skin cream.

C. Motivations At the Time of Purported Invention

81. As a practicing, professional pharmaceutical formulator for the past 30+ years, I am aware of the motivations, knowledge, and expectations that a POSA at the time of the purported invention would have had and would have considered.

82. It was known that if a treatment containing a lower amount of active ingredient and/or administered less frequently was effective, then there were good reasons to use that lower amount and/or provide the pharmaceutical treatment at that lower frequency. The lower amount of active ingredient and/or less frequent administration (“dosing regimen”) would be suitable, provided it was still effective (achieved the desired “therapeutic index”).

83. It was generally understood and accepted by POSAs, by November 2018 and long before, that lower dosing frequencies of drugs such as, e.g., once a day rather than twice a day, while staying within the therapeutic index, provide for multiple predictable and known benefits.

84. One was a decreased risk of adverse effects. POSAs understand that the lowest dosing frequency effective at achieving the treatment goals is widely recommended, as it reduces dose-related effects. With a topical cream administered for site target therapy to treat plaque psoriasis, a lower dosing frequency administers less active ingredient and excipients. With a lower amount of active ingredient and excipients administered, there would be less systemic exposure of active ingredient and excipients, hence reducing the risk of adverse effects. Therefore, the expected decreased adverse effects would have been an additional known reason to use a lower administration frequency.

85. The Sonti reference echoes and confirms this known principle. Sonti 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 continues on to explain that its formulations “can provide lower systemic exposure of the active ingredient to the patient during use.” *Id.*

86. Another was a decrease in cost for the medical treatment. There was a known motivation and market pressure to decrease the cost of topical skin treatments. A POSA in my field would have known that a once daily administration (as compared to a more frequent administration, such as twice daily) would require less amount/volume of the pharmaceutical, and therefore entail less cost. Where feasible, reducing dose frequency may offer benefits for the health care budget holder in terms of costs. Therefore, the expected decreased cost would have been an additional known reason to use a lower administration frequency.

87. Another is an increase in patient compliance. POSAs understood that reducing the number of daily doses had frequently been shown to provide the patient with better symptom control in a number of disease states. Overall improvements are typically seen in adherence, patient quality of life, and patient satisfaction. This is so, for example, because with fewer administrations, there are fewer chances the patient will forget (or be unable) to successfully carry out the prescribed administration at the desired time. Reducing dose frequency may offer benefits for the patient in terms of health outcomes. Therefore, the expected increased patient compliance would have been an additional known reason to use a lower administration frequency.

D. Dependent Claims 2-4 Are Anticipated by Sonti

1. The Formulations Taught by Sonti

88. As I explained above, with respect to the formulations, Sonti discloses various formulations that comprise a “topical...emulsion” having a therapeutically effective amount of tapinarof or a pharmaceutically acceptable salt thereof, “an oil phase, a water phase, a surfactant, and an antioxidant.” Ex-1005, Abstract. Sonti then describes the various parts of the emulsion in more detail, with subsections for each. For example, there is a subsection for the “oil phase” (Ex-1005, [0056]-[0072]), the surfactant (Ex-1005, [0074]-[0098]), etc.

89. While Sonti often uses the phrasing “in one embodiment” or “in a further embodiment” when describing the ingredients in the formulations, a POSA would have immediately envisaged using each of the disclosed options for the portion of the emulsion (e.g., each of the options disclosed for the “oil phase” portion of the emulsion) in each composition. Sonti provides the formulations as menus of acceptable options. For example, Sonti teaches that “exemplary antioxidants include...” (Ex-1005, [0094]), “exemplary chelating agents include...” (Ex-1005, [0107]), “exemplary co-solvents include...” (Ex-1005, [0119]), “exemplary penetration enhancers include...” (Ex-1005, [0123]), etc. Sonti then explains that the amount of active ingredient (tapinarof) can be 1.0 wt. %: “In all of the compositions described herein, the amount of 3,5-Dihydroxy-

4-isopropyl-trans-stilbene or 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 another embodiment, the amount is about 1.0% by weight, based on the total weight of the composition.” Ex-1005, [0196]; *see also id.*, [0055]. As I noted above, many of the specific formulation examples Sonti provides also contain 1% tapinarof. Ex-1005, Table 1 (Formulation 1a), Table 4 (Formulation 13), Table 8 (Formulation 21), and Table 9 (Formulations 30-33).

90. The way Sonti is structured was (and is) also a common way to describe formulations in the field. A POSA would read Sonti for all that it discloses and would not understand Sonti to be teaching a series of discrete and separate embodiments. Instead, a POSA would immediately understand that Sonti was teaching various examples (that Sonti often called “embodiments”) for each portion of the emulsion (e.g., the oil phase or the water phase.) that can be used with each exemplary composition.

91. This is further confirmed by the '088 patent itself, which expressly incorporates by reference the formulations of tapinarof compositions disclosed in Sonti: “the topical compositions may be formulated in any formulation suitable for topical administration...Formulations described in [Sonti, which is US Patent Pub. No. 2016/0338973] are incorporated herein by reference in their entirety.” Ex-1001, 8:60-63 (emphasis added). Given this, it is also not at all surprising that Sonti discloses the formulations that are then recited by the claims of the '088 patent.

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

92. In my opinion, Sonti discloses the elements of claim 2 and therefore anticipates that claim.

93. Sonti explains that the “terms ‘emulsion’ and ‘oil-in-water emulsion’” should be understood to refer to the same thing in Sonti’s disclosure. Ex-1005,

[0054].

94. 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...”).

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*”

95. In my opinion, Sonti discloses the elements of claim 3 and therefore anticipates that claim.

96. Claim 3 merely lists a set of common ingredients for the oil phase of an oil-in-water emulsion, which would have been well-known by November 2018. It does not require any particular amount of any particular ingredient.

Unsurprisingly, Sonti teaches using each of these in the oil phase of its tapinarof oil-in-water emulsion formulations.

I note that Sonti teaches formulations that comprise a “topical...emulsion” having a therapeutically effective amount of tapinarof and “an oil phase, a water phase, a surfactant, and an antioxidant.” Ex-1005, Abstract. As I explained above, Sonti

describes the emulsion by providing menus of options for the ingredients, and then more specifically identifying various specific amounts for each ingredient in specific exemplary formulations (*e.g.*, those shown in tables 1-4 and 7-9). Given how Sonti is structured, a POSA would not understand Sonti to be teaching a series of discrete and separate embodiments. Instead, while Sonti frequently uses the phrasing “in one embodiment,” a POSA would have at once envisaged using each such disclosed option for the phase of the formulation being discussed.

97. Sonti discloses topical pharmaceutical emulsion compositions that include an oil phase, wherein the oil phase of the emulsion includes medium chain triglycerides. Ex-1005, [0061] (“the oil phase comprises an ester of glycerin. Exemplary esters of glycerin include...medium chain triglycerides (MCT)”), [0071], [0351] (Example 7 and Table 7), [0370] (Example 9 and Table 9) (“MCT” in the oil phase). Example 9 specifically includes formulations having 1% tapinarof. Ex-1005, Table 9 (formulations 30-33).

98. Sonti also teaches that the oil phase of the emulsion includes propylene glycol. For example, Sonti teaches that the “compositions may further comprise a penetration enhancer...[and] exemplary penetration enhancers include...diols.” Ex-1005, [0122]-[0123]. Sonti then explains that “exemplary diols include...*propylene glycol*”. Ex-1005, [0130]. Sonti further explains that the “co-solvent...may function as a penetration enhancer.” Ex-1005, [0122]. And Sonti

explains that an “oil miscible co-solvent may be used” (Ex-1005, [0117]), indicating to a POSA that the penetration enhancer (which may include propylene glycol) can be part of the oil phase. *See also* Ex-1005, [0119]-[0120], [0144], [0146], [0194], [0198], [0205], [0213], [0215], [0224], [0239], [0255], [0351] (Table 7, formulations 15-20), [0354], [0355] (Table 8, formulations 17-26 and 28), [0370] (Table 9, formulations 30-40), claim 9. Tables 8 and 9 specifically include formulations having 1% tapinarof. Ex-1005, Table 8 (formulation 21), Table 9 (formulations 30-33).

99. Sonti also teaches inclusion of a surfactant or mixture of two or more surfactants (Ex-1005, [0074]), such as a non-ionic surfactant (Ex-1005, [0077]), that include *emulsifying waxes* (Ex-1005, [0078]). *See also* Ex-1005, [0087] (“In an embodiment, the non-ionic surfactant is an emulsifying wax, e.g. a non-ionic emulsifying wax also known as emulsifying wax NF, or emulsifying wax BP. In an embodiment, the emulsifying wax is a mixture of cetearyl alcohol and polysorbate 60. In another embodiment, the emulsifying wax is a proprietary blend known as ‘Polawax NF’™ (Croda Inc, Edison, N.J., USA).”). Sonti further teaches that the emulsifying wax can be a non-ionic emulsifying wax and can be part of the oil phase. Ex-1005, [0323] (Table 1, formulations 1-1(a), “emulsifying Wax, BP” listed as part of “Oil phase” of a 1 wt.% tapinarof composition), [0325] (Table 2, formulations 2-4, “Non-ionic emulsifying wax” listed as part of “Oil phase” of a

0.5 wt.% tapinarof composition), [0327] (Table 4, formulations 10-14, “Non-ionic emulsifying wax” listed as part of “Oil phase” of a 0%-2 wt.% tapinarof composition), claims 16-17. Tables 1 and 4 specifically include formulations having 1% tapinarof. Ex-1005, Table 1 (formulation 1a), Table 4 (formulation 13).

100. Sonti also teaches that the oil phase can further include a co-solvent, such as *diethylene glycol monoethyl ether*. Ex-1005, [0119], [0120], [129], [0194], [0198], [0205], [0213], [0215], [0224], [0239], [0255], [0351] (Table 7, formulations 15-20), [0357] (Example 8 and Table 8). Additionally, Sonti teaches that the co-solvent can be “an oil miscible co-solvent” to help “solubilize the active ingredient in the oil phase”. Ex-1005, [0117]. This indicates to a POSA that the diethylene glycol monoethyl ether can be part of the oil phase (as also shown, for example, in Tables 7 and 8 of Sonti). Table 8 specifically includes a formulation having 1% tapinarof, with diethylene glycol monoethyl ether in the oil phase. Ex-1005, Table 8 (formulation 21). Additionally, Ex-1005 teaches that the topical pharmaceutical emulsion compositions can further include a penetration enhancer, wherein the co-solvent described therein may function as the penetration enhancer. Ex-1005, [0122]. Ex-1005 teaches that the penetration enhancer can be an alcohol (Ex-1005, [0123]), and that the alcohol can be *diethylene glycol monoethyl ether*. Ex-1005, [0129].

101. Sonti also teaches topical pharmaceutical emulsion compositions that

include a surfactant (Ex-1005, [0074]), such as a non-ionic surfactant (Ex-1005, [0077]), wherein the non-ionic surfactant includes an ethoxylated fatty alcohol ether (Ex-1005, [0078]), such as “steareth-2” (Ex-1005, [0079]). A POSA would have known that “steareth-2” corresponds to *polyoxyl stearyl ether-2*. Ex-1022, for example, provides for synonyms and mappings of STEARETH-2 that include “POLYOXYL 2 STEARYL ETHER.” *See also* Ex-1023 (explaining that “Steareth-2” has synonyms that include “POLYOXYL 2 STEARYL ETHER). Ex-1025 similarly states that “VTAMA cream also contains the following inactive ingredients: . . . polyoxyl 2 stearyl ether” at pages 3-4, and then in the table listing the ingredients of VTAMA cream at page 9 identifies “Steareth-2.” Sonti also teaches including “steareth-2” (which is *polyoxyl stearyl ether-2*” in the oil phase of the formulations at other places. *See* Ex-1005, [0088]-[0089], [0091]-[0092], [0323] (Table 1, formulations 1-1(a)), [0325] (Table 2, formulations 2-5), [0326] (Table 3, formulations 6-9), [0327] (Table 4, formulations 10-14), [0329] (example 5), [0351] (Table 7, formulations 15-20), [0355] (Table 8, formulations 17-29), [0357] (example 8), [0370] (Table 9, formulations 30-40), claims 11, 13, 15, and 17. Tables 1, 4, 8, and 9 specifically include formulations having 1% tapinarof. Ex-1005, Table 1 (formulation 1a), Table 4 (formulation 13), Table 8 (formulation 21), Table 9 (formulations 30-33).

102. Sonti also teaches topical pharmaceutical emulsion compositions that

include an oil phase, wherein the oil phase of the emulsion includes a surfactant (Ex-1005, [0074]), such as a non-ionic surfactant (Ex-1005, [0077]), including a sorbitan derivative (Ex-1005, [0078]), such as polysorbate 80 (Ex-1005, [0085]). *See also* Ex-1005, [0089], [0091]-[0092], [0351] (Table 7, formulations 15-20), [0355] (Table 8, formulations 17-29), [0357] (Example 8), [0370] (Table 9, formulations 30-40), claims 13, 15, and 17. Tables 8 and 9 specifically include formulations having 1% tapinarof. Ex-1005, Table 8 (formulation 21), Table 9 (formulations 30-33).

103. Sonti also teaches topical pharmaceutical emulsion compositions that include a surfactant (Ex-1005, [0074]), such as a non-ionic surfactant (Ex-1005, [0077]), wherein the non-ionic surfactant includes an ethoxylated fatty alcohol ether (Ex-1005, [0078]), such as “steareth-20” (Ex-1005, [0079]). A POSA would have known that “steareth-20” corresponds to polyoxyl stearyl ether-20. Ex-1021, for example, provides for synonyms and mappings of STEARETH-20 that include “POLYOXYL 20 STEARYL ETHER.” *See also* Ex-1024 (explaining that “Steareth-20” has synonyms that include “POLYOXYL 20 STEARYL ETHER”). Sonti also teaches “steareth-20” (which is polyoxyl stearyl ether-20) in the “oil phase” of the formulations. *E.g.*, Ex-1005, [0088]-[0089], [0091]-[0092], [0323] (Table 1, formulations 1-1(a)), [0325] (Table 2, formulations 2-5), [0326] (Table 3, formulations 6-9), [0327] (Table 4, formulations 10-14), [0329] (example 5),

[0351] (Table 7, formulations 15-20), [0355] (Table 8, formulations 17-29), [0357] (example 8), [0370] (Table 9, formulations 30-40), claims 11, 13, 15, and 17. Tables 1, 4, 8, and 9 specifically include formulations having 1% tapinarof. Ex-1005, Table 1 (formulation 1a), Table 4 (formulation 13), Table 8 (formulation 21), Table 9 (Formulations 30-33).

104. Sonti also teaches that the topical pharmaceutical emulsion compositions can further include a pH adjusting agent (Ex-1005, [0103]), that is an acid, such as benzoic acid. Ex-1005, [0104]. Additionally, Ex-1005 teaches that the topical pharmaceutical emulsion compositions can further include a preservative (Ex-1005, [0112]), such as benzoic acid. Ex-1005, [0113]-[0115], [0191]-[0192], [0194], [0241], [0254], [0257]. Additionally, Ex-1005 teaches topical pharmaceutical emulsion compositions that include an oil phase, wherein the oil phase of the emulsion includes benzoic acid. Ex-1005, [0326] (Table 3, formulations 6-9), [0327] (Table 4, formulations 10-14), [0351] (Table 7, formulations 15-20), [0355] (Table 8, formulations 17-29), [0357] (Example 8), [0370] (Table 9, formulations 30-40). Tables 4, 8, and 9 specifically include formulations having 1% tapinarof. Ex-1005, Table 4 (formulation 13), Table 8 (formulation 21), Table 9 (Formulations 30-33).

105. Sonti also teaches topical pharmaceutical emulsion compositions that include an antioxidant (Ex-1005, [0093]), such as butylated hydroxytoluene. Ex-

1005, [0094]-[0095], [0187]-[0188], [0191]-[0192], [0194], [0214], [0226], [0238], [0253], claim 5. “Butylated hydroxytoluene” was commonly known as “BHT”. Ex-1005, [0094] (“butylated hydroxytoluene (BHT)”). Sonti teaches examples of topical pharmaceutical emulsion compositions that include an oil phase, wherein the oil phase of the emulsion includes BHT. Ex-1005, [327], [0351]-[0374] (Examples 4, 7-9, describing method of cream preparation indicating that “BHT” (which s butylated hydroxytoluene) is part of oil phase). Tables 4, 8 and 9 specifically include formulations having 1% tapinarof. Ex-1005, Table 4 (formulation 13, showing “BHT” in the oil phase), Table 8 (formulation 21, showing “BHT” in the oil phase); Table 9 (formulations 30-33, showing “BHT” in the oil phase).

106. As I explained above, Sonti also discloses that the amount of active ingredient (tapinarof) in the formulations can be 1.0 wt.%. Ex-1005, [0196]; *see also id.*, [0055].

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*”

107. In my opinion, Sonti discloses the elements of claim 4 and therefore anticipates that claim.

108. Sonti discloses exemplary formulations where the water phase of the oil-in-water emulsion comprises sodium citrate, edetate disodium, citric acid

monohydrate, and water, as claimed. This includes such formulations where the amount of tapinarof (the “active ingredient”) is 1 wt.%. Such examples include Formulation 13 of Example 4, Formulation 21 of Example 8, and Formulations 30-33 of Example 9. I have reproduced the tables from Sonti showing these formulations below, with highlighting added:

TABLE 4

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

TABLE 8

Ingredient	Formulation Number									
	17	21	22	23	24	25	26	27	28	29
	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w	% w/w
Water Phase										
Purified water	65.18	64.68	63.68	63.18	61.18	65.58	62.68	75.18	67.18	77.18
Sodium citrate	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19
Citric acid	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08	0.08
Disodium EDTA	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Oil Phase										
Active ingredient	0.50	1.00	2.00	2.00	4.00	0.10	3.00	0.50	0.50	0.50
Propylene glycol	10.00	10.00	10.00	10.00	10.00	10.00	10.00	—	10.00	—
Diethylene glycol monoethyl ether	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	—	—
BHT	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Benzoic Acid	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25
Emulsifying wax, NF	7.20	7.20	7.20	—	—	7.20	7.20	7.20	7.20	7.20
Cetostearyl alcohol	—	—	—	5.90	5.90	—	—	—	—	—
MCT	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Polysorbate 80	1.50	1.50	1.50	2.10	2.10	1.50	1.50	1.50	1.50	1.50
Steareth 2	1.80	1.80	1.80	2.50	2.50	1.80	1.80	1.80	1.80	1.80
Steareth 20	1.10	1.10	1.10	1.60	1.60	1.10	1.10	1.10	1.10	1.10
	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

TABLE 9

Ingredient	Formulation Number										
	30	31	32	33	34	35	36	37	38	39	40
	%	%	%	%	%	%	%	%	%	%	%
Ingredient	w/w	w/w	w/w	w/w	w/w	w/w	w/w	w/w	w/w	w/w	w/w
Water Phase											
Purified water	48.18	52.68	56.68	60.68	57.75	56.75	60.67	59.67	69.18	66.38	65.18
Sodium citrate	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19	0.19
Citric acid	0.08	0.08	0.08	0.08	0.09	0.09	0.09	0.09	0.08	0.08	0.08
(anhydrous or monohydrate)											
Disodium EDTA	0.10	0.10	0.10	0.10	0.09	0.09	0.09	0.09	0.10	0.10	0.10
Oil Phase											
Active ingredient	1.00	1.00	1.00	1.00	2.00	2.00	2.00	2.00	0.50	0.50	0.50
Propylene glycol	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Diethylene glycol monoethyl ether	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00	2.00
BHT	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10	0.10
Benzoic Acid	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.25	0.10	0.10	0.10
Emulsifying wax, NF	7.20	7.20	7.20	7.20	7.20	7.20	7.20	7.20	7.20	10.00	7.20
White Petrolatum	16.50	12.00	8.00	4.00	—	4.00	2.00	4.00	3.00	3.00	—
MCT	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	—	—	—
Mineral Oil	—	—	—	—	6.00	3.00	1.00	—	3.00	3.00	10.00
Polysorbate 80	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50	1.50
Steareth 2	1.80	1.80	1.80	1.80	1.80	1.80	1.80	1.80	1.80	1.80	1.80
Steareth 20	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10
	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Ex-1005, [0327] (Example 4), [0355] (Example 8), and [0370] (Example 9).

109. Each of these formulations contained a water phase that included the four claimed ingredients: sodium citrate (“sodium citrate”), edetate disodium (“disodium EDTA”), citric acid monohydrate (“citric acid”), and water (“water”). Each of these is highlighted in the tables above.

110. A POSA would have known that “disodium EDTA” is edetate disodium. EDTA refers to ethylenediaminetetraacetic acid. EDTA is available as several salts, notably disodium EDTA. Edetate and EDTA were often used interchangeably by POSAs. Ex-1031 at 23-24 (entry for “Edetate Disodium,”

noting that “Synonyms” include “disodium EDTA”). In addition, Sonti teaches topical pharmaceutical emulsion compositions that include a chelating agent (Ex-1005, [0107]), such as “ethylene diamine tetraacetic acid (EDTA)” or salts thereof. Ex-1005, [0108]. *See also id.*, [0109] (“In one embodiment, the chelating agent is EDTA or a salt thereof, such as potassium, sodium or calcium salts of EDTA. In an embodiment, the EDTA or a salt thereof is disodium EDTA.”).

111. A POSA also would have known that “citric acid” is “citric acid monohydrate,” or at a minimum, includes “citric acid monohydrate.” This is so because “citric acid” within a topical formulation can only reasonably be “citric acid anhydrous” or “citric acid monohydrate.” These are the two choices. Because Sonti discloses “citric acid” as part of the water phase, I understand the substance to be “citric acid monohydrate.” This is so because citric acid anhydrous, upon contacting the water phase, would absorb water and would no longer exist in the anhydrous form. Upon absorbing water, it would exist in the monohydrate form. Hence, adding citric acid monohydrate to the water layer is preferred. Additionally, citric acid monohydrate has a higher solubility in a water phase, compared to citric acid anhydrous. Sonti’s disclosure of “citric acid” is therefore understood to mean “citric acid monohydrate.”

112. Each of the formulations in Examples 4, 8, and 9 were also “cream” compositions that included a “water phase” and an “oil phase,” that were blended

into an “emulsion.” Ex-1005, [0327] (Table 4, showing “water phase” and “oil phase”) and [0334]-[0344] (describing the “emulsification” of Example 4); *id.*, [0355] (Table 8, showing “water phase” and “oil phase”) and [0359]-[0369] (describing “emulsification” of Example 8); *id.*, [0370] (Table 9, showing “water phase” and “oil phase”) and [0370]-[0374] (describing “the emulsion composition”). A POSA would understand formulations comprising oil and water phases “emulsified” to be an “oil-in-water emulsion.”

113. Sonti also teaches the common ingredients recited in claim 4 in its overview of the formulations. Examples include:

- Sonti also teaches topical pharmaceutical emulsion compositions that include a water phase (Ex-1005, Abstract), wherein the water phase of the emulsion includes sodium citrate dihydrate. Ex-1005, [0325] (Table 2, formulations 2-5), [0326] (Table 3, formulations 6-9).
- Sonti also teaches topical pharmaceutical emulsion compositions that include a chelating agent (Ex-1005, [0107]), such as ethylene diamine tetraacetic acid (EDTA) or salts thereof (e.g., disodium EDTA). Ex-1005, [0108]. *See also* Ex-1005, [0109] (“In one embodiment, the chelating agent is EDTA or a salt thereof, such as potassium, sodium or calcium salts of EDTA. In an embodiment, the EDTA or a salt thereof is disodium EDTA.”).

- Sonti also teaches the topical pharmaceutical emulsion compositions can include a pH adjusting agent (Ex-1005, [0103]) such as an acid, including citric acid (Ex-1005, [0104]). *See also* Ex-1005, [0194], [0258]. EX-1005 also teaches that the pH adjusting agent can be a buffer, such as citrate/citric acid. Ex-1005, [0105]. Ex-1005 also teaches the topical pharmaceutical emulsion compositions can include a chelating agent, such as citric acid. Ex-1005, [0108]-[0110].
- Sonti teaches topical pharmaceutical emulsion compositions that include water in the water phase. Ex-1005, Abstract, [0021], [0023]-[0033], [0035]-[0040], claims 1, 18, 20, and 24-29; *see also id.*, [0073] (“The present topical pharmaceutical emulsion compositions comprise an aqueous or water phase comprising water. Suitably, the water is present in the composition in an amount from about 25% to about 85% by weight, based on the total weight of the composition. In an embodiment, the water is present in the composition in an amount from about 30% to about 80% by weight, based on the total weight of the composition. In another embodiment, the water is present in an amount from about 55% to about 75% by weight, based on the total weight of the composition.”). *See also* Ex-1005, [0154], [0157]-[0162], [0174]-[0184], [0186]-[0188], [0190]-[0194], [0200]-[204],

[0206]-[0212], [0216]-[0223], [0242]-[0251], [0323] (Table 1, formulations 1-1(a)), [0325] (Table 2, formulations 2-5), [0326] (Table 3, formulations 6-9), [0328]-[0344] (Example 5), [0351] (Table 7, formulations 15-20).

E. Dependent Claims 2-4 Are Obvious in View of Sonti and the Knowledge of a POSA

114. Sonti discloses the formulations recited by claims 2-4, as I explained above.

115. However, even if the elements of these claims could be viewed as taught in different embodiments in Sonti, which I do not believe they are, a POSA also would have been motivated to combine the teachings of Sonti into a single embodiment and would have expected to easily be able to do so,

116. A POSA also would have been motivated to combine the formulation teachings of Sonti into a single embodiment in order to provide standard oil-in-water emulsion that would have been expected to work as a topical cream.

117. There are several additional reasons why, in my opinion, a POSA would have been motivated to arrive at the ingredient lists of claims 2, 3 and 4, for an oil-in-water emulsion, in view of Sonti's teachings, and would have expected that to be a predictable, straightforward thing to do.

118. **One**, a POSA would have been motivated to consider all of Sonti's teachings when formulating compositions for the tapinarof active ingredient, and

not just the specific “examples” of formulations Sonti provides. A POSA would also consider Sonti’s general teachings. Sonti explains that “[w]hile particular embodiments of the present invention are described, the skilled artisan will appreciate that various changes and modifications can be made without departing from the spirit and scope of the invention.” Ex-1005, [0322]. Sonti also teaches that “[t]hese formulations include any of the various known excipients which may be 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].

119. Also, an oil-in-water emulsion (as recited by Claim 2, and as further recited by Claim 3 (for the oil phase) and Claim 4 (for the water phase)) was an extremely common, well-known formulation for topical pharmaceuticals by November 2018. Oil-in-water emulsions were known to have the benefit of allowing an active ingredient that could not be sufficiently dissolved in water to be uniformly dispersed in a spreadable form suitable for topical application. *E.g.*, Ex-1030, 10.

120. **Two**, the oil-phase ingredients recited by claim 3 were known constituents of an oil phase of an oil-in-water emulsion, and had predictable functions in the formulation art. Examples include:

- *Medium chain triglycerides* were known to improve spreading and

penetrance properties of topical preparations for the skin and provide stability against oxidation. Ex-1031, 26.

- *Propylene glycol* was known to improve solvency and alter skin barrier properties for the treatment of impaired skin barrier conditions. *Id.*, 30.
- *Nonionic emulsifying wax* was commonly used in barrier creams as an emulsifying agent. *Id.*, 37.
- *Diethylene glycol monoethyl ether* was a solubilizing agent known to enhance skin penetration in creams and lotions. *Id.*, 20.
- *Benzoic acid* was widely used as an antimicrobial preservative. *Id.*, 10.
- *Polysorbate 80* was known as a common ingredient in a surfactant, *E.g.*, Ex-1005, [0085], [0092]. Surfactants were used in creams to stabilize the emulsion. Surfactants were (and still are) typically employed in creams (e.g., oil-in-water or water-in-oil emulsion) to stabilize the emulsion. Surfactants were known to decrease the interfacial tension between oil and water and hinder the coalescence of the dispersed phase in an oil-in-water or water-in-oil emulsion.
- *Butylated hydroxytoluene* was known to delay oxidative rancidity of fats and oils and commonly used as an antioxidant. Ex-1031, 14.

- *Steareth 2* and *Steareth 20* were well-known ingredients in surfactants used for topical creams. Ex-1005, [0088]-[0089], [0091]-[0092].

And it was well-known that one would want to include a surfactant in an oil-in-water emulsion to use as a topical skin composition. E.g., Ex-1005, [0074] (“a surfactant is a compound that lowers the surface tension between two liquids or between a liquid and a solid” and is equivalent to a “emulsifier”). As I explained above, surfactants were known to decrease the interfacial tension between oil and water and hinder the coalescence of the dispersed phase in an oil-in-water or water-in-oil emulsion.

121. The ingredients of the water phase recited by claim 4 were also known, common constituents of the water phase of an oil-in-water emulsion, with well-known functions. For example:

- *Sodium citrate* was known to serve as a buffering agent and complexing agent in solution. Ex-1031, 34.
- *Edetate disodium* was known to have a stabilizing effect in topical formulations gels and was commonly used as a complexing agent. *Id.*, 23.
- *Citric acid monohydrate* was known to adjust the pH of solutions. *Id.*, 17.

122. As I explained above, the ingredients listed for the oil phase (claim 3) and water phase (claim 4) were common, known ingredients of the oil and water phases of an oil in water emulsion, and each already had known, predictable functions. Because of this, a formulator such as myself would have expected to use them when creating an oil in water emulsion, and would have expected to use only normal, routine skill to do so.

123. **Three**, Sonti discloses the ingredients recited by claim 3 by listing them as options for various parts of a formulation, indicating to a POSA that Sonti is not disclosing each ingredient only as part of one discrete embodiment, but rather as a known, potential ingredients intended to be used predictably in many different embodiments. As some examples, Sonti teaches that “exemplary antioxidants include...” (Ex-1005, [0094], “exemplary chelating agents include...” (Ex-1005, [0107]), “exemplary co-solvents include...” (Ex-1005, [0119], “exemplary penetration enhancers include...” (Ex-1005, [0123]), et cetera.

124. **Four**, Sonti itself teaches that its formulation ingredients can be used in combination with each other. Some examples are below:

- Ex-1005 teaches topical pharmaceutical emulsion compositions that include a combination of polyoxyl stearyl ether-2 and polyoxyl stearyl ether-20. Ex-1005, [0088] (“In one embodiment, the surfactant comprises one or more ethoxylated fatty alcohol ethers. In another

embodiment, the ethoxylated fatty alcohol ether is a mixture of steareth-2 and steareth-20.”)

- Ex-1005 teaches topical pharmaceutical emulsion compositions that include a combination of polyoxyl stearyl ether-2, polyoxyl stearyl ether-20, and polysorbate 80. Ex-1005, [0089] (“In one embodiment, the surfactant comprises a mixture of an ethoxylated fatty alcohol ether and a sorbitan derivative. In another embodiment, the mixture of an ethoxylated fatty alcohol ether and a sorbitan derivative is a mixture of steareth-2, steareth-20 and polysorbate 80.”).
- Ex-1005 teaches topical pharmaceutical emulsion compositions that include a combination of steareth-2, steareth-20, polysorbate 80, and the emulsifying wax, Polawax™ NF. Ex-1005, [0091] (“In one embodiment, the surfactant comprises a mixture of an ethoxylated fatty alcohol ether and an emulsifying wax. In another embodiment, the surfactant comprises a mixture of an ethoxylated fatty alcohol ether, a sorbitan derivative and an emulsifying wax. Suitably, the mixture of an ethoxylated fatty alcohol ether and an emulsifying wax is a mixture of steareth-2, steareth-20, and Polawax™ NF. Suitably, the mixture of an ethoxylated fatty alcohol ether, a sorbitan derivative and an emulsifying wax is a mixture of steareth-2, steareth-20,

polysorbate 80 and Polawax™ NF.”).

- Ex-1005 teaches topical pharmaceutical emulsion compositions that include a combination of citric acid and BHT.² Ex-1005, [0110] (“In an embodiment, the compositions of the invention comprise a mixture of a chelating agent and an antioxidant which is a mixture of citric acid and BHT.”).
- Ex-1005 teaches topical pharmaceutical emulsion compositions that include a combination of co-solvents propylene glycol and diethylene glycol. Ex-1005, [0120] (“In another embodiment, the co-solvent is a mixture of propylene glycol and diethylene glycol monoethyl ether.”).

125. **Five**, there is nothing about the formulations recited by claims 2-4 of the '088 patent that would have been unusual or unexpected to a formulator tasked with creating a topical emulsion prior to November 2018. Each claim recites well-known ingredients used for its common and well-known, predictable purpose. Further, the claims do not specify specific amounts of any particular ingredient in the formulation.

126. **Six**, the '088 patent specification also indicates that the specific

² BHT refers to butylated hydroxytoluene. *See* Ex-1005, [0094] (“Exemplary antioxidants include, but are not limited to, butylated hydroxytoluene (BHT),...”).

formulations for tapinarof topical compositions were routine and within the ordinary skill of a POSA at the time. For example, the '088 patent explains that “the person of ordinary skill in the art can refer to various pharmacological references, such as” the Banker & Rhodes and Goodman & Gilman’s reference books “for guidance” in formulating specific topical compositions:

combinations thereof. The person of ordinary skill in the art can refer to various pharmacologic references such as, for example, Modern Pharmaceutics, Banker & Rhodes, Marcel Dekker, Inc. (1979) and Goodman & Gilman’s The Pharmaceutical Basis of Therapeutics, 6th Edition, MacMillan Publishing Co, New York (1980) for guidance in determining the amount of such components in the topical compositions and formulations of embodiments.

Ex-1001, 8:23-29.

127. Given that the ingredient lists recited by claims 3 and 4 were just standard ingredient lists for oil-in-water emulsions, a POSA would have expected to be able to combine the teachings of Sonti using only routine formulating skill. In my opinion, combining the formulation teachings in Sonti’s patent, in view of Sonti’s teaching and the knowledge of a POSA experienced in formulation, would have been just combining known features in a routine and common-sense manner to yield a predictable oil in water emulsion.

**F. Dependent Claims 2-4 Are Obvious in View of Bissonnette,
Further In View of Sonti and/or Chen**

128. I see that the Bissonnette reference (Ex-1008) teaches applying a “1% WBI-1001 cream” topically to treat plaque psoriasis. Ex-1008, 1-2 . “WBI-1001” is tapinarof, as I explained above. Bissonnette does not teach what the specific ingredients of the tapinarof cream are, other than it contains 1% by weight of tapinarof (“WBI-1001,” the active ingredient).

129. However, the formulation recited by claims 2-4 is anticipated by Sonti, for the reasons I describe above. It also would have been obvious, in view of the teachings of Sonti and the knowledge of a POSA in the field, for the reasons I describe above.

130. To a POSA, in view of the teachings of Sonti, it also would have been a common sense, predictable approach to use a formulation as recited in claims 2-4 for the 1% tapinarof cream taught by Bissonnette. A POSA formulating a topical cream of 1 wt.% tapinarof would have been motivated to look to the teachings of Sonti and would have reasonably expected to be successful in doing so, for several reasons.

131. **First**, Bissonnette and Sonti are in the same field of art. In fact, each teaches applying exactly the same active ingredient (tapinarof) to exactly the same skin condition (plaque psoriasis) at the same strength (1 wt.% tapinarof). *E.g.*, Ex-1008, 1; Ex-1005, Abstract, [0285]-[0296], [0008]-[0010], [0055] and [0196] (“1%...by weight” of tapinarof). *Supra*, § IX(A). I explained above that the active ingredient Sonti, Bissonnette, and Chen disclose is tapinarof, even though they use different nomenclature. *Supra, id.* It would have been common sense for a POSA looking to formulate a topical cream for tapinarof, for the treatment of plaque psoriasis, to look to a reference that discusses formulations for topical tapinarof compositions for treating plaque psoriasis. And in doing so, because both the active ingredient and the intended use was the same, a POSA would reasonably expect to be successful.

132. **Second**, Bissonnette disclosed using the 1 wt.% tapinarof as a “cream.” Ex-1008, 2; Ex-1013, 32:25-37; *see also id.*, 32:46-47 (“The cream of the invention contained 1% 3,5-dihydroxy-4-isopropylstilbene”). A POSA looking to create a formulation for that “cream” would be motivated to look to another reference that teaches formulations for a tapinarof cream. That is exactly what Sonti teaches. Sonti s teaches that a “cream” may be an oil-in-water emulsion. “Suitably, the emulsion may be formulated as a cream. The cream may be an oil-in-water cream... In one particular embodiment, the cream is an oil-in-water cream.” Ex-1005, [0100]-[0101].

133. **Third**, formulating a 1 wt.% tapinarof cream to use according to Bissonnette’s method (to treat plaque psoriasis), according to the teachings of Sonti, would have been no more than the combination of known elements in a predictable manner. As I explained above, Sonti already taught tapinarof emulsion formulations for treating plaque psoriasis, including specifically for 1 wt.% tapinarof emulsion formulations. In addition, Bissonnette chose to not describe exactly how the 1 wt.% tapinarof cream was formulated. This is not at all surprising, and is additional evidence supporting my opinion that specific formulations for 1 wt.% tapinarof topical creams, including those recited by claims 2-4 and described by Sonti, were routine and well within the ordinary skill of a POSA by November 2018.

G. The US Clinical Trials (Ex-1026) Were Published and Publicly Available

134. During my 30+ years as a practicing pharmaceutical formulator, I have become very familiar with the various publicly accessible databases that provide access to clinical trial documentation and results.

135. I commonly looked up studies using publicly available clinical trial databases prior to 2018, and I continue to do so today.

136. Prior to 2018, and continuing through today, I commonly used the database provided at <https://clinicaltrials.gov/search> to search and retrieve clinical studies of pharmaceutical treatments.

137. I have reviewed the set of studies taken from the <https://clinicaltrials.gov/search> database and compiled as Ex-1026. I can confirm that a POSA at the relevant time (prior to November 13, 2018) would have looked to this database for relevant information regarding methods of treating psoriasis. I can also confirm that the studies in Ex-1026, all dated prior to November 13, 2018, would have been publicly accessible on that database to a POSA, prior to November 13, 2018.

138. Confirming that the database available at <https://clinicaltrials.gov/search> (and the studies in it) were publicly available prior to 2018, the WayBack Machine internet archive website shows this:

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

Dated: 04/21/2024



Paul T. Sudhakar, MS, MBA