

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

**BIOFRONTERA INCORPORATED,
BIOFRONTERA BIOSCIENCE GMBH,
BIOFRONTERA PHARMA GMBH,**

AND

BIOFRONTERA AG

Petitioners

v.

DUSA PHARMACEUTICALS, INC.

Patent Owner

PATENT 10,357,567

DECLARATION OF HOWARD ROGERS, MD, PHD

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DECLARATION OF DR. HOWARD ROGERS

1. I, Howard Rogers, declare as follows:

2. My name is Howard Rogers. I am over the age of twenty-one (21) years, of sound mind, and capable of making the statements set forth in this Declaration. I am competent to testify about the matters set forth herein. All the facts and statements contained herein are within my personal knowledge and they are, in all things, true and correct.

3. I have been asked by Biofrontera Incorporated, Biofrontera Bioscience GmbH, Biofrontera Pharma GmbH, and Biofrontera AG (collectively, “Biofrontera”) to submit this declaration in support of their challenge to the validity of all claims of U.S. Patent No. 10,357,567 (“the ‘567 patent”).

I. Education and Experience

4. My *curriculum vita* is attached as Exhibit 1004.

5. I am a board-certified dermatologist and a fellowship-trained Mohs micrographic surgeon. I received a Bachelor of Science degree in Biology from Harvard University in 1989, where I graduated magna cum laude. My undergraduate thesis research focused on the immunological response of mast cells. I attended medical school at Washington University School of Medicine in St. Louis from 1989-1996. I graduated with honors, with both an M.D. and a Ph.D. My Ph.D. thesis involved seminal research into mechanisms of infectious immunity. At graduation,

I was awarded the Olin Fellowship (in recognition of my advanced medical research) and the Yalem Dermatology Award (for excellence in Dermatology scholarship).

6. I completed my internship in internal medicine at University Hospital in Baltimore, Maryland. I completed my residency in dermatology at Washington University School of Medicine in 2000 as the chief dermatological resident at Barnes Hospital in St. Louis, MO. While a dermatology resident, I won numerous awards including being elected chief resident.

7. I practiced general and dermatologic surgery at the Chelsea Clinic in Norwich, CT from 2000-2004. I then founded Advanced Dermatology, a private dermatology practice specializing in skin cancer diagnosis, treatment and prevention, in Norwich, CT. I completed a fellowship in Mohs micrographic surgery and cutaneous surgical oncology specializing in difficult to treat skin cancers at the Skin Cancer Center at the University of Cincinnati Hospital in Cincinnati, OH in 2008. Following this training, I founded a second dermatology office, Shoreline Mohs Surgery, in Guilford, CT.

8. I have nearly twenty-five years of experience with skin cancer treatment and photodynamic therapy. My education and experience in photodynamic therapy started with residency training in the procedure in 1997. Since then, in my own private practice, I have treated patients with photodynamic therapy for a variety

of conditions for around 15 years. I have also served as an advisor to the American Medical Association Relative Value Update Committee in defining photodynamic therapy methods and work for incorporation into Current Procedural Terminology and for procedure valuation in the Medicare physician fee schedule.

9. I am an author or co-author on over twenty publications relating to dermatology and skin cancer. I have also testified before Congress in 2019 on the administrative, economic, and medical effects of prior authorization and step therapy policies on practitioners and patients. I am board certified by the American Board of Dermatology, and my fellowship training was accredited by the American College of Mohs Micrographic Surgery. I have served on numerous committees and boards of national dermatological organizations. My leadership in the field has been recently recognized by election to the Presidency of the American College of Mohs Surgery where I currently serve as Vice President and President-elect.

10. Having the foregoing knowledge and experience, I am well qualified to offer the opinions I express in this declaration. A summary of my experience, education, publications and other qualifications is provided in my CV, a copy of which is submitted separately as Exhibit 1004.

II. Compensation

11. In consideration for my services, my work on this case is being billed to Biofrontera at an hourly rate of \$600 per hour, independent of the outcome of this

proceeding. For any work requiring me to be away from the office, I am being reimbursed at a daily rate of \$8000/day. I am also being reimbursed for reasonable expenses I incur in relation to my services provided for this proceeding.

III. Legal Considerations

12. I understand from counsel that the following standards govern the determination of whether a patent claim is invalid as anticipated by and/or obvious in light of the prior art. I have applied these standards in my analysis of whether claims of the '567 patent were anticipated and rendered obvious by January 12, 2018.

A. Anticipation

13. I understand that patents or printed publications that qualify as prior art can be used to invalidate a patent claim as anticipated or as obvious.

14. I understand that a patent claim is “anticipated” by a single prior art reference if that reference discloses each element of the claim.

15. I understand that the test for anticipation is performed in two steps. First, the claims are interpreted to determine their meaning. Second, a potentially invalidating prior art reference is analyzed on an element-by-element basis to determine whether each claim element, as interpreted during the first step, is present in that reference. If all of the elements of a patent claim are present in the prior art reference, then that claim is anticipated and is therefore invalid.

16. I further understand that a prior art reference can anticipate a patent claim without expressly disclosing a feature or element of the claim if the missing feature or element is necessarily present, or inherent, in the anticipating reference.

17. I also understand that it is acceptable to examine extrinsic evidence outside the prior art reference in determining whether a feature, while not expressly discussed in the reference, is necessarily present within that reference.

B. Obviousness

18. I understand that a claimed invention is not patentable for obviousness if the differences between the invention and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter of the invention pertains.

19. I understand that a person of ordinary skill in the art is a hypothetical person who is presumed to have known the relevant art at the time of the invention. As discussed above, I understand that the relevant art for the purpose of this declaration at least includes references that were published or publically available before January 12, 2018, the filing date for the '567 patent.

20. I have been instructed that a determination of obviousness requires inquiries into: (1) the scope and content of the state of the art when the invention was made; (2) the differences between the art and the claims of the patent at issue;

(3) the level of ordinary skill in the pertinent art when the invention was made; and, (4) to the extent they exist, any secondary considerations, such as, unexpected results, long-felt but unresolved needs, failure of others, etc.

21. I understand that a claim can be found to be obvious if all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable and expected results to one of ordinary skill in the art.

22. I understand that improper hindsight must not be used when comparing the prior art to the invention for obviousness. Thus, a conclusion of obviousness must be firmly based on the knowledge and skill of a person of ordinary skill in the art at the time the invention was made.

23. I have been informed that obviousness may also be shown by demonstrating that it would have been obvious to modify what is taught in a single piece of prior art to create the patented invention. I further understand that obviousness may be demonstrated by showing that it would have been obvious to combine the teachings of more than one item of prior art.

24. I understand that in order for a combination of references or teachings to render the claimed invention obvious, there must be some supporting rationale for

combining the cited references or teachings as proposed. I understand further that prior art references themselves may provide a suggestion, motivation, or reason to combine, but that at other times the linkage between two or more prior art references is common sense.

25. I have been informed that the application of the teaching, suggestion or motivation test should not be rigidly applied, but rather is an expansive and flexible test. For example, I have been informed that the common sense of a person of ordinary skill in the art can serve as motivation for combining references.

26. In addition, I understand that a person of ordinary skill in the art must have had a reasonable expectation of success in deriving the claimed invention from the combination of references or teachings. I understand that obviousness does not require absolute predictability of success but instead requires only a reasonable expectation of success.

27. I further understand that exemplary rationales that may support a conclusion of obviousness include: (1) simply arranging old elements in a way in which each element performs the same function it was known to perform, and the arrangement yields expected results; (2) merely substituting one element for another known element in the field, and the substitution yields no more than a predictable result; (3) the use of a known technique to improve similar methods or products in

the same way; (4) the application of a known technique to a known method or product ready for improvement to yield predictable results; (5) combining elements in a way that was “obvious to try” because of a design need or market pressure, where there was a finite number of identified, predictable solutions; (6) whether design incentives or other market forces in a field prompted variations in a work that were predictable to a person of ordinary skill in the art; and (7) that some teaching, suggestion, or motivation in the prior art would have led one of ordinary skill in the art to modify the prior art reference or to combine prior art references to arrive at the claimed invention, among other rationales.

C. Claim Construction

28. I understand that terms appearing in the patent claims are to be interpreted according to their “ordinary and customary meaning” at the time the alleged invention was made in an *inter partes* review proceeding. I understand that this date corresponds to the filing date of the ‘567 patent, which is January 12, 2018.

29. In determining the ordinary and customary meaning, the words of a claim are given their plain meaning as they would have been understood by a person of ordinary skill in the art at the time of the alleged invention in light of the claims, the specification, and the file history. I have followed this approach in my analysis, and have applied the ordinary and customary meaning of those terms throughout my analysis in this declaration.

IV. Level of Ordinary Skill in the Art

30. I have been advised that for purposes of this declaration a person of ordinary skill in the art is a hypothetical person who is presumed to know all of the relevant art as of January 12, 2018. I understand from counsel that (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) the prior art solutions to those problems; (4) the rapidity with which innovations are made; (5) the sophistication of the technology; and (6) the educational level of active workers in the field are non-exhaustive factors that provide a guide for determining the appropriate level of ordinary skill in the art. I further understand that a person of ordinary skill in the art is also a person of ordinary creativity. I have been instructed by counsel that the relevant timeframe for assessing the validity of the claims of the ‘567 patent for the purposes of this declaration is assumed to be January 12, 2018. Unless otherwise specifically noted, all of my opinions expressed herein regarding a person of ordinary skill in the art apply to a person of ordinary skill in the art as of January 12, 2018.

31. By virtue of my education, experience, and training, I am familiar with the level of skill in the art of the ‘567 patent as of January 12, 2018. In my opinion, a person of ordinary skill in the art relevant to the ‘567 patent and its related applications would have had at least a Ph.D., M.D. or D.O., with background in

dermatology, cell biology, molecular biology, or a related field or at least 2-3 years of professional experience in one or more of those fields.

V. Task Summary

32. I have been asked to review the ‘567 patent. I have been asked to provide my opinion regarding the validity of the ‘567 patent from the perspective of a person of ordinary skill in the art, having knowledge of the relevant art as of January 12, 2018, the ‘567 patent’s filing date. The qualifications and abilities of such a person are described in Section IV above.

33. In preparing this declaration, I have considered the available prior art, the ‘567 patent in its entirety, the prosecution history of the ‘567 patent, and the general knowledge of those familiar with the field of dermatological photodynamic therapy as of January 12, 2018. The references I discuss herein relate generally to dermatology and dermatological photodynamic therapy.

34. I have also reviewed the following exhibits:

Exhibit	Description
1001	U.S. Patent No. 10,357,567 (“the ‘567 patent”).
1002	Excerpts from U.S. Patent Application No. 15/869,164 (“the ‘164 Application”).
1003	Declaration of Dr. Howard Rogers MD, PHD (this document)
1004	CV of Dr. Howard Rogers MD, PHD

Exhibit	Description
1005	PCT Publication No. WO 96/06602 (“Noven Pharma”).
1006	Sakamoto FH, Torezan L, Anderson RR. Photodynamic therapy for acne vulgaris: a critical review from basics to clinical practice: part II. Understanding parameters for acne treatment with photodynamic therapy. J Am Acad Dermatol. 2010 Aug;63(2):195-211 (“Sakamoto”).
1007	Berardesca E, Vignoli GP, Fideli D, Maibach H. Effect of occlusive dressings on the stratum corneum water holding capacity. The American Journal of the Medical Sciences. 1992 Jul;304(1):25-28 (“Berardesca”).
1008	Fauteck JD, Ackermann G, Birkel M, Breuer M, Moor AC, Ebeling A, Ortland C. Fluorescence characteristics and pharmacokinetic properties of a novel self-adhesive 5-ALA patch for photodynamic therapy of actinic keratoses. Arch Dermatol Res. 2008 Feb;300(2):53-60 (“Fauteck”).
1009	U.S. Patent Publication No. US2009/0324727 A1 (“Biofrontera”).
1010	Ameluz Prescribing Information (2016) (“Ameluz”).
1011	Levulan Label (2002).
1012	BLU-U Operating Manual (2006).
1013	Willey A, Anderson RR, Sakamoto FH. Temperature-modulated photodynamic therapy for the treatment of actinic keratosis on the extremities. Dermatologic Surgery. 2014 Oct;40(10):1094-1102. (“Willey”).
1014	Calderhead RG. Light-emitting diode phototherapy in dermatological practice in lasers in dermatology and medicine. Lasers in Dermatology and Medicine. 2011 Aug;231-265. (“Calderhead”).

Exhibit	Description
1015	Palm M., Goldman PM. Aminolevulinic acid: actinic keratosis and photorejuvenation. In: Gold M.H., editor. Photodynamic Therapy in Dermatology. Springer Science and Business Media, LLC. 2011 Nov;5-30. (“Palm”).
1016	MacCormack MA. Photodynamic therapy in dermatology: an update on applications and outcomes. Semin Cutan Med Surg. 2008 Mar;27(1):52-62. (“MacCormack”).
1017	Sotiriou E, Apalla Z, Maliamani F, Zaparas N, Panagiotidou D, Ioannides D. Intraindividual, right-left comparison of topical 5-aminolevulinic acid photodynamic therapy vs. 5% imiquimod cream for actinic keratoses on the upper extremities. J Eur Acad Dermatol Venereol. 2009 Sep;23(9):1061-5. (“Sotiriou”).
1018	Bissonnette R. Photodynamic therapy. In: Gold M.H., editor. Photodynamic Therapy in Dermatology. Springer Science and Business Media, LLC; New York, NY, USA: 2011. pp. 221–229. (“Bissonnette”).
1019	McLaren G. Photodynamic therapy. In; Pfenninger and Fowler's procedures for primary care. Third Ed. Mosby Elsevier; Philadelphia, PA: 2011. pp 397-400. (“McLaren”).
1020	Harris DR. Percutaneous absorption and the surface area of occluded skin: a scanning electron microscopic study. British Journal of Dermatology. 1974; 91(27-32). (“Harris”).
1021	Levulan Label (2009).
1022	Wachowska et al., Aminolevulinic acid (ALA) as a prodrug in photodynamic therapy of cancer. Molecules. 2011 May;16(5): 4140-4164. (“Wachowska”).
1023	Agostinis et al. Photodynamic therapy of cancer: an update. CA: A Cancer Journal for Clinicians. 2011 May;61(4):250-281. (“Agostinis”).

Exhibit	Description
1024	Wolf P., Rieger E. and Kerl H. Topical photodynamic therapy with endogenous porphyrins after application of 5-aminolevulinic acid: an alternative treatment modality for solar keratoses, superficial squamous cell carcinomas, and basal cell carcinomas? Journal of the American Academy of Dermatology 28.1 (1993): 17-21 (“Wolf”).
1025	Jeffes E., McCullough J., Weinstein G., Fergin P., Nelson J., Shull T., Simpson K., Bukaty L., Hoffman W., Fong N. Photodynamic therapy of actinic keratosis with topical 5-aminolevulinic acid. A pilot dose-ranging study. Arch Dermatol. 1997 Jun;133(6):727-32 (“Jeffes”).
1026	Hongcharu W., Taylor C., Chang, Y., Aghasi, D., Suthamjariya, K., Anderson, R. Topical ALA-photodynamic therapy for the treatment of acne vulgaris. J Invest Dermatol. 2000 Aug;115(2):183-92 (“Hongcharu”).
1027	Ozog, D., Rkein, A., Fabi, S., Gold M., Goldman, M., Lowe, N., Martin, G., Munavalli, G. Photodynamic therapy: A clinical consensus guide. Dermatol Surg. 2016 Jul;42(7):804-27 (“Ozog”).
1028	Aktelite CL128 Operators Manual with Metvixia (2008) (“Metvixia”).
1029	DUSA Levulan Press Release (1999).
1030	European Medicines Agency CHMP Assessment Report (excerpts) (2011).
1031	Affidavit of Duncan Hall
1032	Willey Pubmed Website Database Listing
1033	Sotiriou Pubmed Website Database Listing
1034	Fauteck Europe PMC Website Database Listing

Exhibit	Description
1035	Rick K, Sroka R, Stepp H, Kriegmair M, Huber RM, Jacob K, Baumgartner R. Pharmacokinetics of 5-aminolevulinic acid-induced protoporphyrin IX in skin and blood. J Photochem Photobiol B. 1997 Oct;40(3):313-9 (“Rick”).

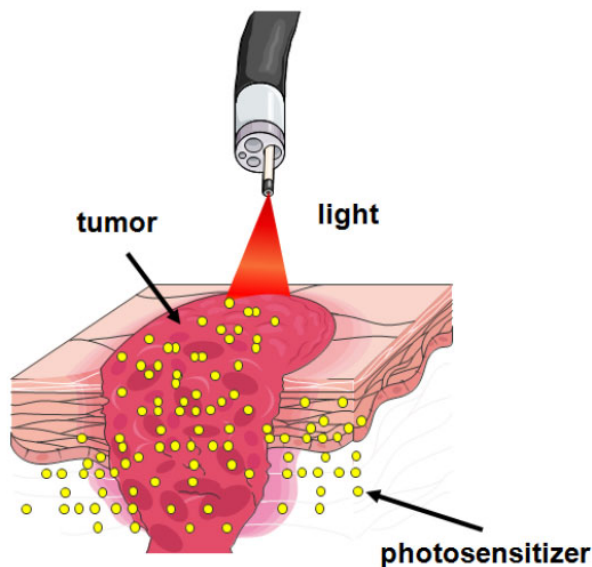
VI. State of the Art

35. The ‘567 patent describes photodynamic therapy with topically applied ALA, using occlusion with low density polyethylene (“LDPE”) film, followed by the application of light. Ex. 1001 at Abstract, Claims 1-10. In the sections below, I briefly summarize what was known about treating actinic keratosis using topically applied ALA and photodynamic therapy, the use of occlusion to enhance penetration of topically applied drug substances such as ALA, and the use of different light sources for photodynamic therapy before the ‘567 patent’s filing date.

A. **5-Aminolevulinic Acid (ALA) Photodynamic Therapy**

36. In photodynamic therapy (“PDT”), a photosensitizing compound (or a photosensitizing compound precursor) is applied to an area of the skin surface to be treated and then exposed to activating light in order to destroy precancerous skin cells called lesions. Ex. 1015 [Palm] at 5. The photosensitizing molecule can be absorbed directly into the skin or when a photosensitizing precursor molecule is applied, the photosensitizer can be generated *in situ* within the absorbing cells. Ex.

1015 [Palm] at 5. Once absorption and/or generation of the photosensitizer has occurred, light is applied to the photosensitized skin cells. Ex. 1015 [Palm] at 5; Ex. 1016 [MacCormack] at 52. The light activates the photosensitizer causing the generation of singlet oxygen and free radicals within the targeted skin cells.



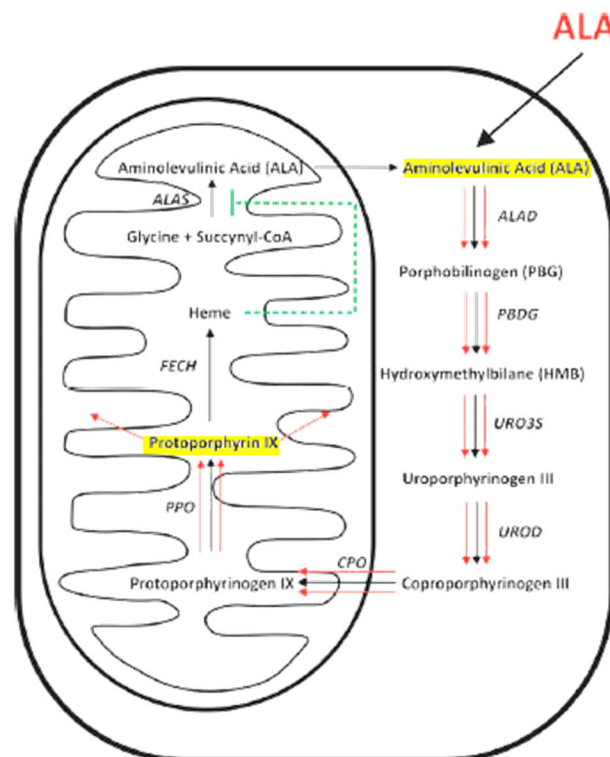
Ex. 1022 [Wachowska] at 4141-4142, Figures 1-2.

37. Because singlet oxygen and free radicals are extremely reactive with biological molecules in the cell interior, their generation inside a targeted cell results in damage and cell death. Ex. 1015 [Palm] at 5; Ex. 1016 [MacCormack] at 52.

38. One photosensitizer precursor compound that has been heavily studied in photodynamic therapy for the past several decades is 5-aminolevulinic acid ("ALA"). Ex. 1005 [Noven Pharma] at 1-2; Ex. 1015 [Palm] at 6; Ex. 1016 [MacCormack] at 52-53. ALA is a non-proteinogenic amino acid that is found

endogenously in humans and other mammals that is used in the biosynthesis of heme—a precursor to hemoglobin. Ex. 1005 [Noven Pharma] at 1-2; Ex. 1015 [Palm] at 6; Ex. 1016 [MacCormack] at 52-53. The heme biosynthetic pathway is depicted in the figure below:

Figure 3. Heme biosynthesis. The graphic presents the most important steps in the heme biosynthetic pathway.



Ex. 1022 [Wachowska] at 4144, Figure 3 (with ALA and Protoporphyrin IX highlighted in yellow).

39. When excess ALA is applied topically, it is readily absorbed through the skin.¹ Ex. 1016 [MacCormack] at 52. Compared to normal cells, cancerous cells treated with excess ALA are unable to complete the final steps in the generation of heme in the heme biosynthesis pathway. Ex. 1016 [MacCormack] at 52. As a result, protoporphyrin IX (“PPIX”)—a strong photosensitizer—accumulates in abnormal/cancerous cells. Ex. 1016 [MacCormack] at 52; Ex. 1015 [Palm] at 5-6. When the accumulated PPIX in the abnormal/cancerous cells is exposed to light, singlet oxygen and free radicals are generated within the cells, which results in cell death. Ex. 1015 [Palm] at 5; Ex. 1016 [MacCormack] at 52.

40. In contrast to the abnormal/cancerous cells, healthy skin cells do not significantly accumulate PPIX. As a result, non-cancerous skin cells surrounding the diseased cells do not generate lethal amounts of reactive oxygen species and free radicals when exposed to light. Ex. 1015 [Palm] at 5-6. Therefore, ALA based photodynamic therapy can be used to preferentially kill precancerous/cancerous

¹ For photodynamic therapy applications, ALA is generally provided in its salt form as 5-aminolevulinic acid hydrochloride (ALA HCl). Ex. 1010 [Ameluz] at 1 (indicating that ALA is present in Ameluz in its aminolevulinic acid hydrochloride form); Ex. 1011 [Levulan Label 2002] at 1 (indicating that the ALA in Levulan Kerastick is supplied as aminolevulinic acid HCl); Ex. 1008 [Fauteck] at 54 (stating that the ALA is “present as 5-aminolevulinic acid hydrochloride”); Ex. 1005 [Noven Pharma] at 5:27-30 (defining ALA as encompassing pharmaceutically acceptable salts of ALA—*i.e.*, ALA HCl). As a result, as used here in the context of photodynamic therapy applications ALA generally refers to ALA in its hydrochloride form.

cells while leaving normal skin cells relatively unharmed. Ex. 1015 [Palm] at 5-6; Ex. 1005 [Noven Pharma] at 1-2.

B. Light Sources Utilized in ALA PDT

41. As noted above, in photodynamic therapy, the administered photosensitizer (e.g., PPIX for ALA) is activated using light. As a result, the light sources utilized for activation must emit light within the absorption spectrum of the photosensitizer. PPIX exhibits a broad absorption spectrum with absorption generally extending from below 350 nm to around 670 nm as reflected in the absorption spectrum below. Ex. 1015 [Palm] at 6-7; Ex. 1016 [MacCormack] at 53.

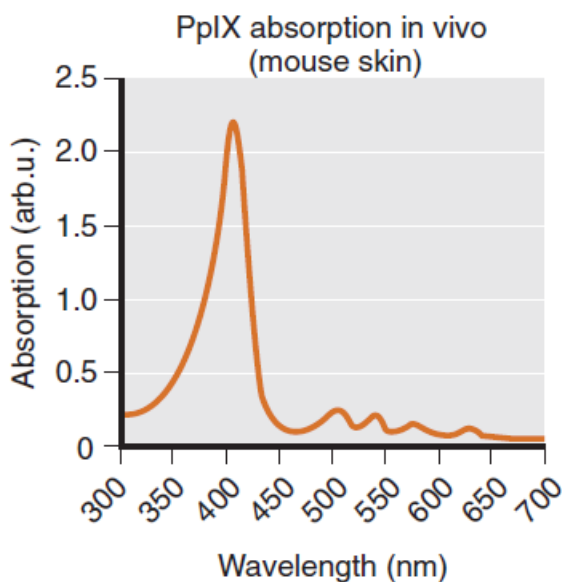


Figure 60-1 The absorption peaks for protoporphyrin IX (PpIX).
(Courtesy of Dusa Pharmaceuticals, Inc., Wilmington, Mass.)

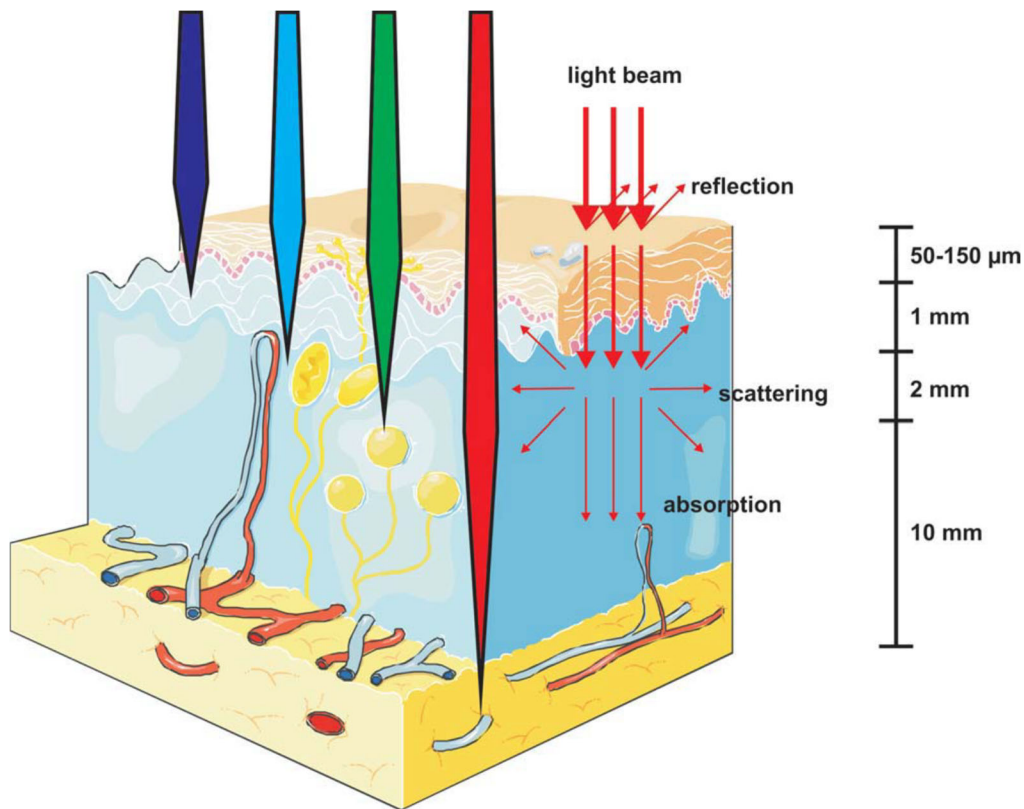
Ex. 1019 [McLaren] at 398, Figure 60-1.

42. As can be seen from the absorption spectrum for PPIX, the amount of light absorbed by PPIX varies depending on the wavelength of light that is irradiated. PPIX exhibits the largest absorption peak in the blue light spectral range at around 409 nm. Ex. 1019 [McLaren] at 397. What this means is that PPIX is able to absorb greater intensities of blue light compared to other colors of light. As a result, lower fluence or energy of blue light is required to activate PPIX to generate free radicals and reactive oxygen species. Ex. 1015 [Palm] at 6-7. PPIX also exhibits absorption peaks in the green, yellow and red wavelength ranges. Ex. 1006 [Sakamoto] at 203; Ex. 1015 [Palm] at 9-15. But, due to lower absorbance at these wavelengths, greater energies in those spectral ranges are required to activate PPIX. Ex. 1015 [Palm] at 6.

43. Red and blue light sources have commonly been utilized for ALA photodynamic therapy. Ex. 1015 [Palm] at 12, 14. For example, the earliest reports of topical ALA photodynamic therapy by Kennedy et al. in the 1990's utilized a slide projector with a red light filter to activate the PPIX photosensitizer. Ex. 1006 [Sakamoto] at 204. More recently, red light sources such as Biofrontera's RhodoLED and Galderma's Aktilite have been developed and utilized. Ex. 1010 [Ameluz] at 3-4; Ex. 1018 [Bissonnette] at 223; Ex. 1015 [Palm] at 10; Ex. 1028 [Metvixia] at 007, 022-040.

44. As noted above, however, because a lower energy dose is required for activation of PPIX using blue light, some doctors and researchers utilize blue light sources for photodynamic therapy. Ex. 1016 [MacCormack] at 53. One blue light source commonly in use for ALA PDT since around 2000 is the BLU-U light source. Ex. 1029 [DUSA Levulan Press Release] at 1; Ex. 1012 [BLU-U Operating Manual]; Ex. 1031 [Affidavit of Duncan Hall] at 072-089.

45. But, because blue light is of a shorter wavelength than red light, blue light penetrates less deeply through the different layers of surface tissue compared to red light and loses its energy more rapidly upon penetration. Blue light has a depth of penetration of around 1.5 to 2 mm, whereas red light can penetrate more deeply (*e.g.*, up to around 8-10 mm). Ex. 1016 [MacCormack] at 53; Ex. 1027 [Ozog] at 806. This is reflected, for example, in the illustration below:



Ex. 1023 [Agostinis] at 255.

46. As a result, red light is considered more effective than blue light for the treatment of lesions that require deeper penetration into the skin (*e.g.*, >1.5-2 mm).

Ex. 1016 [MacCormack] at 53.

47. As noted above, because PPIX exhibits different absorbance at different wavelengths of light, the light dose used in PDT varies with the wavelength of the light source employed. In general, the required light dose for blue light is less than that for red light given the greater absorbance of blue light by PPIX compared to red light. Ex. 1027 [Ozog] at 807.

48. In application, the light dose provided by a particular light source for PDT treatment is based on different factors. These factors include, for example, the light intensity and wavelength(s) of the emitted light, exposure time of the skin surface being treated with the light, distance between the light source and skin surface being treated, the size of the light field, and the light source used. Ex. 1014 [Calderhead] at 240-242; Ex. 1023 [Agostinis] at 255. Light dosing parameters for PDT are generally provided by commercial light source providers based on recommended distance of the treatment site from the light source and exposure time and, in some instances, may be controllable from the light source control panel. Ex. 1012 [BLU-U Operating Manual] at 9-13 (specifying a 16 min. and 40 sec. illumination time with light source placement 2-4 inches from the treatment surface for a blue light source); Ex. 1028 [Aktelite CL128 Operators Manual] at 5 (specifying a calculated illumination time (generally between 7 to 10 minutes) with lamp placement 2 to 3.2 inches from the lesion for a 37 J/cm² light dose). In addition, devices that measure the light dose can also be used to determine the light dose applied during irradiation. Ex. 1023 [Agostinis] at 254.

49. Traditionally, light doses used for ALA-PDT have ranged from between 10-100 J/cm². Ex. 1005 [Noven Pharma] at 12:8-12; Ex. 1009 [Biofrontera] at [0031]. The standard light dose approved by the FDA for ALA-PDT with blue

light sources like the BLU-U is around 10 J/cm². Ex. 1011 [Levulan Label 2002] at 13; Ex. 1013 [Willey] at 1095. The standard light dose approved by the FDA for ALA-PDT with red light using the BF-RhodoLED light source is around 37 J/cm². Ex 1010 [Ameluz] at 3.

C. Treating Actinic Keratosis using PDT

50. Actinic keratosis (“AK”) is a precancerous skin condition of the keratinocytes—*i.e.*, cells on the upper layer (epidermis) of the skin that provide a barrier function. Ex. 1008 [Fauteck] at 53; Ex. 1015 [Palm] at 7; Ex. 1009 [Biofrontera] at [0066]. AKs result from chronic exposure to UV rays from the sun. AKs generally present as scaly plaques or patches on portions of the skin commonly exposed to the sun including the scalp, face, trunk, upper extremities (forearms and hands), and lower extremities (legs and feet). Ex. 1015 [Palm] at 7-8. If left untreated, AKs may develop into a type of skin cancer referred to as squamous cell carcinoma. Ex. 1015 [Palm] at 7-8, 10; Ex. 1009 [Biofrontera] at [0066].

51. Traditionally, AKs have been treated using cryotherapy and other methods. However, since 1990, when Kennedy et al. determined that AKs could be successfully treated using ALA-PDT, doctors have studied and used ALA-PDT to treat AK lesions on various portions of the body including the face, scalp, hands, and forearms, among others. Ex. 1015 [Palm] at 10-11; Ex. 1016 [MacCormack] at 54. Some of this work has resulted in the approval of two ALA-PDT products for

treating AKs that are currently being marketed in the United States—DUSA’s Levulan product and Biofrontera’s Ameluz product.

52. The FDA granted approval for DUSA’s Levulan product in 1999. Ex. 1027 [Ozog] at 809; Ex. 1029 [DUSA Levulan Press Release] at 1. Concurrently with Levulan, the FDA also approved DUSA’s BLU-U blue light source for use with Levulan. Ex. 1018 [Bissonnette] at 222, 225. DUSA’s approved Levulan protocol employed a 20% ALA solution (marketed as Levulan Kerastick) applied to AK lesions for a period of 14 - 18 hours. Following the 14-18 hour incubation time, DUSA’s approved protocol specifies a 16-minute, 40-second exposure to blue light for a light dose of 10 J/cm². Ex. 1016 [MacCormack] at 53; Ex. 1018 [Bissonnette] at 222, 225; Ex. 1027 [Ozog] at 808. Although the FDA approved treatment time for Levulan Kerastick specifies an incubation period of 14-18 hours, a subsequent study by Touma et al. published in 2004 found shortened incubation times of 1-3 hours to be sufficient. This study has led to wide use of the shorter incubation time over the FDA approved longer incubation time which would require an additional office visit. Ex. 1018 [Bissonnette] at 222; Ex. 1027 [Ozog] at 808.

53. Biofrontera’s ALA-PDT product marketed as Ameluz was approved in Europe in 2011 and in the United States in 2016. Ex. 1010 [Ameluz] at 3-1; https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/208081Orig1s000TOC.

cfm; <https://www.ema.europa.eu/en/medicines/human/EPAR/ameluz>. Ameluz is provided in the United States as a 10% ALA nanoemulsion gel. Biofrontera's Ameluz ALA-PDT is coupled with Biofrontera's BF-RhodoLED red light-emitting diode (LED) light system for activation of the resulting PPIX photosensitizer. Ex. 1010 [Ameluz] at 1. Biofrontera's FDA approved treatment protocol for AKs using Ameluz includes:

- application of Ameluz ALA gel to the treatment area and surrounding skin;
- allowing the gel to dry for approximately 10 minutes;
- occlusion of the area where the gel is applied with a light-blocking, occlusive dressing;
- removal of the occlusive dressing after 3 hours and wiping away any remaining gel; and
- illumination of the treatment area with the BF-RhodoLED red light source for a light dose of 37 J/cm² with the lamp head positioned 5-8 cm from the skin's surface.

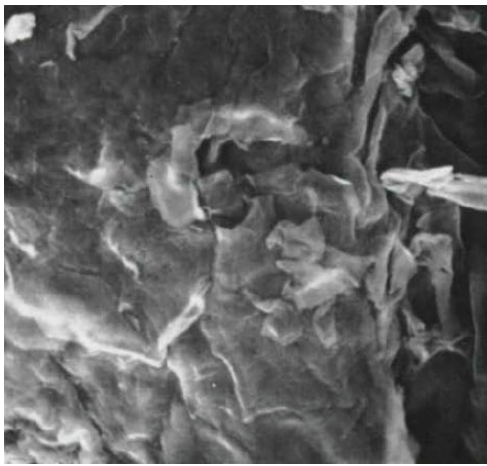
Ex. 1010 [Ameluz] at 3-4. As noted above, Biofrontera's Ameluz treatment protocol has specified the use of an occlusive dressing for around a 3 hour incubation of ALA since at least 2011. Ex. 1030 [EMA Assessment Rpt.] at 9.

D. Occlusion with plastic wrap to minimize transepidermal water loss and enhance penetration of ALA was well known

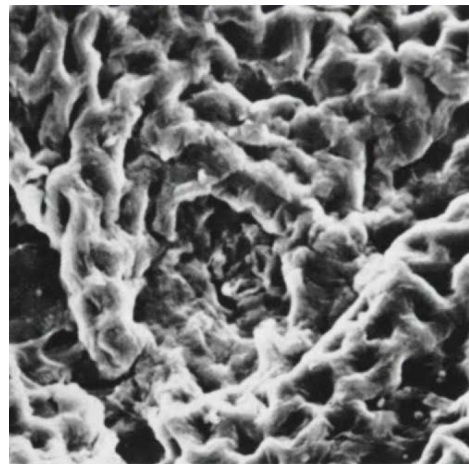
54. It has been long known in the dermatology field that occlusion of the skin with plastic prevents transepidermal water loss, increases the absorption of certain topically applied drugs, and promotes wound healing. Ex. 1020 [Harris] at 27 (“The most widely used method of increasing percutaneous absorption of topically applied therapeutic agents is by the use of occlusive plastic films.” (citing papers published between 1960 and 1970)); Ex. 1007 [Berardesca] at 25 (“Occlusion of the skin is used in clinical dermatology to promote wound healing and to increase the transcutaneous penetration of topically applied drugs.”). Further, it has been found using this technique that absorption of some topical agents can be increased by almost 100 times. Ex. 1020 [Harris] at 27. This is the result of the creation of persistent reservoirs through the outer most layer of the skin called the “stratum corneum” or “horny layer.” Ex. 1020 [Harris] at 27

55. Indeed, studies have shown substantial modifications to the stratum corneum resulting from occlusion of the skin with plastic. Ex. 1020 [Harris] at 27. When an occlusive covering is applied over the skin, water loss from the skin is inhibited. This type of water loss—transepidermal water loss or TEWL—occurs when water passes through the layers of the epidermis and evaporates from the skin’s surface (upper layer of the epidermis) (stratum corneum). Ex. 1007 [Berardesca] at

25. Application of a plastic covering results in an occlusive environment surrounding the skin that approaches 100% relative humidity with the upper layer of the epidermis becoming well hydrated. Ex. 1020 [Harris] at 27. A demonstration of this hydration effect is shown in the figures below which are scanning electron microscope (SEM) micrographs comparing non-occluded skin (left) with skin occluded using a plastic film (polyethylene) (right). Ex. 1020 [Harris] at 29-30.



Non-occluded skin (Fig. 4).



Skin occluded with plastic film (polyethylene) for 72 hrs (Fig. 3).

Ex. 1020 [Harris] at 29-31, Figures 3 and 4. As shown in the figures above, occlusion with plastic inhibits TEWL, resulting in the retention of water and the swelling of the interfibrillary structure of the stratum corneum. Ex. 1020 [Harris] at 31. This creates aqueous pathways through the stratum corneum which allow water-soluble substances (*e.g.*, ALA) applied to the skin—under occlusion with the plastic film—

to experience an increased rate of transport into the occluded, hydrated skin compared to non-occluded skin. Ex. 1020 [Harris] at 31.

56. It was also well known since at least the early 1990's that different covering materials, such as different plastic films, minimize TEWL to different degrees depending on "the physicochemical nature of the dressing." Ex. 1007 [Berardesca] at 25. Berardesca et al. published a journal article in 1992 titled "Effect of Occlusive Dressings on Stratum Corneum Water Holding Capacity." Ex. 1007 [Berardesca] at 25. In that article, Berardesca published the results of a study on the ability of four commercial occlusive dressings used in dermatology to minimize TEWL and promote water holding capacity, including: (1) a polypropylene plastic chamber; (2) Duoderm hydrocolloid dressing; (3) Saran Wrap polyethylene film; and (4) Tegaderm polyurethane film. Ex. 1007 [Berardesca] at 25. After applying the occlusive dressings to the forearms of 10 male subjects for 24 hours, the coverings were removed and TEWL was measured using an Evaporimeter probe. Ex. 1007 [Berardesca] at 25. Berardesca found that the order of occlusion starting with the most occlusive was: (1) the polypropylene plastic chamber; (2) the Duoderm hydrocolloid dressing; (3) the Saran Wrap polyethylene film; and (4) the Tegaderm polyurethane film. Ex. 1007 [Berardesca] at 26-27. This is reflected in Figure 2 from Berardesca shown below:

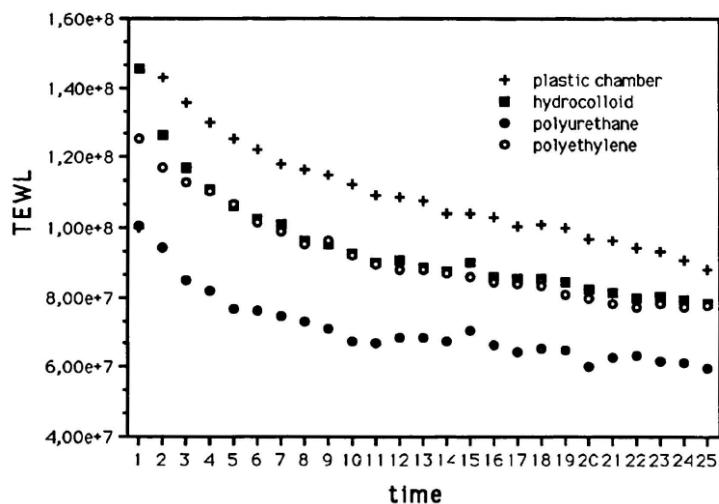


Figure 2. Transepidermal water loss (TEWL) decay curves after removal of the dressings (values in log g/m²h). Polyurethane film shows the lowest decay curve because of the least occlusive capability compared to the other dressings.

Ex. 1007 [Berardesca] at 26-27; Figure 2. In accordance with the study, Berardesca determined that Saran Wrap polyethylene films are more occlusive—*i.e.*, that they are better at minimizing TEWL and increasing the transcutaneous penetration of topically applied drugs—compared to Tegaderm polyurethane occlusive dressings. Ex. 1007 [Berardesca] at 25.

57. More recently, in the context of photodynamic therapy, practitioners have recognized that occlusion with plastic films minimize transepidermal water loss and enhance penetration of ALA. For example, Sakamoto described in 2010 that: “[o]cclusion is known to reduce transepidermal water loss, hydrating the stratum corneum and generally enhancing drug penetration, especially for hydrophilic molecules such as ALA.” Ex. 1006 [Sakamoto] at 205. Likewise Ozog in 2016 stated that “[f]or nonfacial areas, such as the extremities, occlusion has been used to increase penetration [of ALA]” and noted that “[t]his can be accomplished with

plastic wrap or some other nonporous flexible material placed over the targeted area after the ALA has been applied.” Ex. 1027 [Ozog] at 808.

E. State of the Art Summary

58. In the following table, I outline in chronological order various aspects of the ‘567 patent claims that were known in the dermatological PDT field as disclosed in selected references before the ‘567 patent filing date.

Publication	Topical ALA	Occlusion	Removing Occlusion within around 3h Incubation	Light Source	Hand/ Forearm Treatment
Wolf 1993 [Ex. 1024]	✓	✓	4-8h	Red 570 nm	✓
Noven Pharma 1996 [Ex. 1005]	✓	✓ “low density polyethylene”	2-48h; 3-24h	Blue 400 nm; Red 635 or 600-700 nm	✓
Jeffes 1997 [Ex. 1025]	✓	✓ “occlusive tape”	✓	Red 630 nm	✓
Hongcharu 2000 [Ex. 1026]	✓	✓ “saran wrap”	✓	Red 550-700 nm	(back)
MacCormack 2008 [Ex. 1016]	✓	✓	1-18h	Blue 409-417 nm, red 635 nm	✓

Publication	Topical ALA	Occlusion	Removing Occlusion within around 3h Incubation	Light Source	Hand/ Forearm Treatment
Sotiriou 2009 [Ex. 1017]	✓	✓	4h	Red 570- 670 nm	✓
Sakamoto 2010 [Ex. 1006]	✓	✓	✓	Blue 405- 415 nm; Red 628- 635 nm	✓
Bissonnette 2011 [Ex. 1018]	✓	✓ (with MAL)	✓ 45 min-2h	Blue 400- 450 nm; Red 630- 640 nm	✓
McLaren (in Pfenninger 2011) [Ex. 1019]	✓	✓ “kitchen plastic wrap”	✓ 2h	Blue 405- 420 nm	✓
Palm 2011 [Ex. 1015]	✓	✓ “Glad Press ‘n Seal”	✓ 1-3h	Blue 405- 409 nm; Red 505- 635 nm	✓
Calderhead 2012 [Ex. 1014]	✓	✓ “cling film”	“up to several hours;” 5h	Blue 415 nm; Red 633 nm	✓
Willey 2014 [Ex. 1013]	✓	✓ “plastic wrap (Saran; SC Johnson)”	✓ 1h	Blue 417 nm	✓

Publication	Topical ALA	Occlusion	Removing Occlusion within around 3h Incubation	Light Source	Hand/ Forearm Treatment
Ozog 2016 [Ex. 1027]	✓	✓ “plastic wrap”	✓	Blue 405-417 nm; Red 635 nm	✓

59. As the foregoing summary table demonstrates, each of the foregoing features—topical ALA based photodynamic therapy; occlusion of the treatment site with different types of coverings including with various LDPE based plastic wraps; incubation periods less than around 3 hours; illumination of the treatment area with blue and red light; and PDT treatments on the hands and forearms—were all well known in the dermatology field prior to 2018.

VII. The ‘567 Patent

A. The ‘567 Patent Description and Claims

60. The ‘567 patent claims relate to methods for using and enhancing penetration of topical ALA into tissue for photodynamic therapy. Ex. 1001 [‘567 patent] at Abstract. The ‘567 patent, entitled “Methods for Photodynamic Therapy,” was filed on January 12, 2018 as U.S. Patent Application No. 15/869,164 and issued on July 23, 2019. Ex. 1001 [‘567 patent] at Cover. The ‘567 patent identifies Scott Lundahl and Michael Guttadauro as inventors and identifies DUSA

Pharmaceuticals, Inc. as both the applicant and assignee. Ex. 1001 [‘567 patent] at Cover.

61. In the “Background” section, the ’567 patent describes general photodynamic therapy used to treat or diagnose “ailments in or near the skin.” Ex. 1001 [‘567 patent] at 1:11-14. For example, the ’567 Patent acknowledges that photodynamic therapy can be used to treat “actinic keratosis of the upper extremities (e.g., the dorsal surface of the hand or forearms), scalp or facial areas ... and other areas of the patient (e.g., the legs or portions of the arms other than the forearms),” in addition to treating “other indications (e.g., acne, warts, psoriasis, photo-damaged skin, cancer).” Ex. 1001 [‘567 patent] at 1:14-22. The ’567 patent also acknowledges the use of ALA as “a precursor of a photoactivatable agent ... which is commonly used in photodynamic therapy” that is metabolically converted to the “PPIX ... photosensitizer which accumulates in the skin.” Ex. 1001 [‘567 patent] at 1:38-43. The ’567 patent also notes that illuminators such as fluorescent tube or LED light sources “are typically used to provide the proper uniformity of light for treatment purposes” in photodynamic therapy. Ex. 1001 [‘567 patent] at 1:44-53.

62. In addition to describing general ALA photodynamic therapy, the ’567 patent includes in the “Detailed Description” section, four subsections, each respectively entitled “Exemplary Illuminator”, “Administration of ALA”,

“Occlusion with Barrier”, and “Treatment Protocols.” Ex. 1001 [‘567 patent] at 3:59-15:26.

63. The first subsection, “Exemplary Illuminator”, references Figures 1A-1B, 2A-2B, and 3 of the ’567 patent and discusses an illuminator made using LED panels connected together with hinges. Ex. 1001 [‘567 patent] at 5:5-8:19. The ’567 patent mentions that the illuminator may include a heating element or heat source that is used to heat the treatment site in order to accelerate conversion of the ALA to porphyrin. Ex. 1001 [‘567 patent] at 7:52-8:6.

64. The second subsection, entitled “Administration of ALA,” discusses ALA supplied in an ampule and mixed with an alcohol solution before application, as well as other ALA formulations in lotions, creams or gels. Ex. 1001 [‘567 patent] at 8:20-9:25.

65. The third subsection, “Occlusion with Barrier,” discusses experiments performed to test the transepidermal water loss rate from the dorsal forearms after being covered by Tegaderm polyurethane material and various commercially available food plastic wraps made from low density polyethylene (LDPE) and polyvinylidene chloride (PVdC). Ex. 1001 [‘567 patent] at 9:26-12:2. The plastic coverings tested are shown and described in Tables 1 and 2 of the ’567 patent.

TABLE 1

Barrier Materials A-E			
Material Code	Name	Distributor or Manufacturer	Material Description
A	Tegaderm™, Style 1629	3M	Polyurethane
B	Glad® Press'n Seal®	The Glad Products Company	LDPE
C	Glad® Cling Wrap	The Glad Products Company	LDPE
D	Stretch-Tite®	Polyvinyl Films, Inc.	Polyvinylidene chloride (PVdC)
E	Saran™ Premium Wrap	SC Johnson	LDPE

TABLE 2

Barrier Materials W-Z, and E			
Material Code	Name	Distributor or Manufacturer	Material Description
W	Best-Yet Clear Plastic Wrap	C&S Wholesale Grocers, Inc.	LDPE
X	Boardwalk® PVC Food Wrap Film, BWK7204	Boardwalk	PVdC
Y	Shurfine® Strong and Stretchy® Plastic Wrap	Western Family Foods, Inc.	LDPE
Z	Premium Plastic Wrap	Foodhold USA, LLC	PVdC
E	Saran™ Premium Wrap	SC Johnson	LDPE

Ex. 1001 ['567 patent] at Tables 1 and 2. The plastic wraps tested include food storage wraps like Saran Wrap (Material code E) and Glad Press'N Seal (Material code B) among others.

66. Regarding the testing, the '567 patent specifically discusses measuring transepidermal water loss (TEWL) rates on the dorsal forearms of around 30 subjects both before (the “pre” measurement) and after the plastic test coverings had been worn for 3 hours (the “post” measurement). Ex. 1001 ['567 patent] at 10:15-30. The '567 patent references using an RG1 Evaporimeter system with a DermaLab TEWL probe to take the “pre” measurements reported in Figures 5 and 7 “after a minimum 25-minute acclimation period in a controlled environment with less than 50% relative humidity and a temperature between 19-22 deg. Celsius.” Ex. 1001 ['567 patent] at 10:19-30. The '567 patent describes that the same equipment was used to take the “post” measurements shown in Figures 5 and 7, 3 hours after the tested plastic coverings had been applied to the subjects' skin. Ex. 1001 ['567 patent] at

10:34-45. The '567 patent further states that the control measurements were performed on an “area of the subjects’ skin without the barrier.” Ex. 1001 [‘567 patent] at 10:45-46. Figures 5 and 7 show the pre and post TEWL rates for the different plastic wraps tested (Material codes A-E and W-Z in Tables 1 and 2) compared to the controls. Ex. 1001 [‘567 patent] at Tables 1 and 2. The underlying TEWL data shown in Figures 5 and 7 of the '567 patent is tabulated and shown in Figures 9 and 10 (for Material codes A-E) and in Figures 12 and 13 (for Material codes E, W-Z).

67. Also reported in the '567 patent are the mean degrees of occlusion determined for the different plastic coverings tested. Ex. 1001 [‘567 patent] at Figures 6 and 8. The '567 patent states that the “degree of occlusion corresponds to the decrease in evaporative water loss rate when the subject wore the barrier ... as compared to the baseline evaporative water loss rate.” Ex. 1001 [‘567 patent] at 10:51-53. The calculated degrees of occlusion for the different plastic coverings tested are reported in Figures 11 and 14 of the '567 patent. Overall, the '567 patent states that LDPE plastic coverings “resulted in lower water loss rates and a superior degree of occlusion” compared to the Tegaderm polyurethane and polyvinylidene chloride plastic wraps tested. Ex. 1001 [‘567 patent] at 9:55-60; 10:47-11:35.

68. The fourth subsection, “Treatment Protocols,” discusses the treatment protocols and results of studies performed with ALA photodynamic therapy on the upper extremities using occlusion with polyethylene film. The ’567 patent summarizes the results of two open-label pharmacokinetic studies as well as the results of a “multi-center randomized, parallel-group, evaluator-blinded and vehicle-controlled study” of subjects with actinic keratosis on the dorsal surface of the hands and forearms. Ex. 1001 [’567 patent] at 13:15-14:51.

69. The ’567 patent also includes 10 claims which cover methods of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into the tissue for photodynamic therapy (claims 1-7) and methods of using 5-aminolevulinic acid (ALA) and a low density polyethylene barrier (claims 8-10). Ex. 1001 [’567 patent] at 15:27-16:41. To enhance penetration of the ALA, claims 1 and 4 claim “covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area” after the ALA is applied. Ex. 1001 [’567 patent] at Claim 1 and 4. Similarly, Claim 8 claims, after the treatment area is wetted with ALA, “covering the wetted treatment site with the low density polyethylene barrier.” Ex. 1001 [’567 patent] at 15:27-16:41.

70. But using occlusion with LDPE films to enhance penetration of ALA for photodynamic therapy was not new as of January 12, 2018 when the '567 patent was filed. As noted above in my declaration, Berardesca had previously demonstrated in 1992 that polyethylene films are superior to polyurethane films at minimizing transepidermal water loss. Ex. 1007 [Berardesca] at 25. Moreover, in the context of photodynamic therapy, Sakamoto and others described what was well known by 2010—*i.e.*, that “[o]cclusion is known to reduce transepidermal water loss, hydrating the stratum corneum and generally enhancing drug penetration, especially for hydrophilic molecules such as ALA.” Ex. 1006 [Sakamoto] at 205; Ex. 1027 [Ozog] at 808 (“For nonfacial areas, such as the extremities, occlusion has been used to increase penetration [of ALA]. This can be accomplished with plastic wrap or some other nonporous flexible material placed over the targeted area after the ALA has been applied.”).

71. Indeed, this is consistent with my own experience. For example, during my fellowship training at The Skin Cancer Center in Cincinnati from 2007-2008, I was instructed to use occlusion with Saran Wrap (LDPE) in ALA photodynamic therapy to enhance penetration of ALA into the tissue to be treated. Since that time, I have continued to use occlusion with Saran Wrap in my ALA-based photodynamic therapy practice.

72. I am not alone in my use of LDPE occlusion in my ALA based photodynamic therapy practice. As discussed herein, other doctors have used occlusion with LDPE films to minimize transepidermal water loss and enhance penetration of ALA into tissue for photodynamic therapy well prior to January 12, 2018. For example, Palm describes in her practice that she “occlude[s] the treated area with Glad Press ‘N Seal®” which, as noted above, the ‘567 patent identifies as an LDPE material. Ex. 1015 [Palm] at 22. In addition, Willey describes in a study that Saran wrap—an LDPE film identified in the ‘567 patent (see above)—was used to occlude forearms and hands treated with topical ALA. Ex. 1013 [Willey] at 1095 (“Topical 20% 5-ALA (Levulan Kerastick; Dusa Pharmaceuticals, Inc., Wilmington, MA) was applied to the entire forearm skin and occluded with *plastic wrap (Saran; SC Johnson).*”) (emphasis added). Similarly, Noven Pharma describes the use of ALA patches having LDPE occlusive backings for photodynamic therapy in the late 1990’s. Ex. 1005 [Noven Pharma] at 8:30-9:34. Accordingly, using LDPE plastic coverings to minimize transepidermal water loss and enhance penetration of ALA into the skin for photodynamic therapy treatments was not a new idea at the time the ‘567 patent was filed in 2018. Rather, myself and others have been using and describing the use LDPE based coverings like Saran wrap and Glad Press ‘N

Seal as occlusive materials in topical ALA based photodynamic therapy since well before the '567 patent was filed.

73. In addition to the three independent claims—claims 1, 4, and 8—the '567 patent also includes dependent claims which add additional features also commonly known in ALA photodynamic therapy prior to January 12, 2018. Based on my review, none of the features added in the dependent claims (claims 2-3, 5-7, and 9-10) adds anything new.

74. Specifically, claims 2 and 5 respectively specify the light dose for a blue light source as 10 J/cm^2 and for a red light source as 10 to 75 J/cm^2 . These light doses for PDT—including for PDT on the upper extremities—were well known prior to January 12, 2018. Ex. 1013 [Willey] at 1095; Ex. 1005 [Noven Pharma] at 12:8-18; Ex. 1016 [MacCormack] at 53; Ex. 1019 [McLaren] at 398-399; Ex. 1027 [Ozog] at 807, 811.

75. Claims 6 and 7 specify that the treatment site is on the dorsal surface of the hand and forearm. The dorsal surface of the hand and forearm are two skin surfaces commonly known to develop actinic keratosis due to long term sun exposure. As a result, the dorsal surfaces of the hand and forearms, often referred to as the “upper extremities,” have been treated using PDT with occlusion since at least as early as the late 1990's. Ex. 1015 [Palm] at 7-8, 10-11 (referencing clinical PDT

studies performed on the forearms and dorsal hands with occlusion); Ex. 1017 [Sotiriou] at 1061-1062; Ex. 1013 [Willey] at 1096-1098; Ex. 1019 [McLaren] at 398-399; Ex. 1005 [Noven Pharma] at 15:1-29.

76. Claim 3 specifies that the plasma concentration of ALA after application does not exceed 110 ng/ml. Based on other pharmacokinetic studies, however, it was known before January 12, 2018 that the endogenous concentration of ALA is about 11 to 20 ng/ml and that topical application of ALA results in little to no increase in ALA plasma concentration. Ex. 1008 [Fauteck] at 57-58, Tables 5-7; Ex. 1010 [Ameluz] at 9; Ex. 1009 [Biofrontera] at [0143] (“The plasma and urine concentrations of these [ALA and protoporphyrin IX] compounds in ALA-treated patients were not increased in comparison to the naturally occurring physiological values in the same individuals”); Ex. 1035 [Rick] at 315, 317. In light of what was known at the time, a practitioner would not expect the ALA plasma concentration after application to exceed 110 ng/ml.

77. Claims 2 and 9 specify that low density polyethylene film is removed within/no later than 3 hours after the treatment site is covered. Ex. 1001 [‘567 patent] at Claim 2; Claim 9. Yet, the use of LDPE plastic wraps for occlusion in ALA PDT and their removal after an incubation period within/no later than 3 hours was also described in publications before January 12, 2018 and used in my own practice. Ex.

1013 [Willey] at 1095; Ex. 1015 [Palm] at 22-24; Ex. 1019 [McLaren] at 398-399; 11:23-25 (specifying incubation times of up to 120 minutes); Ex. 1014 [Calderhead] at 246 (“At the end of incubation, the occlusive dressing is removed”); Ex. 1010 [Ameluz] at 3 (“Following 3 hours of occlusion, remove the dressing and wipe off any remaining gel.”); Ex. 1018 [Bissonnette] at 226.

78. Claim 10 specifies that the blue light source is positioned between 2-4 inches from the treatment site. The positioning of a blue light source between 2 to 4 inches from the treatment surface was also not new as of January 12, 2018. In fact, the placement of a blue light source between 2 to 4 inches from the treatment surface was previously disclosed by DUSA almost 20 years earlier in the BLU-U operating manual and adopted by the FDA in the instructions for use for using Levulan. Ex. 1012 [BLU-U Operating Manual] at 9-11; Ex. 1011 [Levulan Label 2002] at 14; Ex. 1013 [Willey] at 1095. Thus, in my opinion, none of the features added by the dependent claims of the ’567 patent are new as of January 12, 2018.

B. ‘567 Patent Application (U.S. Patent Application No. 15/869,164)

79. In addition to reviewing the ’567 Patent’s specification, I was also asked to review the prosecution history of the ’567 Patent. As explained in the Legal Considerations Section above, I understand that the prosecution history is relevant to interpreting the claims of the ’567 patent.

80. As shown on the face of the ‘567 patent, on January 12, 2018, DUSA (which I understand is a subsidiary of Sun Pharmaceuticals) filed U.S. Patent Application No. 15/869,164 (“the ‘164 Application”), entitled “Methods for Photodynamic Therapy.” The ‘164 Application originally names Scott Lundahl and Michael Guttadauro as inventors. The ‘164 Application does not appear to claim priority to any earlier filed applications.

81. On August 9, 2018, during prosecution of the patent application, the patent examiner rejected then claims 1-8 and 16-20 based on DUSA’s use of the term “low density polyethylene” in the claims because “low density” was unclear and not defined. Ex. 1002 [‘164 Application] at 177-179. The patent examiner further rejected claims 1, 2, 5, and 16 as anticipated by Foguet Roca, U.S. Application Publication No. 2009/0324727 and claims 1 and 16 as anticipated by Trigiante, U.S. Application Publication No. 2011/0053965. Ex. 1002 [‘164 Application] at 177; 179-181. In rejecting the claims, the patent examiner noted “in the Background section of the instant application, the applicant describes the use of ALA composition[s] for photodynamic therapy is well known in the art.” Ex. 1002 [‘164 Application] at 180. Finally, the patent examiner indicated that then claims 3-8 and 17-20 would be allowable if rewritten to include all the features of the base claim. Ex. 1002 [‘164 Application] at 181. The examiner does not appear to have

rejected any of the claims as obvious based on the Trigante or Foguet Roca references.

82. In response to the patent examiner's rejections, on November 2, 2018, DUSA amended some of the independent claims to add in features from the claims that the examiner said would be allowable if rewritten. Ex. 1002 ['164 Application] at 101 ("Amendments To The Claims"). Some examples of the claim amendments made by DUSA are shown below:

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application:

1. (Currently Amended) A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:

topically applying ALA to a treatment area to be treated with photodynamic therapy;

[[and]]

after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area; and

removing the low density polyethylene barrier within 3 hours and then applying light to the treatment area.

5. (Currently Amended) A method ~~as set forth in claim 1,~~ of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:

topically applying ALA to a treatment area to be treated with photodynamic therapy; and
after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area,

wherein the treatment area is located on a hand or a forearm ~~an upper extremity~~.

16. (Currently Amended) A method of using 5-aminolevulinic acid (ALA) and a low density polyethylene barrier, comprising:

contacting a treatment site with a composition comprising the ALA so as to wet the treatment site; [[and]]

following wetting of the treatment site, covering the wetted treatment site with the low density polyethylene barrier;

removing the low density polyethylene barrier so as to expose the treatment site; and
illuminating the exposed treatment site with an illuminator so as to deliver a 10 J/cm² dose of blue light.

Ex. 1002 [‘164 Application] at 101-102.

83. DUSA also addressed the patent examiner’s “low density” polyethylene concern by identifying documents providing evidence that low density polyethylene was known in the art because it “was the first type of polyethylene that was commercially produced” and was “**developed in 1933.**” Ex. 1002 [‘164 Application] at 098. DUSA further told the patent examiner that “low density

polyethylene’ is a well-known term of art [that was] developed ... over 80 years ago” and admitted that “the specification identifies trade names for various brands of low density polyethylene products in Tables 1 and 2.” Ex. 1002 [‘164 Application] at 098.

84. After some additional prosecution, the ‘567 patent application was allowed on June 3, 2019 [Ex. 1002 [‘164 Application] at 015] and issued around a month later on July 23, 2019. Ex. 1001 [‘567 patent] at Cover. In allowing the claims of the ‘567 patent, the examiner provided the following reasons for allowance:

[T]he prior art of record does not teach a photodynamic therapy method for enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into a tissue, the method comprising: topically applying ALA to a treatment area to be treated with photodynamic therapy; after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize trans-epidermal water loss from the treatment area; and removing the low density polyethylene barrier applied to the treatment area prior to applying light to the treatment area. The prior art further fails to teach a method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, wherein the treatment area is located on a hand or a forearm as claimed. Ex. 1002 [‘164 Application] at 015.

85. Yet, as reflected in this declaration, each of the foregoing features is found in prior art well before the January 12, 2018 filing date of the ‘567 patent.

VIII. Claim Construction

86. I have been asked to provide my opinion regarding the meaning of the phrases “dorsal surface of the hand” and “dorsal surface of the forearm” which appear in claims 6 and 7 respectively to one of ordinary skill in the art as of January 12, 2018 in light of the specification and prosecution history.

87. Based on my reading of the ‘567 patent specification and the prosecution history—which is consistent how one of ordinary skill in the art would interpret these phrases—it is my opinion that: (1) “dorsal surface of a hand” means “the top portion of the hand between the wrist and the base of the fingers”; and (2) “dorsal surface of the forearm” means “the top portion of the forearm between the elbow and the wrist”.

88. These proffered meanings are supported by the specification which describes that “the dorsal surface of the hands and / or the forearm” is the “area between the elbow and the base of the fingers”. Ex. 1001 [‘567 patent] at 14:30-34. Elsewhere, the ‘567 patent specification identifies the “the dorsal hands/forearms” as “the extensor surface of both distal upper extremities.” Ex. 1001 [‘567 patent] at 13:35-38. The latter citation to the specification also supports my interpretation of these phrases because the extensor surface of both distal upper extremities encompasses the top surface of the hands and forearms.

89. My interpretation is also supported by others' use of these phrases in the field around or before January 12, 2018. For example, Willey describes an ALA photodynamic treatment area as on “the forearms and dorsal hands of 24 subjects” Ex. 1013 [Willey] at 1096-1097. Willey also provides photographs showing the treatment area on the dorsal surface of the hand and forearm—*i.e.*, the top portion of the hand and forearm.

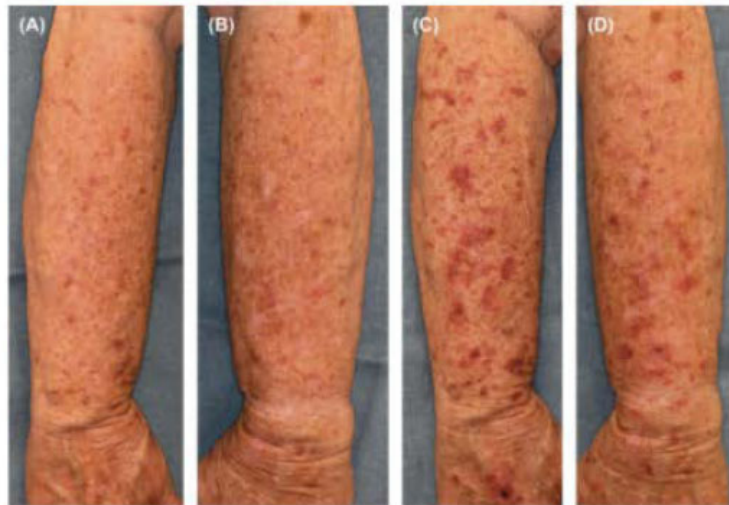


Figure 1. (A) Right arm of Subject 3 at baseline. (B) Left arm of Subject 3 at baseline. (C) Right arm of Subject 3 one week after PDT (heated). Note the increased PDT reaction on heated side compared with control at 1 week, despite similar baseline lesion counts. (D) Left arm of Subject 3 one week after PDT (control).

Ex. 1013 [Willey] at 1096, 1098, Figures 1 and 2.

IX. Application of the Prior Art to the Challenged Claims

90. In the sections below, I demonstrate on a claim-by-claim basis that all of the elements of the ‘567 patent’s claims were well known in the prior art. The publications I use in my analysis for Grounds 1-6 below are within the field of dermatological photodynamic therapy.

A. Ground 1: Claims 1-4 and 6-10 Are Taught by Willey

91. The Willey publication—*i.e.*, Willey A, Anderson RR, Sakamoto FH. Temperature-modulated photodynamic therapy for the treatment of actinic keratosis on the extremities. *Dermatologic Surger*,. 2014 Oct;40(10):1094-1102 (“Willey”)—describes the methods and results of a pilot study examining the effect of temperature on the ALA photodynamic therapy treatment of actinic keratosis on the upper and lower extremities of 20 subjects. In the study, subjects were treated with 20% ALA (Levulan Kerastick) occluded with Saran plastic wrap for a 1 hour incubation period with heat and at room temperature (control) prior to irradiation with the BLU-U blue light source. Ex. 1013 [Willey] at 1095. The researchers found that application of heat under the conditions tested improved the efficacy of ALA PDT treatments of actinic keratosis on the extremities compared to the controls which did not use heat. Ex. 1013 [Willey] at 1094, 1097-1100.

92. Based on my knowledge, investigation and experience, Willey was published and publicly available by at least November 2014. Specifically, Willey was published in the October 2014 edition of the journal entitled *Dermatologic Surgery*, Volume 40 - Issue 10. Ex. 1031 [Affidavit of Duncan Hall] at 005; Ex. 1032 [Willey Pubmed] at 001. Indeed, the Internet Archive site that catalogs webpages, shows that Willey was available for access and review by the public online by at least November 2014. Ex. 1031 [Affidavit of Duncan Hall] at 005.

93. I also confirmed using Pubmed, a medical research website operated by NIH/National Center for Biotechnology Information (“NCBI”), that Willey was available to the public prior to January 12, 2018—the filing date of the ’567 patent. The Pubmed website shows seven publications that cite to Willey dated between 2015 to 2017. Ex. 1032 [Willey Pubmed] at 002-004. The foregoing evidence combined with my experience accessing, reviewing, and publishing in dermatology journals—both in online and print versions—confirms to me that Willey was available to the public before January 12, 2018.

94. I was asked to provide an opinion regarding whether Willey teaches each and every element of claims 1-4 and 6–10 of the ‘567 patent. Based on my review and analysis, Willey discloses all the elements, either expressly or implicitly, in claims 1-4 and 6-10 of the ‘567 patent as discussed in further detail below:

1. Claim 1

95. Claim 1 preamble of the ‘567 patent claims:

1. A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:

96. Willey discloses a method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy. In particular, Willey discloses occluding the treatment site after application of the topical ALA to enhance penetration. Ex. 1013 [Willey] at 1095. (“Treatment

Protocol ... Topical 20% 5-ALA (Levulan Kerastick; Dusa Pharmaceuticals, Inc., Wilmington, MA) was applied to the entire forearm skin and **occluded with plastic wrap (Saran; SC Johnson).**”) (emphasis added). Based on my knowledge, experience and practice, occlusion of the treatment site, such as the forearm skin, with Saran plastic wrap after the application of ALA enhances its penetration into the tissue. This understanding is confirmed by others in the field, including by two of the same authors identified on the Willey publication, Drs. Sakamoto and Anderson. Ex. 1006 [Sakamoto]. The Sakamoto reference, which identifies Drs. Sakamoto and Anderson as co-authors, expressly states that “[o]cclusion is known to reduce transepidermal water loss, hydrating the stratum corneum and generally enhancing drug penetration, especially for hydrophilic molecules such as ALA.”) Ex. 1006 [Sakamoto] at 205. Similarly Ozog describes that “occlusion has been used to increase penetration [of ALA]” and notes that “[t]his can be accomplished with plastic wrap or some other nonporous flexible material placed over the targeted area after the ALA has been applied.” Ex. 1027 [Ozog] at 808.

97. As a result, Willey meets all the elements of Claim 1 preamble of the ‘567 patent.

2. Claim 1a

98. Claim 1a of the ‘567 patent claims:

1a. topically applying ALA to a treatment area to be treated with photodynamic therapy

99. Willey discloses topically applying ALA to an area to be treated with photodynamic therapy. Specifically, Willey discloses that “[t]**opical 20% 5-ALA** (Levulan Kerastick; Dusa Pharmaceuticals, Inc., Wilmington, MA) **was applied** to the entire forearm skin” and specifies that “[o]ne stick [of Levulan] (1.5 mL) was used to cover each distal extremity.” Ex. 1013 [Willey] at 1095; 1094 (referencing photodynamic therapy).

100. As a result, Willey meets all the elements of Claim 1a of the ‘567 patent.

3. Claim 1b

101. Claim 1b of the ‘567 patent claims:

1b. after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area; and

102. Willey discloses that after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss therefrom.

103. As noted above, Willey discloses occluding the treatment site with Saran plastic wrap—a well-known low density polyethylene barrier material—after application of the topical ALA. Ex. 1013 [Willey] at 1095 (**Topical 20% 5-ALA** (Levulan Kerastick; Dusa Pharmaceuticals, Inc., Wilmington, MA) **was applied** to

the entire forearm skin and occluded with plastic wrap (Saran; SC Johnson)” (emphasis added). The ’567 patent specifically identifies SC Johnson’s Saran plastic wrap as a low density polyethylene material:

TABLE 1

Barrier Materials A-E			
Material Code	Name	Distributor or Manufacturer	Material Description
A	Tegaderm™, Style 1629	3M	Polyurethane
B	Glad® Press’n Seal®	The Glad Products Company	LDPE
C	Glad® Cling Wrap	The Glad Products Company	LDPE
D	Stretch-Tite®	Polyvinyl Films, Inc.	Polyvinylidene chloride (PVdC)
E	Saran™ Premium Wrap	SC Johnson	LDPE

Ex. 1001 [‘567 patent], Table 1 (highlighting added).

104. I also note that SC Johnson’s website identifies Saran plastic wrap as made from low density polyethylene. Ex. 1031 (Affidavit of Duncan Hall) at 025.

105. Based on my knowledge, education, and experience, a person of ordinary skill in the art at the time would have recognized that occluding the skin with low density polyethylene films like the Saran plastic wrap disclosed in Willey minimizes transepidermal water loss from the portion of the skin to which the plastic wrap is applied. This understanding is confirmed, for example, by Sakamoto which expressly states that “[o]cclusion is known to reduce transepidermal water loss.” Ex. 1006 [Sakamoto] at 205 (emphasis added). Other references like Berardesca also

describe the application of occlusive barriers such as polyethylene films to minimize transepidermal water loss. Ex. 1007 [Berardesca] at 26, Figure 2 (showing the minimization of transepidermal water loss (TEWL) by different plastic coverings). As such, it was well known before January 12, 2018 that occlusion of the skin minimizes transepidermal water loss resulting in the enhanced penetration of ALA. Ex. 1027 [Ozog] at 808.

106. Thus, Willey meets all the elements of Claim 1b of the '567 patent.

4. Claim 1c

107. Claim 1c of the '567 patent claims:

1c. removing the low density polyethylene barrier within 3 hours and then applying light to the treatment area.

108. Willey discloses removing the low density polyethylene barrier within 3 hours and then applying light to the treatment area. In this regard, Willey discloses, after a 1 hour incubation period, applying blue light from a BLU-U light source and cooling of the treated area with a small portable fan. Ex. 1013 [Willey] at 1095 (“Treatment Protocol ... **After 1 hour, both of the treated sites (heated and control) were irradiated with 10 J/cm² blue light (BLU-U; Dusa Pharmaceuticals, Inc.) ... “During light irradiation, the treated areas were cooled by a small portable fan ... for comfort.”)** (emphasis added). Based on my knowledge, education and experience, cooling the treated area using a small fan during

irradiation indicates to me that the Saran wrap was removed at the end of the incubation prior to irradiation with light. This is because, if the Saran wrap is not removed prior to irradiation, cooling of the treated area by the small fan would be impeded because the Saran wrap would occlude the area and prevent evaporative cooling promoted by the fan.

109. In addition, based on my knowledge, education, and experience, a person of ordinary skill in the art would understand from reading Willey that the Saran wrap is removed at the end of the 1 hour incubation period before light from the BLU-U is applied. Based on my knowledge, education, and experience and the use of the term “incubation period,” a person of ordinary skill in the art would understand “incubation period” as used in Willey to refer to the time that the treated area is covered with the ALA and occluded by the Saran plastic wrap.

110. Based on my knowledge, education, and experience, a person of ordinary skill in the art before January 12, 2018 would further understand that at the end of the specified incubation period, the Saran wrap is removed and the remaining ALA wiped away from the skin in order to bring the incubation period to an end at the specified time.

111. My understanding of “incubation period” as used in Willey is demonstrated in other photodynamic therapy references. Calderhead, for example,

expressly states that at the end of the incubation period, the occlusive dressing is removed and excess ALA is wiped away. Ex. 1014 [Calderhead] at 246 (“At the end of incubation, the occlusive dressing is removed and any excess 5-ALA wiped off. Activation of the porphyrins induced in the target tissue is then achieved with 633 nm light ...”). Similarly, the Ameluz Prescribing Information specifies that after 3 hours of occlusion, the occlusive dressing is removed and any ALA gel is wiped off. Ex. 1010 [Ameluz] at 3 (“Step. 3. Occlusion for 3 Hours ... Following 3 hours of occlusion, remove the dressing and wipe off any remaining gel.”). Other prior art references indicate the same. Ex. 1017 [Sotiriou] at 1061 (“20% 5-ALA ... was applied on the lesions ... and left under occlusion for 4 h. Immediately after removal of the [occlusive] dressing and the cream remnants, [the] treatment area was illuminated.”); Ex. 1005 [Noven Pharma] at 15:7-21 (“After the patch is removed ... the lesion is wiped ... [and] then exposed to a 634 nm wavelength light source.”); Ex. 1018 [Bissonnette] at 226 (“Three hours later the occlusion is removed, the [MAL] cream wiped out of the treatment field and the device (Aktelite) positioned at 5–8 cm from the skin.”); Ex. 1015 [Palm] at 24 (specifying that after a 60 minute incubation period the ALA (Levulan) should be removed “prior to any light treatment.”); Ex. 1019 [McLaren] at 399 (recommending to “[w]ash the treated areas with a gentle cleanser and water after incubation, before starting the light

treatment.”). A person of ordinary skill in the art at the time would therefore interpret the incubation time in Willey the same way—*i.e.*, that following the specified 1 hour incubation period, the Saran wrap is removed and the treatment area cleaned prior to application of the light.

112. Thus, Willey meets all the elements of Claim 1c of the ‘567 patent.

113. Accordingly, Willey meets all the elements of Claim 1 of the ‘567 patent.

5. Claim 2

114. Claim 2 of the ‘567 patent claims:

2. A method as set forth in Claim 1, wherein the low density polyethylene barrier is removed from the treatment area within 3 hours and then blue light is applied to the treatment area for a 10 J/cm² light dose.

115. Willey meets all the elements of Claim 1, as shown above. See Claim 1 discussion; Ex. 1013 [Willey] at 1095; Ex. 1006 [Sakamoto] at 205.

116. Further, as I discuss above, Willey discloses a 1 hour ALA incubation period with occlusion of the treatment area using Saran plastic wrap. Ex. 1013 [Willey] at 1095. As I also discuss above, a person of ordinary skill in the art at the time would understand that the Saran wrap is removed at the end of the incubation period based on the teachings of Willey. Ex. 1013 [Willey] at 1095.

117. Additionally, Willey discloses that blue light from the BLU-U illuminator is applied to the treatment site for a 10 J/cm² dose after the specified 1 hour incubation period. Ex. 1013 [Willey] at 1095 (“**After 1 hour, both of the treated sites** (heated and control) **were irradiated with 10 J/cm² blue light (BLU-U; Dusa Pharmaceuticals, Inc.)** for 1,000 seconds with the light positioned 2 to 4 inches from the skin surface.”) (emphasis added).

118. Thus, Willey meets all the elements of Claim 2 of the ‘567 patent.

6. Claim 3

119. Claim 3 of the ‘567 patent claims:

3. The method of Claim 1, wherein a maximum plasma concentration of ALA following application of the ALA is less than about 110 ng/mL.

120. Willey meets all the elements of Claim 1, as shown above. See Claim 1 discussion; Ex. 1013 [Willey] at 1095; Ex. 1006 [Sakamoto] at 205.

121. Regarding the subject matter of claim 3, the ‘567 patent describes studies involving the “topical application of the ALA to the upper extremities” with the “application of up to two topical solution compositions each containing about 354 mg of ALA.” Ex. 1001 [‘567 patent] at col. 13:47-50; 13:30-33. The ‘567 patent goes on to state that “topical dosing was observed to result in a mean plasma concentration (C_{max}) value of ALA of less than about 110 ng/mL.” Ex. 1001 [‘567

patent] at col. 13:47-50. The '567 patent further states that the “term ‘C_{max}’ as used herein refers to the maximum observed plasma concentrations based on actual values measured following study medication application.” Ex. 1001 [‘567 patent] at col. 13:55-58. In addition, the '567 patent reports in one experiment a “geometric mean maximum plasma concentration [of] about 98 ng/mL” and a “baseline correct[ed] ALA geometric mean maximum plasma concentration [of] 80 ng/mL.” Ex. 1001 [‘567 patent] at col. 13:59-66. In a second experiment, the '567 patent reports a “geometric mean maximum plasma concentration [of] about 61 ng/mL” and a “baseline correct[ed] ALA geometric mean maximum plasma concentration [of] 39 ng/mL.” Ex. 1001 [‘567 patent] at col. 14:6-13.

122. Willey necessarily discloses a maximum plasma concentration of ALA following application of the ALA of less than about 110 ng/mL. Specifically, Willey discloses the topical application of one stick (1.5 mL) of 20% ALA (Levulan) to each upper extremity (including the hands and forearms) for 1 hour under occlusion with a Saran wrap low density polyethylene film. The 1 hour incubation period is followed by illumination of the treatment area with blue light. Ex. 1013 [Willey] at 1095.

123. Based on my review of Willey and the '567 patent, the amount of ALA applied to patients in Willey and the area of application—one stick of Levulan to each distal extremity—is the same amount of ALA applied in the '567 patent.

124. Specifically, Willey discloses the application of up to two sticks of Levulan which contain 354 mg of ALA each to cover each upper extremity. Ex. 1013 [Willey] at 1095; Ex. 1011 [Levulan Label 2002] at 1. Similarly, the '567 patent discloses that “up to two topical solution compositions each containing about 354 mg ALA” were applied to the upper extremities and further states that “topical dosing was observed to result in a mean plasma concentration (C_{max}) value of ALA less than about 110 ng/mL.” Ex. 1001 ['567 patent] at 13:45-14:19.

125. Based on my knowledge, education, and experience, because the same amount of ALA (Levulan) is described as administered to the upper extremities of patients in both Willey and the '567 patent, the patients in Willey would necessarily have maximum plasma concentrations of ALA following application of the ALA that are consistent with the maximum plasma concentrations of ALA reported in the '567 patent. That is, the patients subjected to the disclosed PDT treatment in Willey would necessarily have maximum plasma concentrations of ALA of less than about 110 ng/mL as disclosed in the '567 patent.

126. Thus, Willey meets all the elements of Claim 3 of the '567 patent.

7. Claim 4

127. Claim 4 preamble of the '567 patent claims:

4. A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:

128. Willey meets all the elements of Claim 1 preamble as discussed above, and hence also meets all the elements of Claim 4 preamble. See Claim 1 preamble discussion above; Ex. 1013 [Willey] at 1095; Ex. 1006 [Sakamoto] at 205; Ex. 1027 [Ozog] at 808.

8. Claim 4a

129. Claim 4a of the '567 patent claims:

4a. topically applying ALA to a treatment area to be treated with photodynamic therapy; and

130. Willey meets all the elements of claim 1a, as discussed above. In my opinion, claim 4a is taught by Willey for the same reasons described above for Claim 1a. See Claim 1a discussion above; Ex. 1013 [Willey] at 1095.

9. Claim 4b

131. Claim 4b of the '567 patent claims:

4b. after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light

treatment to minimize transepidermal water loss from the treatment area

132. Willey meets all the elements of claim element 1b, as discussed above.

In my opinion, claim element 4b is taught by Willey for the same reasons described above for Claim 1b. See Claim 1b discussion above; Ex. 1013 [Willey] at 1095; Ex. 1006 [Sakamoto] at 205.

10. Claim 4c

133. Claim 4c of the ‘567 patent claims:

4. wherein the treatment area is located on a hand or a forearm.

134. Willey discloses the treatment area is located on a hand or a forearm.

Willey describes, for example, the treatment of lesions on “the **forearms and dorsal hands** of 24 subjects.” Ex. 1013 [Willey] at 1096-1097 (emphasis added). Willey further states that “[t]opical 20% 5-ALA ... was applied to **the entire forearm skin**” and provides exemplary photos showing treatment of the hand and forearm. Ex. 1013 [Willey] at 1095 (emphasis added); Figures 1 and 2.

135. Thus, Willey meets all the elements of Claim 4c, and also meets all the elements of Claim 4.

11. Claim 6 / Claim 7

136. Claims 6 and 7 of the ‘567 patent claim:

6. The method as set forth in Claim 4, wherein the treatment area is a dorsal surface of the hand.

7. The method as set forth in Claim 4, wherein the treatment area is a dorsal surface of the forearm.

137. Willey meets all the elements of Claim 4, as shown above. See Claim 4 discussion above; Ex. 1013 [Willey] at 1095; Ex. 1006 [Sakamoto] at 205.

138. Willey further discloses a treatment area located on a dorsal surface of the hand and forearm as claimed in claims 6 and 7.

139. As I discuss above, the '567 patent specifically states that "the dorsal surface of the hands and/or the forearm [is the] area between the elbow and the base of the fingers." Ex. 1001 ['567 patent] at col. 14:26-28. This disclosure is consistent with my interpretation of these terms as I discuss in further detail in the claim construction section of this declaration. In that section, I provide my opinion that: (1) "dorsal surface of a hand" means "the top portion of the hand between the wrist and the base of the fingers"; and (2) "dorsal surface of the forearm" means "the top portion of the forearm between the elbow and the wrist". Applying these interpretations, Willey discloses treatment areas located on a dorsal surface of the hand and forearm.

140. For example, Willey states that the treatment area is on “the **forearms and dorsal hands** of 24 subjects.” Ex. 1013 [Willey] at 1096-1097 (emphasis added). Relatedly, Willey further states that “[t]opical 20% 5-ALA ... was applied to **the entire forearm skin**” and provides exemplary photos showing treatment of the dorsal surfaces of the hand and forearm. Ex. 1013 [Willey] at 1096 (emphasis added).

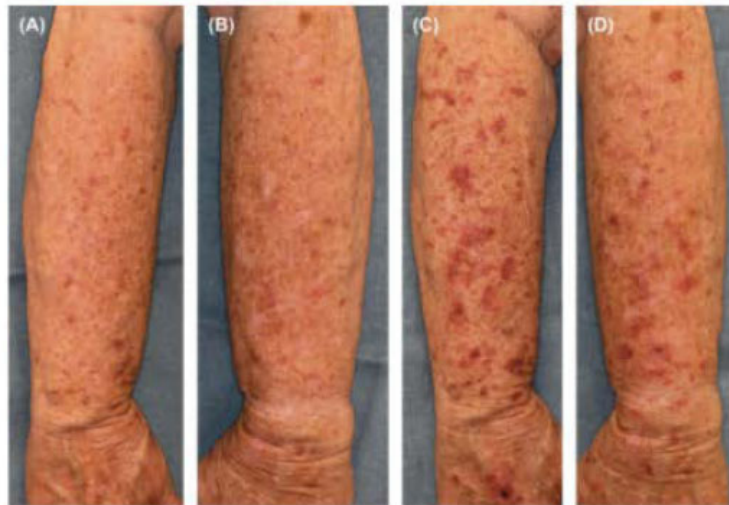


Figure 1. (A) Right arm of Subject 3 at baseline. (B) Left arm of Subject 3 at baseline. (C) Right arm of Subject 3 one week after PDT (heated). Note the increased PDT reaction on heated side compared with control at 1 week, despite similar baseline lesion counts. (D) Left arm of Subject 3 one week after PDT (control).

Ex. 1013 [Willey] at 1096, 1098, Figures 1 and 2.

141. Thus, Willey meets all the elements of claims 6 and 7 of the ‘567 patent.

12. Claim 8

142. Claim 8 preamble of the ‘567 patent claims:

8. A method of using 5-aminolevulinic acid (ALA) and a low density polyethylene barrier, comprising:

143. Willey discloses using 5-aminolevulinic acid (ALA) and a low density polyethylene barrier. As I discuss above, Willey discloses applying 20% ALA to the entire forearm skin and occluding it with Saran plastic wrap thereafter. Ex. 1013 [Willey] at 1095 (“Treatment Protocol ... Topical 20% 5-ALA (**Levulan Kerastick**; Dusa Pharmaceuticals, Inc., Wilmington, MA) was applied to the entire forearm skin and occluded with **plastic wrap (Saran; SC Johnson).**”) (emphasis added). As I discuss above at paragraphs 103-104, Saran plastic wrap provides a low density polyethylene barrier.

144. As a result, Willey meets all the elements of Claim 8 preamble of the ‘567 patent.

13. Claim 8a

145. Claim 8a of the ‘567 patent claims:

8a. contacting a treatment site with a composition comprising the ALA so as to wet the treatment site

146. Willey discloses contacting the treatment site with a 20% ALA solution to wet it. The ‘567 Patent describes wetting the treatment site, in one example, as applying a topical solution of ALA to the skin. Ex. 1001 [‘567 patent] at 9:50-54. In another example, the ‘567 Patent also describes the application of an ALA admixture “to achieve a substantially uniform wetting of the lesion surface with the ALA by contacting the ALA with the lesion surface.” Ex. 1001 [‘567 patent] at 9:12-18.

Consistent with these examples, Willey discloses contacting the treatment site with ALA so as to wet the treatment site. In particular, Willey states that “[t]**opical 20% 5-ALA (Levulan Kerastick;** Dusa Pharmaceuticals, Inc., Wilmington, MA) **was applied** to the entire forearm skin” and that “[o]ne stick (1.5 mL) was used to cover each distal extremity.” Ex. 1013 [Willey] at 1095 (emphasis added).

147. Based on my background, knowledge, and experience, a person of ordinary skill in the art at the time would appreciate that Levulan Kerastick, as discussed in Willey, is applied as a liquid ALA composition to the skin using the Kerastick applicator which wets the skin upon application. In fact, this is confirmed by the Levulan Kerastick labeling information supplied therewith. Ex. 1011 [Levulan Label 2002] at 13 (“Enough solution should be applied to **uniformly wet the lesion** surface.”) (emphasis added).

148. As a result, Willey meets all the elements of Claim 8a of the ‘567 patent.

14. Claim 8b

149. Claim 8b of the ‘567 patent claims:

8b. following wetting of the treatment site, covering the wetted treatment site with the low density polyethylene barrier

150. Willey discloses following wetting of the treatment site, covering the wetted treatment site with the low density polyethylene barrier. Specifically, Willey discloses covering the wetted treatment site with low density polyethylene Saran

plastic wrap after wetting the forearm skin with the liquid ALA solution. Ex. 1013 [Willey] at 1095 (“Treatment Protocol ... Topical 20% 5-ALA (Levulan Kerastick; Dusa Pharmaceuticals, Inc., Wilmington, MA) was applied to the entire forearm skin and **occluded with plastic wrap (Saran; SC Johnson)**”) (emphasis added).

151. As a result, Willey meets all the elements of Claim 8b of the ‘567 patent.

15. Claim 8c

152. Claim 8c of the ‘567 patent claims:

8c. removing the low density polyethylene barrier so as to expose the treatment site; and

153. Willey discloses removal of the low density polyethylene Saran plastic wrap to expose the treatment site. In this regard, Willey discloses, following a 1 hour incubation period, applying blue light from a BLU-U light source and cooling of the treated area with a small portable fan. Ex. 1013 [Willey] at 1095 (“Treatment Protocol ... **After 1 hour, both of the treated sites (heated and control) were irradiated with 10 J/cm² blue light (BLU-U; Dusa Pharmaceuticals, Inc.)** ... “During light irradiation, **the treated areas were cooled by a small portable fan** ... for comfort.”) (emphasis added); Ex. 1013 [Willey] at 1096-1097 (referencing the “1-hour incubation period”). Based on my knowledge, education and experience, Willey’s cooling of the treated area using a small fan during irradiation indicates to

me that the Saran wrap was removed at the end of the incubation period to expose the treatment site prior to its irradiation with light. As I discuss above, this is because if the Saran wrap is not removed prior to irradiation, cooling of the treated area by the small portable fan would be impeded because the Saran wrap would not allow fresh air to contact the skin and would prevent evaporative cooling of the treated area promoted by the fan.

154. In addition, based on my knowledge, education, and experience, a person of ordinary skill in the art would understand from reading Willey that the Saran wrap is removed at the end of the 1 hour incubation period before the light from the BLU-U is applied. Based on my knowledge, education, and experience and the use of the term “incubation period” in the PDT field, a person of ordinary skill in the art would understand “incubation period” as used in Willey to refer to the time that the treated area is covered with the ALA and occluded by the Saran plastic wrap. Based on my knowledge, education, and experience a person of ordinary skill in the art would further understand that at the end of the specified incubation period, the Saran wrap is removed and the remaining ALA wiped away from the skin in order to bring the incubation period to end within the specified time.

155. My understanding of Willey’s incubation period is demonstrated in other photodynamic therapy references, such as in Calderhead. Calderhead, for

example, expressly states that at the end of the incubation period, the occlusive dressing is removed and excess ALA is wiped away which exposes the treatment site. Ex. 1014 [Calderhead] at 246 (“**At the end of incubation, the occlusive dressing is removed** and any excess 5-ALA wiped off. Activation of the porphyrins induced in the target tissue is then achieved with 633 nm light ...”) (emphasis added). Similarly, the Ameluz Prescribing Information specifies that after 3 hours of occlusion, the occlusive dressing is removed and any ALA gel is wiped off. Ex. 1010 [Ameluz] at 3 (“Step. 3. Occlusion for 3 Hours ... **Following 3 hours of occlusion, remove the dressing** and wipe off any remaining gel.”) (emphasis added). Other prior art references indicate the same. Ex. 1017 [Sotiriou] at 1061 (“20% 5-ALA ... was applied on the lesions ... and left under occlusion for 4 h. Immediately after removal of the [occlusive] dressing and the cream remnants, [the] treatment area was illuminated.”); Ex. 1018 [Bissonnette] at 226 (“**Three hours later the occlusion is removed**, the [MAL] cream wiped out of the treatment field and the device (Aktilite) positioned at 5–8 cm from the skin.”) (emphasis added); Ex. 1015 [Palm] at 24 (specifying that after a 60 minute incubation period, that the ALA (Levulan) should be removed “prior to any light treatment.”); Ex. 1019 [McLaren] at 399 (recommending after incubation to “[w]ash the treated areas with a gentle cleanser and water after incubation, before starting the light treatment.”). A person of

ordinary skill in the art at the time would therefore interpret the incubation time in Willey in the same way—*i.e.*, that following the specified incubation period that the Saran wrap is removed to expose the treatment site.

156. As a result, Willey meets all the elements of Claim 8c of the ‘567 patent.

16. Claim 8d

157. Claim 8d of the ‘567 patent claims:

8d. illuminating the exposed treatment site with an illuminator so as to deliver a 10 J/cm² dose of blue light.

158. Willey discloses illuminating the exposed treatment site with an illuminator so as to deliver a 10 J/cm² dose of blue light. In this regard, Willey states that the light used to irradiate the treatment area is 10 J/cm² blue light from the BLU-U illuminator. Ex. 1013 [Willey] at 1095 (“After 1 hour, both of the treated sites (heated and control) were irradiated with **10 J/cm² blue light (BLU-U; Dusa Pharmaceuticals, Inc.)**”) (emphasis added).

159. As a result, Willey meets all the elements of Claim 8d of the ‘567 patent.

160. Accordingly, Willey teaches every limitation of the ‘567 patent, Claim 8

17. Claim 9

161. Claim 9 of the ‘567 patent claims:

9. The method of Claim 8, wherein the low density polyethylene barrier is removed no later than three hours after the treatment site is covered.

162. Willey meets all the elements of Claim 8, as discussed above. See Claim 8 discussion; Ex. 1013 [Willey] at 1095.

163. Willey further discloses that low density polyethylene barrier is removed no later than three hours after the treatment site is covered. Specifically, Willey discloses that after a 1 hour incubation, the treatment area is irradiated with 10 J/cm² blue light and cooled using a small portable fan. Ex. 1013 [Willey] at 1095 (“Treatment Protocol ...during the 1-hour incubation ... After 1 hour, both of the treated sites (heated and control) were irradiated with 10 J/cm² blue light ... During light irradiation, the treated areas were cooled by a small portable fan.”) As I discuss above, a person of ordinary skill in the art at the time would understand from the disclosure in Willey that the Saran wrap is removed at the end of the incubation period prior to irradiation with light. This is confirmed by the disclosure in the ’567 patent because cooling the treatment area with a fan as described therein would be ineffective if it was still covered by the Saran plastic wrap.

164. In addition to the express disclosure in Willey regarding the cooling of the treatment site, a person of ordinary skill in the art at the time would also understand from Willey that a 1 hour incubation period means that the low density

polyethylene Saran wrap barrier is removed 1 hour after the treatment site is covered.

See my further discussion above at Claim 8c.

165. Thus, Willey meets all the elements of Claim 9 of the '567 patent.

18. Claim 10

166. Claim 10 of the '567 patent claims:

10. The method of Claim 8, further comprising: positioning the treatment site between two inches and four inches from a surface of the illuminator.

167. Willey meets all the elements of Claim 8, as discussed above. See Claim 8 discussion above; Ex. 1013 [Willey] at 1095.

168. In addition, Willey discloses positioning the treatment site between two inches and four inches from a surface of the illuminator. In this regard, Willey discloses that the BLU-U illuminator was positioned between two to four inches from the skin surface. Ex. 1013 [Willey] at 1095 (“**[B]oth of the treated sites (heated and control) were irradiated** with 10 J/cm² blue light (BLU-U; Dusa Pharmaceuticals, Inc.) ... **with the light positioned 2 to 4 inches from the skin surface.**”) (emphasis added).

169. Thus, Willey meets all the elements of Claim 10 of the '567 patent.

170. Based on my analysis discussed above, and the claim chart provided below, it is my opinion that Willey discloses expressly and/or implicitly what is claimed in claims 1–4 and 6-10 of the ‘567 patent.

B. Ground 2 – Claim 3 Is Met by the Combination of Willey with Ameluz

171. To the extent DUSA asserts that Willey does not necessarily disclose what is claimed in Claim 3 of the ‘567 Patent, as I explain further below and in the claim chart, it is my opinion that the combination of Willey and Ameluz further discloses what is claimed therein.

172. My discussion of Willey is provided above. As I note above, Willey was published and accessible to the public by at least around November 2014.

173. The Ameluz prescribing information publication (“Ameluz”) describes the results of clinical studies performed by Biofrontera examining the pharmacokinetic properties of Ameluz 10% ALA gel, including the plasma concentrations of ALA and PPIX after application. Ex. 1010 [Ameluz] at 9. In the Ameluz study, 2 g of Ameluz gel (with 10 % ALA) was applied under occlusion at a concentration of 10 mg/cm² to 12 adult subjects over a 20 cm² treatment area for a period of 3 hours. Ex. 1010 [Ameluz] at 9. Biofrontera determined the mean baseline plasma concentration of ALA before ALA application to be 20.16 ± 16.53 ng/mL

and the mean maximum concentration (C_{\max}) for baseline corrected² aminolevulinic acid after the ALA was applied topically to be 27.19 ± 20.02 ng/mL. Ex. 1010 [Ameluz] at 9.

174. Based on my investigation and experience, the Ameluz prescribing information was published and publicly available by at least October 2016 on the FDA website (<https://www.accessdata.fda.gov/>). Ex. 1031 [Affidavit of Duncan Hall] at 060-061. Specifically, the Internet Archive site that catalogs webpages, shows that the Ameluz prescribing information was available to the public at least by October 2016. Ex. 1031 [Affidavit of Duncan Hall] at 060-061. This date is consistent with when Ameluz was approved for marketing in the United States by the FDA. This evidence confirms to me that the Ameluz prescribing information was published and available to the public well before January 2018 when the '567 Patent was filed.

175. My additional analysis of Claim 3 is provided below.

1. Claim 3

176. Claim 3 of the '567 patent claims:

² The baseline corrected plasma concentration of ALA reflects the amount of ALA in the blood plasma resulting from external sources of ALA such as topically applied ALA. This value is generally determined by assessing the plasma concentration of ALA in a patient after application of ALA and subtracting out the baseline concentration of ALA that is attributable to endogenous levels in the blood plasma.

3. The method of Claim 1, wherein a maximum plasma concentration of ALA following application of the ALA is less than about 110 ng/mL.

177. Willey meets all the elements of Claim 1, as shown above. See Claim 1 discussion; Ex. 1013 [Willey] at 1095; Ex. 1006 [Sakamoto] at 205.

178. As I discuss above for Ground 1, Willey meets all the elements of claims 1 and 3 of the '567 patent. In addition, if DUSA asserts that claim 3 is not necessarily disclosed by Willey, it is also my opinion that Claim 3 is disclosed by Willey combined together with the Ameluz prescribing information. Ex. 1010 [Ameluz].

179. As I discussed above, for example, in the Ameluz study, 2 g of Ameluz gel (with 10 % ALA)—*i.e.*, 200 mg of ALA—was applied under occlusion to 12 adult subjects over a 20 cm² treatment area for a period of 3 hours. Ex. 1010 [Ameluz] at 9. Biofrontera determined the mean baseline plasma concentration of ALA to be 20.16 ± 16.53 ng/mL and the mean maximum concentration (C_{\max}) for baseline corrected ALA to be 27.19 ± 20.02 ng/mL. Ex. 1010 [Ameluz] at 9. Based on the Ameluz prescribing information data, the mean non-baseline corrected maximum plasma concentration is estimated to be around 47.35 ng/mL ($20.16 + 27.19$). The maximum ALA plasma concentrations reported in the Ameluz

prescribing information are thus well below the plasma concentration limit of about 110 ng/mL in Claim 3 of the '567 patent.

180. In my opinion, a person of skill in the art performing PDT and assessing the application of less ALA to fewer lesions or smaller lesions than those in Willey, would combine Willey's disclosure with that from the Ameluz prescribing information which indicates that less topical ALA (*i.e.*, 200 mg) can be safely and effectively applied under occlusion for a maximum plasma concentration of ALA around 47.35 ng/mL. Based on my education, background, and experience, it is my opinion that a person of ordinary skill in the art would be motivated to combine the teachings of Willey and the Ameluz prescribing information.³ Both relate to the use of topically applied ALA compositions to administer ALA for photodynamic therapy with occlusion and the Ameluz prescribing information indicates that the application of 200 mg of ALA is safe and effective with a maximum plasma concentration of ALA at around 47.35 ng/mL. As a result, a person of ordinary skill in the art wanting to assess the application of topical ALA compositions like those discussed in Willey (*i.e.*, Levulan) applied at an amount of around 200 mg of ALA with occlusion to treat fewer or smaller lesions would consult the Ameluz

³ In addition to other reasons, a person of ordinary skill in the art would be motivated to combine Willey with the Ameluz prescribing information because the Ameluz prescribing information includes ALA pharmacokinetic information from one of the few reported topically applied ALA pharmacokinetic studies.

prescribing information, which describes the pharmacokinetics of a similar FDA approved ALA composition and provides a maximum plasma concentration for topical application of ALA that is below 110 ng/mL. Ex 1010 [Ameluz] at 9; Ex. 1013 [Willey] at 1095-1096. Although Willey describes the application of up to 2 sticks of Levulan (up to 708 mg of ALA), a person of ordinary skill in the art would understand that less ALA would be applied to treat fewer lesions over smaller areas of skin—such as 200 mg of ALA over 20 cm² of skin as reported in the Ameluz prescribing information. Indeed, in my experience, a person of ordinary skill in the art would adjust the amount of ALA applied to a patient based on the size and number of AK lesions present on the portion of the patient being treated. Ex. 1011 [Levulan Label 2002] at 13 (stating that “[e]nough solution should be applied to uniformly wet the lesion surface”); Ex 1010 [Ameluz] at 3 (indicating that a “sufficient amount of gel” should be used “to cover the single lesions or if multiple lesions, the entire area.”). In such cases, one of skill in the art would appreciate that when less ALA is used (*e.g.*, ≤ 200 mg) to treat fewer/smaller AK lesions (*e.g.*, over a skin surface area of ≤ 20 cm²), that the maximum plasma concentrations of ALA would also decrease and be similar to or less than the maximum plasma concentration reported in the Ameluz prescribing information—*i.e.*, less than or around 47.35 ng/mL which is less than about 110 ng/mL. Indeed, based on the

pharmacokinetic information in the Ameluz prescribing information, a person of ordinary skill could readily adjust the amount of ALA applied to given areas of the skin so that the maximum plasma concentration of ALA did not exceed 110 ng/mL.

181. It is also my opinion that a person of ordinary skill in the art would have reasonably expected success in combining Willey with the Ameluz prescribing information. Specifically, in light of the results reported in the Ameluz prescribing information, a person of ordinary skill in the art would not expect a maximum plasma concentration above 110 ng/mL after topical application of the ALA compositions described in Willey especially when applied at concentrations at or below 200 mg—e.g., to treat fewer or smaller surface areas of lesions (at or below 20 cm²). This understanding is confirmed by the Ameluz prescribing information itself, as well as an earlier study by Rick, et al. In Rick, 200 mg of ALA was topically applied in a water-in-oil based cream and covered for 6 hours with occlusion. Ex. 1035 [Rick] at 315. In that study Rick determined that the maximum plasma concentration of ALA did not exceed the detection limit of 0.1 mg/L (*i.e.*, 100 ng/mL). Ex. 1035 [Rick] at 317. This further confirms my understanding that Willey and the Ameluz prescribing information could be combined with a reasonable expectation of success especially when fewer lesions are treated and less ALA is applied. Moreover, as noted above, based on the pharmacokinetic information in the Ameluz prescribing

information, a person of ordinary skill could readily adjust the amount of ALA applied to given areas of the skin so that the maximum plasma concentration of ALA did not exceed 110 ng/mL.

182. Thus, based on the foregoing and the claim chart below, it is my opinion that the '567 patent's Claim 3 is obvious in light of the combination of Willey and the Ameluz prescribing information.

C. Ground 3 – Claim 5 Is Met by the Combination of Willey with Sotiriou

183. As I explain below and in the claim chart, it is my opinion that the combination of Willey and Sotiriou discloses what is claimed in Claim 5 of the '567 Patent.

184. My discussion of Willey is provided above. As I also note above, Willey was published and accessible to the public by at least around October to November 2014.

185. The Sotiriou publication—*i.e.*, Sotiriou E, Apalla Z, Maliamani F, Zaparas N, Panagiotidou D, Ioannides D. Intraindividual, right-left comparison of topical 5-aminolevulinic acid photodynamic therapy vs. 5% imiquimod cream for actinic keratoses on the upper extremities. *J Eur Acad Dermatol Venereol*. 2009 Sep;23(9):1061-5. ("Sotiriou")—describes a study conducted between September 2007 and July 2008 comparing the efficacy and safety of treating AKs on the upper

extremities (dorsa of the hands and forearms) using ALA-PDT versus treatment using 5% imiquimod cream. Ex. 1017 [Sotiriou] at 1061-1062. In the study, 30 patients with comparable AK lesions on both the right and the left upper extremities were selected and treated randomly with ALA-PDT on one upper extremity and with imiquimod cream on the other. Ex. 1017 [Sotiriou] at 1062. For the ALA-PDT treatment, ALA was applied to the lesions and surrounding skin and maintained under occlusion for 4 hours. Ex. 1017 [Sotiriou] at 1062. After removal of the occlusive dressing, the treated area was irradiated with red light for a light dose of 75 J/cm². Ex. 1017 [Sotiriou] at 1062. As a result of the study, Sotiriou determined that ALA-PDT shows better efficacy than 5% imiquimod cream for grade II actinic keratosis (more sun damage) and had comparable efficacy to 5% imiquimod cream for treating grade I AK lesions (less sun damage) on the dorsal surface of the hands and forearms. Ex. 1017 [Sotiriou] at 1065.

186. Based on my investigation and experience, Sotiriou was published and publicly available before January 12, 2018. Specifically, Sotiriou was published in the September 2009 edition of the Journal of the European Academy of Dermatology and Venereology (“JEADV”), Volume 23, Issue 9 [Ex. 1017] and lists an E-publication date of April 8, 2009. Ex. 1033 [Sotiriou Pubmed] at 001. Further, the

Internet Archive website, demonstrates that Sotiriou was accessible to the public at least by March 2011. Ex. 1031 [Affidavit of Duncan Hall] at 013.

187. In addition, I confirmed using Pubmed that Sotiriou was available to the public prior to January 12, 2018. The Pubmed website identifies four publications that cite to Sotiriou dated between 2010 and 2016. Ex. 1033 [Sotiriou Pubmed] at 002. The foregoing evidence, combined with my experience accessing, reviewing, and publishing in dermatology journals—both online and print versions—confirms that Sotiriou was publicly available prior to January 12, 2018.

188. My analysis of Claim 5 is provided below.

2. Claim 5

189. Claim 5 of the '567 patent claims:

5. A method as set forth in Claim 4, wherein the low density polyethylene barrier is removed from the treatment area and then red light is applied to the treatment area for a 10 to 75 J/cm² light dose.

190. Willey meets all the elements of Claim 4, as shown above. See Claim 4 discussion; Ex. 1013 [Willey] at 1095.

191. While Willey does not disclose using a red light for a 10 to 75 J/cm² light dose, as specified in Claim 4, Claim 4 is obvious when the disclosure of Willey is combined with Sotiriou, which discloses using a red light source for a 75 J/cm² light dose to treat AK lesions on the hands and forearms. Ex. 1017 [Sotiriou] at 1062.

Indeed, as I discuss above, it was well known at the time that PPIX absorbs light in the blue and red wavelength ranges and can be activated by irradiating with wavelengths of light falling within the PPIX absorption spectrum. Ex. 1019 [McLaren] at 398.

192. Sotiriou reports results from the examination of the efficacy of ALA photodynamic therapy (“ALA-PDT”) using red light compared with the efficacy of 5% imiquimod cream administered to patients with AK lesions on the dorsal surfaces of the hands and forearms. Ex. 1017 [Sotiriou] at 1062. As part of the ALA-PDT treatment method employed, Sotiriou discloses: the application of 20% ALA to AK lesions on the dorsal surface of the hands and forearms under occlusion for 4 hours; removal of the occlusive dressing and any treatment remnants; and irradiation of the treated area with red light for a light dose of 75 J/cm^2 . Ex. 1017 [Sotiriou] at 1062. As a result of the study, Sotiriou determined that ALA-PDT provided around the same or better efficacy for treating AKs on the upper extremities when compared to 5% imiquimod cream. Ex. 1017 [Sotiriou] at 1065.

193. It is my opinion that a person of ordinary skill in the art at the time would have been motivated to combine the disclosures of Willey regarding ALA treatments using occlusion with Saran wrap with the disclosure of Sotiriou regarding using a red light source for a 75 J/cm^2 light dose. In this regard, a person of ordinary

skill in the art seeking to try to improve the efficacy of treating AK lesions—especially deeper lesions—on the hands and forearms would have been motivated to combine the disclosures of Willey with Sotiriou to, at the very least, examine whether a red light source improves efficacy for treating such lesions. In this regard, Willey expressly references and characterizes Sotiriou as demonstrating “high clearance rates” for PDT. Ex. 1013 [Willey] at 1094, 1101. Given this characterization of Sotiriou in Willey, it is my opinion that one of skill in the art would have been motivated to combine the disclosures of the two.

194. In addition, as I discuss above, it was well known at the time that red light is capable of penetrating deeper into the skin than blue light for photodynamic therapy treatment of lesions. Ex. 1016 [MacCormack] at 53; Ex. 1023 [Agostinis] at 255. Thus, a person of ordinary skill in the art at the time would have been motivated to combine the disclosure in Willey regarding the treatment of AKs on the hands and forearms (with topical ALA and occlusion with Saran plastic wrap) with the disclosure of Sotiriou regarding irradiation of the lesions with red light for a light dose of 75 J/cm^2 .

195. It is also my opinion that a person of ordinary skill in the art would have reasonably expected success in combining the disclosures of Willey with those of Sotiriou. The disclosures in Willey and Sotiriou are compatible because both relate

to topically treating AKs with 20% ALA compositions with occlusion. Ex. 1013 [Willey] at 1094; Ex. 1017 [Sotiriou] at 1062. Moreover, as I discuss in more detail above, both blue light sources (i.e., the BLU-U) and red light sources (i.e., BF-RhodoLED) can be used to treat AK lesions using PDT. Ex. 1015 [Palm] at 12, 14. Indeed, as I also discuss above, two of the currently FDA approved light sources for performing ALA photodynamic therapy are a blue light source (the BLU-U) and a red light source (BF-RhodoLED). Thus, it is my opinion that a person of ordinary skill in the art at the time would reasonably expect success in combining the disclosures of Willey with Sotiriou's red light source for irradiation in place of the blue light source disclosed in Willey. Ex. 1027 [Ozog] at 811.

196. Thus, in light of the foregoing and the claim chart, it is my opinion that the '567 patent's Claim 5 is obvious in light of the combined teachings of Willey and Sotiriou.

D. Ground 4: Claims 1-9 Are Taught by Noven Pharma

197. Noven Pharma—International Publication No. WO 96/06602—is a PCT Application Publication with an international publication date of March 7, 1996. Ex. 1005 [Noven Pharma], Cover. It lists Juan Mantelle and Allyn Golub as inventors and Noven Pharmaceuticals, Inc. as the applicant. Noven Pharma seeks to solve a need at the time to create a storage-stable composition of ALA in a form that can be administered to a patient. Ex. 1005 [Noven Pharma] at 3:17-19. In this regard,

Noven Pharma discloses two types of skin patches for administering ALA—both adhesive matrix patches and reservoir-type patches—containing ALA stable compositions (e.g., with a weak proton donor or a saccharide) which allow ALA to penetrate into tissue when applied to lesions for photodynamic therapy treatment. Ex. 1005 [Noven Pharma] at 8:30-15:29.

198. Based on the information on the cover of Noven Pharma, I understand Noven Pharma to have International Publication Number WO 96/06602 and an International Publication Date of March 7, 1996. Ex. 1005 [Noven Pharma], Cover. As I understand it, this means that Noven Pharma would have been published and accessible to the public by at least around March 7, 1996—*i.e.*, over twenty years before the January 12, 2018 filing date of the '567 Patent.

199. I was asked to provide an opinion regarding whether Noven Pharma teaches each and every element of claims 1–9 of the '567 patent. Based on my review and analysis, Noven Pharma discloses all the elements of claims 1-9 of the '567 patent, either expressly or implicitly, as discussed in further detail below:

1. Claim 1

200. Claim 1 preamble of the '567 patent claims:

1. A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:

201. Noven Pharma discloses a method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy. In particular, Noven Pharma discloses both adhesive matrix and reservoir-type patches having a backing material made from low density polyethylene for administering compositions of ALA dispersed in an adhesive matrix or in solvent through a membrane into tissue for photodynamic therapy. Ex. 1005 [Noven Pharma] at 9:1-7 (“ALA is dispersed in a pressure sensitive adhesive. ... The additional ingredients are added to the mixture and then the solvents are removed to form the patch.”); 9:27-34 (“The backing materials, which are preferably water resistant, and occlusive ... can be selected from such material as ... low density polyethylene”.); 10:1-12 (“Where the topical device is a reservoir-type device, the ALA in a solvent ... is used to fill the reservoir. ... The solution or gel is retained in the reservoir by a suitable rate-controlling membrane ... Backing materials [for reservoir-type devices] are similar to those described above for matrix devices.”). Noven Pharma further describes that its patches using solid formulations of ALA “appear to improve the fluorescence produced ... compared to ALA in a fluid carrier” and generate a “pattern of fluorescence [that] is more even and uniform over the area of application than with topical creams and salves, and may even provide increased fluorescence”. Ex. 1005 [Noven Pharma] at 3:32–4:6. Improved,

increased, and more uniform fluorescence—*i.e.*, resulting from formation of PPIX—are indicative of the enhanced penetration of topical compositions of ALA.

202. In addition to the foregoing, Noven Pharma also teaches a “penetration enhancer” and explains that “[a]dditional substances which increase passage of the drug into the skin” can be added to the ALA formulations to enhance penetration into the skin being treated. Ex. 1005 [Noven Pharma] at 10:20–27, 11:11–13.

203. As a result, Noven Pharma meets all the elements of Claim 1 preamble of the ‘567 patent.

2. Claim 1a

204. Claim 1a of the ‘567 patent claims:

1a. topically applying ALA to a treatment area to be treated with photodynamic therapy

205. Noven Pharma discloses topically applying ALA to a treatment area to be treated with photodynamic therapy. Noven Pharma states in the Background of the Invention section that ALA “is especially useful in the treatment of malignant and non-malignant abnormal growths” such as those on the skin and notes that “ALA has been administered ... especially by topical application to the skin”. Ex. 1005 [Noven Pharma] at 1:29-2:2. Moreover, Noven Pharma describes that the “target tissues for which the present invention may be used are any visible, cutaneous lesion or other undesired rapidly growing cells.” Ex. 1005 [Noven Pharma] at 12:19-25.

For applying ALA, Noven Pharma describes that “ALA can be prepared in a stable formulation for topical use by incorporation into a **topical** drug delivery carrier” that “is contained in a patch.” Ex. 1005 [Noven Pharma] at 5:15-20 (emphasis added). Noven Pharma further states that “the **topical** device must contain a pharmacologically effective amount of ALA” and that “[t]he duration of application is that period sufficient to achieve ALA penetration into the diseased tissue.” Ex. 1005 [Noven Pharma] at 11:29-35; 15:7-15 (emphasis added).

206. Thus, Noven Pharma meets all the elements of Claim 1a of the ‘567 patent.

3. Claim 1b

207. Claim 1b of the ‘567 patent claims:

1b. after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area; and

208. Noven Pharma discloses, after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss therefrom.

209. As noted above, Noven Pharma describes the use of topical patches to administer ALA to the treatment area. Ex. 1005 [Noven Pharma] at 8:30-9:4; 10:1-12. As further described in Noven Pharma, the “ALA is dispersed in a pressure

sensitive adhesive” for the adhesive matrix patches or is in solution or gel in the reservoir-type patches. Ex. 1005 [Noven Pharma] at 9:1-3; 10:1-12. Noven Pharma also discloses that both types of patch have “a suitable backing material” made from “water resistant” “low density polyethylene”. Ex. 1005 [Noven Pharma] at 9:27-34; 10:11-12.

210. Based on my experience and use of similar instruments for the topical administration of pharmaceuticals and other compounds such as Cordran tape, the ALA in the Noven Pharma patches contacts with the treatment area and is subsequently covered by low density polyethylene backing material. That is, ALA in the adhesive matrix or in the reservoir device comes into contact with and is applied the skin, prior to the treatment area becoming covered by the low density polyethylene backing material. This is because, as described in Noven Pharma, the ALA is on the skin facing side of the patch while the low density polyethylene is on the exterior facing side of the patch. Ex. 1005 [Noven Pharma] at 3:27-30.

211. Noven Pharma also discloses that the low density polyethylene backing material of the patch minimizes transepidermal water loss. As noted above, Noven Pharma states that the patch backing material is “preferably water resistant.” Ex. 1005 [Noven Pharma] at 9:29-34. This indicates to a person of ordinary skill in the art that the low density polyethylene backing material in Noven Pharma resists the

passage of water through the material and therefore minimizes transepidermal water loss from the treatment area where the patch is applied.

212. Also as discussed elsewhere in my declaration, it was well known before January 12, 2018 that occluding the skin with water resistant materials like low density polyethylene reduces transepidermal water loss and enhances the penetration of ALA into the tissue. Ex. 1006 [Sakamoto] at 205 (“Occlusion is known to reduce transepidermal water loss, hydrating the stratum corneum and generally enhancing drug penetration, especially for hydrophilic molecules such as ALA.”); Ex. 1007 [Berardesca] at 26, Figure 2 (demonstrating empirically that polyethylene and other occlusive coverings minimize transepidermal water loss).

213. Thus, Noven Pharma meets all the elements of Claim 1b of the ‘567 patent.

4. Claim 1c

214. Claim 1c of the ‘567 patent claims:

1c. removing the low density polyethylene barrier within 3 hours and then applying light to the treatment area.

215. Noven Pharma discloses removing the low density polyethylene barrier within 3 hours and then applying light to the treatment area. For example, Noven Pharma describes examples where the ALA patch with the low density polyethylene backing material is applied to the diseased tissue for about 2 or 3 hours. Ex. 1005

[Noven Pharma] at 11:23-27 (stating that ALA may be “applied to the area of the skin to be diagnosed or treated **for about 2–48 hours**”); 11:29-12:5 (“The duration of application is that period sufficient to achieve ALA penetration into the diseased tissue and that permits high localized concentrations of protoporphyrin IX resulting from the conversion of ALA. **This period may be about 3-24 hours.**”) (emphasis added).

216. While I note that Noven Pharma also discloses a range of incubation periods that are longer than 3 hours, I understand that a reference that discloses an overlapping range can still anticipate the claims, even where the prior art range only slightly overlaps with the range appearing in the claim. Based on my knowledge and practice, use of an incubation time of less than 3 hours after which the low density polyethylene covering is removed and light is applied is not critical to the operability of the claims. For example, I note that the specification indicates that an incubation time of 14 to 18 hours can be used when treating the face or scalp. Ex. 1001 [’567 Patent] at 12:17-23. Further, claims 4-7 do not impose any incubation time requirement or time after which to remove the low density polyethylene barrier and apply the light. Further, based on my experience, practice and knowledge, longer incubation times can be used. Indeed, the ALA-PDT literature is replete with published clinical studies using ALA-PDT with occlusion having incubation times

ranging between 1 to 20 hours. Ex. 1015 [Palm] at 10-11 (Table 2.1); see also my State of the Art Summary table above. While shorter incubation times (e.g., less than 3 hours) are often preferred in order to minimize patient waiting time and limit the PDT treatment to a single office visit, longer incubation times—e.g., 4 hours or longer—would not make the ALA-PDT treatment referenced in the claims cease to work.

217. Noven Pharma further discloses that after the ~2-3 hour incubation time, the patch is removed and activating light is then applied to the lesion. Ex. 1005 [Noven Pharma] at 15:7-21 (“After the patch is removed, the lesion is wiped with an alcohol swab to remove any residual adhesive. The lesion is then exposed to activating UV light ... Finding the levels suitable, the lesion is then exposed to a 634 nm wavelength light source”); 11:29-12:5 (“ALA photodynamic therapy (ALA PDT™) involves the exposure of the ALA-treated lesion with light.”).

218. Thus, Noven Pharma meets all the elements of Claim 1c of the ‘567 patent.

219. Accordingly, Noven Pharma meets all the elements of Claim 1 of the ‘567 patent.

5. Claim 2

220. Claim 2 of the ‘567 patent claims:

2. A method as set forth in Claim 1, wherein the low density polyethylene barrier is removed from the treatment area within 3 hours and then blue light is applied to the treatment area for a 10 J/cm² light dose.

221. Noven Pharma meets all the elements of Claim 1, as shown above. See Claim 1 discussion; Ex. 1005 [Noven Pharma] at 9:1-7; 9:27-34; 10:1-12.

222. In addition, Noven Pharma discloses removing the low density polyethylene barrier within 3 hours and then applying blue light to the treatment area for a 10 J/cm² light dose. In this regard, as discussed above, Noven Pharma describes removing the ALA patch with the low density polyethylene barrier within 3 hours and then applying light to the treatment area. See Claim 1c.

223. Further, Noven Pharma specifically discloses examples where the light applied to the treatment area is blue light—400 nm—for a light dose of 10 J/cm²:

Topical ALA photodynamic therapy (ALA PDT™) involves the exposure of the ALA-treated lesion with light. **A suitable wavelength is 400 nm**, 634 nm or 600-700 nm, at an intensity of 10-100 milliwatts per centimeter squared (mW/cm²) **to provide a light dose of 10-100 Joules/cm²**. Exposure time may vary from 3 to 30 minutes, but preferably is about 10 minutes.

Ex. 1005 [Noven Pharma] at 12:8-18 (emphasis added).

224. Based on my review, the ‘567 patent identifies light having a wavelength at or above 400 nm as “blue light.” Ex. 1001 [‘567 patent] at 5:24-29 (“the LED arrays 60 preferably emit **blue light having wavelengths at or above**

400 nanometers (nm), for example, about 430 nm, about 420 nm or, for example, 417 nm.”) (emphasis added).

225. In light of the foregoing, I understand the teachings of Noven Pharma to indicate that the treatment site where the patch is applied is irradiated with blue light for a light dose of 10 J/cm² light dose.

226. Further, I note that Noven Pharma teaches a range of light doses, including light doses in excess of 10 J/cm². Based on my knowledge, practice, and experience, use of a blue light dose of 10 J/cm² is not critical to the operation of the claims. For example, the ‘567 patent describes examples of lesions treated with blue light for a light dose between 0.1 J/cm² to about 2 J/cm²). Ex. 1001 [’567 Patent] at 7:23. I also note that the light color and light dose are both specified in a dependent claim—*i.e.*, they are not specified in independent claims 1 or 4—suggesting that any reasonable light dose is suitable. Further, based on my experience, practice and knowledge, a 10 J/cm² blue light dose is not critical to enhancing penetration of ALA into tissue or for performing blue light photodynamic therapy using ALA. Increased blue light doses as disclosed in Noven Pharma could and have been used in topical photodynamic therapy. Ex. 1019 [McLaren] at 399 (specifying that the recommended energy for the Omnilux blue 415-nm light is 48 J/cm² for 20 minutes,

but suggesting that one should start with a setting of 24 J/cm² for 20 minutes to minimize discomfort).

227. Thus, Noven Pharma meets all the elements of Claim 2 of the ‘567 patent.

6. Claim 3

228. Claim 3 of the ‘567 patent claims:

3. The method of Claim 1, wherein a maximum plasma concentration of ALA following application of the ALA is less than about 110 ng/mL.

229. Noven Pharma meets all the elements of Claim 1, as shown above. See Claim 1 discussion above; Ex. 1005 [Noven Pharma] at 9:1-7; 9:27-34; 10:1-12.

230. In addition, Noven Pharma discloses the topical application of ALA using a patch having LDPE backing material, removing the ALA patch within 3 hours, followed by the application of light to the treatment area. Ex. 1001 [‘567 patent] at Claim 1. Based on my knowledge, practice, and experience, by January 12, 2018, topical application of ALA for up to a 3 hour period with patches like those taught in Noven Pharma—with sizes between 2.5 to 20 cm² and ALA concentrations between 0.1-3.0 mg/cm²—would not substantially increase the blood plasma concentration of ALA above endogenous levels which are well below 110 ng/mL. Ex. 1005 [Noven Pharma] at 11:20-28.

231. This understanding is borne out by topical ALA pharmacokinetic studies performed by others using ALA prior to January 12, 2018. Those studies demonstrate that the mean endogenous concentration of ALA is around 11 ng/ml (Fauteck) or 20.16 ng/mL (Ameluz) and that topical application of ALA results in an increase in the mean maximum ALA plasma concentration to around 28.36 ng/mL (Fauteck when 64 mg of ALA is applied with patches) or to around 47.35 ng/mL (Ameluz when 200 mg of ALA is applied using a gel). Ex. 1008 [Fauteck] at 58; Ex. 1010 [Ameluz] at 9.

232. In this regard, Fauteck examined the pharmacokinetic properties of ALA supplied via patch for a 4 hour duration to 12 subjects. According to Fauteck, eight patches were applied to each subject, each with a size of 4 cm² and containing 2 mg of ALA per cm² (for a total of 64 mg of ALA). Ex. 1008 [Fauteck] at 53-55. In connection with these studies, Fauteck found the mean endogenous level of ALA present in human plasma—the amount normally present before topical application of the ALA—to be around 11.23 µg/l (*i.e.*, 11.23 ng/mL). Ex. 1008 [Fauteck] at 57, Table 5. Following the 4 hour application period, Fauteck observed only a small increase in ALA plasma concentrations (a mean C_{max} of 28.36 µg/l (*i.e.*, 28.36 ng/mL) and did not observe C_{max} values exceeding 53.08 µg/l (*i.e.*, 53.08 ng/mL). Ex. 1008 [Fauteck] at 57-58, Tables 5-7. The maximum ALA plasma concentration

reported by Fauteck is substantially less than the plasma concentration limit of about 110 ng/mL in Claim 3 of the '567 patent.

233. Similarly, Biofrontera performed a pharmacokinetic study in connection with its FDA submission of its Ameluz ALA-based product and observed results consistent with those of Fauteck. In the Biofrontera study, 2 g of Ameluz gel (with 10 % (200 mg) of ALA) was applied under occlusion at a concentration of 10 mg/cm² to 12 adult subjects over a 20 cm² treatment area for a period of 3 hours. Ex. 1010 [Ameluz] at 9. Biofrontera determined the mean baseline plasma concentration of ALA to be 20.16 ± 16.53 ng/mL and the maximum concentration (C_{\max}) for baseline corrected ALA to be 27.19 ± 20.02 ng/mL. Ex. 1010 [Ameluz] at 9. Based on the Ameluz prescribing information data, the mean (non-baseline corrected) C_{\max} was around 47.35 ng/mL (*i.e.*, $20.16 + 27.19$). The maximum ALA plasma concentration reported in the Ameluz prescribing information is thus also well below the maximum plasma concentration limit of about 110 ng/mL in Claim 3 of the '567 patent.

234. The pharmacokinetic studies performed by Fauteck and by Biofrontera in connection with the Ameluz prescribing information confirm my understanding that the ALA patches described in Noven Pharma—*e.g.*, the 5 cm² ALA patch with an ALA concentration between 0.1-3.0 mg/cm² for up to 15 mg of ALA (see

Example 3)⁴—when applied topically would not result in a maximum plasma concentration of ALA in excess of 110 ng/mL. In the pharmacokinetic studies reported in both Fauteck and the Ameluz prescribing information, greater amounts of ALA were applied to larger surface areas of skin when compared to the disclosure regarding in the ALA patch applied in Noven Pharma. Yet, in both Fauteck and the Ameluz prescribing information the maximum plasma concentrations of ALA reported were both well below 110 ng/mL—*i.e.*, around 28.36 ng/mL with no measured value exceeding 53.08 ng/mL (Fauteck when 64 mg of ALA is applied with patches) or around 47.35 ng/mL (Ameluz when 200 mg of ALA is applied using a gel). Ex. 1008 [Fauteck] at 58; Ex. 1010 [Ameluz] at 9.

235. Accordingly, the pharmacokinetic data in Fauteck and the Ameluz prescribing information confirm my opinion, that topical application of the Noven Pharma patch would necessarily result in a maximum plasma concentration of ALA less than 110 ng/mL.

⁴ As noted above, Noven Pharma describes ALA patches with sizes between 2.5 to 20 cm² and ALA concentrations between 0.1-3.0 mg/cm². Thus, the largest patch having the highest concentration of ALA identified in Noven Pharma is a 20 cm² patch with a total concentration of ALA at 60 mg. This is also less than the amount of ALA applied over the same or greater surface area in Fauteck and the Ameluz prescribing information and would hence also necessarily result in mean maximum plasma concentrations of ALA below 110 ng/mL.

236. Thus, Noven Pharma meets all the elements of Claim 3 of the '567 patent.

7. Claim 4

237. Claim 4 preamble of the '567 patent claims:

4. A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:

238. Noven Pharma meets all the elements of Claim 1 preamble, as shown above and hence also meets all the elements of Claim 4 preamble. See Claim 1 preamble discussion above; Ex. 1005 [Noven Pharma] at 9:1-7; 9:27-34; 10:1-12; Ex. 1006 [Sakamoto] at 205; Ex. 1027 [Ozog] at 808.

8. Claim 4a

239. Claim 4a of the '567 patent claims:

4a. topically applying ALA to a treatment area to be treated with photodynamic therapy; and

240. Noven Pharma meets all the elements of Claim 1a, as shown above. In my opinion, Claim 4a is taught by Noven Pharma for the same reasons noted above for Claim 1a. See Claim 1a discussion above; Ex. 1005 [Noven Pharma] at 1:29-2:2; 5:15-20; 11:29-35; 12:19-25; 15:7-15.

9. Claim 4b

241. Claim 4b of the '567 patent claims:

4b. after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area

242. Noven Pharma meets all the elements of Claim 4b, as shown above. In my opinion, claim element 4b is taught by Noven Pharma for the same reasons described above for Claim 1b. See Claim 1b discussion above; Ex. 1005 [Noven Pharma] at 3:27-30; 8:30-9:4; 9:27-34; 10:1-12; Ex. 1006 [Sakamoto] at 205; Ex. 1007 [Berardesca] at 26.

10. Claim 4c

243. Claim 4c of the '567 patent claims:

4c. wherein the treatment area is located on a hand or a forearm.

244. Noven Pharma discloses a treatment area located on a hand or a forearm. Noven Pharma explicitly states that “[t]he target tissues for which the present invention may be used are **any visible, cutaneous lesion.**” Ex. 1005 [Noven Pharma] at 12:19-21 (emphasis added). Any visible, cutaneous lesion refers to lesions on the skin which include lesions on a hand or forearm. In addition, Example 3 of Noven Pharma specifically describes the treatment of a lesion on a patient’s

right forearm. Ex. 1005 [Noven Pharma] at 15:2-6 (“A single lesion is evident on her right forearm covering approximately 22 mm², and topical aminolevulinic acid photodynamic therapy (ALA PDTTM) is prescribed.”).

245. Thus, Noven Pharma meets all the elements of Claim 4c of the ‘567 patent.

246. Accordingly, Noven Pharma meets all the elements of Claim 4 of the ‘567 patent.

11. Claim 5

247. Claim 5 of the ‘567 patent claims:

5. A method as set forth in Claim 4, wherein the low density polyethylene barrier is removed from the treatment area and then red light is applied to the treatment area for a 10 to 75 J/cm² light dose.

248. Noven Pharma meets all the elements of Claim 5, as shown above.

249. In addition, Noven Pharma discloses removing the ALA patch with the low density polyethylene backing material and then applying red light to the treatment area. See discussion for Claim 1c above; Ex. 1005 [Noven Pharma] at 3:27-30; 8:30-9:4; 9:27-34; 10:1-12; Ex. 1006 [Sakamoto] at 205; Ex. 1007 [Berardesca] at 26.

250. Noven Pharma further describes examples where red light is applied to the treatment area—e.g., 634 nm light—for a 10 to 75 J/cm² light dose.

“Topical ALA photodynamic therapy (ALA PDT™) involves the exposure of the ALA-treated lesion with light. A suitable wavelength is 400 nm, 634 nm or 600-700 nm, at an intensity of 10-100 milliwatts per centimeter squared (mW/cm²) to provide a light dose of 10-100 Joules/cm². Exposure time may vary from 3 to 30 minutes, but preferably is about 10 minutes.”

Ex. 1005 [Noven Pharma] at 12:8-18 (emphasis added). Light having wavelengths of 634 nm and 600-670 nm are examples of red light. Indeed, based on my review, the ‘567 patent identifies light having wavelengths between 570 to 670 nm as red light. Ex. 1001 [‘567 patent] at 5:44-46 (“the LED arrays may also emit **red light having wavelengths of 570 to 670 nm.**”) (emphasis added). Further, the red light dose range of 10-100 J/cm² identified in Noven Pharma includes the range of a 10 to 75 J/cm² light dose appearing in Claim 5.

251. In light of the foregoing, I understand the teachings of Noven Pharma to indicate that the treatment site where the patch is applied is irradiated with red light for a light dose of 10 to 75 J/cm².

252. In addition, I note that Noven Pharma teaches a range of light doses, including light doses in excess of 75 J/cm². Based on my knowledge, practice, and experience, use of a red light dose between of 10 to 75 J/cm² is not critical to the operation of the claims. For example, the ‘567 Patent describes treating lesions with doses between 30 J/cm² to 150 J/cm². Ex. 1001 ‘567 Patent] at 7:26-29. In addition, it appears that the light color and light dose are both specified in a dependent claim—

i.e., because they are not included in independent claims 1 or 4—suggesting that any reasonable red light dose can be used. Further, based on my experience, practice and knowledge, a 10 to 75 J/cm² red light dose is not critical to enhancing penetration of ALA into tissue or for performing red light photodynamic therapy using ALA. Different red light doses as disclosed in Noven Pharma could and have been used in topical photodynamic therapy with ALA. Ex. 1014 [Calderhead] at 246-247 (describing ALA PDT treatment with red light for a 96 J/cm² light dose).

253. Thus, Noven Pharma meets all the elements of Claim 5 of the ‘567 patent.

12. Claim 6 / Claim 7

254. Claims 6 and 7 of the ‘567 patent claim:

6. The method as set forth in Claim 4, wherein the treatment area is a dorsal surface of the hand.

7. The method as set forth in Claim 4, wherein the treatment area is a dorsal surface of the forearm.

255. Noven Pharma meets all the elements of Claim 4, as shown above. See Claim 4 discussion above; Ex. 1005 [Noven Pharma] at 9:1-7; 9:27-34; 10:1-12.

256. Noven Pharma further discloses a treatment area located on a dorsal surface of the hand and forearm as claimed in claims 6 and 7. As I discuss above, the ‘567 patent specifically states that “the dorsal surface of the hands and/or the

forearm [is the] area between the elbow and the base of the fingers.” Ex. 1001 [‘567 patent] at col. 14:26-28. This disclosure is consistent with my interpretation of these terms as I discuss in further detail in the claim construction section of this declaration. In that section, I provide my opinion that: (1) “dorsal surface of a hand” means “the top portion of the hand between the wrist and the base of the fingers”; and (2) “dorsal surface of the forearm” means “the top portion of the forearm between the elbow and the wrist”. Applying these interpretations, Noven Pharma discloses treatment areas located on a dorsal surface of the hand and forearm.

257. For example, Noven Pharma states that the treatment area can be any visible, cutaneous lesion. Ex. 1005 [Noven Pharma] at 12:19-21. This would include a lesion on the dorsal surface of the hand or forearm. Indeed, the dorsal surface of the hand and forearm are common areas of the body that are known to develop actinic keratosis and other lesions. Ex. 1015 [Palm] at 8 (“As AKs often result from a long history of UV exposure, the lesions usually arise in heavily sun-exposed areas including the ... dorsal hands, and extensor forearms.”).

258. Moreover, as I discuss above, Noven Pharma discusses a specific example (Example 3) where an ALA patch was used to treat a lesion on a patient’s forearm. Ex. 1005 [Noven Pharma] at 15:2-6 (“**A single lesion** is evident **on her right forearm** covering approximately 22 mm², and topical aminolevulinic acid

photodynamic therapy (ALA PDT™) is prescribed.”) (emphasis added). As I understand the foregoing statement in Noven Pharma, it would include the dorsal surface of the forearms. In my experience, these portions of the skin are likely to have visible lesions due to long term UV exposure and photodamage. Ex. 1015 [Palm] at 8.

259. Thus, Noven Pharma meets all the elements of Claim 6 and 7 of the ‘567 patent.

13. Claim 8

260. Claim 8 preamble of the ‘567 patent claims:

8. A method of using 5-aminolevulinic acid (ALA) and a low density polyethylene barrier, comprising:

261. Noven Pharma discloses using 5-aminolevulinic acid (ALA) and a low density polyethylene barrier. As I discuss above, Noven Pharma discloses using adhesive matrix or reservoir-type patches having a water resistant, low density polyethylene backing material to administer 5-aminolevulinic acid (ALA) topically for photodynamic therapy. Ex. 1005 [Noven Pharma] at 9:27-10:4 (“The backing materials [for the adhesive matrix devices], which are preferably water resistant... can be selected from ... low density polyethylene”); 10:11-12 (“Backing materials [for reservoir-type devices] are similar to those described above for matrix devices.”).

262. As a result, Noven Pharma meets all the elements of Claim 8 preamble of the '567 patent.

14. Claim 8a

263. Claim 8a of the '567 patent claims:

8a. contacting a treatment site with a composition comprising the ALA so as to wet the treatment site

264. Based on my review, Noven Pharma discloses examples of adhesive patch compositions containing ALA together with proton donors, penetration enhancers, and other substances that are applied to wet the site to be treated. In this regard, the '567 Patent describes wetting the treatment site, in one example, as applying a topical solution of ALA to the skin. Ex. 1001 ['567 patent] at 9:50-54. In another example, the '567 Patent describes the application of an ALA admixture “to achieve a substantially uniform wetting of the lesion surface with the ALA by contacting the ALA with the lesion surface.” Ex. 1001 ['567 patent] at 9:12-18.

265. Consistent with these examples, Noven Pharma discloses contacting the treatment site with ALA compositions so as to wet the treatment site. For example, Noven Pharma teaches adhesive patches containing ALA with “an optional carrier [that] may contain from 0 to 40% by weight of other components, such as a proton donor, penetration enhancer and other substances known for use in transdermal formulations.” Ex. 1005 [Noven Pharma] at 10:24-27. Noven Pharma

further states that “[a]dditional substances which increase the passage of the drug into the skin also can be added.” Ex. 1005 [Noven Pharma] at 11:11-14. Based on my knowledge and experience, such carriers and penetration enhancers are typically liquids and would, therefore, together with the ALA assist with wetting the treatment site when applied.

266. In addition, I note that Example 2 of Noven Pharma discloses other ALA compositions in solvents such as propylene glycol and glycerin. Ex. 1005 [Noven Pharma] at 14:1-21. Based on my knowledge and experience, a person of ordinary skill in the art would understand that ALA compositions with propylene glycol and glycerin applied to the skin would wet the treatment site.

267. Moreover, with respect to the reservoir-type patch examples, Noven Pharma states that such patches include non-aqueous solvents for delivery of ALA to the treatment site. Ex. 1005 [Noven Pharma] at 10:1-12 (“Where the topical device is a reservoir-type device, the ALA [is] in a solvent, preferably in a non-aqueous solvent such as an alkanediol”). Based on my knowledge and experience, ALA compositions with liquid solvents like those mentioned in Noven Pharma would wet the treatment site when they are contacted with it.

268. As a result, Noven Pharma meets all the elements of Claim 8a of the ‘567 patent.

15. Claim 8b

269. Claim 8b of the '567 patent claims:

8b. following wetting of the treatment site, covering the wetted treatment site with the low density polyethylene barrier

270. Noven Pharma discloses covering the wetted treatment site with the low density polyethylene barrier following wetting of the treatment site. As I discuss above, Noven Pharma discloses using ALA dispersed in an adhesive matrix patch having a low density polyethylene backing material. Ex. 1005 [Noven Pharma] at 8:30-9:33 (“ALA is dispersed in a pressure sensitive adhesive ... The backing materials ... can be selected from ... low density polyethylene”); 10:32-11:14; 14:1-21. Noven Pharma also describes reservoir-type patches having a low density polyethylene backing material for the delivery of ALA and liquid solvent to treat lesions. Ex. 1005 [Noven Pharma] at 10:11-12. (“Backing materials are similar to those described above for matrix devices.”) Because the ALA and the liquid components of the composition are contained in the adhesive matrix or reservoir on the skin-directed surface of the patch, the treatment site becomes covered by the low density polyethylene backing material after the treatment site is contacted/wetted by the ALA composition. The patch is then left in place for the specified incubation period to allow ALA to penetrate into the lesions and be converted to the PPIX photosensitizer.

271. As a result, Noven Pharma meets all the elements of Claim 8b of the ‘567 patent.

16. Claim 8c

272. Claim 8c of the ‘567 patent claims:

8c. removing the low density polyethylene barrier so as to expose the treatment site; and

273. Noven Pharma discloses removing the low density polyethylene barrier so as to expose the treatment site. In this regard, Noven Pharma describes the application of the ALA patches having a low density polyethylene backing material for a specific duration after which the patch is removed. Ex. 1005 [Noven Pharma] at 11:29-12:5 (“The duration of application is that period sufficient to achieve ALA penetration into the diseased tissue and that permits high localized concentrations of protoporphyrin IX resulting from the conversion of ALA”). Noven Pharma further states that following the removal of the patch, the lesion is cleaned. Ex. 1005 [Noven Pharma] at 15:7-21 (“After the patch is removed, the lesion is wiped with an alcohol swab to remove any residual adhesive.”). This demonstrates that the low density polyethylene barrier (the patch backing material) is removed and the treatment site is exposed.

274. As a result, Noven Pharma meets all the elements of Claim 8c of the ‘567 patent.

17. Claim 8d

275. Claim 8d of the '567 patent claims:

8d. illuminating the exposed treatment site with an illuminator so as to deliver a 10 J/cm² dose of blue light.

276. As I discuss above for Claim 1c, Noven Pharma discloses removing the ALA patch with low density polyethylene backing and then applying light to the exposed treatment site. See Ground 4, Claim 1c discussion above. Further, as I discuss above for Claim 2, Noven Pharma discloses examples where the treatment site is illuminated with blue light—400 nm light—for a 10 J/cm² light dose. See Claim 2 discussion above; Ex. 1005 [Noven Pharma] at 12:8-18; Ex. 1001 ['567 patent] at 5:24-29.

277. As a result, Noven Pharma meets all the elements of Claim 8a of the '567 patent.

278. Accordingly, Noven Pharma meets all the elements of Claim 8 of the '567 patent.

18. Claim 9

279. Claim 9 of the '567 patent claims:

9. The method of Claim 8, wherein the low density polyethylene barrier is removed no later than three hours after the treatment site is covered.

280. Noven Pharma meets all the elements of Claim 8, as shown above. See Claim 8 discussion; Ex. 1005 [Noven Pharma] at 9:27-10:4; 10:11-12.

281. Noven Pharma further discloses removing the low density polyethylene barrier no later than three hours after the treatment site is covered. For example, Noven Pharma discloses applying an ALA patch for 2-3 hours. See Ground 4, Claim 1c discussion above; Ex. 1005 [Noven Pharma] at 11:23-27 (stating that ALA may be “applied to the area of the skin to be diagnosed or treated **for about 2–48 hours**”) (emphasis added); 11:29-12:5 (“The duration of application ... may be **about 3-24 hours.**”) (emphasis added). A duration of application of an ALA patch for about 2 or 3 hours indicates to one of skill in the art that the patch is removed no later than 3 hours after the treatment site is covered.

282. As a result, Noven Pharma meets all the elements of Claim 9 of the ‘567 patent.

283. Based on my analysis discussed above, and the claim charts provided below, it is my opinion that Noven Pharma discloses expressly and implicitly what is claimed in claims 1–9 of the ‘567 patent.

E. Ground 5 – Claim 3 Is Met by the Combination of Noven Pharma and Fauteck

284. As I explain below and in the claim chart, it is my opinion that the combination of Noven Pharma together with Fauteck further discloses what is claimed in Claim 3 of the '567 Patent.

285. My discussion of Noven Pharma is provided above. As I note above, Noven Pharma was published and accessible to the public by at least around March 7, 1996.

286. The Fauteck publication—Fauteck JD, Ackermann G, Birkel M, Breuer M, Moor AC, Ebeling A, Ortland C. Fluorescence characteristics and pharmacokinetic properties of a novel self-adhesive 5-ALA patch for photodynamic therapy of actinic keratoses. Arch Dermatol Res. 2008 Feb;300(2):53-60 (“Fauteck”)—describes the results of clinical studies examining the pharmacokinetic properties of a self-adhesive ALA patch identified as PD P 506 A, including the absorption of ALA after patch application and the generation of PPIX. Ex. 1008 [Fauteck] at 53. Following patch application, Fauteck observed a small increase in ALA plasma concentration for ten of the twelve patients tested, with a maximum observed plasma concentration in one patient of 53.08 ug/L (*i.e.*, 53.08 ng/mL). Ex. 1008 [Fauteck] at 57-58. The amounts of PPIX generation after patch

application were found to be below the lower limit of quantification for all patients tested. Ex. 1008 [Fauteck] at 58.

287. Based on my investigation and experience, Fauteck was published and publicly available prior to January 12, 2018. In this regard, Fauteck expressly states on the cover of the article that was published online on October 25, 2007. Ex. 1008 [Fauteck] at 53 (“Published online: 25 October 2007”). I also note that Fauteck was published in the February 2008 edition of the journal entitled Archives of Dermatological Research, Volume 300, Issue 2. Ex. 1008 [Fauteck] at 53; Ex. 1031 [Affidavit of Duncan Hall] at 009.

288. I also confirmed using the Europe Pubmed Central (“Europe PMC”), that Fauteck was available to the public prior to January 12, 2018. The Europe PMC site identifies nine publications that cite to Fauteck, eight of which are dated between 2008 to 2015. Ex. 1034 [Fauteck EuropePMC] at 002-005. In addition, the Internet Archive site that catalogs webpages shows that Fauteck was available to the public at least by 2015. Ex. 1031 [Affidavit of Duncan Hall] at 009. Taken together, based on my experience accessing, reviewing, and publishing in dermatology journals—both online and print versions—this evidence confirms to me that Fauteck was available to the public well before January 2018 when the ’567 Patent was filed.

289. My additional analysis of Claim 3 is provided below.

3. Claim 3

290. Claim 3 of the '567 patent claims:

3. The method of Claim 1, wherein a maximum plasma concentration of ALA following application of the ALA is less than about 110 ng/mL.

291. Noven Pharma meets all the elements of Claim 1, as shown above. See Claim 1 discussion; Ex. 1005 [Noven Pharma] at 9:1-7; 9:27-34; 10:1-12.

292. As I discuss above for Ground 4, Noven Pharma meets all the elements of claims 1 and 3 of the '567 patent.

293. In addition, if DUSA asserts that claim 3 is not necessarily disclosed by Noven Pharma, it is also my opinion that Claim 3 is obvious over the disclosures of Noven Pharma combined with Fauteck. That is, one of skill in the art would understand from the combination of Noven Pharma and Fauteck that more lesions or larger lesions could be safely treated with maximum plasma concentrations of ALA after application that are similar to those reported in Fauteck—*i.e.*, less than about 110 ng/mL.

294. In this regard, Fauteck examined the pharmacokinetic properties of ALA supplied via patches for a 4 hour duration to 12 subjects. According to Fauteck, eight patches were applied, each with a size of 4 cm² and containing 2 mg of ALA per cm²—*i.e.*, for a total of 64 mg of ALA. Ex. 1008 [Fauteck] at 53-55. In

connection with these studies, Fauteck found the mean endogenous level of ALA present in human plasma—the amount normally present before topical application of the ALA—to be around 11.23 µg/l (*i.e.*, 11.23 ng/mL). Ex. 1008 [Fauteck] at 57, Table 5. Following the 4 hour application period, Fauteck observed only a small increase in the mean maximum ALA plasma concentrations (a mean C_{\max} of around 28.36 µg/l (*i.e.*, 28.36 ng/mL) and did not observe C_{\max} values exceeding 53.08 µg/l (*i.e.*, 53.08 ng/mL). Ex. 1008 [Fauteck] at 57-58, Tables 5-7.

Table 6 PK study: descriptive characteristics of pharmacokinetic parameters for 5-ALA ($N = 12$)

Parameter	Geometric mean (SD)	Median (range)
C_{\max} (µg/l)	28.36 (1.44)	25.64 (18.05–53.08)
AUC _(0–t) (µg*h/l)	350.00 (1.60)	393.81 (109.37–565.64)
T_{\max} (h)	4.58 (1.73)	3.99 (3.00–23.97)

Ex. 1008 [Fauteck] at 57, Table 6 (providing concentration information in µg/l which is equivalent to ng/ml). The maximum ALA plasma concentrations reported by Fauteck are less than the plasma concentration limit of about 110 ng/mL in Claim 3 of the ‘567 patent.

295. Based on my education, background, and experience, it is my opinion that one of skill in the art seeking to use Noven Pharma’s patches to attempt to treat more lesions and/or lesions with greater surface area (*i.e.*, greater than 20 cm²),

would consult Fauteck which describes that 64 mg of ALA can be safely applied over 32 cm² using multiple ALA patches to achieve a mean maximum plasma concentration of around 28.36 ng/mL. As noted above, Noven Pharma describes that ALA patch sizes can range between “2.5 to 20 cm²” and have “0.1-3.0 mg/cm²” of ALA. Ex. 1005 [Noven Pharma] at 11:20-28.

296. A person of ordinary skill in the art would be motivated to combine Noven Pharma with Fauteck to treat more lesions or larger lesions, because Fauteck describes that eight 4 cm² ALA patches applied over 32 cm² for a total of 64 mg of ALA results in a mean maximum plasma concentration of 28.36 ng/mL (with no observed C_{max} values exceeding 53.08 µg/l) and is safe and well-tolerated. Ex. 1008 [Fauteck] at Abstract; 59. As a result, one of skill in the art wanting to try to treat more lesions or larger lesions would appreciate based on Fauteck that they could safely apply up to 64 mg of ALA over 32 cm² using Noven Pharma’s ALA patches.⁵

297. One of skill in the art would have also appreciated a reasonable expectation of success when seeking to try to treat more lesions or larger lesions

⁵ A person of ordinary skill in the art would understand that the patch size, number of patches applied, and concentration of ALA in the patches could be adjusted to modify the maximum plasma concentration of ALA in a patient. Indeed, based on the pharmacokinetic data supplied in Fauteck, a person of ordinary skill could select the size, number of patches applied, and concentration of ALA in the patches (like those in Noven Pharma) applied to a subject’s lesions to achieve a maximum plasma concentration of ALA like in Fauteck which is well below 110 ng/mL.

using Noven Pharma's patches based on the teachings of Fauteck. When up to 64 mg of ALA is applied over up to 32 cm² of skin surface area using the patches of Noven Pharma, one of skill in the art would reasonably expect a maximum observed plasma concentration of ALA around or less than 53.08 ng/mL with a mean maximum plasma concentration of ALA around or below 28.36 ng/mL as reported by Fauteck. Ex. 1008 [Fauteck] at 57-58, Tables 5-7. This is well below the 110 ng/mL figure specified in claim 3 of the '567 patent.

298. Thus, the '567 patent's Claim 3 is also obvious in light of the Noven Pharma's description of ALA patches and Fauteck's description of ALA patch pharmacokinetics.

F. Ground 6 – Claim 10 Is Met by the Combination of Noven Pharma with the BLU-U Operating Manual

299. As I explain further below and in the claim chart, it is my opinion that the combination of Noven Pharma and the BLU-U Operating Manual also discloses what is claimed in Claim 10 of the '567 Patent.

300. My discussion of Noven Pharma is provided above. As discussed above, Noven Pharma was published and accessible to the public by at least around March 7, 1996.

301. The BLU-U Operating Manual—is an instruction manual supplied with the BLU-U Blue Light Photodynamic Therapy Illuminator device and also published

online by DUSA and its affiliates (e.g., at www.dusapharma.com). The BLU-U operating manual provides product specification information, explains the different instrument controls and indications on the BLU-U, and provides instructions for the set up and use of the BLU-U for blue light photodynamic therapy treatments. Ex. 1012 [BLU-U Operating Manual] at 4-13; Ex. 1031 [Affidavit of Duncan Hall] at 078-085.

302. Based on my investigation and knowledge, the BLU-U Operating Manual was published and publicly available by at least 2006 or before. For example, the Food and Drug Administration's CDRH portal for medical devices, provides a link to an early version of the BLU-U Operating Manual with a decision date of December 3, 1999. <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P990019>.

303. In addition, the Internet Archive site that catalogs webpages shows that the BLU-U Operating manual could be viewed and downloaded by the public from DUSA's own website (www.dusapharma.com) at least by 2006. Ex. 1031 [Affidavit of Duncan Hall] at 072-089.

304. In addition, based on my own experience, I can recall working with the BLU-U and consulting the BLU-U operating manual in connection with my fellowship training in 2007. The foregoing evidence and my own experience

confirms that the BLU-U operating manual was available prior to January 2018 when the '567 Patent was filed.

305. My further analysis of Claim 10 is provided below.

2. Claim 10

306. Claim 10 of the '567 patent claims:

10. The method of Claim 8, further comprising: positioning the treatment site between two inches and four inches from a surface of the illuminator.

307. Noven Pharma meets all the elements of Claim 8, as shown above. See Claim 8 discussion; Ex. 1005 [Noven Pharma] at 9:27-10:4; 10:11-12.

308. In addition, Noven Pharma when combined with the BLU-U operating manual also demonstrates that Claim 10 is obvious. Specifically, Noven Pharma describes examples where blue light (400 nm light) for a 10 J/cm² light dose is applied to the lesion after removal of the ALA patch. Ex. 1005 [Noven Pharma] at 13:8-18. As I note above, the BLU-U blue light source provides a 10 J/cm² light dose and is the only FDA approved blue light source for ALA photodynamic therapy. Because the BLU-U operating manual describes placing the blue light source 2 to 4 inches from the patient's skin [Ex. 1012 [BLU-U Operating Manual] at 9-12; Ex. 1031 [Affidavit of Duncan Hall] at 081-084; see also Ex. 1031 at 036-040], Noven

Pharma together with the BLU-U operating manual demonstrates that Claim 10 is obvious.

309. It is also my opinion that a person of ordinary skill in the art seeking to apply the teachings of Noven Pharma for photodynamic therapy would be motivated to combine the teachings of Noven Pharma with the BLU-U operating manual. The BLU-U Operating Manual states that the “BLU-UTM blue light photodynamic therapy illuminator ... is indicated for the treatment of non-hyperkeratotic actinic keratoses of the face and scalp.” Ex. 1012 [BLU-U Operating Manual] at 9-12. As I note above, the BLU-U blue light source is the only FDA approved blue light source for ALA photodynamic therapy and Noven Pharma does not specify a particular blue light source to use. Further, Noven Pharma teaches an example where blue light (*e.g.*, ~400 nm light) is applied for a 10 J/cm² light dose [EX. 1005 [Noven Pharma] and the BLU-U is the only FDA approved blue light source for ALA photodynamic therapy that provides a 10 J/cm² light dose. Because the BLU-U operating manual specifically instructs users that the light source should be positioned around between 2 to 4 inches from the patient’s skin [Ex. 1012 [BLU-U Operating Manual] at 9-11; Ex. 1031 [Affidavit of Duncan Hall] at 081-084; see also Ex. 1031 at 037-040], it is my opinion that a person of ordinary skill in the art would have been motivated to combine the teachings of Noven Pharma with the BLU-U operating manual to meet

Claim 10's requirement that the illuminator surface be 2 to 4 inches from the treatment site.

310. While DUSA may argue that one of ordinary skill in the art would not be motivated to combine the teachings of Noven Pharma with the BLU-U operating manual because the BLU-U Operating Manual states that the BLU-U is indicated "in combination with the Levulan Kerastick™" and should not be used "with other photosensitizing drugs" [BLU-U Operating Manual] at 4], I disagree that one of the skill in the art would be dissuaded by this statement. As I discuss elsewhere in my declaration, both the Levulan Kerastick™ and the Noven Pharma patches use ALA (converted to PPIX) as the photosensitizing drug. Ex. 1016 [MacCormack] at 53. As a result, one of skill in the art would not view other forms of ALA (such as ALA patches) as another photosensitizing drug. As a result, any such contrary assertion made by DUSA would be incorrect.

311. It is further my opinion that a person of ordinary skill in the art would reasonably expect success in combining the teachings of Noven Pharma with the BLU-U operating manual. Based on my education, knowledge and experience, the BLU-U is one of the first light sources used for ALA photodynamic therapy to provide blue light for a 10 J/cm² light dose. As I note above, Noven Pharma also describes the use of a blue light source at a 10 J/cm² light dose in connection with

ALA supplied to a lesion using an ALA patch. Given that both Noven Pharma and the BLU-U Operating Manual concern the same photosensitizer, it is my opinion that a person of ordinary skill in the art would reasonably expect the BLU-U light source and its specified positioning to be compatible and work well in PDT using the ALA patches disclosed in Noven Pharma.

X. Claim Charts

A. Ground 1: Claims 1-4 and 6-10 are taught by Willey

Claim	Willey
1 [preamble] A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:	<p>Willey describes a method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy.</p> <p>“Areas to be treated were swabbed with acetone and gauze and allowed to dry. Topical 20% 5-ALA (Levulan Kerastick; Dusa Pharmaceuticals, Inc., Wilmington, MA) was applied to the entire forearm skin and occluded with plastic wrap (Saran; SC Johnson).”</p> <p>Ex. 1013 [Willey] at 1095.</p> <p>One of skill in the art would recognize that occlusion with plastic films like Saran wrap reduces transepidermal water loss and enhances penetration of topically applied ALA. This is reflected, for example, in various prior art publications, including publications from some of the same authors of Willey—<i>i.e.</i>, Anderson and Sakamoto.</p> <p>“Occlusion is known to reduce transepidermal water loss, hydrating the stratum corneum and generally enhancing drug penetration,</p>


Claim	Willey
	<p>especially for hydrophilic molecules such as ALA.”</p> <p>Ex. 1006 [Sakamoto] at 205.</p> <p>Others in the field have recognized the same:</p> <p>“[O]cclusion has been used to increase penetration [of ALA]. This can be accomplished with plastic wrap or some other nonporous flexible material placed over the targeted area after the ALA has been applied.”</p> <p>Ex. 1027 [Ozog] at 808.</p>
<p>[a] topically applying ALA to a treatment area to be treated with photodynamic therapy;</p>	<p>Willey describes topically applying ALA to a treatment area to be treated with photodynamic therapy.</p> <p>“Areas to be treated were swabbed with acetone and gauze and allowed to dry. Topical 20% 5-ALA (Levulan Kerastick; Dusa Pharmaceuticals, Inc., Wilmington, MA) was applied to the entire forearm skin and occluded with plastic wrap (Saran; SC Johnson).”</p> <p>Ex. 1013 [Willey] at 1095.</p>
<p>[b] after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize</p>	<p>Willey describes covering the treatment area with a low density polyethylene barrier, namely Saran plastic wrap, after ALA application and prior to light treatment, to minimize transepidermal water loss from the treatment area. See my discussion at Claim 1 [preamble]</p> <p>“Areas to be treated were swabbed with acetone and gauze and allowed to dry. Topical 20% 5-ALA (Levulan Kerastick; Dusa Pharmaceuticals, Inc., Wilmington, MA) was applied to the entire</p>

Claim	Willey																												
transepidermal water loss from the treatment area; and	<p>forearm skin and occluded with plastic wrap (Saran; SC Johnson).”</p> <p>Ex. 1013 [Willey] at 1095.</p> <p>The ’567 Patent admits that Saran wrap is a low density polyethylene barrier material.</p> <p style="text-align: center;">TABLE 1</p> <table><tr><th colspan="4">Barrier Materials A-E</th></tr><tr><th>Material Code</th><th>Name</th><th>Distributor or Manufacturer</th><th>Material Description</th></tr><tr><td>A</td><td>Tegaderm™, Style 1629</td><td>3M</td><td>Polyurethane</td></tr><tr><td>B</td><td>Glad® Press’n Seal®</td><td>The Glad Products Company</td><td>LDPE</td></tr><tr><td>C</td><td>Glad® Cling Wrap</td><td>The Glad Products Company</td><td>LDPE</td></tr><tr><td>D</td><td>Stretch-Tite®</td><td>Polyvinyl Films, Inc.</td><td>Polyvinylidene chloride (PVdC)</td></tr><tr><td>E</td><td>Saran™ Premium Wrap</td><td>SC Johnson</td><td>LDPE</td></tr></table> <p>Ex. 1001 [’567 Patent], Table 1.</p> <p>One of skill in the art at the time would recognize that occlusive barriers like Saran Wrap low density polyethylene, when applied to the treatment area, minimize transepidermal water loss. See Claim 1 [preamble]; Ex. 1006 [Sakamoto] at 205; Ex. 1007 [Berardesca] at 26, Figure 2.</p>	Barrier Materials A-E				Material Code	Name	Distributor or Manufacturer	Material Description	A	Tegaderm™, Style 1629	3M	Polyurethane	B	Glad® Press’n Seal®	The Glad Products Company	LDPE	C	Glad® Cling Wrap	The Glad Products Company	LDPE	D	Stretch-Tite®	Polyvinyl Films, Inc.	Polyvinylidene chloride (PVdC)	E	Saran™ Premium Wrap	SC Johnson	LDPE
Barrier Materials A-E																													
Material Code	Name	Distributor or Manufacturer	Material Description																										
A	Tegaderm™, Style 1629	3M	Polyurethane																										
B	Glad® Press’n Seal®	The Glad Products Company	LDPE																										
C	Glad® Cling Wrap	The Glad Products Company	LDPE																										
D	Stretch-Tite®	Polyvinyl Films, Inc.	Polyvinylidene chloride (PVdC)																										
E	Saran™ Premium Wrap	SC Johnson	LDPE																										
[c] removing the low density polyethylene barrier within 3 hours and then applying light to the treatment area.	<p>Willey discusses removing the low density polyethylene barrier within 3 hours and then applying light to the treatment area.</p> <p>For example, Willey discusses an incubation period of 1 hour with occlusion of the treated area with Saran Wrap low density polyethylene film. One of skill in the art would recognize that the Saran Wrap low density polyethylene barrier must be removed at the end of the 1 hour incubation</p>																												

Claim	Willey
	<p>period prior to the application of light given Willey’s description that, during light irradiation, the treatment areas were cooled by a small portable fan. One of skill in the art would recognize that the intended cooling effect of the fan would be impeded if the treatment sites were still covered with Saran Wrap low density polyethylene film.</p> <p>“After 1 hour, both of the treated sites (heated and control) were irradiated with 10 J/cm² blue light (BLU-U; Dusa Pharmaceuticals, Inc.) for 1,000 seconds with the light positioned 2 to 4 inches from the skin surface. During light irradiation, the treated areas were cooled by a small portable fan set on a mayo stand for comfort.”</p> <p>Ex. 1013 [Willey] at 1095.</p> <p>In addition, one of skill in the art would recognize that the Saran Wrap low density polyethylene barrier would be removed at the end of the incubation period so that the excess ALA could be cleaned from the treatment area prior to application of the light. See, for example, Ex. 1014 [Calderhead] at 246 (“At the end of incubation, the occlusive dressing is removed and any excess 5-ALA wiped off.”); Ex. 1017 [Sotiriou] at 1062; Ex. 1010 [Ameluz] at 3; Ex. 1018 [Bissonnette] at 226; Ex. 1015 [Palm] at 24; Ex. 1019 [McLaren] at 399.</p>
<p>2. A method as set forth in Claim 1, wherein the low density polyethylene barrier is removed from the treatment area within 3 hours and then blue light is</p>	<p>Willey describes the method of Claim 1, wherein the low density polyethylene barrier is removed from the treatment area within 3 hours and then blue light is applied to the treatment area for a 10 J/cm² light dose. For example, Willey teaches using an incubation period of 1 hour with occlusion of the treated area with Saran plastic wrap. One of skill in the art would recognize that the Saran Wrap low density polyethylene barrier is removed at the end of the 1 hour incubation period prior to the application of light. See my</p>

Claim	Willey
<p>applied to the treatment area for a 10 J/cm² light dose.</p>	<p>discussion above at Claim 1[c]; Ex. 1013 [Willey] at 1095; Ex. 1014 [Calderhead] at 246; Ex. 1017 [Sotiriou] at 1062; Ex. 1010 [Ameluz] at 3; Ex. 1018 [Bissonnette] at 226; Ex. 1015 [Palm] at 24; Ex. 1019 [McLaren] at 399.</p> <p>Further, Willey describes that, after the 1 hour incubation period, blue light is applied to the treatment area for a 10 J/cm² light dose.</p> <p>“After 1 hour, both of the treated sites (heated and control) were irradiated with 10 J/cm² blue light (BLU-U; Dusa Pharmaceuticals, Inc.) for 1,000 seconds with the light positioned 2 to 4 inches from the skin surface. During light irradiation, the treated areas were cooled by a small portable fan set on a mayo stand for comfort.”</p> <p>Ex. 1013 [Willey] at 1095.</p>
<p>3. The method of Claim 1, wherein a maximum plasma concentration of ALA following application of the ALA is less than about 110 ng/mL.</p>	<p>Willey teaches the method of Claim 1, wherein a maximum plasma concentration of ALA following application of the ALA is less than about 110 ng/mL.</p> <p>For example, Willey describes the application of up to two sticks of Levulan, which contain 354 mg of ALA each, to each patient’s skin. Ex. 1013 [Willey] at 1095 (“One stick (1.5 ml) was used to cover each distal extremity.”); Ex. 1011 [Levulan Label 2002] at 1. Similarly, the ’567 patent states that “up to two topical solution compositions each containing about 354 mg ALA” were applied and further states that “topical dosing was observed to result in a mean plasma concentration (C_{max}) value of ALA less than about 110 ng/mL.” Ex. 1001 [’567 patent] at 13:45-58. Because the same amount of ALA is described as administered to the upper extremities of patients in both Willey and the ’567 patent, the patients in Willey would necessarily have</p>

Claim	Willey
	<p>maximum plasma concentrations of ALA following application of the ALA that are consistent with the maximum plasma concentrations of ALA reported in the '567 patent—<i>i.e.</i>, less than 110 ng/mL.</p>
<p>4. A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:</p>	<p>Willey discusses a method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy.</p> <p>See my discussion above at Claim 1[preamble]; 1[b]; Ex. 1013 [Willey] at 1095; Ex. 1006 [Sakamoto] at 205; Ex. 1027 [Ozog] at 808.</p>
<p>[a] topically applying ALA to a treatment area to be treated with photodynamic therapy; and</p>	<p>Willey describes topically applying ALA to a treatment area to be treated with photodynamic therapy.</p> <p>See my discussion above at Claim 1[a]; Ex. 1013 [Willey] at 1095.</p>
<p>[b] after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area,</p>	<p>Willey describes covering the treatment area with a low density polyethylene barrier, after the ALA is applied to the treatment area and prior to light treatment, to minimize transepidermal water loss from the treatment area.</p> <p>See my discussion above at Claim 1[b]; Ex. 1013 [Willey] at 1095; '567 Patent, Table 1; Sakamoto at 205; Berardesca (1992) at 26.</p>
<p>[c] wherein the treatment area is</p>	<p>Willey describes a treatment area located on a hand or a forearm.</p>

Claim	Willey
located on a hand or a forearm.	<p data-bbox="597 281 1321 575">“Twenty subjects aged 57 to 90 years (median, 70) were enrolled in this study between June 22, 2010 and June 15, 2011. Subjects included 5 women and 15 men with skin Type II. Areas treated included the low legs of 3 subjects and the forearms and dorsal hands of 24 subjects. All 20 subjects completed the 6-month study.”</p> <p data-bbox="505 621 992 663">Ex. 1013 [Willey] at 1096-1097.</p>  <p data-bbox="505 1228 1154 1270">Ex. 1013 [Willey] at 1096, Figures 1 and 2.</p>
<p data-bbox="168 1318 475 1564">6. The method as set forth in Claim 4, wherein the treatment area is a dorsal surface of the hand.</p>	<p data-bbox="505 1318 1300 1482">Willey discusses the method of Claim 4, wherein the treatment area is a dorsal surface of the hand. See my discussion above at Claim 4; Claim 4[c]; Ex. 1013 [Willey] at 1096-1097, Figures 1 and 2.</p>
<p data-bbox="168 1577 475 1814">7. The method as set forth in Claim 4, wherein the treatment area is a dorsal surface of the forearm.</p>	<p data-bbox="505 1577 1312 1740">Willey discusses the method of Claim 4, wherein the treatment area is a dorsal surface of the forearm. See my discussion above at Claim 4; Claim 4[c]; Ex. 1013 [Willey] at 1096-1097, Figures 1 and 2.</p>

Claim	Willey
<p>8. A method of using 5-aminolevulinic acid (ALA) and a low density polyethylene barrier, comprising:</p>	<p>Willey discusses a method of using 5-aminolevulinic acid (ALA) and a low density polyethylene barrier for photodynamic therapy.</p> <p>See my discussion above at Claim 1; Ex. 1013 [Willey] at 1095.</p>
<p>[a] contacting a treatment site with a composition comprising the ALA so as to wet the treatment site;</p>	<p>Willey describes contacting a treatment site with a composition comprising the ALA so as to wet the treatment site.</p> <p style="padding-left: 40px;">“Areas to be treated were swabbed with acetone and gauze and allowed to dry. Topical 20% 5-ALA (Levulan Kerastick; Dusa Pharmaceuticals, Inc., Wilmington, MA) was applied to the entire forearm skin and occluded with plastic wrap (Saran; SC Johnson).”</p> <p>Ex. 1013 [Willey] at 1095.</p>
<p>[b] following wetting of the treatment site, covering the wetted treatment site with the low density polyethylene barrier;</p>	<p>Willey describes covering the wetted treatment site with a low density polyethylene barrier after the treatment site is wetted with the ALA.</p> <p>Willey describes covering the ALA wetted treatment area with Saran plastic wrap. Saran plastic wrap is a low density polyethylene material. See my discussion above at Claim 1; Claim 1[b]; Ex. 1013 [Willey] at 1095; ‘567 Patent, Table 1.</p>
<p>[c] removing the low density polyethylene barrier so as to expose the treatment site; and</p>	<p>Willey describes removing the low density polyethylene barrier so as to expose the treatment site.</p> <p>See my discussion above at Claim 1; Claim 1[c]; Ex. 1013 [Willey] at 1095; Calderhead at 246; Sotiriou at 1062; Ex. 1010 [Ameluz] at 3; Ex. 1018 [Bissonnette] at 226; Ex. 1015 [Palm] at 24; Ex. 1019 [McLaren] at 399.</p>

Claim	Willey
[d] illuminating the exposed treatment site with an illuminator so as to deliver a 10 J/cm ² dose of blue light.	<p>Willey discusses illuminating the exposed treatment site with an illuminator so as to deliver a 10 J/cm² dose of blue light.</p> <p>See my discussion above at Claim 2; Ex. 1013 [Willey] at 1095 (“treated sites were irradiated with 10 J/cm² blue light”).</p>
9. The method of Claim 8, wherein the low density polyethylene barrier is removed no later than three hours after the treatment site is covered.	<p>Willey describes the method of Claim 8, wherein the low density polyethylene barrier is removed no later than three hours after the treatment site is covered.</p> <p>See my discussion above at Claim 2; Ex. 1013 [Willey] at 1095 (specifying a 1 hour incubation time); Calderhead at 246; Sotiriou at 1062; Ex. 1010 [Ameluz] at 3; Ex. 1018 [Bissonnette] at 226; Ex. 1015 [Palm] at 24; Ex. 1019 [McLaren] at 399.</p>
10. The method of Claim 8, further comprising: positioning the treatment site between two inches and four inches from a surface of the illuminator.	<p>Willey describes the method of Claim 8, further comprising: positioning the treatment site between two inches and four inches from a surface of the illuminator.</p> <p>For example, Willey teaches that the BLU-U blue light source is positioned 2 to 4 inches from the treatment surface.</p> <p>“After 1 hour, both of the treated sites (heated and control) were irradiated with 10 J/cm² blue light (BLU-U; Dusa Pharmaceuticals, Inc.) for 1,000 seconds with the light positioned 2 to 4 inches from the skin surface. During light irradiation, the treated areas were cooled by a small portable fan set on a mayo stand for comfort.”</p> <p>Ex. 1013 [Willey] at 1095.</p>

B. Ground 2: Claim 3 is met by the combination of Willey with Ameluz

‘567 Patent	Willey Combined with Ameluz
<p>3. The method of Claim 1, wherein a maximum plasma concentration of ALA following application of the ALA is less than about 110 ng/mL.</p>	<p>Willey teaches the method of Claim 1, wherein a maximum plasma concentration of ALA following application of the ALA is less than about 110 ng/mL.</p> <p>For example, Willey teaches the topical application of ALA with an incubation period of 1 hour and occlusion of the treated area with Saran plastic wrap.</p> <p style="padding-left: 40px;">“Areas to be treated were swabbed with acetone and gauze and allowed to dry. Topical 20% 5-ALA (Levulan Kerastick; Dusa Pharmaceuticals, Inc., Wilmington, MA) was applied to the entire forearm skin and occluded with plastic wrap (Saran; SC Johnson). One stick (1.5 ml) was used to cover each distal extremity. ... After 1 hour, both of the treated sites (heated and control) were irradiated with 10 J/cm² blue light.”</p> <p>Ex. 1013 [Willey] at 1095.</p> <p>To the extent that DUSA asserts that Willey does not necessarily disclose all the elements of claims 3, a person of ordinary skill in the art would be motivated to combine the teachings of Willey and the Ameluz prescribing information to arrive at what is claimed in Claim 3. For example, a person of skill in the art seeking to assess the application of less ALA to fewer or smaller lesions than those treated in Willey, would combine Willey’s disclosure with that from the Ameluz prescribing information which indicates that less topical ALA (i.e., 200 mg) can be safely and effectively applied under occlusion for a mean maximum plasma concentration of ALA around 47.35 ng/mL.</p>

'567 Patent	Willey Combined with Ameluz
	<p>A person of ordinary skill in the art would be motivated to combine the teachings of Willey and the Ameluz prescribing information. Both relate to the use of topically applied ALA compositions to administer ALA for photodynamic therapy with occlusion and the Ameluz prescribing information indicates that the application of 200 mg of ALA is safe and effective with a mean maximum plasma concentration of ALA at around 47.35 ng/mL. As a result, a person of ordinary skill in the art wanting to assess the application of topical ALA compositions like those discussed in Willey (i.e., Levulan) applied at an amount of less than or around 200 mg of ALA with occlusion to treat fewer or smaller lesions would consult the Ameluz prescribing information, which describes the pharmacokinetics of a similar FDA approved ALA composition and provides a maximum plasma concentration for topical application of ALA that is below 110 ng/mL. Ex 1010 [Ameluz] at 9; Ex. 1013 [Willey] at 1095-1096.</p> <p>A person of ordinary skill in the art would have reasonably expected success in combining Willey with the Ameluz prescribing information. In light of the results reported in the Ameluz prescribing information, a person of ordinary skill in the art would not expect a maximum plasma concentration above 110 ng/mL after topical application of the ALA compositions described in Willey especially when applied at concentrations at or below 200 mg—<i>e.g.</i>, to treat fewer or smaller lesions (covering surface areas at or below 20 cm²). This understanding is confirmed by the Ameluz prescribing information itself, as well as an earlier study by Rick, et al. Ex. 1035 [Rick] at 315, 317. Moreover, based on the pharmacokinetic information provided in the Ameluz prescribing information, a person of ordinary skill could readily adjust the amount of ALA applied to given areas of the skin to ensure that the maximum plasma concentration of ALA was less than or around 47.35 ng/mL (as specified in the Ameluz prescribing information)—i.e., did not exceed around 110 ng/mL.</p>

C. Ground 3: Claim 5 is met by the combination of Willey with Sotiriou

‘567 Patent	Willey Combined with Sotiriou
<p>5. A method as set forth in Claim 4, wherein the low density polyethylene barrier is removed from the treatment area and then red light is applied to the treatment area for a 10 to 75 J/cm² light dose.</p>	<p>Willey describes the method of Claim 4, wherein the low density polyethylene barrier is removed from the treatment area and then red light is applied to the treatment area for a 10 to 75 J/cm² light dose. See my discussion above at Claim 4; Ex. 1013 [Willey] at 1095.</p> <p>Although Willey does not expressly identify the use of a red light or its dose, one of skill in the art would know that a red light with a dose of 10 to 75 J/cm² could be used in place of the blue light source and dose taught in Willey.</p> <p>For example, Willey references various photodynamic therapy clinical trials, including a clinical trial performed by Sotiriou et al. using ALA with red light PDT and occlusion for treating actinic keratosis on the upper extremities including the hands and forearms. Ex. 1013 [Willey] at 1094, 1101; Ex. 1017 [Sotiriou] at 1062 (“20% 5-ALA . . . was applied on the lesions as well as on 5 mm of normal surrounding skin and left under occlusion for 4 h. Immediately after removal of the dressing and the cream remnants, treatment area was illuminated with red light (570-670 nm) by a non-coherent light source (Waldmann PDT 1200. Waldmann-Medizinn-Technik, Villingen-Schwenningen, Germany) at a light dose of 75 J/cm² and a fluence rate of 75 mw/cm².”).</p> <p>As a result, one of skill in the art reading Willey together with Sotiriou would know and be motivated to apply red light to the treatment area for a light dose of 10 to 75 J/cm². Moreover, one of skill in the art would reasonably expect success in making the combination because red and blue light sources have long been used with ALA photodynamic therapy including light with light doses between 10 to 75 J/cm².</p>

D. Ground 4: Claims 1-9 are taught by Noven Pharma

‘567 Patent	Noven Pharma
<p>1 [preamble] A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:</p>	<p>Noven Pharma describes using a patch with a low density polyethylene backing material to topically administer ALA for photodynamic therapy.</p> <p>“It has now been found that ALA can be prepared in a stable formulation for topical use by incorporation into a topical drug delivery carrier, optionally containing a mild organic proton donor or saccharide containing substance. In a preferred embodiment, the delivery carrier is contained in a patch.”</p> <p>Ex. 1005 [Noven Pharma] at 5:15-21.</p> <p>“The most convenient form for manufacture of a matrix device is one in which the ALA is dispersed in a pressure sensitive adhesive . . . The backing materials, which are preferably water resistant, and occlusive or non-occlusive, can be selected from such material as foam, metal foil, polyester, low density polyethylene, copolymers of vinyl chloride and polyvinylidene chloride and laminates thereof.”</p> <p>Ex. 1005 [Noven Pharma] at 9:1-5; 9:27-34; 10:1-12.</p> <p>Noven Pharma further describes “penetration enhancers” and discloses that its occlusive patches using formulations of ALA “appear to improve the fluorescence produced . . . compared to ALA in a fluid carrier” and generate a “pattern of fluorescence [that] is more even and uniform over the area of application than with topical creams and salves, and may even provide increased fluorescence”. Ex. 1005 [Noven</p>

'567 Patent	Noven Pharma
	<p>Pharma] at 3:32–4:6; 10:20–27, 11:11–13. One of skill in the art would recognize that improved, increased, and more uniform fluorescence—<i>i.e.</i>, resulting from formation of PPIX—are indicative of the enhanced penetration of topical compositions of ALA.</p> <p>In addition, one of skill in the art would recognize that occlusion with a patch having a water resistant low density polyethylene backing reduces transepidermal water loss and enhances penetration of topically applied ALA, as reflected, for example, in various prior art publications.</p> <p style="padding-left: 40px;">“Occlusion is known to reduce transepidermal water loss, hydrating the stratum corneum and generally enhancing drug penetration, especially for hydrophilic molecules such as ALA.”</p> <p>Ex. 1006 [Sakamoto] at 205; see also Ex. 1007 [Berardesca] at 26, Figure 2; Ex. 1027 [Ozog] at 808.</p>
<p>[a] topically applying ALA to a treatment area to be treated with photodynamic therapy;</p>	<p>Noven Pharma describes the topical application of ALA to the photodynamic therapy treatment site using a patch.</p> <p style="padding-left: 40px;">“It now has been found that ALA can be prepared in a stable formulation for topical use by incorporation into a topical drug delivery carrier, optionally containing a mild organic proton donor or saccharide containing substance. In a preferred embodiment, the delivery carrier is contained in a patch.</p> <p>Ex. 1005 [Noven Pharma] at 5:15-21</p> <p style="padding-left: 40px;">“The size of the topical device of the present invention depends on the dose of ALA to be utilized, with the preferred patch area being about 2.5 to 20 cm² preferably 5 to 15 cm². ... As</p>

'567 Patent	Noven Pharma
	<p>a minimum, the topical device must contain a pharmacologically effective amount of ALA."</p> <p>Ex. 1005 [Noven Pharma] at 11:20-30.</p> <p>"Topical ALA photodynamic therapy (ALA PDT™) involves the exposure of the ALA-treated lesion with light."</p> <p>Ex. 1005 [Noven Pharma] at 12:8-9.</p>
<p>[b] after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area; and</p>	<p>Noven Pharma describes using a patch with a low density polyethylene backing material with ALA dispersed in a pressure sensitive adhesive. Because the ALA is on the skin-facing surface of the patch, the ALA is applied to the treatment area and subsequently covered by the low density polyethylene backing material of the patch.</p> <p>"The most convenient form for manufacture of a matrix device is one in which the ALA is dispersed in a pressure sensitive adhesive . . . The backing materials, which are preferably water resistant, and occlusive or non-occlusive, can be selected from such material as foam, metal foil, polyester, low density polyethylene, copolymers of vinyl chloride and polyvinylidene chloride and laminates thereof."</p> <p>Ex. 1005 [Noven Pharma] at 9:1-5; 9:27-34.</p> <p>One of skill in the art would recognize that occlusion with a patch having a water resistant low density polyethylene backing reduces transepidermal water loss and enhances penetration of topically applied ALA. See my discussion in Claim 1[preamble]; Ex. 1006 [Sakamoto] at 205; see also Ex. 1007 [Berardesca] at 26, Figure 2; Ex. 1027 [Ozog] at 808.</p>

'567 Patent	Noven Pharma
<p>[c] removing the low density polyethylene barrier within 3 hours and then applying light to the treatment area.</p>	<p>Noven Pharma describes an example where the ALA patch with the low density polyethylene backing is applied to the treatment area for about a 2 to 3 hour duration. One of skill in the art would understand this to mean that the patch is removed after 2-3 hours.</p> <p>“The preferred delivery rate for ALA is at least 0.1 ug. per cm² per hour, giving a preferred daily dosage of at least 0.25 mg. per day applied to the area of the skin to be diagnosed or treated for about 2-48 hours.”</p> <p>Ex. 1005 [Noven Pharma] at 11:23-27.</p> <p>“As a minimum, the topical device must contain a pharmacologically effective amount of ALA. Generally, this is at least 0.25 mg. The duration of application is that period sufficient to achieve ALA penetration into the diseased tissue and that permits high localized concentrations of protoporphyrin IX resulting from the conversion of ALA. This period may be about 3-24 hours. The effective amount and duration will vary depending on the nature of the lesion and may be determined empirically by those skilled in the art by testing localized fluorescence of the lesion after administration.”</p> <p>Ex. 1005 [Noven Pharma] at 11:29-12:5.</p> <p>“Topical ALA photodynamic therapy (ALA PDT™) involves the exposure of the ALA-treated lesion with light . . . Upon exposure, activation of protoporphyrin IX leads to in situ breakdown of protoporphyrin IX and the</p>

'567 Patent	Noven Pharma
	<p data-bbox="634 243 1279 317">generation of singlet oxygen, leading to the destruction of diseased cells.”</p> <p data-bbox="540 369 1097 405">Ex. 1005 [Noven Pharma] at 12:8-18.</p> <p data-bbox="540 457 1333 573">Noven Pharma further describes that after the ALA patch is removed that light is applied to the treatment area.</p> <p data-bbox="630 625 1373 831">“After the patch is removed, the lesion is wiped with an alcohol swab to remove any residual adhesive . . . [T]he lesion is then exposed to a 634 nm wavelength light source at 100 mW/cm² for 15 minutes.”</p> <p data-bbox="540 884 1117 919">Ex. 1005 [Noven Pharma] at 15:14-21.</p>
<p data-bbox="204 972 511 1476">2. A method as set forth in Claim 1, wherein the low density polyethylene barrier is removed from the treatment area within 3 hours and then blue light is applied to the treatment area for a 10 J/cm² light dose.</p>	<p data-bbox="540 972 1455 1178">Noven Pharma describes an example where the ALA patch with the low density polyethylene backing is applied to the treatment area for a 2-3 hour duration after which the patch is removed. See my discussion above for Claim 1[c]; Ex. 1005 [Noven Pharma] at 9:1-5; 11:23-27; 11:29-12:5; 15:14-21.</p> <p data-bbox="540 1230 1458 1346">Further, Noven Pharma describes an example where, after the patch is removed from the ALA treated area, blue light at 400 nm is applied for a 10 J/cm² light dose.</p> <p data-bbox="634 1398 1377 1692">“Topical ALA photodynamic therapy (ALA PDT™) involves the exposure of the ALA-treated lesion with light. A suitable wavelength is 400 nm, 634 nm or 600-700 nm, at an intensity of 10-100 milliwatts per centimeter squared (mW/cm²) to provide a light dose of 10-100 Joules/cm².”</p> <p data-bbox="540 1745 1097 1780">Ex. 1005 [Noven Pharma] at 12:8-18.</p>

'567 Patent	Noven Pharma
	<p>The '567 patent identifies light with a wavelength at or above 400 nm as “blue light.” Ex. 1001 ['567 Patent] at 5:24-29.</p>
<p>3. The method of Claim 1, wherein a maximum plasma concentration of ALA following application of the ALA is less than about 110 ng/mL.</p>	<p>Noven Pharma describes the topical application of ALA to the treatment site using a patch for photodynamic therapy for a 2-3 hour duration. See my discussion above for Claim 1; Ex. 1005 [Noven Pharma] at 5:15-21; 11:20-12:5; 12:8-9.</p> <p>The ALA patches of Noven Pharma (<i>e.g.</i>, 2.5-20 cm² patches or the 5 cm² patch of Example 3) when applied topically for 2-3 hours would not substantially increase the blood plasma levels of ALA above endogenous ALA concentrations, and, therefore, maximum blood plasma levels would remain below about 110 ng/mL.</p> <p>For example, Fauteck observed only a small increase in 5-ALA plasma concentration (a mean C_{max} of 28.36 µg/l (<i>i.e.</i>, 28.36 ng/mL) with topically applied ALA using eight 4 cm² patches containing 2 mg of ALA per cm² (for a total of 64 mg of ALA) and did not observe any C_{max} values above 53.08 µg/l (<i>i.e.</i>, 53.08 ng/mL).</p> <p>“A small increase or 5-ALA plasma concentrations was observed in 10 or 12 patients after applying 8 patches for 4 h, which rapidly declined to normal values after patch removal. The maximum increase was 3.7-fold of the predose 5-ALA plasma concentration.”</p> <p>Ex. 1008 [Fauteck] at 53.</p> <p>“5-ALA plasma concentrations increased from endogenous 11.23 µg/l (measured pre-dose) to a maximum of 27.57 µg/l (geometric means of 12 patients; values not baseline corrected).”</p>

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	<p>Ex. 1008 [Fauteck] at 57.</p> <p>“The maximum increase in 5-ALA plasma concentrations was 3.7-fold of the pre-dose concentration (C_{\max} 53.08 µg/l in one patient).”</p> <p>Ex. 1008 [Fauteck] at 58; see also Ex. 1004 [Fauteck] at 57, Tables 5-7; Ex. 1009 [Biofrontera] at [0140]-[0142] (“The plasma and urine concentrations of these compounds in ALA-treated patients were not increased in comparison to the naturally occurring physiological values in the same individuals.”); Ex. 1010 [Ameluz] at 9 (the “maximum concentration (C_{\max}) for baseline corrected aminolevulinic acid (n=12) w[as] . . . 27.19 ± 20.02 ng/ml.”).</p>
<p>4 [preamble] A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:</p>	<p>Noven Pharma describes using a patch with a low density polyethylene backing material to topically administer ALA for photodynamic therapy.</p> <p>See my discussion above at Claim 1 [preamble]; Ex. 1005 [Noven Pharma] at 5:15-21; 9:1-5; 9:27-34; Ex. 1006 [Sakamoto] at 205; Ex. 1007 [Berardesca] at 26; Ex. 1027 [Ozog] at 808.</p>
<p>[a] topically applying ALA to a treatment area to be treated with photodynamic therapy; and</p>	<p>Noven Pharma describes the topical application of ALA to the treatment site using a patch for photodynamic therapy.</p> <p>See my discussion above for Claim 1[a]; Ex. 1005 [Noven Pharma] at 5:15-21; 11:20-30; 12:8-9.</p>
<p>[b] after the ALA is applied to the treatment area,</p>	<p>Noven Pharma describes using a patch with a low density polyethylene backing material with ALA dispersed in a pressure sensitive adhesive. Because the ALA is on the skin-</p>

'567 Patent	Noven Pharma
<p>covering the treatment area with a low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area,</p>	<p>facing surface of the patch, the ALA is applied to the treatment area and subsequently covered by the low density polyethylene backing material of the patch. One of skill in the art would recognize that occlusion with a patch having a low density polyethylene backing reduces transepidermal water loss and enhances penetration of topically applied ALA.</p> <p>See my discussion above for Claim 1[b]; Ex. 1005 [Noven Pharma] at 9:1-5; 9:27-34; Ex. 1006 [Sakamoto] at 205; Ex. 1007 [Berardesca] at 26; Ex. 1027 [Ozog] at 808.</p>
<p>[c] wherein the treatment area is located on a hand or a forearm.</p>	<p>Noven Pharma discusses that a treatment area can be any visible portion of a patient's skin having a lesion, which would include a hand or a forearm.</p> <p style="padding-left: 40px;">“The target tissues for which the present invention may be used are any visible, cutaneous lesion or other undesired rapidly growing cells.”</p> <p>Ex. 1005 [Noven Pharma] at 12:19-21.</p> <p>In addition, in one example, Noven Pharma describes treatment of a lesion on a subject's forearm.</p> <p style="padding-left: 40px;">“A thirty-two year old female is diagnosed with basal cell carcinoma. A single lesion is evident on her right forearm covering approximately 22 mm², and topical aminolevulinic acid photodynamic therapy (ALA PDT™) is prescribed.”</p> <p>Ex. 1005 [Noven Pharma] at 15:2-6.</p>

'567 Patent	Noven Pharma
<p>5. A method as set forth in Claim 4, wherein the low density polyethylene barrier is removed from the treatment area and then red light is applied to the treatment area for a 10 to 75 J/cm² light dose.</p>	<p>Noven Pharma describes an example where, after the patch is removed from the ALA treated area, red light at 634 nm is applied for a 10 J/cm² light dose.</p> <p>“Topical ALA photodynamic therapy (ALA PDT™) involves the exposure of the ALA-treated lesion with light. A suitable wavelength is 400 nm, 634 nm or 600-700 nm, at an intensity of 10-100 milliwatts per centimeter squared (mW/cm²) to provide a light dose of 10-100 Joules/cm².”</p> <p>Ex. 1005 [Noven Pharma] at 12:8-18.</p>
<p>6. The method as set forth in Claim 4, wherein the treatment area is a dorsal surface of the hand.</p>	<p>Noven Pharma describes that the treatment area can be any visible portion of a subject's skin having a lesion, which would include the dorsal surface of the hand.</p> <p>“The target tissues for which the present invention may be used are any visible, cutaneous lesion or other undesired rapidly growing cells.”</p> <p>Ex. 1005 [Noven Pharma] at 12:19-21.</p>
<p>7. The method as set forth in Claim 4, wherein the treatment area is a dorsal surface of the forearm.</p>	<p>Noven Pharma describes that the treatment area can be any visible portion of a subject's skin having a lesion, which would include the dorsal surface of the forearm.</p> <p>“The target tissues for which the present invention may be used are any visible, cutaneous lesion or other undesired rapidly growing cells.”</p> <p>Ex. 1005 [Noven Pharma] at 12:19-21.</p>

'567 Patent	Noven Pharma
	<p>In addition, in one example, Noven Pharma describes treatment of a lesion on a subject's forearm.</p> <p style="padding-left: 40px;">“A thirty two year old female is diagnosed with basal cell carcinoma. A single lesion is evident on her right forearm covering approximately 22 mm², and topical aminolevulinic acid photodynamic therapy (ALA PDT™) is prescribed.”</p> <p>Ex. 1005 [Noven Pharma] at 15:2-6.</p> <p>Noven Pharma's discussion regarding a lesion on the right forearm encompasses the dorsal surface of the forearm. Further, one of skill in the art would recognize that Noven Pharma's disclosure of a lesion on the right forearm refers to the dorsal surface of the forearm as this is the expected location for lesions on the forearm due to sun exposure.</p>
<p>8 [preamble] A method of using 5-aminolevulinic acid (ALA) and a low density polyethylene barrier, comprising:</p>	<p>Noven Pharma describes using a patch with a low density polyethylene backing material to topically administer ALA for photodynamic therapy.</p> <p>See my discussion above at Claim 1 [preamble]; Ex. 1005 [Noven Pharma] at 5:15-21; 9:1-5; 9:27-34; Ex. 1006 [Sakamoto] at 205; Ex. 1027 [Ozog] at 808.</p>
<p>[a] contacting a treatment site with a composition comprising the ALA so as to wet the treatment site;</p>	<p>Noven Pharma describes examples of adhesive patch compositions containing ALA together with solvents, liquids, and other compositions that are applied to wet the treatment site.</p> <p>The '567 Patent describes wetting the treatment site, in one example, as applying a topical solution of ALA to the skin. Ex. 1001 ['567 Patent] at 9:50-54. In another example, the '567 Patent describes the application of an ALA admixture “to achieve a substantially uniform wetting of the lesion</p>

'567 Patent	Noven Pharma
	<p>surface with the ALA by contacting the ALA with the lesion surface.” Ex. 1001 [‘567 Patent] at 9:12-18.</p> <p>Like these examples, Noven Pharma describes contacting the treatment site with ALA so as to wet the treatment site using adhesive patches containing ALA with a carrier and other components such as penetration enhancers. Ex. 1005 [Noven Pharma] at 10:24-27; 11:8-13.</p> <p>Noven Pharma also describes examples of a reservoir-type device for ALA delivery to the treatment site using a non-aqueous solvent such as an alkanediol.</p> <p>“Where the topical device is a reservoir-type device, the ALA in a solvent, preferably in a non-aqueous solvent such as an alkanediol or an organic acid such as citric acid is used to fill the reservoir. . . . Backing materials are similar to those described above for matrix devices.”</p> <p>Ex. 1005 [Noven Pharma] at 10:1-12</p>
<p>[b] following wetting of the treatment site, covering the wetted treatment site with the low density polyethylene barrier;</p>	<p>Noven Pharma describes using patches with a low density polyethylene backing material with ALA dispersed in a pressure sensitive adhesive. Because the ALA is on the skin-facing surface of the patch, the patch backing material is applied to cover the treatment site after it is wetted/contacted with ALA.</p> <p>“The most convenient form for manufacture of a matrix device is one in which the ALA is dispersed in a pressure sensitive adhesive. . . . The backing materials, which are preferably water resistant, and occlusive or non-occlusive,</p>

'567 Patent	Noven Pharma
	<p>can be selected from such material as foam, metal foil, polyester, low density polyethylene, copolymers of vinyl chloride and polyvinylidene chloride and laminates thereof.”</p> <p>Ex. 1005 [Noven Pharma] at 9:1-5; 9:27-34.</p> <p>“Where the topical device is a reservoir-type device, the ALA in a solvent, preferably in a non-aqueous solvent such as an alkanediol or an organic acid such as citric acid is used to fill the reservoir. . . . Backing materials are similar to those described above for matrix devices.”</p> <p>Ex. 1005 [Noven Pharma] at 10:1-12.</p>
<p>[c] removing the low density polyethylene barrier so as to expose the treatment site; and</p>	<p>Noven Pharma describes that the patch is removed to expose the treatment site.</p> <p>“After the patch is removed, the lesion is wiped with an alcohol swab to remove any residual adhesive.”</p> <p>Ex. 1005 [Noven Pharma] at 15:14-21.</p> <p>Noven Pharma also describes an examples where the ALA patch with the low density polyethylene backing is applied to the treatment area for a set duration. One of skill in the art would understand this to mean that the patch is removed after the specified duration to expose the treatment site.</p> <p>“The preferred delivery rate for ALA is at least 0.1 ug. per cm² per hour, giving a daily dosage of at least 0.25 mg. per day applied to the area of the skin to be diagnosed or treated for about 2-48 hours.”</p>

'567 Patent	Noven Pharma
	<p data-bbox="537 281 1117 321">Ex. 1005 [Noven Pharma] at 11:23-27.</p> <p data-bbox="634 365 1369 705">“As a minimum, the topical device must contain a pharmacologically effective amount of ALA. Generally, this is at least 0.25 mg. The duration of application is that period sufficient to achieve ALA penetration into the diseased tissue and that permits high localized concentrations of protoporphyrin IX resulting from the conversion of ALA. This period may be about 3-24 hours.”</p> <p data-bbox="537 749 1146 789">Ex. 1005 [Noven Pharma] at 11:29-12:5.</p> <p data-bbox="634 833 1330 1129">“Topical ALA photodynamic therapy (ALA PDT™) involves the exposure of the ALA-treated lesion with light . . . Upon exposure, activation of protoporphyrin IX leads to in situ breakdown of protoporphyrin IX and the generation of singlet oxygen, leading to the destruction of diseased cells.”</p> <p data-bbox="537 1173 1097 1213">Ex. 1005 [Noven Pharma] at 12:8-18.</p>
<p data-bbox="203 1266 500 1514">[d] illuminating the exposed treatment site with an illuminator so as to deliver a 10 J/cm² dose of blue light.</p>	<p data-bbox="537 1266 1455 1388">Noven Pharma describes an example where, after the patch is removed from the ALA treated area, blue light at 400 nm is applied for a 10 J/cm² light dose.</p> <p data-bbox="634 1432 1377 1728">“Topical ALA photodynamic therapy (ALA PDT™) involves the exposure of the ALA-treated lesion with light. A suitable wavelength is 400 nm, 634 nm or 600-700 nm, at an intensity of 10-100 milliwatts per centimeter squared (mW/cm²) to provide a light dose of 10-100 Joules/cm².”</p> <p data-bbox="537 1772 1377 1812">Ex. 1005 [Noven Pharma] at 12:8-18; see also 15:14-21.</p>

'567 Patent	Noven Pharma
	<p>The '567 patent defines light with a wavelength at or above 400 nm as “blue light.” Ex. 1001 ['567 Patent] at 5:42-29.</p>
<p>9. The method of Claim 8, wherein the low density polyethylene barrier is removed no later than three hours after the treatment site is covered.</p>	<p>Noven Pharma describes an example where the ALA patch with the low density polyethylene backing is applied to the treatment area for about a 2-3 hour duration. One of skill in the art would understand this to mean that the patch is removed after no later than 2-3 hours after the treatment site is covered.</p> <p>“The preferred delivery rate for ALA is at least 0.1 ug. per cm² per hour, giving a preferred daily dosage of at least 0.25 mg. per day applied to the area of the skin to be diagnosed or treated for about 2-48 hours.”</p> <p>Ex. 1005 [Noven Pharma] at 11:23-27.</p> <p>“As a minimum, the topical device must contain a pharmacologically effective amount of ALA. Generally, this is at least 0.25 mg. The duration of application is that period sufficient to achieve ALA penetration into the diseased tissue and that permits high localized concentrations of protoporphyrin IX resulting from the conversion of ALA. This period may be about 3-24 hours. The effective amount and duration will vary depending on the nature of the lesion and may be determined empirically by those skilled in the art by testing localized fluorescence of the lesion after administration.”</p> <p>Ex. 1005 [Noven Pharma] at 11:29-12:5.</p>

E. Ground 5: Claim 3 is met by the combination of Noven Pharma with Fauteck.

‘567 Patent	Noven Pharma with Fauteck
<p>3. The method of Claim 1, wherein a maximum plasma concentration of ALA following application of the ALA is less than about 110 ng/mL.</p>	<p>Noven Pharma describes the method of Claim 1, wherein a maximum plasma concentration of ALA following application of the ALA is less than about 110 ng/mL. See my discussion above at Claim 1 [preamble]; Ex. 1005 [Noven Pharma] at 5:15-21; 11:20-30; 12:8-9.</p> <p>To the extent that DUSA asserts that Noven Pharma does not necessarily disclose all the elements of claims 3, a person of ordinary skill in the art would be motivated to combine the teachings of Noven Pharma and the Fauteck to arrive at what is claimed in Claim 3. Based on the combination of Noven Pharma with Fauteck, one of skill in the art would understand that the ALA patches of Noven Pharma (<i>e.g.</i>, the 2.5 to 20 cm² patches or the 5 cm² patch of Example 3) when applied topically for 2-3 hours would not substantially increase the blood plasma levels of ALA above endogenous ALA concentrations, and, therefore, maximum blood plasma levels would remain below about 110 ng/mL.</p> <p>For example, Fauteck observed only a small increase in 5-ALA plasma concentration (a mean C_{max} of 28.36 µg/l (<i>i.e.</i>, 28.36 ng/mL) with topically applied ALA using eight 4 cm² patches containing 2 mg of ALA per cm² (for a total of 64 mg of ALA) and did not observe any C_{max} values above 53.08 µg/l (<i>i.e.</i>, 53.08 ng/mL).</p> <p>“A small increase or 5-ALA plasma concentrations was observed in 10 or 12 patients after applying 8 patches for 4 h, which rapidly declined to normal values after patch removal. The maximum increase was 3.7-fold of the predose 5-ALA plasma concentration.”</p> <p>Ex. 1008 [Fauteck] at 53.</p>

“5-ALA plasma concentrations increased from endogenous 11.23 µg/l (measured pre-dose) to a maximum of 27.57 µg/l (geometric means of 12 patients; values not baseline corrected).”

Ex. 1008 [Fauteck] at 57.

“The maximum increase in 5-ALA plasma concentrations was 3.7-fold of the pre-dose concentration (C_{\max} 53.08 µg/l in one patient).”

Ex. 1008 [Fauteck] at 58; see also Ex. 1004 [Fauteck] at 57, Tables 5-7.

A person of skill in the art seeking to use Noven Pharma’s patches to attempt to treat more lesions and/or lesions with greater surface area (i.e., greater than 20 cm²), would consult Fauteck which describes that 64 mg of ALA can be safely applied over 32 cm² using multiple ALA patches to achieve a mean maximum plasma concentration of around 28.36 ng/mL. Noven Pharma describes that ALA patch sizes can range between “2.5 to 20 cm²” and contain “0.1-3.0 mg/cm²” of ALA. Ex. 1005 [Noven Pharma] at 11:20-28.

A person of ordinary skill in the art would be motivated to combine Noven Pharma with Fauteck to treat more lesions or larger lesions, because Fauteck describes that eight 4 cm² ALA patches applied over 32 cm² for a total of 64 mg of ALA results in a mean maximum plasma concentration of 28.36 ng/mL and is safe and well-tolerated. EX. 1008 [Fauteck] at Abstract; 59. As a result, one of skill in the art assessing the treatment of more lesions or larger lesions would appreciate based on Fauteck that they could safely apply up to 64 mg of ALA over 32 cm² using Noven Pharma’s ALA patches.

	<p>One of skill in the art would have also appreciated a reasonable expectation of success. When up to 64 mg of ALA is applied over up to 32 cm² of skin surface area, one of skill in the art would reasonably expect an observed maximum plasma concentration of ALA between around or less than 53.08 ng/mL with a mean maximum plasma concentration of ALA around or less than 28.36 ng/mL as reported by Fauteck. Ex. 1008 [Fauteck] at 57-58, Tables 5-7. This is well below the about 110 ng/mL amount specified in claim 3 of the '567 patent.</p>
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F. Ground 6: Claim 10 is met by the combination of Noven Pharma with the BLU-U operating manual


Claim	Noven Pharma with BLU-U Operating Manual
10. The method of Claim 8, further comprising: positioning the treatment site between two inches and four inches from a surface of the illuminator.	<p>Noven Pharma describes the method of Claim 8, further comprising: positioning the treatment site between two inches and four inches from a surface of the illuminator.</p> <p>One of skill in the art seeking to use a blue light illumination source would be motivated to combine Noven Pharma with the instruction manual for BLU-U (a commercially available blue light source) with a reasonable expectation of success. The BLU-U operating manual specifies that the BLU-U illuminator should be positioned between two and four inches from the surface of the treatment site.</p> <p>“Position the BLU-U® around the patient's head so the entire surface area to be treated lies between 2” and 4” from the BLU-U® surface:</p> <p>a.) The patient's scalp should be no closer than 2” from the surface and</p> <p>b.) The patient's scalp should be no further than 4” from the surface and</p> <p>c.) The sides of the patient's face and the patient's ears should be no closer than 2” from the BLU-U® surface.”</p> <p>Ex. 1012 [BLU-U Operating Manual] at 9-10; 12; Ex. 1031 [Affidavit of Duncan Hall] at 081-084; see also Ex. 1031 [Affidavit of Duncan Hall] at 037-040.</p>

XI. Additional Remarks

312. I currently hold the opinions expressed in this declaration, but my analysis may continue, and I may acquire additional information and attain further insights that may result in added observations.

313. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

10/19/2021
Date


Name
Howard Rogers MD