

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

AND

BIOFRONTERA AG**

Petitioner

v.

DUSA PHARMACEUTICALS, INC.

Patent Owner

***Inter Partes* Review No. IPR2022-00056**

Patent 10,357,567

PETITION FOR *INTER PARTES* REVIEW UNDER 35 U.S.C. 312

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Petitioner's Exhibit List

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
1004	CV of Dr. Howard Rogers MD, PHD
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, Ortlund 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. <i>Dermatologic Surgery</i> . 2014 Oct;40(10):1094-1102. (“Willey”)
1014	Calderhead RG. Light-emitting diode phototherapy in dermatological practice in lasers in dermatology and medicine. <i>Lasers in Dermatology and Medicine</i> . 2011 Aug;231-265. (“Calderhead”)
1015	Palm M., Goldman PM. Aminolevulinic acid: actinic keratosis and photorejuvenation. In: Gold M.H., editor. <i>Photodynamic Therapy in Dermatology</i> . Springer Science and Business Media, LLC. 2011 Nov;5-30. (“Palm”)
1016	MacCormack MA. Photodynamic therapy in dermatology: an update on applications and outcomes. <i>Semin Cutan Med Surg</i> . 2008 Mar;27(1):52-62. (“MacCormack”)
1017	Sotiriou E, Apalla Z, Maliamani F, Zapparas 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. <i>J Eur Acad Dermatol Venereol</i> . 2009 Sep;23(9):1061-5. (“Sotiriou”)
1018	Bissonnette R. Photodynamic therapy. In: Gold M.H., editor. <i>Photodynamic Therapy in Dermatology</i> . 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. <i>British Journal of Dermatology</i> . 1974; 91(27-32). (“Harris”)
1021	Levulan® Label (2009)

1022	Wachowska et al., Aminolevulinic acid (ALA) as a prodrug in photodynamic therapy of cancer. <i>Molecules</i> . 2011 May; 16(5): 4140-4164. (“Wachowska”)
1023	Agostinis et al. Photodynamic therapy of cancer: an update. <i>CA: A Cancer Journal for Clinicians</i> . 2011 May; 61(4):250-281. (“Agostinis”).
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? <i>Journal of the American Academy of Dermatology</i> 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. <i>Arch Dermatol</i> . 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. <i>J Invest Dermatol</i> . 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. <i>Dermatol Surg</i> . 2016 Jul;42(7):804-27 (“Ozog”)
1028	Aktelite CL128 Operators Manual with Metvixia
1029	DUSA Levulan Press Release
1030	European Medicines Agency CHMP Assessment Report (excerpts)
1031	Affidavit of Duncan Hall

1032	Willey Pubmed Website Database Listing
1033	Sotiriou Pubmed Website Database Listing
1034	Fauteck Europe PMC Website Database Listing
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”)
1036	International Patent Reviews, LLC review of U.S. Patent No. 10,357,567 dated July 26, 2021 available at https://patent-reviews.com/
1037	News article entitled “DUSA Pharmaceuticals To Pay U.S. \$20.75 Million To Settle False Claims Act Allegations Relating To Promotion Of Unsupported Drug Administration Process” available at https://www.justice.gov/opa/pr/dusa-pharmaceuticals-pay-us-2075-million-settle-false-claims-act-allegations-relating

Pursuant to 35 U.S.C. §§ 311-319, Biofrontera Incorporated, Biofrontera Bioscience GmbH, Biofrontera Pharma GmbH, and Biofrontera AG (collectively, “Petitioner”) hereby respectfully request *inter partes* review of claims 1–10 (“Challenged Claims”) of U.S. Patent No. 10,357,567 (“the ’567 Patent”), which issued on July 23, 2019 and is assigned to DUSA Pharmaceuticals, Inc. (“DUSA” or “PO”). As explained herein, there is a reasonable likelihood that Petitioner will prevail in establishing that the ’567 Patent is unpatentable as anticipated and obvious.

I. INTRODUCTION

Petitioner and PO are competitors in the marketplace for photodynamic therapy treatments for actinic keratosis—a pre-cancerous skin condition that can lead to squamous cell carcinoma. Petitioner’s product is marketed in the United States as Ameluz® and was first approved by the Food and Drug Administration (“FDA”) in 2016. PO’s product is marketed in the United States as Levulan® and was first approved by the FDA in 2000.

PO has previously asserted that its photodynamic therapy treatment with Levulan® was covered by five different patents (EX1021, 015) but the last of PO’s identified patents expired in October 2017. Facing the prospect of not having any Orange Book listed patents to protect its Levulan® product, PO pursued a purportedly new indication for Levulan®: treatment of pre-cancerous lesions on the

hands and forearms using occlusion with low density polyethylene (LDPE) and 5-aminolevulinic acid (ALA) photodynamic therapy. EX1021. Concurrently, PO filed the application that led to the '567 Patent on January 12, 2018 and requested prosecution on an expedited basis. But the claims that PO sought in its application and eventually received in the '567 Patent reflected a common off-label use of ALA photodynamic therapy that was already employed by researchers and doctors in the field for more than a decade. EX1003, ¶¶57-58;71-72.

Noven Pharma filed a PCT application in 1994 disclosing ALA patches for photodynamic therapy using an occlusive, water-resistant backing material made from LDPE for treating actinic keratosis on the forearms and elsewhere. EX1005. Likewise, Palm in 2011 disclosed using ALA photodynamic therapy to treat lesions on the hands and forearms including the occlusion of areas having thicker lesions “with Glad Press ‘N Seal®”—a well-known LDPE film. EX1015, 22. Similarly, Willey in 2014 described the off-label treatment of actinic keratosis (AK) lesions on the hands and forearms using PO’s product, Levulan®, coupled with occlusion by Saran® plastic wrap—another, well-known LDPE film. EX1013, 1095. As a result, the new indication that PO sought to protect with the '567 Patent—topical ALA photodynamic therapy using occlusion with LDPE film to enhance penetration of ALA into tissue, such as that on the hands and forearms—was already well known in the art prior to January 12, 2018. PO’s attempt to extend patent protection on its

Levulan® product by seeking to cover off-label uses that were commonplace in the prior art should not be countenanced. The '567 Patent should be held unpatentable. *See* EX1036.

II. MANDATORY NOTICES

A. Real Party in Interest (37 C.F.R. § 42.8(b)(1))

The real parties-in-interest for Petitioner are Biofrontera Incorporated, Biofrontera Bioscience GmbH, Biofrontera Pharma GmbH, and Biofrontera AG. No unnamed entity is funding, controlling, or otherwise has an opportunity to control or direct this Petition or Petitioner's participation in any resulting IPR. Also, Petitioner notes that Biofrontera Inc. has several commonly owned entities, and each of these entities agrees to be estopped under the provisions of 35 U.S.C. § 315 as a result of any final written decision in the requested IPR to the same extent that Petitioner is estopped.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

At the time of filing of this Petition, Petitioner is unaware of any related matters concerning the '567 Patent. Petitioner is presently involved in litigation filed in the District of Massachusetts originally captioned as *Dusa Pharmaceuticals, Inc. v. Biofrontera Inc. et al.* (Civil Action No. 1:18-cv-10568) involving U.S. Patent No. 9,723,991 ("the '991 Patent") and U.S. Patent No. 8,216,289 ("the '289 Patent"). Neither the '991 Patent nor the '289 Patent are in the same family as the '567 Patent.

C. Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))

Lead counsel: Lauren L. Fornarotto (Reg. No. 76,470) of McKool
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Back-up counsel: John F. Garvish (*pro hac vice* to be filed), Geoffrey
L. Smith (*pro hac vice* to be filed), and Matthew T. Cameron (Reg. No.
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D. Service Information (37 C.F.R. § 42.8(b)(4))

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Petitioner consents to electronic service.

E. Payment of Fees (37 C.F.R. §§ 42.15(a) and 42.103(a))

The Office is authorized to charge the fees specified by 37 C.F.R. §§ 42.103(a)
and 42.15(a) to Deposit Account No. 50-5723.

III. GROUNDS FOR STANDING (37 C.F.R. § 42.104(A))

Petitioner certifies that the '567 Patent is available for *inter partes* review, and
that Petitioner is not barred or estopped from requesting an *inter partes* review
challenging the claims on the grounds identified in this Petition.

IV. STATEMENT OF PRECISE RELIEF REQUESTED FOR EACH CLAIM CHALLENGED

A. Claims for Which Review Is Requested (37 C.F.R. § 42.104(b)(1))

Petitioner requests the review and cancellation of claims 1–10 (the “Challenged Claims”) of the ’567 Patent.

B. Statutory Grounds of Challenge (37 C.F.R. § 42.104(b)(2))

The Challenged Claims should be canceled for the following reasons:

Ground 1: Claims 1-4 and 6-10 are invalid under 35 U.S.C. § 102(a)(1) based on Willey (EX1013).

Ground 2: Claim 3 is invalid under 35 U.S.C. § 103 based on the combination of Willey (EX1013) and the Ameluz® prescribing information (EX1010).

Ground 3: Claim 5 is invalid under 35 U.S.C. § 103 based on the combination of Willey (EX1013) and Sotiriou (EX1017).

Ground 4: Claims 1-9 are invalid under 35 U.S.C. §§ 102(a)(1) and 102(a)(2) based on PCT Publication No. WO 96/06602 (“Noven Pharma”) (EX1005).

Ground 5: Claim 3 is invalid under 35 U.S.C. § 103 based on the combination of Noven Pharma (EX1005) and Fauteck (EX1008).

Ground 6: Claim 10 is invalid under 35 U.S.C. § 103 based on the combination of Noven Pharma (EX1005) and the Blu-U Operating Manual (EX1012).

The '567 Patent's earliest effective filing date is January 12, 2018—*i.e.*, its actual filing date. Willey is a journal article published online by October-November 2014 [EX1003, ¶¶92-93; EX1031, 005], and thus qualifies as prior art under 35 U.S.C § 102(a)(1). Noven Pharma is an international patent application publication that was filed on August 26, 1994 and published on March 7, 1996, and thus qualifies as prior art under 35 U.S.C §§ 102(a)(1) and 102(a)(2). EX1005. Sotiriou is a journal article published in the September 2009 edition of the Journal of the European Academy of Dermatology and Venereology [EX1003, 186-187], and was publicly available online by March 2011 [EX1031, 013], and thus qualifies as prior art under 35 U.S.C § 102(a)(1). Fautek is a journal article published online by February 2008 in the journal Archives of Dermatological Research, [EX1003, 287-288; EX1008, 53; EX1031, 009], and thus qualifies as prior art under 35 U.S.C § 102(a)(1). Ameluz® Prescribing Information was published on the Food and Drug Administration Website by October 2016 [EX1003, 92-93; EX1031, 060-071], and thus qualifies as prior art under 35 U.S.C § 102(a)(1). Likewise, the Blu-U Operating Manual was published on PO's website by at least 2006 [EX1003, 287-288; EX1031, 072-089], and thus qualifies as prior art under 35 U.S.C § 102(a)(1). Evidence of the public availability of Willey, Sotiriou, Fauteck, the Ameluz® Prescribing Information and the BLU-U Operating Manual before January 12, 2018 is found in EX1031, which is an affidavit from the Internet Archive. EX1031.

Further evidence of public availability of Willey, Fauteck, and Sotiriou is found in Exhibits 1032-1034.

Ground 1 asserts that the Challenged Claims are invalid based on published descriptions of ALA photodynamic therapy treatments on the hands and forearms using PO's own marketed product—Levulan®—together with Saran Wrap—a known low density polyethylene material used in the art. Ground 2 is not cumulative with Ground 1 because it adds the Ameluz® prescribing information reference to Ground 1, which addresses elements in claim 3 that PO may contend are not inherently present. Ground 3 is not cumulative with Ground 1 because it adds the use of red light as an illumination source to the disclosure in Ground 1, which is focused on the application of blue light.

Ground 4 is not cumulative with Grounds 1-3 because Noven Pharma specifically references the use of low density polyethylene as an occlusive material for ALA photodynamic therapy treatments, to the extent that PO contends Willey's use of Saran Wrap is insufficient to disclose low density polyethylene. Ground 5 is not cumulative with Ground 4 because it adds the Fauteck reference, which addresses elements in claim 3 that PO may contend are not inherently present. Ground 6 is not cumulative with Ground 4 because it adds the BLU-U Operating Manual reference, which addresses elements in claim 10 concerning the distance of the light source from the treatment area.

Grounds 1-6 are also not cumulative with the art of record, including the art of record expressly considered by the Examiner during prosecution of the '567 Patent. During prosecution, the Examiner determined that the prior art of record does not teach the claimed methods also including “removing the low density polyethylene barrier applied to the treatment area prior to applying light to the treatment area” and “wherein the treatment area is located on a hand or a forearm as claimed.” EX1002, 015. Grounds 1-6 address these and other purported deficiencies identified by the Examiner during prosecution.

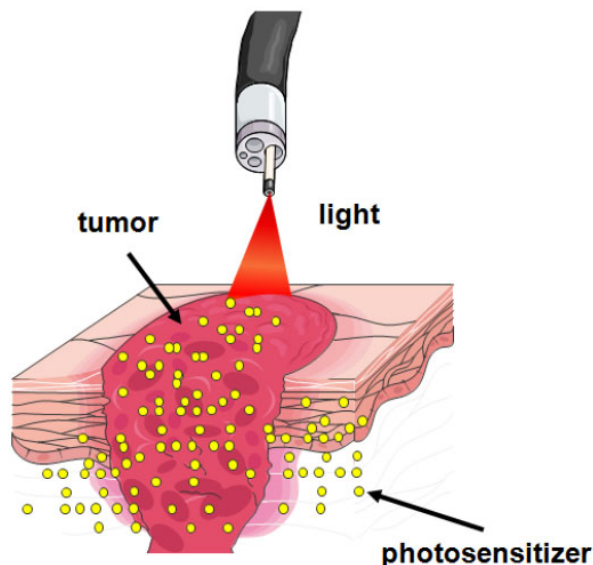
Moreover, each of the asserted references is analogous art that is usable in an obviousness combination. *Unwired Planet, LLC v. Google Inc.*, 841 F.3d 995, 1000 (Fed. Cir. 2016). Each reference is from the same field of endeavor as the '567 patent, *e.g.*, dermatological photodynamic therapy. EX1003, ¶¶33;¶90; *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). As analogous art, a person of ordinary skill in the art (POSITA) is presumed to have been aware of these references. *In re Nilssen*, 851 F.2d 1401, 1403 (Fed. Cir. 1988).

V. FIELD OF TECHNOLOGY

The '567 Patent states that “[t]he present disclosure relates generally to methods for photodynamic therapy.” EX1001, Abstract; Claims 1-10.

A. Photodynamic Therapy

Topical photodynamic therapy (PDT) involves the administration of a photosensitizing compound or a photosensitizer precursor compound to an area of the skin to be treated, followed by exposure to light. EX1003, ¶36; EX1015, 5. The photosensitizer is either absorbed directly into the skin when a photosensitizer compound is applied, or may be generated within the cells being treated when a photosensitizer precursor is applied. *Id.* Application of light to the photosensitized cells results in the generation of singlet oxygen and free radicals. EX1003, ¶36; EX1015, 5; EX1016, 52.



EX1022, 4141-42. Singlet oxygen and free radicals are highly reactive, and can result in damage or death to the cells that they are present within. EX1003, ¶37; EX1015, 5; EX1016, 52. Thus, if targeted to harmful cells like malignant cells,

photosensitizers and light (and the resulting generation of singlet oxygen and free radicals) can be used for treatment. EX1003, ¶39; EX1015, 5-6.

B. 5-Aminolevulinic Acid (ALA)

In the 1990s, scientists discovered that pre-cancerous and cancerous skin lesions could be treated and destroyed using a photosensitizer precursor known as 5-aminilevulinic acid (ALA), followed by administration of light. EX1003, ¶38; EX1016, 52-54; EX1018, 221. When ALA is applied to skin lesions, pre-malignant and malignant cells selectively generate and accumulate more protoporphyrin IX (PpIX)—a photosensitizer—than normal cells. EX1003, ¶39; EX1016, 52; EX1018, 221. Because ALA causes pre-malignant and malignant cells to selectively accumulate PpIX, and because PpIX causes cell death under certain wavelengths of light, ALA can be used to preferentially kill precancerous and cancerous cells while leaving normal skin cells relatively unharmed. EX1003, ¶¶39-40; EX1016, 52; EX1005, 1-2.

ALA is a non-proteinogenic amino acid that is present naturally in humans and used by the body in the heme biosynthesis pathway to help make hemoglobin—a protein found in blood. EX1003, ¶38; EX1005, 1-2; EX1015, 6; EX1016, 52-53. When ALA is topically applied to the skin, it is readily absorbed through abnormal skin cells, but not as readily through normal skin cells. EX1003, ¶39; EX1016, 52. Due to limited amounts of iron—a necessary substance for the generation of heme—

present in skin cells, the cells treated with ALA are unable to complete the final steps in the generation of heme. EX1003, ¶¶38-39; EX1016, 52. This results in the accumulation of PpIX—a potent photosensitizer—especially in the abnormal skin cells. EX1003, ¶39; EX1016, 52; EX1015, 6. As noted above, PpIX—especially at high concentrations—when exposed to certain light in the presence of oxygen generates reactive oxygen species that may result in the destruction of cells. EX1003, ¶¶39-40; EX1015, 5; EX1016, 52.

C. Photodynamic Therapy Light Sources

The light sources used for photodynamic therapy are generally those capable of emitting light within the absorption spectrum of the selected photosensitizer. For example, PpIX—the photosensitizer that results after application of ALA—has a fairly broad absorption spectrum with a number of absorption peaks spanning from around 353 nm to around 670 nm. EX1003, ¶41; EX1015, 6-7; EX1016, 53. As shown in the figure below, the largest absorption peak for PpIX occurs at 409 nm—which corresponds to blue light—and a smaller absorption peak occurs at 635 nm—which corresponds to red light. EX1003, ¶41-42; EX1016, 53.

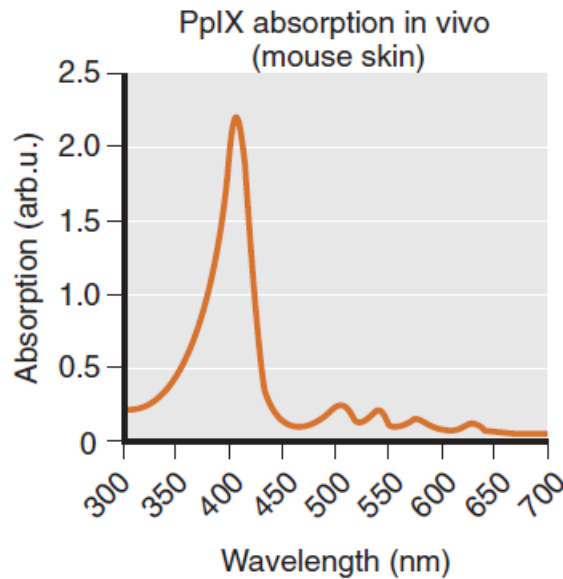
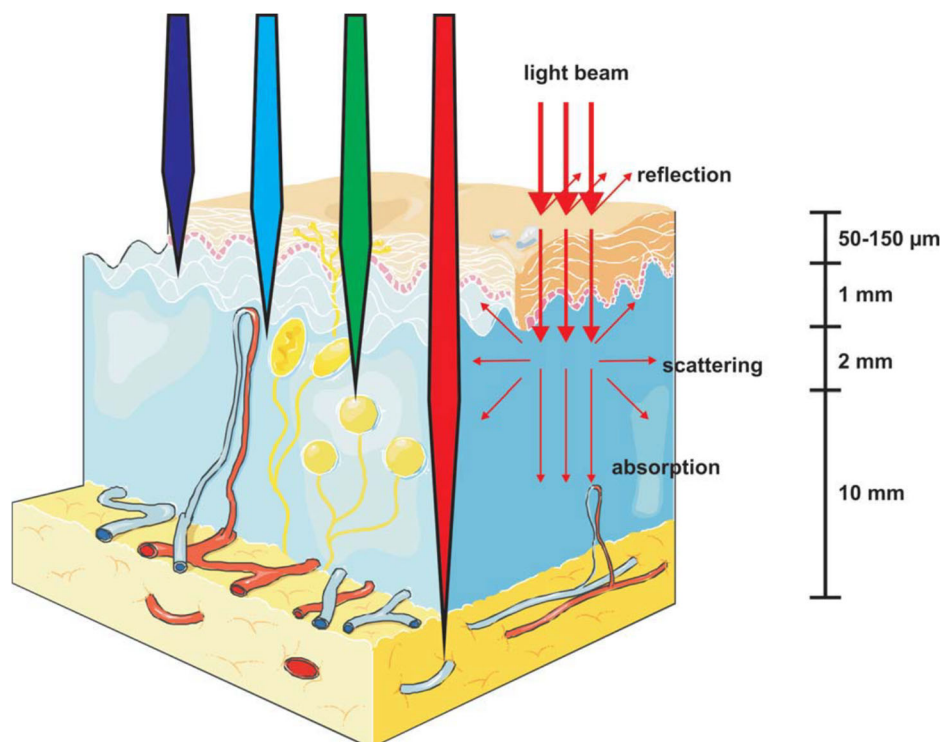


Figure 60-1 The absorption peaks for protoporphyrin IX (PpIX).
(Courtesy of Dusa Pharmaceuticals, Inc., Wilmington, Mass.)

EX1019, 397-398.

Given the absorbance of PpIX in the blue and red light wavelength ranges, blue and red light sources have been developed and traditionally utilized for topical ALA photodynamic therapy since at least the early 2000s. EX1003, ¶¶42-43; EX1015, 12-14. Further, because a lower energy dose is required for higher absorption peaks, some researchers and doctors have preferred to use blue light sources for photodynamic therapy. EX1003, ¶¶42-44; EX1016, 53. Because of its shorter wavelength, however, blue light may not penetrate as deeply into tissue as red light and is also known to lose its energy more rapidly upon penetration. EX1003, ¶45; EX1016, 53. For this reason, red light is considered more effective than blue light for the treatment of thicker lesions that require deeper light

penetration into the skin (*e.g.*, up to 8-mm deep). EX1003, ¶¶45-46; EX1016, 53-54. The ability of different wavelengths of light to penetrate tissue is shown in the figure below:



EX1003, ¶45; EX1023, 254-255.

The light dose provided by a light source is determined by factors such as the size of the light field, the light intensity, the distance between lamp and skin surface, the illumination time, and the light source used. EX1003, ¶48. So that the appropriate light dose can be administered, information regarding these factors is generally provided by commercial photodynamic therapy light source providers or can be measured using a detector. EX1003, ¶48; EX1012, 9-13. The standard light dose approved by the FDA for ALA-PDT with blue light sources like the BLU-U is 10

J/cm², and with red light sources like the BF-RhodoLED is around 37 J/cm² for. EX1003, ¶49; EX1011, 13; EX1010, 3.

D. Photodynamic Therapy Treatment of Actinic Keratosis

Keratinocytes are cells in the epidermis (top layer) of the skin that serve a protective, barrier function. EX1003, ¶50. Over time, as a result of sun exposure and other factors, keratinocytes may become precancerous—a condition known as actinic keratosis (“AK”). EX1003, ¶50; EX1015, 7. AKs generally present as discolored, scaly patches on portions of the skin commonly exposed to the sun, including the face, scalp, upper extremities (hands and forearms), lower extremities (legs and feet) and the chest. *Id.* at 7-8. If not treated, AKs have been found to develop into cancerous lesions called squamous cell carcinomas. EX1003, ¶50; EX1015, 7. Since early work performed by Kennedy et al. in 1990, which found that AKs could be successfully treated using ALA photodynamic therapy, numerous doctors and researchers have studied and used ALA photodynamic therapy to treat AKs on different portions of the human body. EX1003, ¶¶51-53; EX1015, 9-11; EX1016, 54.

In 1999, the FDA granted approval for an AK treatment protocol to PO. This approved protocol involved the use of a 20% ALA solution (marketed by PO as Levulan Kerastick®) to individual AKs for a period of 14 to 18 hours followed by a 16-minute, 40-second exposure to blue light for a total dose of 10 J/cm². EX1003,

¶52; EX1016, 53; EX1018, 222, 225. The FDA also approved the Blu-U® device, which emits blue light, for use with Levulan Kerastick®. EX1003, ¶52; EX1018, 222, 225. While the original FDA approved treatment time for Levulan Kerastick® specifies an incubation period of 14-18 hrs, a subsequent study found shortened incubation times of 1-3 hours to be sufficient. EX1003, ¶52; EX1018, 222. This study, along with DUSA's apparent off-label promotion of the shorter 1-3 hour incubation time and convenience, has resulted in substantial use of the shorter incubation time by practitioners over the FDA-approved longer incubation time. EX1037, 1-2; EX1027, 808; EX1018, 222.

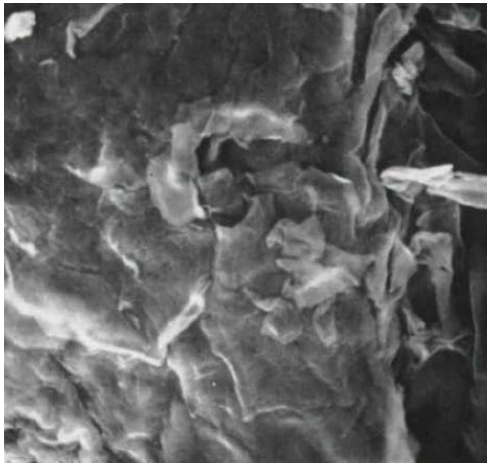
Petitioner's ALA product—Ameluz®—was approved for marketing in Europe in 2011 and in the United States in 2016. EX1003, ¶53. Ameluz® is marketed in the U.S. as a 10% ALA nanoemulsion gel. Ameluz® uses a red light-emitting diode (LED) light system with a compact LED array called BF-RhodoLED® for activation of the PpIX photosensitizer. EX1003, ¶53; EX1010, 1. The treatment protocol for Ameluz® approved by the FDA in 2016 involves: (1) applying Ameluz® ALA gel to the treatment area; (2) allowing the gel to dry; (3) occluding (*e.g.*, covering) the area where the gel is applied with a light-blocking, occlusive dressing; (4) after 3 hours of occlusion, removing the occlusive dressing and wiping off any remaining gel; and (5) illuminating of the treatment area with the BF-RhodoLED® red light source for around 10 minutes for a light dose of 37 J/cm²

with the lamp head positioned 5-8 cm from the skin's surface. EX1003, ¶53; EX1010, 3-4.

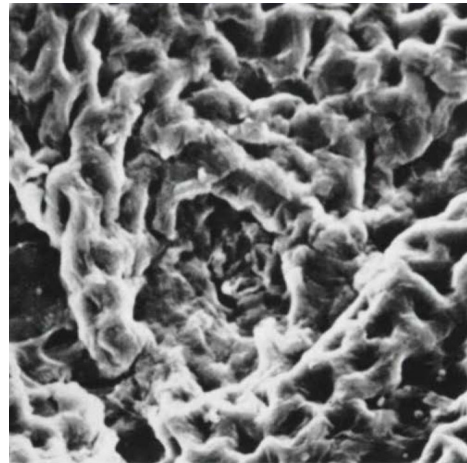
E. Use of Occlusion to Minimize Transepidermal Water Loss and Enhance Penetration of ALA Was Well-Known in the Art

Since at least the 1960s it has been known that occlusion, such as covering, of the skin with plastic increases the percutaneous absorption of topically applied agents. EX1003, ¶54; EX1020, 27. Studies have shown that by occluding with plastic films, absorption of some topical agents can be increased by almost 100 fold. EX1003, ¶54; EX1020, 27. Studies have further shown that the increased absorption is mostly due to improved hydration of the outermost layer of the skin, which is referred to as the “stratum corneum”. EX1003, ¶54; EX1020, 27. When an occlusive cover is applied on the skin, the transepidermal water loss (“TEWL”)¹ from the skin is inhibited and the skin becomes hydrated. EX1003, ¶¶54-55; EX1007, 25. This is reflected in the figures below showing micrographs comparing non-occluded skin (left) with skin occluded using a plastic film (right).

¹ Transepidermal water loss (TEWL) occurs when water passes through the layers of the epidermis (upper layer of skin) and evaporates from the skin's surface (stratum corneum). EX1003, ¶55; EX1007, 25.



Non-occluded skin



Skin occluded with plastic
(polyethylene) film

EX1003, ¶55; EX1020, 29-31. As demonstrated above, occlusion with plastic film—in this case polyethylene film—limits TEWL, resulting in the retention of water and the swelling of the fibrous structure of the stratum corneum. EX1003, ¶¶55-57; EX1020, 31. As a result, water soluble substances—like ALA—applied under the film experience an increased rate of transport into the occluded skin compared to non-occluded skin. *Id.*; *see also* EX1006, 205 (“Occlusion is known to reduce transepidermal water loss ... generally enhancing drug penetration, especially for ... ALA.”); EX1027, 808 (“[O]cclusion has been used to increase penetration ... with plastic wrap ... after the ALA has been applied.”); EX1007, 26-27 (Saran Wrap polyethylene film minimizes TEWL); EX1003, ¶56. Consequently, practitioners in the field have long used LDPE films like Saran Wrap to minimize transepidermal water loss and enhance penetration of ALA into tissue for photodynamic therapy. EX1003, ¶¶57-58; EX1013, 1095; EX1015, 22; EX1005, 9.

VI. THE '567 PATENT

A. Claims and Specification of the '567 Patent

The '567 Patent was filed on January 12, 2018 as U.S. Patent Application No. 15/869,164, issued on July 23, 2019 and is entitled “Methods for Photodynamic Therapy”. EX1001, Cover. In order to enhance penetration of ALA, the claims specify that after ALA is applied, the treatment area is covered with an LDPE barrier—*e.g.*, plastic food storage wraps like Saran Wrap and Glad Press'n Seal, as described in Table 1 of the '567 Patent—to minimize TEWL. *Id.* at Table 1. In experimental results disclosed in the '567 Patent, PO determined that plastic wraps made from LDPE when worn for 3 hours resulted in lower evaporative water loss rates than polyurethane and polyvinylidene chloride films. EX1001, Figures 5-13. On this basis, PO concluded that LDPE-based food storage wraps were superior to polyurethane and polyvinylidene chloride films at minimizing TEWL. EX1001, Col. 9:55-60. As a result, all of the claims of the '567 Patent specify covering the treatment site using LDPE in order to minimize TEWL. EX1001, Claims 1-10.

But occlusion with LDPE to minimize TEWL and enhance ALA penetration into the skin was already known in the art years before the '567 Patent's 2018 priority date. EX1003, ¶¶54-58. For example, Berardesca demonstrated in 1992 that LDPE films were superior to polyurethane films at minimizing TEWL after removal. EX1003, ¶56; EX1007, 25-27. Likewise, Sakamoto taught 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.” EX1003, ¶57; EX1006, 205. Further, Ozog described in 2016 that “occlusion has been used to increase penetration ... with plastic wrap ... after the ALA has been applied.” EX1003, ¶57; EX1027, 808.

As a result, prior to the ’567 Patent, many practitioners in the field were teaching and publishing information on their research and practice of performing occlusion with LDPE films to minimize TEWL and enhance penetration of ALA into the treatment area for photodynamic therapy. EX1003, ¶¶57-58, 70-72. For example, Palm teaches to “occlude the treated area with *Glad Press ‘N Seal®*”—a LDPE film. EX1015, 22 (emphasis added). Similarly, Willey teaches that “Topical 20% 5-ALA ... was applied ... and occluded with *plastic wrap (Saran; SC Johnson)*”—also an LDPE film. EX1013, 1095 (emphasis added). Thus, the use of LDPE films to minimize TEWL and enhance penetration of ALA into the area to be treated using photodynamic therapy was not new as of January 2018. EX1003, ¶¶57-58, 70-72.

The dependent claims do not meaningfully narrow the independent claims (claims 1, 4, and 8). EX1003, ¶¶73-78. Claims 2, 5, and 9 specify the light dose to be used for blue light and red light photodynamic therapy and/or specify that the LDPE film is removed no later than 3 hours. EX1001, Claims 2, 5, and 9. But the

claimed light doses, ALA incubation periods under occlusion, and removal of the occlusive covering after incubation were also known in the prior art. EX1003, ¶¶74, 77; EX1013, 1095; EX1005, 11:29-12:18; 15:7-21; EX1027, 811; EX1014, 246; EX1010, 3. Claims 6 and 7 specify that the treatment site is on the dorsal surface of the hand and forearm—two areas known to develop actinic keratosis due to exposure to the sun, which were long treated using ALA photodynamic therapy. EX1003, ¶75; EX1015, 7-8, 10-11; EX1017, 1061-1062; EX1013, 1096-1098 (depicting treatment of AKs on hands and forearms). Claim 3 specifies that the plasma concentration of ALA after application does not exceed 110 ng/ml. EX1001, Claim 3. Yet, it was already known at the time of filing that the endogenous concentration of ALA is around 11 to 20 ng/ml and that topical application of ALA results in small (often unmeasurable) increases in ALA plasma concentration. EX1003, ¶76; EX1008, 57-58, Tables 5-7; EX1010, 9. Finally, claim 10 specifies that the blue light source is positioned between 2-4 inches from the treatment site. This positioning of a blue light source, however, was already disclosed by DUSA over 10 years earlier in its BLU-U light source operating manual. EX1003, ¶78; EX1012, 9-11. As a result, none of the dependent claims lend novelty to the independent claims of the '567 Patent.

B. Prosecution History of the '567 Patent

PO filed the '164 Application on January 12, 2018. Concurrent with the application, PO submitted a Track One request for prioritized examination under 37 CFR §1.102(e)(1) as an original non-provisional application. EX1002, 300. PO's Track One request for prioritized examination was granted on March 20, 2018. EX1002, 223.

On August 8, 2018, the Examiner issued a non-final rejection, rejecting certain of the then-pending claims as anticipated by Foguet Roca, U.S. Application Publication No. 2009/0324727 and Trigiante, U.S. Application Publication No. 2011/0053965. EX1002, 176,179-181. The Examiner also issued an indefiniteness rejection based on PO's use of the term "low density polyethylene." EX1002, 178-179.

In an attempt to overcome the Examiner's anticipation rejections, PO canceled certain dependent claims and amended select independent claims to add in elements from the cancelled dependent claims—including claim elements specifying the removal of the LDPE barrier prior to the application of light. EX1002, 099,101-103.

PO also sought to overcome the Examiner's indefiniteness rejection by citing to documents indicating that low density polyethylene "was the first type of polyethylene that was commercially produced" and that it was "developed in 1933." EX1002, 098. PO further told the Examiner that "'low density polyethylene' is a

well-known term of art [that was] developed ... over 80 years ago” and noted that “the specification identifies trade names for various brands of low density polyethylene products in Tables 1 and 2.” *Id.*

The Examiner issued a second office action on February, 25, 2019, allowing all pending claims but one, which was rejected due to a drafting defect. EX1002, 042-044. The Examiner then issued a notice of allowance on June 3, 2019. EX1002, 015. The ’567 Patent ultimately issued on July 23, 2019. EX1001, Cover.

C. Claim Construction

The Challenged Claims should be construed “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b), including construing the claim in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. §42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005). For terms not explicitly construed below, Petitioner has applied their plain meaning.

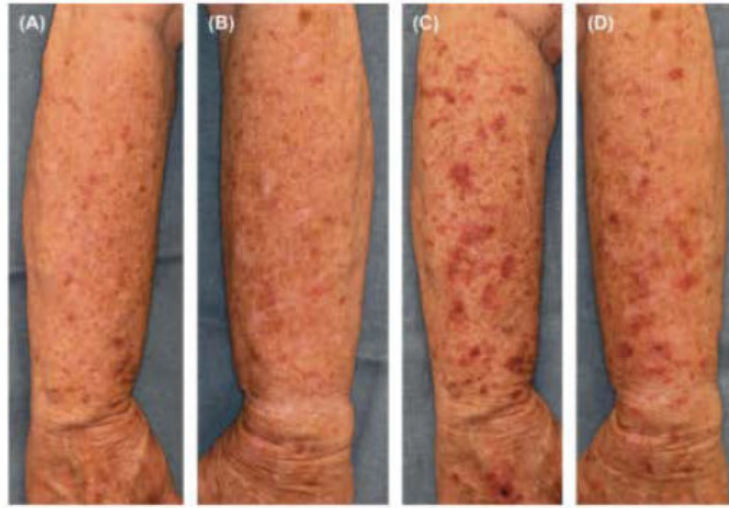
1. “dorsal surface of the hand” (claim 6) / “dorsal surface of the forearm” (claim 7)

The terms “dorsal surface of the hand” and “dorsal surface of the forearm” appear in claims 6 and 7 respectively. The proper construction under *Phillips* of “dorsal surface of a hand” is “the top portion of the hand between the wrist and the

base of the fingers.” The proper construction under *Phillips* of “dorsal surface of the forearm” is “the top portion of the forearm between the elbow and the wrist.”

These constructions are consistent with the specification, which states that “the dorsal surface of the hands and / or the forearm” is the “area between the elbow and the base of the fingers”. EX1001, 14:30-34. They are also consistent with the specification’s reference to “the dorsal hands/forearms” as “the extensor surface of both distal upper extremities”—*i.e.*, the top surface of the hands and forearms. EX1001, 13:35-38.

Petitioner’s proposed constructions are consistent with the specification, and they also comport with the understanding of a POSITA. EX1003, ¶¶87-89. This is reflected, for example, in contemporaneous publications such as Willey, which describes an ALA photodynamic treatment area on “**the forearms and dorsal hands** of 24 subjects” EX1013, 1096-1097 (emphasis added). 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.



EX1013, 1096, 1098, Figures 1 and 2.

VII. REASONS FOR THE RELIEF REQUESTED UNDER 37 C.F.R. §§ 42.22(A)(2) AND 42.104(B)(4)

A. The Scope and Content of the Prior Art

1. The Prior Art Teaches that Occlusive Barriers Like LDPE Minimize Transepidermal Water Loss

Prior to January 12, 2018, it was known that occlusion of the skin with plastics—like LDPE—minimize transepidermal water loss (TEWL) and increase the percutaneous absorption of topically applied agents. *See supra*, Part V.E. EX1003, ¶¶54-57; EX1020, 27, 29-31. This was known to occur because minimization of TEWL results in the retention of water and the swelling of the outer layer of the skin (epidermal layer). EX1003, ¶¶55; EX1020, 31; EX1007, 25. As a result, water soluble compounds—like ALA—applied under the occlusive barrier experience an increased rate of transport into the occluded skin compared to non-occluded skin. EX1003, ¶57; EX1006, 205; EX1020, 31.

Prior to January 12, 2018, it was also known that different occlusive materials—such as different types of plastic—vary in occlusivity and hence, minimize TEWL to different degrees. EX1003, ¶56. For example, acknowledging that occlusive films enhance the skin penetration of topically applied compounds, Berardesca, studied several occlusive coverings commonly used in dermatology at the time, and found Saran Wrap polyethylene films to be superior at minimizing TEWL compared to Tegaderm polyurethane films. EX1007, 26-28. Hence, by January 12, 2018, low density polyethylene (like Saran Wrap) was known to minimize transepidermal water loss and enhance penetration of topical agents, and to do so better than certain other available occlusive materials tested in the '567 patent, such as the Tegaderm polyurethane films. EX1003, ¶¶56-58; EX1006, 205; EX1027, 808; EX1001, Table 1; EX1007, 26-28.

Consequently, by January 12, 2018, many practitioners in the field were teaching and publishing information on their practice of performing occlusion with LDPE films to minimize transepidermal water loss and enhance penetration of ALA into tissue for photodynamic therapy. EX1003, ¶¶57-58. Willey teaches, for example, that “Topical 20% 5-ALA ... was applied to the entire forearm skin and occluded with *plastic wrap (Saran; SC Johnson)*”—an LDPE film. EX1013, 1095 (emphasis added). Similarly, Palm teaches photodynamic therapy using “occlu[sion

of] the treated area with *Glad Press ‘N Seal®*”—also an LDPE film. EX1015, 22 (emphasis added).

2. The Prior Art Teaches Removal of Occlusive Coverings for Photodynamic Therapy Prior to Illumination

Prior to January 12, 2018, in the context of photodynamic therapy it was known that when occlusive barriers are used for incubation of ALA, they should be removed at the end of the incubation period prior to illumination with light. EX1003, ¶¶77, 110-111. For example, Calderhead describes that the occlusive cling film is removed at the end of incubation and excess ALA is wiped off prior to the application of light to the treatment area. EX1014, 246 (“**At the end of incubation, the occlusive dressing is removed and any excess 5-ALA wiped off.** Activation ... is then achieved with 633 nm light ...”) (emphasis added). Similarly, Sotiriou specifies that “[i]mmmediately after removal of the [occlusive] dressing and the cream remnants, [the] treatment area was illuminated.” EX1017, 1062. Likewise, the Ameluz® prescribing information teaches that following 3 hours of occlusion, “remove the dressing and wipe off any remaining gel.” EX1010, 3. Indeed, it was common knowledge prior to January 12, 2018 that the “incubation period” specifies the time during which the treatment site with ALA is occluded and that the incubation is stopped by removing the occlusive barrier and wiping away the excess ALA. EX1003, ¶¶109-111. As a result, prior to January 12, 2018, in the context of

photodynamic therapy a POSITA would have understood that occlusive barriers used for incubation of ALA should be removed following the specified incubation period prior to illumination with light. EX1003, ¶¶77, 108-111.

3. The Prior Art Teaches PDT Treatment using LDPE Occlusive Barriers on the Hands and Forearms

It was also known, prior to January 12, 2018, that ALA photodynamic therapy with occlusive coverings could be used to treat lesions such as AKs on the hands and forearms. EX1003, ¶¶58, 75, 140, 243; EX1015, 7-8, 10-11; EX1017, 1061-1062; EX1013, 1096-1098 (depicting treatment of AKs on hands and forearms). Indeed, Sotiriou studied the efficacy of ALA photodynamic therapy (“ALA-PDT”) with occlusion using a red light illumination source on patients with AKs on the dorsal surfaces of the hands and forearms. EX1017, 1061-1062. Likewise, Willey describes the treatment of AK on “the forearms and dorsal hands of 24 subjects” using occlusion with Saran wrap (an LDPE barrier) and ALA photodynamic therapy with a blue light source. EX1013, 1095-1098, Figures 1 and 2; *see also*, EX1005, 12:19-21; 15:2-6. Accordingly, prior to January 12, 2018, it was known that the penetration of topical ALA on the hands and forearms could be enhanced by using an LDPE occlusive barrier. EX1003, ¶¶58, 75, 140, 244.

B. Level of Ordinary Skill in the Art

A POSITA relevant to the subject matter disclosed in the '567 Patent and the earlier applications in its family would have had at least a Ph.D., M.D. or D.O., with a 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. EX1003, ¶30-31. For purposes of this Petition, the anticipation and obviousness analysis is performed from the perspective of a POSITA as of the '567 Patent's January 12, 2018 filing date. EX1003, ¶31.

C. Ground 1 – Claims 1-4 and 6-10 Are Unpatentable as Anticipated by Willey

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

To the extent that the preamble of claim 1 is determined to be a limitation on the claims, Willey teaches a method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy. For example, Willey teaches using occlusion with Saran plastic wrap after application of ALA to the treatment area to improve penetration of ALA. *See* EX1013, 1095. (“Treatment Protocol ... **Topical 20% 5-ALA ... was applied ... and occluded with plastic wrap** (Saran; SC Johnson).”) (emphasis added). A POSITA would recognize that occlusion with plastic films like Saran wrap enhances penetration of topically applied ALA. EX1003, ¶96. This background knowledge is

reflected in various prior art publications, including a publication from some of the same authors of Willey.² Sakamoto, for example, teaches that it was known, in 2010, that occlusion (*e.g.*, with Saran plastic wrap) enhances penetration of ALA into tissue. EX1006, 205; EX1027, 808 (“[O]cclusion has been used to increase penetration [of ALA] ... with plastic wrap.”).

2. *Claim 1a: “topically applying ALA to a treatment area to be treated with photodynamic therapy”*

Willey describes topically applying ALA to the area to be treated with photodynamic therapy. EX1003, ¶99. For example, Willey describes 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 (1.5 mL) was used to cover each distal extremity.” EX1013, 1095 (emphasis added).

3. *Claim 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”*

Willey teaches occluding the treatment area after the application of ALA with Saran plastic wrap from SC Johnson. EX1003, ¶¶102-106; EX1013, 1095 (**Topical 20% 5-ALA ... was applied to the entire forearm skin and occluded with plastic**

² Both Willey and Sakamoto were co-authored by R. Rox Anderson, MD and Sakamoto, Fernanda H. MD, PhD.

wrap (Saran; SC Johnson)). As acknowledged by PO, SC Johnson Saran plastic wrap is a low density polyethylene (“LDPE”) barrier. EX1001, Table 1 (identifying SaranTM Premium Wrap from SC Johnson as LDPE)³.

A POSITA would recognize that occlusion with Saran plastic wrap—as is taught by Willey—minimizes TEWL from the area being treated.⁴ EX1003, ¶¶54-57,105. As discussed above, Sakamoto recognizes that “[o]cclusion is known to **reduce transepidermal water loss.**” EX1006, 205. And Berardesca also demonstrates that occlusive barriers, such as polyethylene films, minimize TEWL. EX1007, 25-26, Figure 2; EX1027, 808 (“[O]cclusion has been used to increase penetration ... after the ALA has been applied.”). Indeed, minimizing TEWL to enhance penetration is generally why occlusion is utilized with ALA photodynamic therapy. EX1003, ¶¶57-58,105.

³ See also EX1031, 025.

⁴ Although demonstrated here that it was known in the art that occlusion with LDPE and other materials minimizes transepidermal loss, clauses describing an intended result are generally non-limiting. *Bristol-Myers Squibb Co v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001); *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1378 (Fed. Cir. 2005).

4. *Claim 1c: “removing the low density polyethylene barrier within 3 hours and then applying light to the treatment area.”*

Willey teaches, following a 1 hour incubation period, application of blue light to the treatment area and cooling of the treatment area using a portable fan:

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.”

EX1013, 1095-1096.

A POSITA would recognize, from the teachings of Willey, that the Saran wrap must be removed at the end of the incubation period prior to the application of light. EX1003, ¶¶108-111; *see also Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (“A reference can anticipate a claim even if it does not expressly spell out all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would at once envisage the claimed arrangement or combination.”) Specifically, a POSITA would understand the term “incubation period” as used in Willey to mean the time during which the treatment area is in contact with ALA and occluded by Saran plastic wrap. EX1003, ¶109. At the end of the incubation period, a POSITA would understand that the plastic wrap and the excess ALA must be removed to start the next phase of treatment (*i.e.*, applying light). EX1003, ¶¶110-111. This understanding is confirmed by other ALA-PDT literature, such as Calderhead and the Levulan Label. *See* EX1014, 246

(“At the end of incubation, **the occlusive dressing is removed and any excess 5-ALA wiped off.**”); EX1011, 13 (specifying that the treated area should be “gently rinsed with water and patted dry” at the end of the incubation period prior to the application of light which would require removal of an LDPE barrier).

Other teachings in Willey would also indicate to a POSITA that the Saran wrap should be removed prior to the application of light. EX1003, ¶108. Willey states that “[d]uring light irradiation, the treated areas were cooled by a small portable fan ... for comfort.” EX1013, 1095. A POSITA would “at once envisage” that the Saran Wrap is removed prior to this phase of treatment because the intended cooling effect of the fan would be hindered if the treatment site was occluded with Saran Wrap. EX1003, ¶108; *Kennametal*, 780 F.3d at 1381.

5. *Claim 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.”*

As discussed above for Ground 1, claim 1c, Willey teaches using an ALA incubation period of 1 hour with occlusion of the treated area using Saran plastic wrap which a POSITA would understand is removed at the end of the incubation period based on the teachings of Willey. *See* Ground 1, claim 1c, *supra*; EX1013, 1095-1096. Willey further teaches that the light source applied to the treatment area after incubation is blue light from a BLU-U illuminator for a 10 J/cm² dose. EX1013,

1095 (“After 1 hour, both of the treated sites (heated and control) were irradiated with 10 J/cm² blue light (BLU-U...”)). EX1003, ¶116-117.

6. *Claim 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.”*

As discussed above for Ground 1, claims 1a and 1c, Willey teaches topical application of one stick (1.5 mL) of 20% ALA (Levulan®) to each distal extremity (e.g., forearm and hand for a total of two extremities) for 1 hour under occlusion with a Saran wrap LDPE film, followed by application of blue light to the treatment area. *See* Ground 1, claims 1a and 1c, *supra*; EX1013, 1095.

The amount of 20% ALA (Levulan®) applied to subjects in Willey—*i.e.*, one Levulan® stick to each upper extremity for a total of up to two sticks—mirrors the amount of 20% ALA applied in the ’567 Patent. Specifically, the ’567 Patent states that “up to two topical solution compositions each containing about 354 mg ALA” were applied to the upper extremities and that “topical dosing was observed to result in a mean plasma concentration (*C_{max}*) value of ALA less than about 110 ng/mL.” EX1001, 13:45-58; 13:30-33; 13:59-66; 14:6-13. Likewise, Willey describes the application of up to two sticks of Levulan® which contain 354 mg of ALA each to the distal extremities. EX1013, 1095; EX1011, 14. Based on the ’567 Patent’s own disclosure, given that both the ’567 Patent and Willey describe administering the same amount of ALA to the upper extremities of patients, the subjects in Willey

necessarily would have had maximum plasma concentrations of ALA following application of the ALA consistent with the disclosure in the '567 Patent—*i.e.*, less than about 110 ng/mL as disclosed. EX1003, ¶¶121-125; *Alcon Research, Ltd. v. Apotex Inc.*, 687 F.3d 1362, 1369 (Fed. Cir. 2012) (analyzing inherency based on the disclosure of the “patent itself”). As a result, claim 3 is inherently present in teachings of Willey. *See In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (finding the pharmacokinetic features of a compound to be an inherent property that “adds nothing of patentable consequence”); *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (“The initial blood serum concentration resulting from administering a PPI dosage is an inherent property of the formulation”).

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

To the extent that the preamble is determined to be a limitation on the claim, this element is satisfied by the teachings of Willey for the same reasons described above for Ground 1, claim 1. *See*, Ground 1, claim 1 preamble discussion *supra*. EX1013, 1095; EX1006, 205.

8. *Claim 4a: “topically applying ALA to a treatment area to be treated with photodynamic therapy; and”*

Claim element 4a is taught by Willey for the same reasons described above for Ground 1, claim 1a. *See* Ground 1, claim 1a, *supra*; EX1013, 1095.

9. *Claim 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,”*

Claim element 4b is taught by Willey for the same reasons described above for Ground 1, claim 1b. *See* Ground 1, claim 1b, *supra*; EX1013, 1095; EX1006, 205.

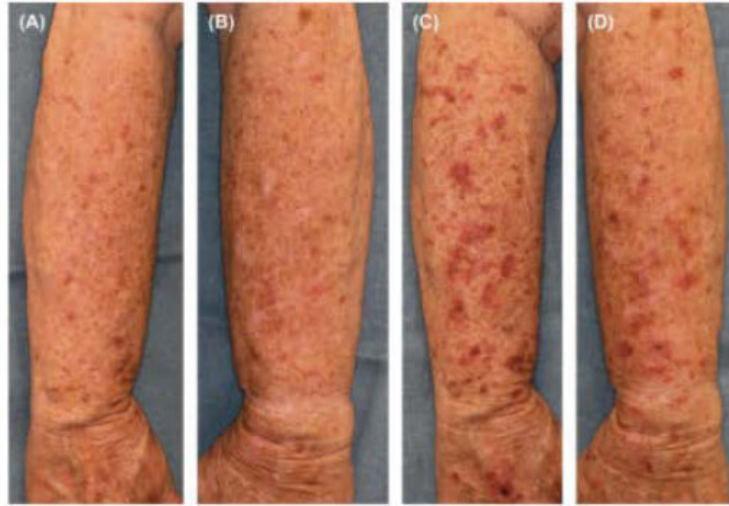
10. *Claim 4c: “wherein the treatment area is located on a hand or a forearm.”*

Willey further teaches a treatment area located on a hand or a forearm. Specifically, Willey describes the treatment of actinic keratosis lesions on “*the forearms and dorsal hands* of 24 subjects” [EX1013, 1096-1097] and states that “[t]opical 20% 5-ALA ... was applied to **the entire forearm skin**”. EX1013, 1095, Figures 1 and 2.

11. *Claim 6: “The method as set forth in claim 4, wherein the treatment area is a dorsal surface of the hand.” / Claim 7: “The method as set forth in claim 4, wherein the treatment area is a dorsal surface of the forearm.”*

Willey also teaches a treatment area located on a dorsal surface of the hand and forearm consistent with Petitioner’s proposed claim construction. EX1003, ¶¶137-141. Willey describes the treatment area as on “**the forearms and dorsal hands** of 24 subjects” [EX1013, 1096-1097] and states that “[t]opical 20% 5-ALA ... was applied to **the entire forearm skin**”. EX1013, 1095. Willey also provides

photographs showing the treatment area on the dorsal surface of the hand and forearm at baseline and at one week following treatment:



EX1013, 1096, 1098, Figures 1 and 2.

- 12.** *Claim 8pre: “A method of using 5-aminolevulinic acid (ALA) and a low density polyethylene barrier, comprising:”*

To the extent that the preamble of claim 8 is determined to be a limitation, Willey teaches a method of using 5-aminolevulinic acid (ALA) and an LDPE barrier. Specifically, Willey teaches using occlusion with Saran plastic wrap (LDPE) after application of ALA to the entire forearm skin. EX1013, 1095. (“Topical 20% 5-ALA ... was applied ... and occluded with plastic wrap (Saran; SC Johnson).”). As noted previously, Saran plastic wrap is an LDPE barrier. EX1003, ¶¶103-104;143.

- 13.** *Claim 8a: “contacting a treatment site with a composition comprising the ALA so as to wet the treatment site;”*

Consistent with the '567 patent disclosure, Willey describes wetting the treatment site by contacting it with a 20% ALA solution. EX1003, ¶¶146-147. For example, Willey describes 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 (1.5 mL) was used to cover each distal extremity.” EX1013, 1095 (emphasis added). A POSITA would appreciate that Levulan Kerastick® is applied as a liquid 20% ALA composition to the treatment area using the Kerastick® applicator which would wet the skin when applied. EX1003, ¶147; EX1011, 13 (“Enough [Levulan] solution should be applied to uniformly wet the lesion surface.”).

14. *Claim 8b: “following wetting of the treatment site, covering the wetted treatment site with the low density polyethylene barrier;”*

After wetting the treatment site with a 20% ALA solution, Willey describes covering the wetted treatment site with low density polyethylene Saran plastic wrap. EX1013, 1095. (“Topical 20% 5-ALA ... was applied to the entire forearm skin **and occluded with plastic wrap (Saran; SC Johnson).**”) (emphasis added); EX1003, ¶¶150-151.

15. *Claim 8c: “removing the low density polyethylene barrier so as to expose the treatment site; and”*

Although Willey does not expressly describe removal of the low density polyethylene Saran plastic wrap, a POSITA would recognize from the teachings of Willey that the Saran wrap is removed at the end of the specified 1 hour incubation period prior to the application of light. *See* Ground 1, Claim 1c; EX1003, ¶153-155; *see also* EX1014, 246; EX1010, 3; EX1017, 1061.

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

As discussed above for Ground 1, claim 1c, Willey describes that the light used to irradiate the treatment area after incubation is blue light from a BLU-U light source for a 10 J/cm² dose. EX1013, 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).

17. *Claim 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.”*

Following a 1 hour incubation period, Willey teaches application of light to the treatment area (*i.e.*, blue light from the BLU-U light source) and cooling of the treatment area using a small portable fan. EX1013, 1095. As discussed above, a POSITA would understand from the teachings of Willey that a 1 hour incubation period means that the low density polyethylene Saran wrap barrier is removed

around 1 hour after the treatment site is covered. EX1003, ¶¶153-155; *see* discussion at Ground 1, claims 1c, 8c.

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

Willey describes that the blue light source—*i.e.*, the BLU-U illuminator—was positioned between two to four inches from the treatment site. EX1013, 1095 (“**[B]oth of the treated sites (heated and control) were irradiated ... with the light positioned 2 to 4 inches from the skin surface.**”) (emphasis added); EX1003, ¶¶168-169.

D. Ground 2 – Claim 3 Is Unpatentable as Obvious Over Willey Combined with Ameluz

1. *Claim 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.”*

As discussed above for Ground 1, Willey anticipates claims 1 and 3 of the Challenged Patent. To the extent that PO argues that Willey does not inherently disclose claim 3, it is obvious based on the teachings of Willey combined with the Ameluz® prescribing information, which teaches an ALA maximum plasma concentration following application of 200 mg ALA of 47.35 ng/mL (*i.e.*, less than 110 ng/mL). EX1003, ¶¶179-182; EX1010, 9; EX1013, 1095; Ground 1, claim 3, *supra*; *see also*, *In re Kao*, 639 F.3d at 1070; *Santarus*, 694 F.3d at 1354 (“[A]n

obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations”).

As noted above, Willey describes the topical application of an ALA composition—*i.e.*, up to 2 sticks of Levulan—for photodynamic therapy treatment. EX1013, 1095. The Ameluz® prescribing information publication describes the pharmacokinetic properties of Ameluz® 10% ALA gel, including the plasma concentrations of ALA both before and after application. EX1010, 9. In the underlying Ameluz experiment, 2 g of Ameluz® gel having 10 % ALA, for a total of 200 mg, was applied under occlusion to 12 patients over a 20 cm² treatment area for 3 hours. EX1010, 9. The mean baseline plasma concentration of ALA (before topical ALA was applied) was determined to be 20.16 ± 16.53 ng/mL and the mean maximum concentration (C_{max}) for baseline corrected aminolevulinic acid (after topical application of ALA)⁵ was determined to be 27.19 ± 20.02 ng/mL. EX1010, 9.

⁵ A “baseline corrected” plasma concentration of ALA represents the amount of ALA in the blood plasma due to topical application of the ALA drug. Baseline corrected values are obtained by subtracting the baseline concentration of ALA from the ALA plasma concentration determined after the ALA has been topically applied. EX1003, ¶173, n.2.

A POSITA, evaluating the application of less ALA for PDT treatment of fewer or smaller lesions, would be motivated to combine Willey's disclosure with that from the Ameluz® prescribing information which demonstrates that less topical ALA (*e.g.*, up to 200 mg) can be safely and effectively applied under occlusion for a maximum plasma concentration of ALA around 47.35 ng/mL (*i.e.*, 20.16+27.19). EX1003, ¶¶179-180. Both references concern the use of topically applied ALA compositions for photodynamic therapy with occlusion, and the Ameluz® prescribing information indicates that application of 200 mg is safe and results in a maximum plasma concentration of around 47.35 ng/mL. EX1003, ¶180; EX1010, 9. Thus, a POSITA seeking to evaluate the use of less ALA (Levulan) than the amount used in Willey with occlusion would consult the Ameluz® prescribing information, which describes the pharmacokinetics of a similar FDA approved topical ALA composition applied at an amount of 200 mg of ALA with occlusion to achieve a maximum plasma concentration of ALA around 47.35 ng/mL (*i.e.*, less than 110 ng/m). EX1003, ¶180; EX1010, 9.

While Willey uses up to two sticks of Levulan or 708 mg of ALA, a POSITA would be motivated to apply less ALA than that used in Willey—such as the 200 mg of ALA tested in the Ameluz® prescribing information—to treat fewer or smaller lesions. EX1003, ¶180. Indeed, a POSITA would understand that lower amounts of ALA would be applied to treat fewer lesions over smaller areas of the

skin and that such reductions in the amount of ALA applied and the size of the treatment area would result in decreases to the maximum plasma concentration of ALA. *Id.*; EX1011, 13 (stating that “[e]nough solution should be applied to uniformly wet the lesion surface”); EX1010, 3 (indicating that a “sufficient amount of gel” should be used “to cover the single lesions or if multiple lesions, the entire area.”). That is, based on the pharmacokinetic information provided in the Ameluz® prescribing information, a POSITA could readily change the amount of ALA applied to given areas of the skin to ensure that the maximum plasma concentration of ALA is around or less than that specified in the Ameluz® prescribing information (around 47.35 ng/mL) which is less than 110 ng/mL. EX1003, ¶180.

A POSITA would also have a reasonable expectation of success in combining Willey with the Ameluz® prescribing information. EX1003, ¶181. Based on the ALA mean maximum plasma concentration results reported in the Ameluz® prescribing information—around 47.35 ng/mL—a POSITA 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, such as when treating fewer or smaller surface areas of lesions (at or below 20 cm²). EX1003, ¶181; EX1010, 9; EX1035, 317 (finding maximum plasma concentration of ALA to be below 0.1 mg/L (*i.e.*, 100 ng/mL)).

E. Ground 3 – Claim 5 Is Unpatentable as Obvious Over Willey Combined with Sotiriou

1. *Claim 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.”*

As discussed above for Ground 1, Willey anticipates claim 4 of the Challenged Patent. Although Willey does not teach using a red light source for a 10 to 75 J/cm² light dose, as specified in claim 5, claim 5 is obvious over the teachings of Willey combined with Sotiriou, where the latter teaches using a red light source for a 75 J/cm² light dose to treat AKs on the hands and forearms. EX1003, ¶190-196; EX1017, 1062.

Sotiriou studied the efficacy of ALA photodynamic therapy (“ALA-PDT”) using red light compared with that of 5% imiquimod cream in patients with actinic keratosis on the dorsal surfaces of the hands and forearms. EX1017, 1061. For ALA-PDT, Sotiriou describes: (1) the application of 20% ALA to AK lesions on the dorsal surface of the hands and forearms under occlusion for 4 hours; (2) removal of the occlusive dressing and cream remnants; and (3) illumination of the treatment area with red light for a light dose of 75 J/cm². EX1017, 1062. Sotiriou found that ALA-PDT provided a better therapeutic response than 5% imiquimod cream for grade II actinic keratosis and had comparable efficacy to 5% imiquimod cream for treating

grade I actinic keratosis on the dorsal surfaces of the hands and forearms. EX1017, 1065.

A POSITA seeking to try to improve efficacy in treating AK lesions on the hands and forearms would have been motivated to combine the teachings of Willey with Sotiriou to at least evaluate the use of a red light source as opposed to the blue light source taught in Willey. EX1003, ¶¶193-194. To start, Willey itself highlights the “high clearance rates” for PDT described in Sotiriou. EX1013, 1094, 1101 (citing Sotiriou). Given that Sotiriou is expressly referenced in Willey, a POSITA would have been motivated to combine these references and use a red dose of 75 J/cm^2 as reported in Sotiriou in place of the blue light dose reported in Willey. EX1003, ¶193. Further, it was known at the time that red light is capable of penetrating deeper into the tissue than blue light for PDT treatment. EX1023, 255; EX1016, 53. As a result, a POSITA would have been motivated to combine the teachings of Willey for treating AKs on the hands and forearms with the teachings of Sotiriou regarding the use of red light for a light dose of 75 J/cm^2 especially for attempting to treat deeper lesions. EX1003, ¶¶193-194.

A POSITA would have had a reasonable expectation of success in combining Willey with Soritiou. EX1003, ¶195. Both Willey and Soritiou are directed to topically treating AKs using 20% ALA under occlusion. *Id.* Likewise, both blue light sources (*i.e.*, the BLU-U) and red light sources (*i.e.*, BF-RhodoLED) are approved

light sources for ALA photodynamic therapy. *Id.*; see also discussion *supra* at “Treatment of Actinic Keratosis”. As a result, a POSITA would reasonably expect success in combining the teachings of Willey with the red light source of Soritiou. EX1003, ¶195.

F. Ground 4 – Claims 1-9 Are Unpatentable as Anticipated by Noven Pharma

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

To the extent that the preamble of claim 1 is determined to be a limitation on the claims, Noven Pharma teaches a method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy. For example, Noven Pharma teaches using patches with an LDPE backing material to topically administer 5-aminolevulinic acid (ALA) dispersed in an adhesive matrix or via a reservoir-type device into tissue for photodynamic therapy. EX1005, 9:1-33 (“ALA is dispersed in a pressure sensitive adhesive ... The backing materials, which are preferably water resistant, and occlusive ... can be selected from ... low density polyethylene”.); *id.* at 10:1-12. Noven Pharma also teaches “penetration enhancer[s]” and “substances which increase passage of the drug into the skin” that can be added to the disclosed ALA compositions to enhance ALA penetration into the tissue being treated. EX1005, 10:20–27, 11:11–13; EX1003, ¶¶201-202. Finally,

Noven Pharma describes embodiments that “appear to improve the fluorescence produced”. EX1005, 3:32–4:6. A POSITA would recognize that improved fluorescence is indicative of enhanced penetration of topically applied ALA. EX1003, ¶201.

2. *Claim 1a: “topically applying ALA to a treatment area to be treated with photodynamic therapy”*

Noven Pharma teaches a method for topically applying ALA to a treatment area to be treated with photodynamic therapy. EX1003, ¶¶205-206. To apply ALA to the desired treatment area, 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.” EX1005, 5:15-20 (emphasis added). Noven Pharma also describes that “[*t*]opical ALA photodynamic therapy (ALA PDT™) involves the exposure of the ALA-treated lesion with light.” EX1005, 12:8-9 (emphasis added). Therefore, Noven Pharma teaches claim 1a of the ’567 Patent.

3. *Claim 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”*

Noven Pharma teaches a method of ALA treatment that uses patches with ALA dispersed in a pressure sensitive adhesive or administered via a reservoir-type device. EX1003, ¶209; EX1005, 8:30-9:4; 10:1-12. Noven Pharma discloses “low density polyethylene” as a preferred backing material for its ALA patches. EX1005,

9:27-34; 10:11-12. Because the ALA is contained in adhesive or in a reservoir on the skin-facing surface of the patch, the low density polyethylene barrier (the patch backing material) is applied to the treatment area after ALA has contacted the skin. EX1003, ¶210.

Noven Pharma further teaches that the LDPE backing material of the patch minimizes TEWL.⁶ Specifically, Noven Pharma describes that the backing material is “preferably water resistant.” EX1005, 9:29-30. A POSITA reading Noven Pharma, would recognize that a water resistant backing material prevents water from passing through and therefore minimizes TEWL from the area being treated. EX1003, ¶211. Likewise, a POSITA would recognize that occlusion with LDPE (like the Noven Pharma patch backing material) minimizes TEWL. *See* Ground 1, claim 1b; EX1003, ¶212. Therefore, Noven Pharma teaches claim 1b of the ’567 Patent.

4. *Claim 1c: “removing the low density polyethylene barrier within 3 hours and then applying light to the treatment area.”*

Noven Pharma describes removing the LDPE barrier within 3 hours and then applying light to the treatment area. EX1003, ¶215. Specifically, Noven Pharma

⁶ *See supra* n.3 (noting that intended results in claims such as minimizing transepidermal water loss are generally non-limiting).

teaches an embodiment where the ALA patch with the LDPE backing material is applied to the treatment area for *about* 2 or 3 hours. EX1005, 11:23-27 (explaining that ALA may be “applied to the area of the skin to be diagnosed or treated **for about 2–48 hours**”). (emphasis added); *see also id.*, 11:29-12:5 (“**The duration of application** is that period sufficient to achieve ALA penetration into the diseased tissue ... **This period may be about 3-24 hours.**”) A prior art reference like Noven Pharma that discloses an overlapping range is anticipatory, even where the prior art range only partially or slightly overlaps with the claimed range. *See Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 870–71 (Fed. Cir. 2015) (affirming summary judgment of anticipation of patent claims for composition with “0.05 to 0.5% by weight of at least one saturated fatty acid amide” lubricant in view of a prior art reference disclosing the same class of lubricant in an overlapping range of “0.1 to 5 parts by weight,” where the parties agreed that a measurement in “% by weight” was equivalent to one in “parts by weight”).⁷

⁷ Patent Owner will be unable to demonstrate that “removing the low density polyethylene barrier **within 3 hours**” is critical to the operability of the alleged invention. EX1003, ¶216; *Ineos*, 783 F.3d at 871. As acknowledged in the ’567 Patent, Patent Owner’s Levulan product is approved by the FDA for ALA-PDT treatment for times ranging between 14 to 18 hours, which the ’567 patent

Following an incubation period of about 2-3 hours, Noven Pharma teaches that the patch is removed and light is then applied to the treatment area. EX1003, ¶217; EX1005, 11:29-12:5; EX1005, 15:7-21 (“**After the patch is removed, the lesion is wiped ... 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**”) (emphasis added).

Accordingly, Noven Pharma teaches every limitation of the ’567 Patent, claim 1.

5. *Claim 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.”*

As discussed above for Ground 4, claim 1c, Noven Pharma teaches removing the low density polyethylene barrier (*i.e.*, the ALA patch) within 2-3 hours and then applying light to the treatment area. *See* Ground 4, claim 1c, *supra*. Noven Pharma

acknowledges is a suitable incubation time. EX1001, 12:17-23; EX1016, 53; Further, other researchers describe longer incubation times including with occlusion for ALA PDT. EX1003, ¶¶58, 216.

further teaches embodiments where the light applied to the treatment area is blue light (*e.g.*, 400 nm light⁸) for a 10 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.”

EX1005, 12:8-12 (emphasis added). A POSITA would understand the teachings of Noven Pharma to indicate that the treatment site can be irradiated with blue light for a 10 J/cm² light dose. EX1003, ¶¶223-225; *Ineos*, 783 F.3d at 870–71 (finding prior art reference that disclosed an overlapping range to be anticipatory).⁹

⁸ The '567 patent defines 400 nm light as “blue light.” EX1001, 5:24-29 (“the LED arrays 60 preferably emit **blue light having wavelengths at or above 400 nanometers (nm)...**”) (emphasis added).

⁹ PO will also be unable to demonstrate that “blue light ... for a 10 J/cm² light dose” is critical to the operability of the alleged invention. EX1003, ¶226. The '567 Patent describes treating lesions with lower blue light doses (0.1 to 2 J/cm²) [EX1001, 7:23] and higher blue light doses for ALA PDT are taught in the prior art. EX1019, 399 (referencing a 10 to 48 J/cm² blue light dose and a 48 J/cm² light dose for the Omnilux blue light).

6. *Claim 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.”*

As discussed above, Noven Pharma teaches topical application of ALA using a patch, removing the ALA patch within 3 hours, and then applying light to the treatment area. *See* Ground 4, claims 1a and 1c, *supra*. A POSITA would appreciate that ALA applied topically using a patch as taught in Noven Pharma—*e.g.*, a 2.5 to 20 cm² patch with an ALA concentration between 0.1-3.0 mg/cm²—for a 3 hour period would not substantially increase the blood plasma levels of ALA above endogenous ALA concentrations levels, and hence, maximum blood plasma levels would remain below about 110 ng/mL. EX1003, ¶¶230-235; *see also, In re Kao*, 639 F.3d at 1070; *Santarus*, 694 F.3d at 1354.

ALA pharmacokinetic studies performed by others confirm this. For example, Fauteck studied the pharmacokinetics of ALA applied to 12 patients for 4 hours using 8 patches, each having a size of 4 cm² with 2 mg of ALA per cm², for a total of 64 mg of ALA for all 8 patches per patient. EX1008, 53-55. Fauteck determined the mean endogenous level of ALA present in human plasma—the amount normally present—to be around 11.23 µg/l (*i.e.*, 11.23 ng/mL). EX1008, 57, Table 5. Fauteck observed only a small increase in ALA plasma concentrations with topically applied ALA via patch—a mean maximum plasma concentration of 28.36 µg/l (*i.e.*, 28.36 ng/mL)—and did not observe any values in any of the patients tested in excess of

53.08 µg/l (*i.e.*, 53.08 ng/mL). EX1008, 57-58, Tables 5-7. Likewise, as discussed above under Grounds 1 and 4, Petitioner performed a pharmacokinetic study in connection with its FDA submission and labeling for its Ameluz® product and observed a (non-baseline corrected) mean maximum plasma concentration of around 47.35 ng/mL (20.16+27.19) when 200 mg of ALA (in 2 g of Ameluz® gel) was applied to 12 subjects with occlusion over a 20 cm² treatment area for a period of 3 hours. EX1010, 9; EX1003, ¶¶230-233.

In sum, the mean maximum plasma concentration of ALA was 28.36 ng/mL in Fauteck for topical application of 64 mg of ALA, and around 47.35 ng/mL in the Ameluz® prescribing information for topical application of 200 mg of ALA—both of which are well below the 110 ng/mL specified in claim 3. Because the ALA patch of Noven Pharma contains a maximum of 60 mg of ALA—less than the amounts of ALA used in Fauteck (64 mg) and the Ameluz® prescribing information (200 mg)—Noven Pharma would also would likewise necessarily result in an ALA plasma concentration of less than 110 ng/mL, as specified in claim 3. EX1003, ¶¶234-235.

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

As described above, for Ground 4, claim 1pre, to the extent that the preamble is determined to be a limitation on the claim, this element is satisfied by the teachings of Noven Pharma. *See* Ground 4, claim 1 preamble discussion *supra*.

8. *Claim 4a: “topically applying ALA to a treatment area to be treated with photodynamic therapy; and”*

Claim element 4a is taught by Noven Pharma for the same reasons described above for Ground 4, claim 1a. *See* Ground 4, claim 1a, *supra*.

9. *Claim 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,”*

Claim element 4b is taught by Noven Pharma for the same reasons described above for Ground 4, claim 1b. *See* Ground 4, claim 1b, *supra*.

10. *Claim 4c: “wherein the treatment area is located on a hand or a forearm.”*

Noven Pharma further teaches a treatment area located on a hand or a forearm. For example, Noven Pharma describes that the treatment area can be any visible portion of a subject’s skin having a lesion—which would include a hand or forearm. EX1005, 12:19-21 (“The target tissues ... are any visible, cutaneous lesion.”); EX1003, ¶244. In addition, in one disclosed example, Noven Pharma describes treatment of a lesion on a subject’s forearm. EX1005, 15:2-6 (“A single lesion is evident on her right forearm ... (ALA PDT™) is prescribed.”) Accordingly, Noven Pharma teaches every limitation of the ’567 Patent, claim 4.

11. *Claim 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.”*

As discussed above for Ground 4, claim 1c, Noven Pharma teaches removing the LDPE barrier (*i.e.*, the ALA patch) and then applying light to the treatment area. *See* Ground 4, claim 1c, *supra*. Noven Pharma further teaches embodiments where the light applied is red light (*e.g.*, 634 nm light¹⁰) for a 10 to 75 J/cm² light dose. EX1005, 12:8-18 (“**A suitable wavelength is ..., 634 nm or 600-700 nm, ...to provide a light dose of 10-100 Joules/cm².**”) (emphasis added). The disclosed light wavelengths of 634 nm and 600-670 nm are examples of red light and the disclosed light dose range of 10-100 J/cm² encompasses and includes the claimed 10 to 75 J/cm² light dose.¹¹ EX1003, ¶¶250-251.

12. *Claim 6: “The method as set forth in claim 4, wherein the treatment area is a dorsal surface of the hand.” / Claim 7:*

¹⁰ The ’567 patent identifies red light as having a wavelength between 570 and 670 nm. EX1001, 5:44-46 (“the LED arrays may also emit red light having wavelengths of 570 to 670 nm.”); EX1003, ¶250.

¹¹ PO will be unable to demonstrate that “red light ... for a 10-75 J/cm² light dose” is critical to the operability of the alleged invention. EX1003, ¶252. The ’567 Patent describes the treatment of lesions with doses between 30 J/cm² to 150 J/cm² [EX1001, 7:26-29] and higher red light doses in ALA PDT are taught in the prior art. EX1014, 246-247 (referencing a 96 J/cm² light dose for 633 nm red light).

“The method as set forth in claim 4, wherein the treatment area is a dorsal surface of the forearm.”

Consistent with Petitioner’s claim construction, Noven Pharma further teaches a treatment area located on a dorsal surface of the hand and forearm. EX1001, 14:26-28; EX1003, ¶¶256-258. As noted above for claim 4, Noven Pharma describes that the treatment area can be any visible portion of a subject’s skin having a lesion—which would include a dorsal surface of the hand or forearm. EX1005, 12:19-21; EX1003, ¶¶257-258.

Also, as noted above, Noven Pharma highlights a particular embodiment in which an ALA patch was used to treat a lesion on a subject’s forearm. EX1005, 15:2-6 (“A single lesion is evident on her right forearm ... and ... (ALA PDT™) is prescribed.”). A POSITA would understand the foregoing disclosure to include and encompass the dorsal surface of the forearm—*i.e.*, the top portion of the forearm. This surface of the forearm is particularly likely to have visible lesions due to sun exposure and photodamage. EX1003, ¶258.

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

To the extent that the preamble of claim 8 is determined to be a limitation, Noven Pharma teaches a method of using 5-aminolevulinic acid (ALA) and a low density polyethylene barrier. For example, as noted above, Noven Pharma teaches using adhesive and reservoir-type patches with a water resistant LDPE backing

material to topically administer 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy. EX1005, 9:27-10:4; 10:11-12.

14. *Claim 8a: “contacting a treatment site with a composition comprising the ALA so as to wet the treatment site;”*

The '567 Patent describes wetting the treatment site as applying an ALA admixture by contacting the ALA with the lesion surface. EX1001, 9:12-18; 9:50-54. Consistent with the '567 patent disclosure and claims, Noven Pharma describes wetting the treatment site by contacting it with ALA compositions. EX1003, ¶¶264-268. Noven Pharma describes, for example, adhesive patches containing ALA compositions with a “carrier” that may contain “a proton donor, penetration enhancer and other substances known for use in transdermal formulations.” EX1005, 10:23-27. Noven Pharma also states that “[a]dditional substances which increase the passage of the drug into the skin also can be added.” EX1005, 11:11-14. Likewise, Example 2 of Noven Pharma expressly discloses compositions of ALA in propylene glycol and glycerin. EX1005, 14:1-21. And for the reservoir-type patch embodiments, Noven Pharma describes that such patches include ALA compositions with liquid non-aqueous solvents for delivery of ALA to the treatment site. EX1005, 10:1-12. A POSITA would appreciate that these various disclosures in Noven Pharma teach compositions comprising ALA that wet the treatment site when applied. EX1003, ¶¶264-268.

15. *Claim 8b: “following wetting of the treatment site, covering the wetted treatment site with the low density polyethylene barrier;”*

As noted above for Ground 4, claim 8a, Noven Pharma teaches embodiments using a patch having a LDPE backing with ALA dispersed in an adhesive matrix or via a reservoir. EX1005, 8:30-9:33; 10:1-12. Because the ALA compositions are contained in the adhesive matrix or reservoir on the skin-facing surface of the patch, the treatment site is covered by the LDPE backing material of both patch embodiments after wetting by the ALA composition. EX1003, ¶270.

16. *Claim 8c: “removing the low density polyethylene barrier so as to expose the treatment site; and”*

Noven Pharma also teaches removing the LDPE barrier to expose the treatment site. EX1003, ¶¶273-274. Specifically, Noven Pharma teaches embodiments where the ALA patch with the LDPE backing material is applied to the treatment area for a certain duration after which time the patch is removed and the lesion is wiped to expose the treatment site. EX1005, 11:29-12:5; *Id.*, 15:7-21 (“After the patch is removed, the lesion is wiped with an alcohol swab.”).

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

As discussed above for Ground 4, claim 1c, Noven Pharma teaches removing the LDPE barrier (*i.e.*, the ALA patch) and subsequently applying light to the exposed treatment site. *See* Ground 4, claim 1c, *supra*. Noven Pharma further

teaches embodiments where the light applied to the treatment area after removal of the patch is blue light (e.g., 400 nm light) for a 10 J/cm² light dose. See Ground 4, claim 2, *supra*; EX1005, 12:8-12; EX1001, 5:24-29. Accordingly, Noven Pharma teaches every limitation of claim 8. EX1003, ¶¶276-278.

18. *Claim 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.”*

Noven Pharma further teaches removing the LDPE barrier no later than three hours after the treatment site is covered. See claim 1c, *supra*; EX1005, 11:23-27 (ALA may be “applied to the area of the skin to be diagnosed or treated for **about 2–48 hours**”); see also *id.*, 11:29-12:5 (“The duration of application is that period sufficient to achieve ALA penetration into the diseased tissue ... This period may be **about 3-24 hours.**”); *Ineos*, 783 F.3d at 870–71 (finding prior art reference that disclosed an overlapping range to be anticipatory).¹² A POSITA would understand that a duration of application of about 2 or 3 hours means that the patch with the low density polyethylene barrier is removed no later than two or three hours after the treatment site is covered. EX1003, ¶281.

¹² See also n.7.

G. Ground 5 – Claim 3 Is Unpatentable as Obvious Over Noven Pharma Combined with Fauteck

1. *Claim 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.”*

As discussed above for Ground 4, Noven Pharma anticipates claims 1 and 3 of the Challenged Patent. To the extent that PO argues that claim 3 is not inherently met by Noven Pharma, Claim 3 is unpatentable as obvious over the teachings of Noven Pharma combined with Fauteck because a POSITA would understand from the combined teachings that the ALA patches of Noven Pharma could be safely used to treat more or larger lesions with maximum plasma concentrations of ALA following application that are around or below 53.08 ng/mL—*i.e.*, less than about 110 ng/mL. EX1003, ¶¶293-298; *see also In re Kao*, 639 F.3d at 1070; *Santarus*, 694 F.3d at 1354.

As discussed above, in connection with Ground 4, claim 3, Fauteck studied the pharmacokinetic properties of ALA patches—like those described in Noven Pharma—to determine, *inter alia*, the maximum plasma concentration of ALA following patch application. EX1003, ¶294. In Fauteck, 8 patches each were applied to 12 patients for 4 hours with each patch having a size of 4 cm² and a concentration of ALA at 2 mg of ALA per cm² (*i.e.*, 64 mg of ALA in total for 8 patches). EX1008, 53-55. Fauteck observed only a small increase in maximum ALA plasma

concentrations with topically applied ALA from the tested patches (from an endogenous level of 11.23 ng/mL up to a mean C_{\max} of 28.36 $\mu\text{g/l}$ (*i.e.*, 28.36 ng/mL)) and did not observe any maximum plasma concentration values in any patients tested above 53.08 $\mu\text{g/l}$ (*i.e.*, 53.08 ng/mL). EX1008, 57-58, Tables 6-7; EX1003, ¶294.

While Noven Pharma teaches the application of a single 5 cm² ALA patch having an ALA concentration between 0.1-3.0 mg/cm² for a maximum of 15 mg of ALA (see Example 3)—a POSITA would be motivated to combine the teachings of Noven Pharma and Fauteck in order to safely evaluate the application of ALA patches like those in Noven Pharma to treat more lesions or larger lesions for PDT.¹³ EX1003, ¶¶295-296. As noted above, both references relate to the use of similar ALA patches to administer ALA for PDT, and Fauteck describes that when eight 4 cm² patches containing a total of 64 mg of ALA are applied to cover 32 cm² of skin,

¹³ Indeed, a POSITA would understand that the size, number, and concentration of ALA in the patches could be adjusted to modify the maximum plasma concentration of ALA in a patient. EX1003, ¶296, n.5. Based on the pharmacokinetic data supplied in Fauteck, a POSITA could readily select the size, number, and concentration of ALA in the patches applied to a subject's lesions to ensure that the maximum plasma concentration of ALA did not exceed 110 ng/mL. *Id.*

the resulting application (which resulted in a mean maximum plasma concentration of 28.36 ng/mL) is safe and well tolerated. EX1008, Abstract; 53; 59; EX1005, 11:20-28; 15:7. Based on Fauteck's teaching, a skilled artisan, when seeking to evaluate the treatment of more lesions or lesions with greater surface area using Noven Pharma's ALA patches, would have been motivated combine Noven Pharma with Fauteck to administer up to 64 mg of ALA over up to 32 cm² of skin surface area. EX1003, ¶¶295-296.

Further, a POSITA would have appreciated a reasonable expectation of success in combining the teachings of Noven Pharma and Fauteck to treat larger lesions or more lesions. EX1003, ¶297. In line with Fauteck, when the patches of Noven Pharma are used to apply up to 64 mg of ALA over up to 32 cm² of skin surface area, a POSITA would reasonably expect a maximum observed plasma concentration of ALA around or less than 53.08 ng/mL with a mean maximum plasma concentration around or less than 28.36 ng/mL as reported by Fauteck. EX1008, 57-58, Tables 5-7; EX1003, ¶297. Accordingly, this combination would result in a maximum plasma concentration of ALA well below the 110 ng/mL limit specified by claim 3.

H. Ground 6 – Claim 10 Is Unpatentable as Obvious Over Noven Pharma Combined with the BLU-U Operating Manual

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

As discussed above for Ground 4, Noven Pharma anticipates claim 8 of the '567 Patent. Claim 10 is also rendered obvious by the teachings of Noven Pharma combined with the BLU-U operating manual, which describes the sole FDA approved blue light source for ALA photodynamic therapy and specifies its positioning from between two to four inches from the treatment site. EX1003, ¶309; EX1012, 9-12 (“the entire surface area to be treated lies between 2” and 4” from the BLU-U surface.”).

In addition, as discussed above in connection with Ground 4, claims 2, 5, and 8d, Noven Pharma teaches embodiments where the light applied to the treatment area after removal of the patch is blue light (*e.g.*, ~400 nm light) for a 10 J/cm² light dose. EX1005, 12:8-14. A POSITA seeking to apply the teachings of Noven Pharma for photodynamic therapy (which does not specify a commercially available blue light source to use) would be motivated to combine the teachings of Noven Pharma with operating documentation for the only blue light source for ALA photodynamic therapy approved by the FDA—*i.e.*, the BLU-U—which provides a 10 J/cm² light dose. EX1003, ¶309. The BLU-U operating manual specifically instructs users that

the treatment area should be positioned “between 2” and 4” from the BLU-U surface” as noted above for a 10 J/cm² light dose. EX1012, 9-12. As a result, a POSITA would have been motivated to combine the teachings of Noven Pharma with the BLU-U operating manual’s instruction to position the light source 2-4 inches from the treatment area. EX1003, ¶309.

A POSITA would have appreciated a reasonable expectation of success in practicing claim 10 by combining the teachings of Noven Pharma with the BLU-U operating manual. EX1003, ¶311. The BLU-U has long been used for ALA based photodynamic therapy (*i.e.*, since ~ 1999) where a blue light source was desired and provides for a 10 J/cm² light dose with a positioning “between 2” and 4” from the BLU-U surface.” EX1003, ¶¶301-302,311. As noted above, this is consistent with Noven Pharma, which also specifies blue light sources and a 10 J/cm² dose. EX1003, ¶311. As a result, a POSITA would reasonably expect that the BLU-U and its positioning relative to the treatment site would be compatible and operable with the ALA patch embodiments described in Noven Pharma. *Id.*

VIII. ANY SECONDARY CONSIDERATIONS PO MAY RAISE DO NOT OVERCOME THE PRIMA FACIE CASE OF OBVIOUSNESS

1. *No Unexpected Results*

No unexpected results are tied to the claims of the ’567 Patent that support a finding of non-obviousness. PO suggests in the ’567 Patent that it was surprising to

find that LDPE was better at minimizing TEWL than other plastic films, like polyurethane films, tested in the '567 Patent. EX1001, col. 2:18-27. However, it was already known—as reflected in Berardesca, for example—that “polyethylene films (Saran Wrap)” were superior to polyurethane films at minimizing transepidermal water loss. EX1007, 26-27; EX1003, ¶¶56, 70.

Indeed, occlusion with LDPE films in connection with ALA photodynamic therapy was already in common use by practitioners by January 2018, including in the treatment of lesions on the hands and forearms of patients. EX1003, ¶¶57-58, 71-72; EX1013, 1095; EX1015, 22-24; EX1005, 8:30-9:33; 10:1-12. As such, there is nothing surprising or unexpected in the claimed inventions of the '567 Patent.

If PO identifies any additional evidence of secondary considerations, Petitioner respectfully requests an opportunity to respond.

IX. CONCLUSION

For the foregoing reasons, Petitioner respectfully requests institution.

Dated: October 19, 2021

Respectfully submitted,

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CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24(a)(i), the undersigned certifies that this Paper—exclusive of the table of contents, table of authorities, grounds for standing under § 42.104, mandatory notices under § 42.8, certificate of service, and this certificate of word count—includes 13943 words.

/ Lauren Fornarotto/
Lauren Fornarotto (Reg. No. 76,470)

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e) and 37 C.F.R. § 42.105(a), the undersigned certifies that on October 19, 2021, a complete copy of this Petition for Inter Partes Review, Petitioner’s power of attorney, and all exhibits were served on Patent Owner at the correspondence addresses of record listed below by EXPRESS MAIL®:

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