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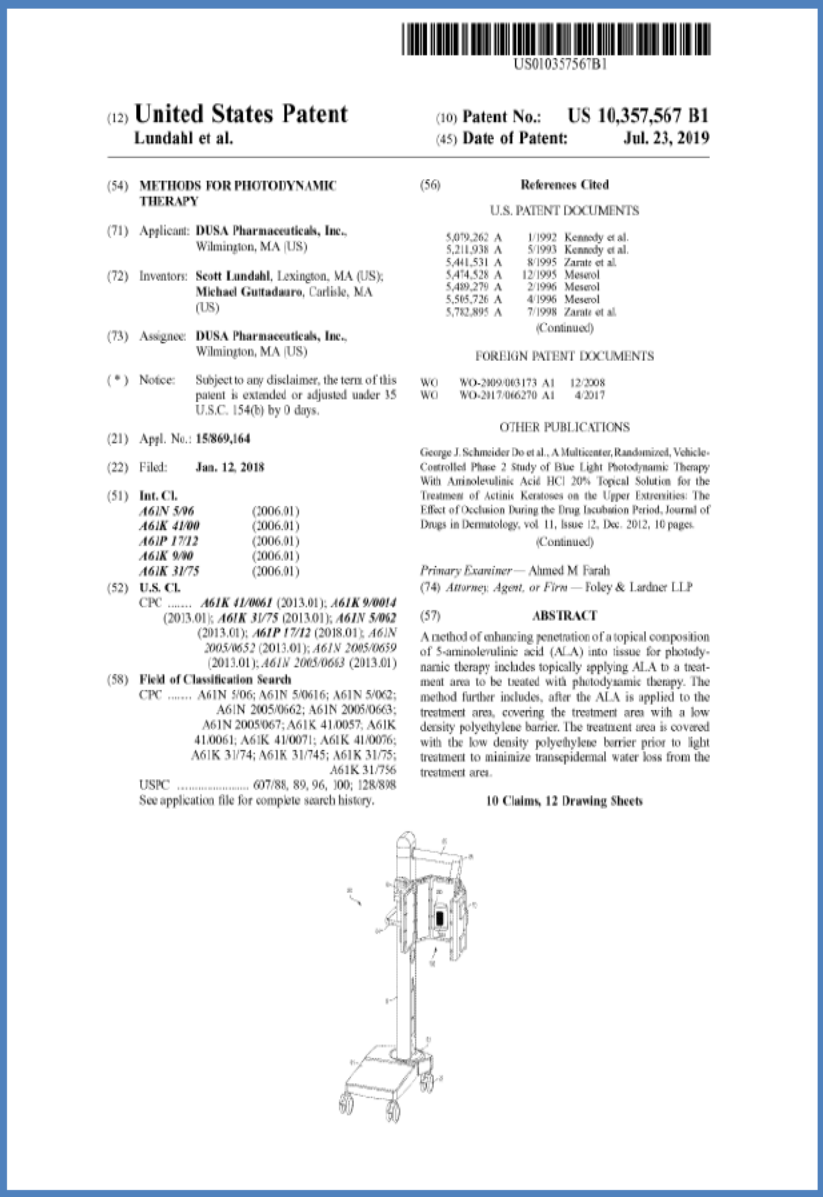

US010357567B1

(12) **United States Patent**
Lundahl et al.

(10) **Patent No.: US 10,357,567 B1**
(45) **Date of Patent: Jul. 23, 2019**

(54) **METHODS FOR PHOTODYNAMIC THERAPY**

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(73) Assignee: **DUSA Pharmaceuticals, Inc.**, Wilmington, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **15/869,164**

(22) Filed: **Jan. 12, 2018**

(51) **Int. Cl.**

A61N 5/06	(2006.01)
A61K 41/00	(2006.01)
A61P 17/12	(2006.01)
A61K 9/00	(2006.01)
A61K 31/75	(2006.01)

(52) **U.S. Cl.**
CPC ***A61K 41/0061*** (2013.01); ***A61K 9/0014*** (2013.01); ***A61K 31/75*** (2013.01); ***A61N 5/062*** (2013.01); ***A61P 17/12*** (2018.01); *A61N 2005/0652* (2013.01); *A61N 2005/0659* (2013.01); *A61N 2005/0663* (2013.01)

(58) **Field of Classification Search**
CPC A61N 5/06; A61N 5/0616; A61N 5/062; A61N 2005/0662; A61N 2005/0663; A61N 2005/067; A61K 41.0057. A61K 41.0061; A61K 41/0071; A61K 41/0076; A61K 31/74; A61K 31/745; A61K 31/75; A61K 31/756
USPC 607/88, 89, 96, 100; 128/898
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,079,262 A	1/1992	Kennedy et al.
5,211,938 A	5/1993	Kennedy et al.
5,441,531 A	8/1995	Zarate et al.
5,474,528 A	12/1995	Meserol
5,489,279 A	2/1996	Meserol
5,505,726 A	4/1996	Meserol
5,782,895 A	7/1998	Zarate et al.

(Continued)

FOREIGN PATENT DOCUMENTS

WO	WO-2009/063173 A1	12/2008
WO	WO-2017/066270 A1	4/2017

OTHER PUBLICATIONS

George J. Schmeider Do et al., A Multicenter, Randomized, Vehicle-Controlled Phase 2 Study of Blue Light Photodynamic Therapy With Aminolevulinic Acid HCl 20% Topical Solution for the Treatment of Actinic Keratoses on the Upper Extremities: The Effect of Occlusion During the Drug Incubation Period, Journal of Drugs in Dermatology, vol. 11, Issue 12, Dec. 2012, 10 pages.

(Continued)

Primary Examiner — Ahmed M Farah
(74) *Attorney, Agent, or Firm* — Foley & Lardner LLP

(57) **ABSTRACT**

A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy includes topically applying ALA to a treatment area to be treated with photodynamic therapy. The method further includes, after the ALA is applied to the treatment area, covering the treatment area with a low density polyethylene barrier. The treatment area is covered with the low density polyethylene barrier prior to light treatment to minimize transepidermal water loss from the treatment area.

10 Claims, 12 Drawing Sheets

Methods for Photodynamic Therapy
Critical Date: January 12, 2018
Expiration Date: January 12, 2038

Initial Patent Review
U.S. 10357567

International Patent Reviews

IPR Initial Review

Patent information

URL	Priority	Expiration	RC*	FC**
https://patents.google.com/patent/US10357567	Jan 12 2018	Jan 12 2038	55	99

*patent and non-patent literature citations ** citing patents

Technology Description & Application Area

Patent Number	Title	Description/Application Area
10357567	Methods for photodynamic therapy	A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy is disclosed. The method includes topically applying ALA to a treatment area to be treated with photodynamic therapy. The method further includes, after the ALA is applied to the treatment area, covering the treatment area with a polymeric barrier ...

Prosecution History

U.S. 10357567	Date	Action/Outcome
Original Filing	Jan 12 2018	Originally filed with claims 1-23.
Request for Restriction/Election	Apr 3 2018	I. Claims 1-8 and 16-23, drawn to alternative methods of enhancing penetration of a topical composition into a tissue for photodynamic therapy, classified in A61 K41 /0061. This application contains claims directed a patentably distinct specie. The invention of Group I contains claims directed to the following patentably distinct species: Species A (claims directed to a method of enhancing penetration of a topical composition into tissue characterized by applying 5-aminolevulinic acid (molecular formula C5H9NQ3) to a body tissue to be treated, see Par. 0007 and 0010 of the specification), and Specie B (claims directed to method of enhancing penetration of a topical composition to a skin tissue characterized by applying 5-aminolevulinic acid hydrochloride (molecular formula: C5H10CINO3) to a body tissue to be treated, see Par. 0011).

		II. Claims 9-15, drawn to a method of photodynamic treatment of a body/skin tissue, classified in A61 N 5/062.
Response to Request for Restriction/Election	Apr 13 2018	Applicant elected Group I, claims 1-8 and 16-23, without traverse and Species A, claims directed to a method of enhancing penetration of a topical composition into a tissue, characterized by applying 5-aminolevulinic acid (molecular formula C5H9N03), with traverse.
Non-Final Rejection	Aug 9 2018	Claims 9-15 and 21-23 withdrawn from consideration. Claims 1-8 and 16-20 rejected. Claims 1-8 and 16-20 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. The term "low" in claim 1 line 5 and claim 16 line 6 is a relative term which renders the claim indefinite. Claim 8 recites the limitation "the maximum plasma" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claims 1, 2, 5 and 16 rejected under 35 U.S.C. 102(a)(1) as being anticipated by Foguet Roca, Pub. No. U.S. 2009/0324727. **Note**: in the Background section of the instant application, the applicant describes the use of ALA compositions for photodynamic therapy as well known in the art. The applicant further indicates that the inventors found 'coving [sic] polyethylene for a period of time over a treatment area is effective to minimize trans-epidermal water loss from the treatment area' (see Par. 006 of the specification). The examiner further notes that the use of surfactants such as polyethylene for coating on a surface to minimize water loss for a period of time, or on a surface of a medical capsule to minimize water absorption is well known in the art (see Pars. 0004 and 0208 of Parent et al., Pub. No. U.S. 2014/0010761; and Pars. 0090 and 0106 of Bonasera et al., Pub. No. U.S 2005/0090429). Claims 1 and 16 rejected under 35 U.S.C. 102(a)(1) as being anticipated by Trigiante, Pub. No. U.S. 2011 /0053965.
Applicant Arguments	Nov 2 1018	Claim 1 amended to include allowable subject matter relating to claim 4. Claims 2, 4, 9-15, 17, 18 and 21-233 were cancelled without prejudice or disclaimer. Claim 5 was rewritten into independent form and revised to include subject matter supported at least by paras. [0022], [0059], [0066] and [0073] of the specification as filed. New claims 24 and 25 include subject matter also supported by at least these portions of the disclosure. Claim 8 was amended for antecedent basis purposes. Claim 16 was amended to include allowable subject matter relating to claim 17. Claim 20 is amended for consistency with the amendments to claim 16. Claim 1 was amended by adding the phrase "removing the low density polyethylene barrier within 3 hours and then applying light to

		the treatment area." Claim 16 was amended by adding the phrase "removing the low density polyethylene barrier so as to expose the treatment site; and illuminating the exposed treatment site with an illuminator so as to deliver a 10 J/cm2 dose of blue light." Upon entry of the amendments, claims 1, 3, 5-8, 16, 19, 20, 24 and 25 will be pending.
Final Rejection	Feb 25 2019	Claims 1, 5-8, 16, 19, 20, 24 and 25 were allowed. Claim 3 was rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends.
Applicant Response	Apr 12 2019	Accepted cancellation of claim 3.
Notice of Allowance	Jun 3 2019	The allowed claim(s) were 1,5-8, 16, 19-20 and 24-25.
Issue Notification	Jul 2 2019	Issue date specified as Jul 23 2019 for US Patent 10357567
Notice of Publication	Jul 18 2019	US-2019-0216927-A 1 published on Jul 18 2019

Litigation History

U.S. Patent 10357567: none

Current Orange Book Patent Data

Active Ingredient: AMINOLEVULINIC ACID HYDROCHLORIDE
Proprietary Name: LEVULAN
Dosage Form; Route of Administration: SOLUTION; TOPICAL
Strength: 20%
Reference Listed Drug: Yes
Reference Standard: Yes
TE Code:
Application Number: N020965
Product Number: 001
Approval Date: Dec 3, 1999
Applicant Holder Full Name: DUSA PHARMACEUTICALS INC
Marketing Status: Prescription

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
001	10357567	01/12/2038			U-804		08/02/2019

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
001	I-766	03/09/2021

Best Potential Prior Art

Relevant Patent or Publication	Publication Date
Dragieva, G., et al. "A randomized controlled clinical trial of topical photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratoses in transplant recipients." British Journal of Dermatology 151.1 (2004): 196-200.	July 2004
Kurwa, Habib A., et al. "A randomized paired comparison of photodynamic therapy and topical 5-fluorouracil in the treatment of actinic keratoses." Journal of the American Academy of Dermatology 41.3 (1999): 414-418.	September 1999
Braathen, Lasse R., et al. "Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: an international consensus." *Journal of the American Academy of Dermatology* 56.1 (2007): 125-143.	January 2007
MacCormack, Mollie A. "Photodynamic therapy in dermatology: an update on applications and outcomes." Seminars in cutaneous medicine and surgery. Vol. 27. No. 1. WB Saunders, 2008.	March 2008
Wolf, Peter, Edgar Rieger, and Helmut Kerl. "Topical photodynamic therapy with endogenous porphyrins after application of 5-aminolevulinic acid: an alternative treatment modality for solar keratoses, superficial squamous cell carcinomas, and basal cell carcinomas?" Journal of the American Academy of Dermatology 28.1 (1993): 17-21.	January 1993
Ozog, David M., et al. "Photodynamic therapy: a clinical consensus guide." Dermatologic Surgery 42.7 (2016): 804-827.	July 2016
Schmieder, George J., Eugene Y. Huang, and Michael Jarratt. "A multicenter, randomized, vehicle-controlled phase 2 study of blue light photodynamic therapy with aminolevulinic acid HCl 20% topical solution for the treatment of actinic keratoses on the upper extremities: the effect of occlusion during the drug incubation period." Journal of drugs in dermatology: JDD 11.12 (2012): 1483-1489.*	November 2012

WO 2009/003173 A1 to Sakamoto *et al.**	December 2008
FDA Label LEVULAN KERASTICK (aminolevulinic acid HCl) for Topical Solution, 20%; Initial U.S. Approval: 1999	October 2006

*Cited during prosecution or on face of the patent.

Prior Art Analysis

Ever-greening of the 5-ALA PDT Technology:

The patentee originally filed an NDA (NDA 20-965) for "for LEVULAN® KERASTICK (aminolevulinic acid HCl) for Topical Solution, 20%, for use in photodynamic therapy with blue light irradiation" on June 29, **1998** which was based at least on U.S. Patents 5,079,262 (issued **1992**); 5,211,938 (issued 1993); 5,422,093 (issued 1995); 5,954,703 (issued 1999); and 6,710,066 (issued 2004). The use of 5-ala in blue-light photodynamic therapy as Levulan® Kerastick was given FDA approval on December 5, 1999.

Patent Number	Issued	Expiration (est)
US 10357567	2019-07-23	**2038-01-12**
US 8758418	2014-06-24	2018-05-01
US 8216289	2012-07-10	2018-05-01
US 7723910	2010-05-25	2019-06-17
US 6709446	2004-03-23	2018-05-01
US 6710066[L]	2004-03-23	2016-03-23
US 6559183	2003-05-06	2019-11-12
US 5954703[L]	1999-09-21	2017-10-31
US 5422093[L]	1995-06-06	2012-06-06
US 5211938[L]	1993-05-18	2014-07-08
US 5079262[L]	1992-01-07	2013-09-30

[L] – on original FDA Label 2006 as approved (NDA 20-965)

U.S Patent 10357567 was filed as U.S. Appl. 15/869,164 on January 12, **2018**. The expected expiration date of the '567 is estimated to be January 12, **2038**. This is a span of **46 years and 5 days** from the time of issuance of the first foundational patent. The '567 patent represents an abuse of the United States Patent system as an inequitable extension of valid patent rights by "ever-greening" the technology and should be invalidated as lacking novelty over the prior art cited below.

The use of 5-aminolevullinic acid in photodynamic therapy using a 3-hour pretreatment under occlusion on the hands and forearms was very well known and developed at the time of the invention (January 12, 2018). Reviews have been published (see e.g., at least MacCormack and Ozog).

During prosecution, the examiner explicitly makes note of this fact and indicates that the patentee was well aware of the knowledge of the art by stating: "in the Background section of the instant application, the applicant describes the use of ALA composition for photodynamic therapy is well known in the art."

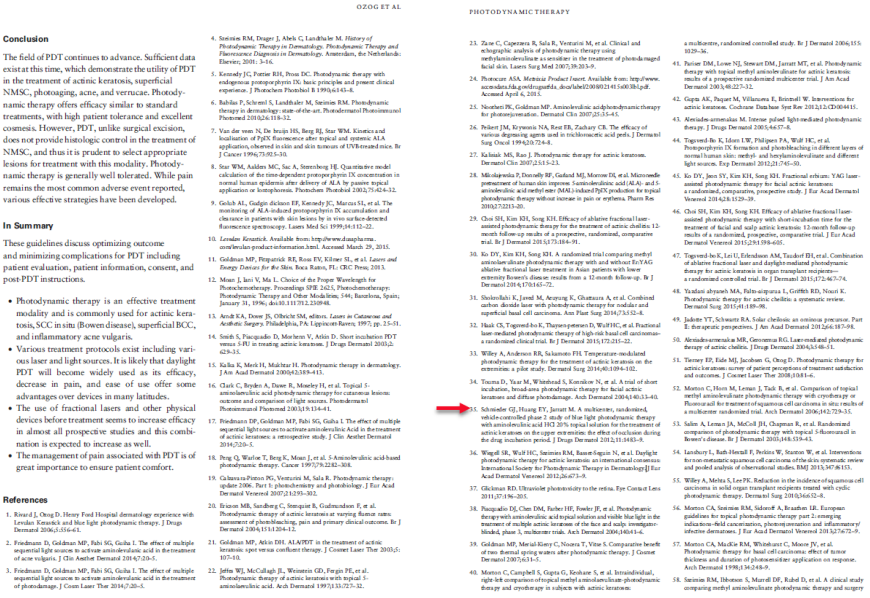
In fact, in Dragieva (2004), the method was so well established that it was used as the control in experiments investigating the use of an alternate photosensistizer.

The supposed differentiating factor for the '567 over the prior art was the addition of an element relating to "removing …[a] low density polyethylene barrier within 3 hours and then applying light to …[a] treatment area." However, this so-called novel element was very well known in the art at the time of the invention.

More specifically, the use of topical 5-ala in photodynamic treatments may be traced back at least as far as 1990. MacCormack lists no fewer than 46 studies on the use of 5-ala/mal for the treatment of actinic keratoses and/or acne prior to 2008 (see Table I extracted from MacCormack 2008, below). Further, many of these citations used occlusive coverings to enhance 5-ala/mal uptake.

Lack of disclosure of the prior art during prosecution of the '567 was rampant.

Ozog discloses the state of the art of 5-ALA PDT as of **2016** (Table 4 below) and presents 93 cited references. Only **one** of the citations from Ozog (Schmieder, describing a clinical trial, red arrow below) is mentioned on the face of the patent or during prosecution. **NONE of the other 92 state of the art references** from Ozog are mentioned on the face of the patent nor during prosecution:

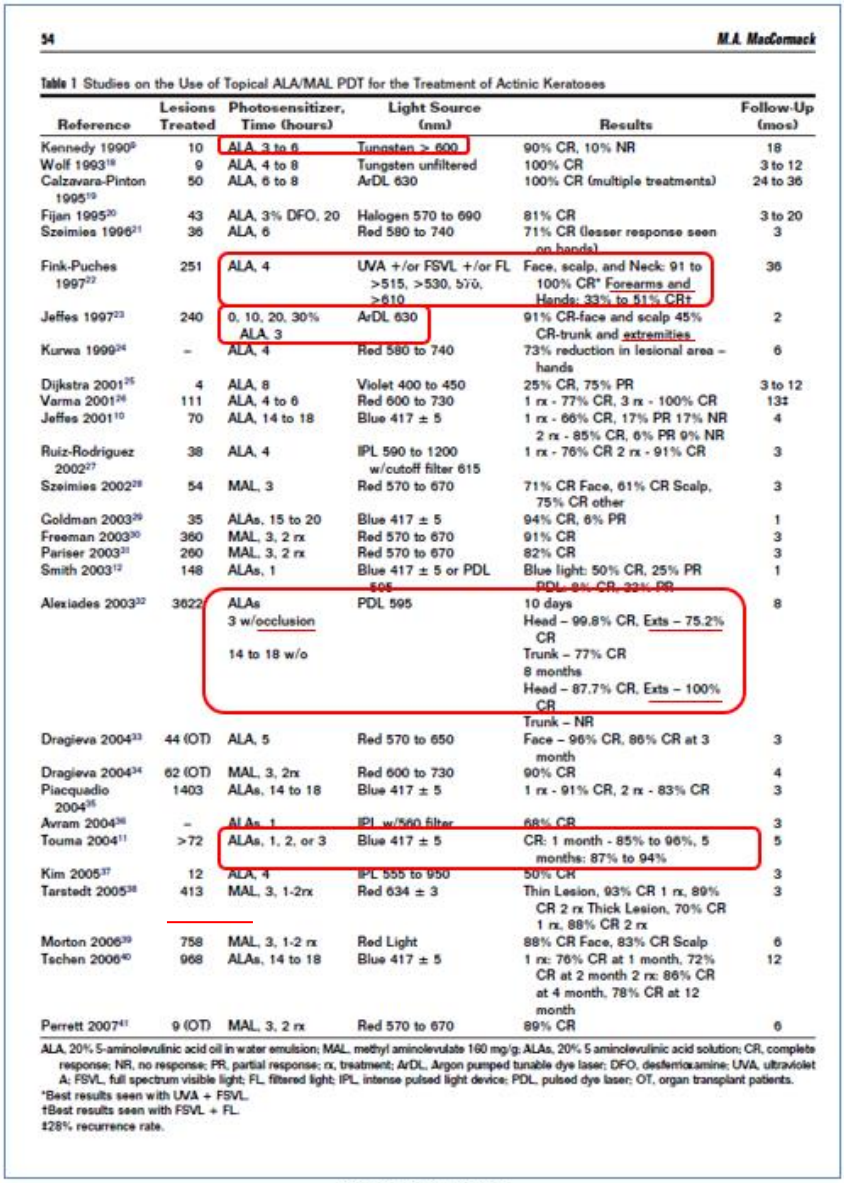


Ozog 2016

As mentioned, from MacCormack, **NONE** of the citations listed in Table 1 entitled "Studies on the Use of 5-ALA/MAL PDT for the Treatment of Actinic Keratoses" (below) is found on the face of the patent nor cited during prosecution:

Kennedy 2009	Wolf 1993	Calzaver-Pinton 1993	Fijan 1995
Szeimies 1996	Fink-Puches 1997	Jeffes 1997	Kurwa 1999
Dijkstra 2001	Varma 2001	Jeffes 2001	Ruiz-Rodriquez 2002
Szeimies 2002	Goldman 2003	Freeman 2003	Pariser 2003
Smith 2003	Alexiades 2003	Dragieva 2003a, 2003b	Piacquadio 2004
Avram 2004	Touma 2004*	Kim 2005	Tarstedt 2005
Morton 2006	Tschen 2006	Perrett 2007	

Of these omitted citations, attention is called to at least Kennedy 2009, Fink-Puches 1997, Jeffes 1997, and Alexiades 2003 as being particularly pertinent to the prior art (indicated below in red).



54 M.A. MacCormack

Table 1 Studies on the Use of Topical ALA/MAL PDT for the Treatment of Actinic Keratoses

Reference	Lesions Treated	Photosensitizer, Time (hours)	Light Source (nm)	Results	Follow-Up (mos)
Kennedy 1999[9]	10	ALA, 3 to 6	Tungsten > 600	90% CR, 10% NR	18
Wolf 1993[18]	9	ALA, 4 to 8	Tungsten unfiltered	100% CR	3 to 12
Calzavara-Pinton 1995[19]	50	ALA, 6 to 8	ArDL 630	100% CR (multiple treatments)	24 to 36
Fijan 1995[20]	43	ALA, 3% DFO, 20	Halogen 570 to 690	81% CR	3 to 20
Szeimies 1996[21]	36	ALA, 6	Red 580 to 740	71% CR (lesser response seen on hands)	3
Fink-Puches 1997[22]	251	ALA, 4	UVA +/or FSVL +/or FL >515, >530, 570, >610	Face, scalp, and Neck: 91 to 100% CR* Forearms and Hands: 33% to 51% CR†	36
Jeffes 1997[23]	240	0, 10, 20, 30% ALA, 3	ArDL 630	91% CR-face and scalp 45% CR-trunk and extremities	2
Kurwa 1999[24]	–	ALA, 4	Red 580 to 740	73% reduction in lesional area – hands	6
Dijkstra 2001[25]	4	ALA, 8	Violet 400 to 450	25% CR, 75% PR	3 to 12
Varma 2001[26]	111	ALA, 4 to 6	Red 600 to 730	1 rx - 77% CR, 3 rx - 100% CR	13‡
Jeffes 2001[10]	70	ALA, 14 to 18	Blue 417 ± 5	1 rx - 66% CR, 17% PR 17% NR 2 rx - 85% CR, 6% PR 9% NR	4
Ruiz-Rodriguez 2002[27]	38	ALA, 4	IPL 590 to 1200 w/cutoff filter 615	1 rx - 76% CR 2 rx - 91% CR	3
Szeimies 2002[28]	54	MAL, 3	Red 570 to 670	71% CR Face, 61% CR Scalp, 75% CR other	3
Goldman 2003[29]	35	ALAs, 15 to 20	Blue 417 ± 5	94% CR, 6% PR	1
Freeman 2003[30]	360	MAL, 3, 2 rx	Red 570 to 670	91% CR	3
Pariser 2003[31]	260	MAL, 3, 2 rx	Red 570 to 670	82% CR	3
Smith 2003[12]	148	ALAs, 1	Blue 417 ± 5 or PDL 595	Blue light: 50% CR, 25% PR PDL: 9% CR, 33% PR	1
Alexiades 2003[32]	3622	ALAs 3 w/occlusion 14 to 18 w/o	PDL 595	10 days Head – 99.8% CR, Exts – 75.2% CR Trunk – 77% CR 8 months Head – 87.7% CR, Exts – 100% CR Trunk – NR	8
Dragieva 2004[33]	44 (OT)	ALA, 5	Red 570 to 650	Face – 96% CR, 86% CR at 3 month	3
Dragieva 2004[34]	62 (OT)	MAL, 3, 2rx	Red 600 to 730	90% CR	4
Piacquadio 2004[35]	1403	ALAs, 14 to 18	Blue 417 ± 5	1 rx - 91% CR, 2 rx - 83% CR	3
Avram 2004[36]	–	ALAs, 1	IPL w/560 filter	68% CR	3
Touma 2004[11]	>72	ALAs, 1, 2, or 3	Blue 417 ± 5	CR: 1 month - 85% to 96%, 5 months: 87% to 94%	5
Kim 2005[37]	12	ALA, 4	IPL 555 to 950	50% CR	3
Tarstedt 2005[38]	413	MAL, 3, 1-2rx	Red 634 ± 3	Thin Lesion, 93% CR 1 rx, 89% CR 2 rx Thick Lesion, 70% CR 1 rx, 88% CR 2 rx	3
Morton 2006[39]	758	MAL, 3, 1-2 rx	Red Light	88% CR Face, 83% CR Scalp	6
Tschen 2006[40]	968	ALAs, 14 to 18	Blue 417 ± 5	1 rx: 76% CR at 1 month, 72% CR at 2 month 2 rx: 86% CR at 4 month, 78% CR at 12 month	12
Perrett 2007[41]	9 (OT)	MAL, 3, 2 rx	Red 570 to 670	89% CR	6

ALA, 20% 5-aminolevulinic acid oil in water emulsion; MAL, methyl aminolevulate 160 mg/g; ALAs, 20% 5 aminolevulinic acid solution; CR, complete response; NR, no response; PR, partial response; rx, treatment; ArDL, Argon pumped tunable dye laser; DFO, desferrioxamine; UVA, ultraviolet A; FSVL, full spectrum visible light; FL, filtered light; IPL, intense pulsed light device; PDL, pulsed dye laser; OT, organ transplant patients.
*Best results seen with UVA + FSVL.
†Best results seen with FSVL + FL.
‡28% recurrence rate.

MacCormack 2008

Ozog is the primary document cited for invalidating prior art in the claim chart, below. Ozog is a **consensus document from a panel of experts** on the understanding of the state of the art and use of 5-ALA PDT. It was published in July 2016, at least a year and a half before the priority date of the '567. Ozog is neither cited not mentioned during prosecution of the application resulting in the issuance of the '567 patent.

Ozog states as follows:

> The American Society of Dermatologic Surgery (ASDS) periodically develops **consensus documents** for its members concerning various aspects of dermatologic surgery. Advances in photodynamic therapy (PDT) have been many and PDT use has been established in a variety of skin conditions.
>
> OBJECTIVE: The ASDS board of directors proposed a **committee of experts** in the field to develop consensus documents on different treatments. An expert panel reviewed the literature on PDT and discussed the findings. **The consensus was reached with evidence-based recommendations on different clinical applications for PDT.** (Abstract; emphasis added)

Ozog specifically delineates the following procedures, particularly pertinent to the prior art:

TABLE 4. Photodynamic Therapy Specific Treatment Protocols for Different Indications

Indication	*Topical Photosensitizer*	*Incubation Period*	*Light Source*	*Dose*	*Comments*
Actinic keratosis	ALA	1–4 h	Blue light	10 J/cm²	Requires 1–2 sessions of PDT for optimal results
		1–4 h	Red light	75–150 J/cm²	Sunscreen necessary for daylight PDT
		0.5 h	Daylight	2 h	
	MAL	1–3 h	Red light	37–75 J/cm²	
Bowen disease	ALA	4 h	Red light	≥100 J/cm²	Requires 2–3 sessions of PDT for optimal results
	MAL	3 h	Red light	75–100 J/cm²	
Superficial BCC	ALA	3–6 h	Red light	≥60 J/cm²	Requires 2–3 sessions of PDT for optimal results
	MAL	3 h	Red light	37–75 J/cm²	
Acne vulgaris	ALA	3 h	Blue light	10 J/cm²	2–3 treatments, repeated biweekly
			Red light	37 J/cm²	
	MAL	3 h	Red light	37 J/cm²	
Photorejuvenation	ALA	30 min–3 h	Blue light	10 J/cm²	2–3 treatments, repeated monthly
			Red light	37 J/cm²	
	MAL	30 min–1 h	Red light	37 J/cm²	

ALA, aminolevulinic acid; BCC, basal cell carcinoma; MAL, methyl aminolevulinate; PDT, photodynamic therapy.

Ozug 2016

The Table below is a very brief summary of some of the pertinent prior art exemplary of various elements of the claims in the '567.

Publication	5-ALA or MAL	Topical application	Occlusion	3 hrs	Light	Hand/Forearm
Piacquadio 2004	5-ALA	✓			Blue	
Alexiades-Armenakas 2003	5-ALA	✓	✓ gauze	✓	PDL (595 nm)	✓
Kurwa 1999	5-ALA	✓	✓	4 hrs	Red (580 to 740 nm)	✓
Tarstedt 2005	MAL	✓	✓	✓	Red (634 nm)	
Dragieva 2003	MAL	✓	✓	✓	Red (600-700 nm)	✓
Hongcharu 2000	5-ALA	✓	✓ Saran wrap	✓	Red (550-700 nm)	
Jeffes 1997	5-ALA	✓	✓	✓	✓	✓
Ozog	5-ALA	✓	✓ plastic wrap	✓	Blue	✓
Ruiz-Rodriquez 2002	5-ALA	✓	✓ plastic film	4 hrs	Red (615 nm)	
Szeimes 1996	5-ALA	✓	✓	6 hrs	Red 580-740 nm	✓
Varma 2000	5-ALA	✓	✓ Tegaderm	4 hrs	Red 640 nm	
Sakamoto 2008	5-ALA	✓	✓ Saran wrap	3 hrs	Blue	✓
MacCormack	5-ALA	✓	✓	✓	Blue and Red	✓
Wolf 1993	5-ALA	✓	✓	4 hrs	Red 570 nm	✓

Ground I

Claims 1, 2, and 4-9 are obvious under 35 U.S.C § 103(a) over the prior art of Ozog in view of Sakamoto.

U.S. 10357567	Ozog in view of Sakamoto
1. A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:	Ozog teaches a method of enhancing penetration ("occlusion has been used to **increase penetration**." Pg. 808, right column, top) of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy ("The **application of the topical ALA** solution…" pg. 808 left column, bottom; "The main types of topical photosensitizer prodrugs used for **PDT** are **5-aminolevulinic acid (5-ALA)** or its derivatives." Pg. 804 left column, bottom).
topically applying ALA to a treatment area to be treated with photodynamic therapy;	Ozog teaches topically applying ALA to a treatment area to be treated with photodynamic therapy ("The **application of the topical ALA** solution…" pg. 808 left column, bottom; "The main types of topical photosensitizer prodrugs used for **PDT** are **5-aminolevulinic acid (5-ALA)** or its derivatives." Pg. 804 left column, bottom).
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	Ozog teaches after the ALA is applied to the treatment area, covering the treatment area with a plastic wrap-type, occlusive barrier prior to light treatment to minimize transepidermal water loss from the treatment area; ("For nonfacial areas, such as the extremities, **occlusion** has been used **to increase penetration**. This can be accomplished with plastic wrap or some other nonporous flexible material placed over the targeted area after the ALA has been applied." Pg. 808 right column top) Ozog does not specifically teach the plastic wrap-type, occlusive barrier is low density polyethylene. However low density polyethylene barriers to enhance penetration were well known in the art at the time of the invention as described by Sakamoto. Sakamoto teaches PDT in which after 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 (para [0106] "An **occlusive, transparent plastic mask or covering such as, e.g., Saran® wrap** or a transparent occlusive ointment may optionally be placed, sprayed or spread on the skin.) Saran wrap was a well known low density polyethylene material. It would have been obvious to POSA that a low density polyethylene barriers such as Saran® wrap could have been used to cover the area of application to minimize tranepidermal water loss as a method to increase penetration of 5-ALA as described without undue experimentation according to the method of Ozog in view of Sakamoto. [Other references to plastic wrap or Saran wrap can be readily found.]
removing the low density polyethylene barrier within 3 hours	Ozog teaches removing the occlusive barrier within 3 hours and then applying light to the treatment area ("A recent multicenter

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and then applying light to the treatment area.	randomized study found the median AK clearance rate at 12 weeks to be 88.7% for extremities, when **treated with ALA under occlusion for 3 hours and irradiated with blue light** (10 J/cm2)" pg. 808, right column, middle; "After incubation, the targeted area may be gently washed with water and a cleanser." pg. 808 right column, bottom. Further "the targeted area may be gently washed" following incubation implies that the barrier has been removed.). [See also Schmieder *et al* 2012]
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.	The method of claim 1 is obvious, as described above. Further, Ozog teaches the occlusive 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 ("A recent multicenter randomized study found the median AK clearance rate at 12 weeks to be 88.7% for extremities, when treated with **ALA under occlusion for 3 hours and irradiated with blue light** (**10 J/cm2**)" pg. 808, right column, middle).
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.	*Not on FDA label under Section 2 "Dosage and Administration" as being required for treatment.*
4. A method of enhancing penetration of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy, the method comprising:	Ozog teaches a method of enhancing penetration ("occlusion has been used to **increase penetration**." Pg. 808, right column, top) of a topical composition of 5-aminolevulinic acid (ALA) into tissue for photodynamic therapy ("The **application of the topical ALA** solution…" pg. 808 left column, bottom; "The main types of topical photosensitizer prodrugs used for **PDT** are **5-aminolevulinic acid (5-ALA)** or its derivatives." Pg. 804 left column, bottom).
topically applying ALA to a treatment area to be treated with photodynamic therapy; and	Ozog teaches topically applying ALA to a treatment area to be treated with photodynamic therapy ("The **application of the topical ALA** solution…" pg. 808 left column, bottom; "The main types of topical photosensitizer prodrugs used for **PDT** are **5-aminolevulinic acid (5-ALA)** or its derivatives." Pg. 804 left column, bottom).
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,	Ozog teaches after the ALA is applied to the treatment area, covering the treatment area with a plastic wrap-type, occlusive barrier prior to light treatment to minimize transepidermal water loss from the treatment area; ("For nonfacial areas, such as the extremities, occlusion has been used to increase penetration. This can be accomplished with plastic wrap or some other nonporous flexible material placed over the targeted area after the ALA has been applied." Pg. 808, right column, top) Ozog does not specifically teach the plastic wrap-type, occlusive barrier is specifically low density polyethylene. However low density polyethylene plastic wrap-type, occlusive barriers to enhance penetration of ALA were well known in the art at the

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	time of the invention as described by Sakamoto. Sakamoto specifically teaches the plastic wrap-type, occlusive barrier is a low density polyethylene barrier covering the treatment area with prior to light treatment to minimize transepidermal water loss from the treatment area and is employed after ALA is applied to the treatment area, (para [0106] "An occlusive, transparent plastic mask or covering such as, e.g., Saran® wrap or a transparent occlusive ointment may optionally be placed, sprayed or spread on the skin.) It would have been obvious to POSA that a low density polyethylene barriers such as Saran® wrap could have been used to cover the area of application to minimize tranepidermal water loss as a method to increase penetration of 5-ALA as described without undue experimentation according to Ozog in further view of Sakamoto.
wherein the treatment area is located on a hand or a forearm.	Ozog teaches the treatment area is located on a hand or a forearm (Figure 5 pg. 814; "For nonfacial areas, such as the **extremities**, occlusion has been used to increase penetration." Pg. 808, right column top; "Sixteen patients with 542 AKs in field-cancerized skin of the scalp, chest, and **extremities** were treated." Pg. 812, left column middle).
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.	The method of claim 4 is obvious as described above. Further, Ozog teaches removing the barrier from the treatment area prior to phototherapy area ("A recent multicenter randomized study found the median AK clearance rate at 12 weeks to be 88.7% for extremities, when **treated with ALA under occlusion for 3 hours** and irradiated with blue light (10 J/cm2)" pg. 808, right column, middle; "After incubation, the targeted area may be gently washed with water and a cleanser." pg. 808 right column, bottom. Wherein "the targeted area may be gently washed" following incubation implies that the barrier has been removed. [See also Schmieder *et al* 2012]), and further that red light is applied to the treatment area following the initial treatment interval of less than 3 hours. (Table 4, pg. 811; "…compared the efficacy of ALA-PDT with that of MAL-PDT…" … Both photosensitizers were applied for 3 hours under occlusion, followed by **irradiation with red light** (635 nm, 37 J/cm2) pg. 817 right column middle; "**red light** (635 nm) is used for thicker lesions because it has a greater than 2-mm penetration." Pg. 806, right column bottom; "**Red light** requires a longer irradiation period because it does not excite PpIX as efficiently as blue light. … In fact, there is evidence to support that cumulative light doses of greater than 40 J/cm2 can deplete all available oxygen sources during the oxidation reaction, making higher doses of energy during PDT unnecessary." Pg. 807 right column, bottom; (3 hours of incubation with illumination with broad-spectrum red light; 75 J/cm2" pg. 810 left column middle.; "Red light (630 nm) irradiation was used for both ALA and MAL; range 37 to 80 J/cm pg. 812 left column bottom; Figure 8; "ALA was applied under occlusion for 4 hour before irradiation with red light (590–700 nm, 70 J/cm2) pg. 820 left column top).

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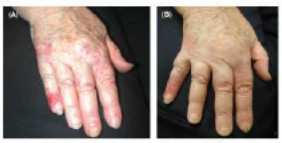
6. The method as set forth in claim 4, wherein the treatment area is a dorsal surface of the hand.	Claim 4 is obvious as above. Further, Ozog teaches the treatment area is a dorsal surface of the hand. (Figure 5 pg. 814).  Figure 5. (A) Right hand with multiple Bowen disease and (B) after 2 sessions of PDT using 20% aminolevulinic acid and blue light combined with pulsed-dye laser. Of note, the residual lesion on the fifth digit was treated with Mohs surgery (courtesy of David M. Ozog, MD).
7. The method as set forth in claim 4, wherein the treatment area is a dorsal surface of the forearm.	Claim 4 is obvious as above. Ozog does not specifically teach the treatment area is a dorsal surface of the forearm. However, Ozog does specifically teach "treatment of extremities", ("For nonfacial areas, such as the **extremities**, occlusion has been used to increase penetration." Pg. 808, right column top; "Sixteen patients with 542 AKs in field-cancerized skin of the scalp, chest, and **extremities** were treated." Pg. 812, left column middle). It would have been readily obvious to POSA that treatment of the dorsal forearm would have been available as a type of well known treatment of extremities. [See also Schmeider which specifically teaches the treatment area is a dorsal surface of a forearm.]
8. A method of using 5-aminolevulinic acid (ALA) and a low density polyethylene barrier, comprising:	Ozog teaches a method using 5-aminolevulinic acid (ALA) ("The **application of the topical ALA** solution…" pg. 808 left column, bottom; "The main types of topical photosensitizer prodrugs used for **PDT** are **5-aminolevulinic acid (5-ALA)** or its derivatives." Pg. 804 left column, bottom) and a plastic wrap-type, occlusive barrier ("Occlusion has been used to **increase penetration**." This can be accomplished with plastic wrap or some other nonporous flexible material placed over the targeted area after the ALA has been applied. Pg. 808, right column, top) Ozog does not specifically teach the barrier is low density polyethylene. However low density polyethylene barriers to enhance penetration were well known in the art at the time of the invention as described by Sakamoto. Sakamoto teaches PDT in which after 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 (para [0106] "An **occlusive, transparent plastic mask or covering such as, e.g., Saran® wrap** or a transparent occlusive ointment may optionally be placed, sprayed or spread on the skin.) Saran wrap was a well-known low density polyethylene material. It would have been obvious to POSA that a low density polyethylene barriers such as Saran® wrap or similar could have been used to cover the area of application to minimize transepidermal water loss as a method to increase

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	penetration of 5-ALA as described by Sakamoto without undue experimentation.
contacting a treatment site with a composition comprising the ALA so as to wet the treatment site; *According to the specifications of the '567, the term "wetting" means simply to apply a topical composition of ALA to the surface of the skin and nothing more. "The method includes contacting a treatment site with a composition comprising the ALA so as to wet the treatment site" (col 2 ln 61—63) and "In one embodiment, ALA may be applied in a topical composition with a concentration of 20 % . The ALA admixture is topically applied to the lesions using a point applicator to control dispersion of the ALA admixture, in at least one embodiment, so as to achieve a substantially uniform wetting of the lesion surface with the ALA by contacting the ALA with the lesion surface." (col 9 ln 11-18)*	Ozog teaches contacting a treatment site with a composition comprising the ALA so as to wet the treatment site ("The **application of the topical ALA** solution…" pg. 808 left column, bottom; "The main types of topical photosensitizer prodrugs used for **PDT** are **5-aminolevulinic acid (5-ALA)** or its derivatives." Pg. 804 left column, bottom; "In the United States, ALA is available as a **20% solution** and is marketed under the trade name Levulan (DUSA Pharmaceuticals, Inc., Wilmington, MA). It is FDA approved since 1999…" pg. 806, left column, middle) Ozog also teaches alternative methods to wet the treatment site ("Many methods exist for pretreatment preparation of skin-cleansing regimens. Cleaning allows for a more uniform penetration of the ALA and subsequent photoactivation. … Isopropyl alcohol, soaps, alpha-hydroxy/salicylic acid cleansers, or towelettes can also be used." Pg. 808 left column, middle).
following wetting of the treatment site, covering the wetted treatment site with the low density polyethylene barrier;	Ozog teaches following wetting of the treatment site, covering the wetted treatment site with a plastic wrap-type, occlusive barrier ("Occlusion has been used to **increase penetration**." This can be accomplished with plastic wrap or some other nonporous flexible material placed over the targeted area after the ALA has been applied." Pg. 808, right column, top)
removing the low density polyethylene barrier so as to expose the treatment site; and	Ozog teaches removing the occlusive barrier so as to expose the treatment site ("After incubation, the targeted area may be gently washed with water and a cleanser." pg. 808 right column, bottom. Wherein "the targeted area may be gently washed" following incubation implies that the barrier has been removed. [See also Schmieder *et al* 2012]).
illuminating the exposed treatment site with an illuminator so as to deliver a 10 J/cm2 dose of blue light.	Ozog teaches illuminating the exposed treatment site with an illuminator so as to deliver a 10 J/cm2 dose of blue light ("A recent multicenter randomized study found the median AK clearance rate at 12 weeks to be 88.7% for extremities, when treated with ALA under occlusion for 3 hours and **irradiated with blue light** (**10 J/cm2**)" pg. 808, right column, middle).
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.	Claim 8 is obvious as above. Further Ozog teaches the occlusive barrier is removed no later than three hours after the treatment site is covered. ("A recent multicenter randomized study found the median AK clearance rate at 12 weeks to be 88.7% for extremities, when **treated with ALA under occlusion for 3 hours** and irradiated with blue light (10 J/cm2)" pg. 808, right column, middle; "After incubation, the targeted area may be gently washed with water and a cleanser." pg. 808 right

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	column, bottom. Wherein "the targeted area may be gently washed" following incubation implies that the barrier has been removed. [See also Schmieder *et al* 2012])

Ground II

Claim 10 is obvious under 35 U.S.C § 103(a) over Ozog and Sakamoto in further view of the FDA Label 2006.

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10. The method of claim 8, further comprising: positioning the treatment site between two inches and four inches from a surface of the illuminator.	Claim 8 is obvious over Ozog in further view of Sakamoto. Neither Ozog nor Sakamoto specifically teach positioning the treatment site between two inches and four inches from a surface of the illuminator. However, such positing of the light source was very well known and widely practiced in the art at the time of the invention as exemplified in an early FDA label for Levulan that specifically teaches positioning the treatment site between two inches and four inches from a surface of the illuminator ("The BLU-U is positioned around the patient's head so the entire surface area to be treated lies between 2" and 4" from the BLU-U surface" pg. 12). It would have been obvious to practice the method of Ozog in view of Sakamoto by positing the light source as claimed since such positing has been taught specifically for ALA PDT since at least 2006 in guidance approved by the FDA Label for commercially available 5-ALA PDTs.