Efficacy of ALA–PDT in the treatment of actinic keratoses on the upper extremities: A post hoc analysis of a phase 3, randomized, vehicle-controlled trial

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BACKGROUND

- Actinic keratoses (AKs) are precancerous, dysplastic epidermal lesions that may progress to squamous cell carcinoma (SCC)[1]
- Aminolevulinic acid (ALA) 20% solution photodynamic therapy (PDT) is indicated for targeted treatment of AK on the face, scalp, and upper extremities[2]
- In a phase 3, randomized, evaluator-blinded, vehicle-controlled trial (NCT02137785), ALA 20% solution–PDT at baseline and week 8 using lesion-targeted treatment and a 3-hour occluded incubation was superior to vehicle (VEH)–PDT for AK clearance of the upper extremities[3]
  - The study assessed response of the entire field to treatment, including new AKs present at follow-up, in calculations of clearance rates

OBJECTIVE

- To assess clearance rate relative to baseline, cumulative disease area clearance, and complete clearance rate by lesion size in treated lesions only in patients treated with ALA-PDT for AKs on the upper extremities

METHODS

Study design

- This is a post hoc analysis of a phase 3, randomized, evaluator-blinded, vehicle-controlled, parallel group trial (NCT02137785) conducted between May 8, 2014, and March 5, 2015[3]
- The study enrolled men and women ≥18 years of age with 4–15 grade 1–2 AKs on ≥1 upper extremity treatment area, defined as the area between the elbow and the base of the fingers
- If both arms qualified for inclusion, the treatment arm was defined as the arm with greater number of lesions, or the arm with higher grade lesions if both had an equal number
- Major exclusion criteria included presence within the treatment area of grade 3 or atypical AKs larger than 1 cm, lesions suspicious for skin cancer, or untreated skin cancer
- Patients were randomized in a 1:1 ratio to receive topical application of ALA 20% or VEH to AKs within the treatment area, followed by 3 h incubation with occlusion and 10 J/cm^2 blue light photodynamic therapy at 10 mW/cm^2
- Treatment was repeated at week 8 if any lesions were present within the treatment area, and patients were followed for up to 12 weeks postbaseline

Endpoints and assessments

- AK lesion count and mapping were performed at baseline and at weeks 4, 8, and 12; lesion size and grade were assessed at baseline and at weeks 8 and 12
- Post hoc assessments included mean AK clearance rate compared to baseline, cumulative disease area clearance, and subgroup analysis of complete clearance rate by lesion size
- Safety assessments included assessment of PDT responses (tolerability) and adverse event (AE) monitoring throughout the study

Statistical analyses

- Continuous variables were summarized using descriptive statistics (n, mean, median, standard deviation [SD], and range), and categorical variables were summarized using frequency counts and percentages
- Lesion clearance rate was calculated as (1 – number of treated AK lesions present at follow-up/ number of AK lesions at baseline) x 100
- Percent cumulative disease area cleared was calculated as (1 – sum of treated lesion sizes at follow-up/sum of lesion sizes at baseline) x 100
- Statistical comparisons of clearance rate and percent cumulative disease area cleared used a linear mixed model with fixed effects for treatment group, time point, and treatment group by time point interaction

RESULTS

- The study enrolled 269 patients,135 and 134 randomized to ALA-PDT and VEH-PDT, respectively; 132 (97.8%) patients who received ALA-PDT and 130 (97.0%) patients who received VEH-PDT treatment completed the study, and all patients were included in the current post hoc analysis
- The mean (SD) age was 67.6 (8.6) and 67.6 (9.4) years for the ALA-PDT and vehicle group respectively; patients were predominantly male (188 [69.9%]) both in the ALA-PDT (92 [68.1%]) and the VEH-PDT group (96 [71.6%], **Table 1**)
- The mean (SD) number of lesions per patient in the treated area at baseline was 8.5 (3.6) for the ALA-PDT group and 8.6 (3.4) for the VEH-PDT group (**Table 1**)
- The mean cumulative disease area at baseline was 149 mm^2 and 154 mm^2 for ALA-PDT and VEH-PDT-treated AKs, respectively (**Table 1**)

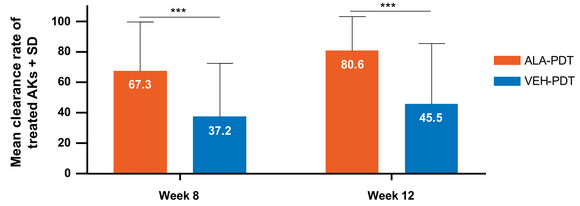
Table 1. Patient demographics and baseline disease characteristics

	ALA-PDT (N = 135)	VEH-PDT (N = 134)
Age, years, mean (SD)	67.6 (8.6)	67.6 (9.4)
Sex, male	92 (68.1)	96 (71.6)
Ethnicity		
Hispanic or Latino	0	3 (2.2)
Not Hispanic or Latino	135 (100.0)	131 (97.8)
Race		
White	135 (100.0)	134 (100.0)
Number of lesions	1150	1149
Grade 1	576 (50.1)	580 (50.5)
Grade 2	574 (49.9)	569 (49.5)
Lesions per patient, mean (SD)	8.5 (3.6)	8.6 (3.4)
Mean cumulative disease area, mm^2	149	154

Data presented as n (%) unless otherwise indicated.
ALA-PDT, aminolevulinic acid combined with photodynamic therapy; SD, standard deviation; VEH-PDT, vehicle combined with photodynamic therapy.

- The mean (SD) AK clearance rate for lesions of all sizes treated with ALA-PDT was 80.6% (22.6%) at 12 weeks (after up to 2 treatments), compared with 45.5% (37.2%) for lesions treated with VEH-PDT (*P* <0.0001, linear mixed model, **Figure 1**)

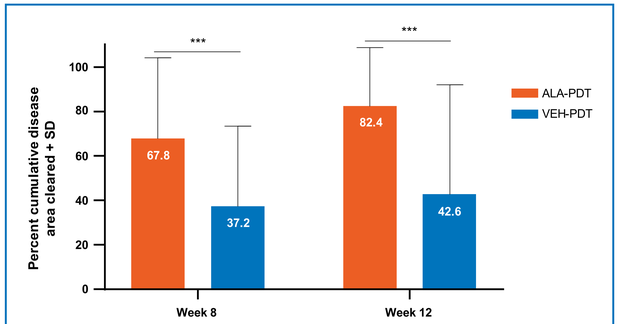
Figure 1. Clearance rate of treated actinic keratoses of all sizes at week 8 and 12



***P <0.0001 using linear mixed model with fixed effects for treatment group, time point, and treatment group by time point interaction.
AK, actinic keratosis; ALA-PDT, aminolevulinic acid combined with photodynamic therapy; SD, standard deviation; VEH-PDT, vehicle combined with photodynamic therapy.

- At week 12, a mean (SD) of 82.4% (26.3%) of the cumulative disease area was cleared after ALA-PDT, compared with 42.6% (49.4%) after VEH-PDT (*P* <0.0001, linear mixed model, **Figure 2**)

Figure 2. Percent cumulative disease area cleared at week 8 and 12



***P <0.0001 using linear mixed model with fixed effects for treatment group, time point, and treatment group by time point interaction.
ALA-PDT, aminolevulinic acid combined with photodynamic therapy; SD, standard deviation; VEH-PDT, vehicle combined with photodynamic therapy.

- More than half of patients treated with ALA-PDT experienced complete clearance of larger lesions at 12 weeks, with 48/68 (70.6%) patients exhibiting complete clearance of lesions 25–36 mm^2 and 25/42 (59.5%) patients exhibiting complete clearance of lesions ≥36 mm^2 (**Table 2**)

Table 2. Clearance of lesions by size at week 8 and 12

	Week 8			Week 12		
BL lesion size	**n**	**Complete clearance**	**≥75% clearance**	**n**	**Complete clearance**	**≥75% clearance**
<10 mm^2						
ALA-PDT	95	44 (46.3)	59 (62.1)	104	59 (56.7)	74 (71.2)
VEH-PDT	90	15 (16.7)	23 (25.6)	104	25 (24.0)	37 (35.6)
10–25 mm^2						
ALA-PDT	103	43 (41.7)	49 (47.6)	115	66 (57.4)	72 (62.6)
VEH-PDT	102	20 (19.6)	24 (23.5)	114	31 (27.2)	38 (33.3)
25–36 mm^2						
ALA-PDT	57	32 (56.1)	33 (57.9)	68	48 (70.6)	50 (73.5)
VEH-PDT	52	18 (34.6)	18 (34.6)	56	18 (32.1)	18 (32.1)
≥36 mm^2						
ALA-PDT	37	20 (54.1)	22 (59.5)	42	25 (59.5)	31 (73.8)
VEH-PDT	40	9 (22.5)	9 (22.5)	43	11 (25.6)	13 (30.2)

Data presented as n (%) unless otherwise indicated.
ALA-PDT, aminolevulinic acid combined with photodynamic therapy; BL, baseline; VEH-PDT, vehicle combined with photodynamic therapy.

- Reactions to PDT were all expected, nonserious, and would typically resolve within several weeks
- As anticipated, pretreatment with ALA resulted in a greater incidence and severity of certain PDT side effects (erythema, edema, stinging/burning, scaling and dryness, and oozing/vesiculation/ crusting) than was seen after pretreatment with VEH
- By the end of the study (4 weeks after the second PDT treatment), most patients had returned to their baseline status with respect to these effects
- No clinically significant AEs were reported for either study group (**Table 3**) and there were no discontinuations due to AEs
- A total of 16 skin carcinomas were diagnosed in the study:
  - Nine SCCs were diagnosed in 7 patients treated with ALA-PDT, all of whom had prior history of SCC; 2 SCCs were within the treatment area
  - Three SCCs were diagnosed in 3 patients treated with VEH-PDT, of whom 2 had prior history of SCC; 1 SCC was within the treatment area
  - Four BCCs were diagnosed in 3 patients treated with VEH-PDT, all of whom had prior history of BCC; no BCCs were within the treatment area

Table 3. Adverse events reported in ≥3 patients in either treatment group

	ALA-PDT (N = 135)	VEH-PDT (N = 134)
Infections and infestations		
Nasopharyngitis	2 (1.5)	4 (3.0)
Sinusitis	3 (2.2)	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)		
Basal cell carcinoma	0	3 (2.2)
Squamous cell carcinoma	3 (2.2)	1 (0.7)
Squamous cell carcinoma of skin	4 (3.0)	2 (1.5)

Data presented as n (%).
ALA-PDT, aminolevulinic acid combined with photodynamic therapy; VEH-PDT, vehicle combined with photodynamic therapy.

CONCLUSIONS

- ALA-PDT resulted in significantly higher clearance rates of treated AKs and significantly higher percent of treated disease area cleared vs VEH-PDT, with good response of large lesions
- Therapy with ALA-PDT was well tolerated, and no safety concerns were raised

REFERENCES

1. Criscione, VD et al. *Cancer.* 2009; 115:2523–30.
2. Levulan Kerastick (aminolevulinic acid HCl) for topical solution, 20%. Full Prescribing Information. DUSA Pharmaceuticals, Inc., Wilmington, MA, USA. 2017.
3. Brian Jiang, SI et al. *Dermatol Surg.* 2019; 45:890–7.

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DISCLOSURES

BB has received grants and consulting fees from Anacor; Pfizer; DUSA Pharmaceuticals, Inc., Sun Pharmaceutical Industries, Inc.; and Biofrontera. **NB** is an advisor, consultant, investigator, and speaker for Anacor, Merz, Sandoz, and Valeant. **DP** is an employee of Therapeutics Inc. **AH** is an employee of DUSA Pharmaceuticals, Inc. **DS** is a member of the Board of Directors for Caliber I.D.; member of the Clinical Advisory Board for Michelson Diagnostics, LTD; and an advisory board attendee for Castle Biosciences Inc.

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