

## ORIGINAL ARTICLE

# The impact of occlusive vs non-occlusive application of 5-aminolevulinic acid (BF-200 ALA) on the efficacy and tolerability of photodynamic therapy for actinic keratosis on the scalp and face: A prospective within-patient comparison trial

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## Abstract

**Background:** Photodynamic therapy (PDT) is an effective treatment for actinic keratoses (AK). PDT is usually performed with occlusion of the photosensitizer prior to subsequent illumination.

**Objectives:** This study aimed to compare the efficacy and tolerability of occlusive versus non-occlusive application of a 5-aminolevulinic acid (BT-200 ALA) for PDT of multiple AK on the scalp or face.

**Methods:** Prospective, investigator-blinded, within-patient comparison study on 45 patients. PDT with occlusion of ALA was performed in a target area on one randomized side of the scalp or face. One week later a contralateral target area received the same treatment except that no occlusion of the ALA gel was performed. 3 and 6 months after PDT, the clearance rate of a predetermined target lesion and the total clearance rate of all AK within the treated areas were determined. PDT-induced pain and skin phototoxicity and cosmetic outcome were also recorded.

**Results:** Clearance rate of the target AK and total AK clearance rate at 3 months after PDT was 88.4% and 90.6% for occlusive PDT and 58.1% ( $P = .001$ ) and 70.4% ( $P = .04$ ) for non-occlusive PDT. The corresponding values at 6 months after PDT were 69.7% and 72.1% for occlusive PDT and 30.2% ( $P < .001$ ) and 35.6% ( $P = .001$ ) for non-occlusive PDT. Pain score and skin phototoxicity were significantly higher after occlusive ALA application. No difference was observed with respect to cosmetic outcome.

**Conclusions:** Occlusive application of ALA significantly improves the efficacy of PDT but is associated with more pain and increased phototoxicity.

## KEYWORDS

5-aminolevulinic acid, actinic keratosis, ALA, BF-200, occlusion, photodynamic therapy

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## 1 | INTRODUCTION

Actinic keratosis (AK) is a very common in-situ squamous cell carcinoma (SCC) that is mainly caused by chronic ultraviolet damage.<sup>1-3</sup> In immunocompetent patients, an estimated 10% of all AK progress into invasive SCC and this rate increases up to 30% in immunosuppressed patients.<sup>2</sup> Due to a substantial risk for SCC development, there is general consensus that AK needs to be treated.

The choice of treatment depends on clinical grade, number and localization of lesions, the extent of the affected areas, the patients' general health status, and both patients' and physicians' individual preferences.<sup>3</sup> Photodynamic therapy (PDT) using 5-aminolevulinic acid (5-ALA) or its methyl ester (methyl aminolevulinate, MAL) is among the first line treatments of AK due to its high efficacy and excellent cosmetic outcome.<sup>4</sup>

BF-200 ALA (Ameluz<sup>®</sup>, Biofrontera Bioscience GmbH) is a nanoemulsion-based 5-ALA gel formulation containing 7.8% 5-ALA. This specific formulation of 5-ALA has been shown to confer increased stability and skin penetration as compared to conventional 5-ALA preparations.<sup>5</sup> BF-200 ALA is registered in the EU for the photodynamic treatment of mild-to-moderate AK on the face and bald scalp, field cancerization and basal cell carcinoma. It is common practice in topical red light PDT to use an occlusive dressing during the incubation period of the photosensitizer. This is also recommended in the summary of product characteristics (SPC) of BF-200 ALA and is assumed to provide enhanced resorption resulting in a better treatment response<sup>6</sup>. However, clinical data regarding the impact of occlusion on the efficacy and tolerability of conventional BF-200 ALA PDT are lacking.

The present prospective within-patient comparison study is the first to evaluate in a controlled setting the difference between occlusive and non-occlusive application of BF-200 ALA with regard to clinical efficacy and adverse reactions in patients with multiple AK in the head region.

## 2 | PATIENTS AND METHODS

### 2.1 | Study population

45 patients with Fitzpatrick skin phototype I-III and mild-to-moderate AK (grade I-II according to Olsen et al<sup>7</sup> on the scalp or face) were enrolled. AK were diagnosed clinically. The size of the AK lesions ranged between 0.5 and 1.5 cm in diameter. Exclusion criteria were an age under 18 or over 90 years, hypersensitivity to ALA, porphyria, chronic immunosuppression, and any other dermatological disease in the treatment areas that would interfere with the assessment of the AK. Patients were given written and verbal information on the nature of the study and signed informed consent was obtained before their enrollment.

The study was approved by the local ethics committee and conducted at the Department of Dermatology, Medical University of Vienna, Austria, between March 2015 and October 2016 (EudraCT number: 2014-003331-18).

### 2.2 | Study design and study medication

This was a prospective investigator-blinded, intraindividual left-right comparison study. The study medication was BF-200 ALA gel (Ameluz<sup>®</sup>) which was provided by Biofrontera AG.

### 2.3 | Treatment procedure

At the first visit, the patients' history was taken and a thorough dermatological examination was performed. Two comparable target areas of approximately 5 × 5 cm with 4-8 AK were selected for comparing the efficacy and tolerability of occlusive versus non-occlusive application of BF-200 ALA. All lesions within the target areas were mapped, and an AK with the highest clinical score was chosen as target lesion. The clinical score was the sum score of redness, scaling (each graded between 0 = none, 1 = slight, 2 = moderate, and 3 = severe) and infiltration (graded between 0 = absent and 1 = present). Photographs were taken under standardized conditions before and after each treatment.

### 2.4 | Photodynamic therapy

In all patients, two target areas were randomly assigned to PDT with either occlusive or non-occlusive application of BF-200 ALA within a 1-week interval. Concealed randomization was done using Randomizer, a web-based program for prospective studies. Every patient was undergoing both treatments and thus served as his own control. Each target area was pretreated with 10% salicylic acid in petrolatum once daily over one week before PDT. For occlusive treatment, BF-200 ALA was applied in a thickness of 1 mm on the target area including a 5 mm margin of surrounding skin and allowed to dry for 10 minutes. The target area was then covered with an non-absorbent, transparent self-adhesive dressing (Suprasorb<sup>®</sup>, Lohmann & Rauscher, Austria). After an incubation period of 3 hours during which the patients remained within the hospital, all remnants of BF-200 ALA were removed with a 0.9% saline solution and illumination was performed with red light (635 ± 9 nm; BF-RhodoLED<sup>®</sup>, Biofrontera Pharma GmbH) at an irradiance of 62 mW/cm<sup>2</sup> and a dose of 37 J/cm<sup>2</sup>. Pain was reduced during PDT by using a cooling airflow of -30° (Criojet, Air Mini, Linde Gas Therapeutics GmbH, Germany) and a fan integrated into the lamp. After PDT, a cooled water gel (Avène Thermal Spring Water Gel, Pierre Fabre) was applied. Since simultaneous treatment with occlusive and non-occlusive PDT would have confounded pain assessment by the patients, the second target area was treated one week later in exactly the same way with the only exception that no occlusion was used after the application of BF-200 ALA. Occlusive and not-occlusive PDT were not done simultaneously since that would have confounded the pain assessment by the patients. Each target area was treated only once. Follow-up examinations were scheduled two and seven days as well as 3 and

6 months after PDT. To increase patients' adherence, assessment at 3 and 6 months after treatment was done on a single day for both treatments and not one week apart. To this purpose, the patients were free to choose a day at their convenience in the week between the respective scheduled follow-up visit for occlusive and non-occlusive PDT. AK not responding to PDT were subsequently treated with cryotherapy.

## 2.5 | Assessments

The following primary (I) and secondary (II–VIII) outcome measures were assessed: (I) complete clearance rate of the target lesion at 3 and 6 months after PDT; (II) total clearance rate of all AK in the target areas at 3 and 6 months after PDT; (III) recurrence rate of target AK at 6 months after PDT; (IV) recurrence rate of total AK at 6 months after PDT; (V) occurrence of new AK in the target areas at 6 months after PDT; (VI) treatment-associated pain that was evaluated on a visual analogue scale (VAS; range between 0 (no pain to 10 (unbearable pain)) during and up to 30 minutes after PDT; (VII) severity of the phototoxic skin reaction (sum score of erythema, edema, and blistering each graded between 0 and 4; 0 = absent, 1 = slight, 2 = moderate, 3 = strong, and 4 = very strong) at 2 and 7 days after PDT; and (VIII) cosmetic outcome which was graded as excellent (absence of erythema and/or hypo-/hyperpigmentation and/or scarring), moderate (slight erythema and/or hypo-/hyperpigmentation and/or scarring) and poor (substantial erythema and/or hypo-/hyperpigmentation and/or scarring) at 6 months after PDT.

Pain and the severity of the phototoxic skin reaction were evaluated by the study physician. Measures of efficacy and cosmetic outcome were determined by a blinded assessor unaware of treatment allocation by side-to-side comparison with sequential photographs that were taken at each study visit.

## 2.6 | Statistical analysis

Based on data in the literature, a clearance rate of 85% was assumed for occlusive PDT and a 20 percent point decrease in efficacy as compared to occlusive application of ALA for non-occlusive PDT. According to these assumptions, a sample size of 45 patients including a drop-out rate of 10% was calculated to ensure a power of 80% according to a one-sided McNemar test. Power and sample size were calculated with nQuery® Advisor version 6.01. Target lesions were classified as completely cleared (yes/no) at 3 months after PDT and tested on a significance level of 0.05 (one-sided, 5%). Additionally, total clearance rate (complete clearance of all AK within the target areas) was analyzed using a paired t test. Pain intensity (arithmetic mean of all values obtained) and the severity of the phototoxic reaction (arithmetic mean of all summary scores) were analyzed by means of paired t test. The difference in cosmetic outcome was tested

using the McNemar-Bowker test. The recurrence rate of target lesions was analyzed using the McNemar test. The recurrence rate of all treated AK within the target areas was assessed using a paired t test. Exploratory statistical analysis was performed on secondary endpoints like pain intensity during PDT, intensity of phototoxic skin reaction, and cosmetic outcome.

## 3 | RESULTS

### 3.1 | Patients

Out of all 45 enrolled patients, two were excluded from the final analysis, one due to intolerable pain during PDT necessitating early termination of illumination and the other because of using imiquimod for treating a basal cell carcinoma adjacent to the target area subsequently to PDT (Figure 1). The patients' demographics and clinical characteristics are given in Table 1.

All target lesions were Olsen grade II. 42% of them were on the bald scalp and 58% on the face. The distribution was comparable for both treatment arms (Table 1). 37% of all occlusive treated lesions (target area A) were on the bald scalp and 63% on the face as compared to 40% on the bald scalp and 60% on the face for non-occlusive treatment (target area B).

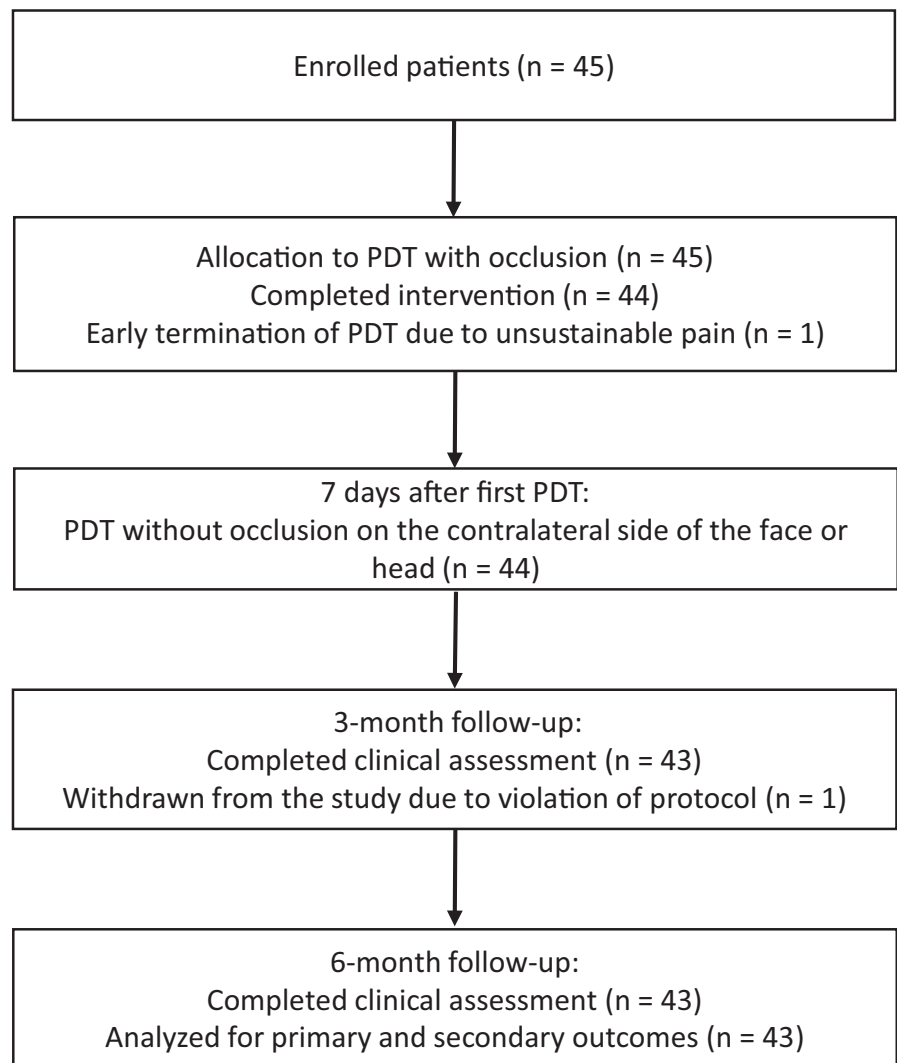
### 3.2 | Efficacy

#### 3.2.1 | Clearance rate of target lesions

The clearance rate of the evaluable target lesions at 3 months after PDT was 88.4% (38/43) for occlusive BF-200 ALA PDT as compared to 58.1% (25/43) for non-occlusive PDT (Figure 2). The difference between the two mode of applications was highly significant ( $P < .001$ ). The recurrence rate of target lesions at 6 months after PDT was 21.1% (8/38) for occlusive PDT and 48% (12/25) for non-occlusive PDT ( $P = .016$ ). The 6-month clearance rate of the target lesions for occlusive PDT thus was 69.7% (30/43) as opposed to 30.2% (13/43) for non-occlusive PDT ( $P < .001$ ) (Figure 2).

#### 3.2.2 | Total clearance rate

Total clearance rate of all AK lesions within the target areas at 3 months after PDT is presented in Figure 3. 90.6% (240/265) of the lesions treated with occlusive PDT and 70.4% (176/250) of AK treated with non-occlusive PDT showed complete clearance ( $P = .04$ ). The recurrence rate within the target areas at 6 months after PDT was 20.4% (49/240) for occlusive PDT as compared to 49.4% (87/176) for non-occlusive PDT ( $P = .003$ ). The total clearance rate of all AK lesions within the target areas at 6 months thus

**FIGURE 1** Flowchart of participants

was 72.1% (191/265) for occlusive PDT and 35.6% (89/250) for non-occlusive PDT, respectively ( $P = .001$ ) (Figure 3).

### 3.2.3 | Occurrence of new lesions in the target areas

One single new AK occurred in the target areas treated with occlusive PDT as compared to 6 AK after non-occlusive PDT. This difference was not statistically significant ( $P = .63$ ).

### 3.3 | PDT-induced pain and phototoxic skin reaction

The mean pain score during illumination after occlusive PDT was 3.3 (min. 0, max. 6.4) as compared to 2.3 (min. 0, max. 5.6) for non-occlusive PDT ( $P < .001$ ; Figure 4). The mean phototoxicity score 2 days and 7 days after PDT was 2.8 and 1.3 for occlusive PDT and 2.1 ( $P < .001$ ) and 0.9 ( $P = .003$ ) for non-occlusive PDT, respectively (Figure 5).

No other side effects besides those specifically related to PDT were observed.

### 3.4 | Cosmetic outcome

The overall cosmetic outcome was rated excellent for both methods without a significant difference between the two treatments ( $P = .508$ ).

## 4 | DISCUSSION

BF-200 ALA is used for PDT of AK. High efficacy of BF-200 ALA PDT in the treatment of AK has been shown in several clinical studies.<sup>5,8,9</sup> An occlusive dressing during the incubation period of BF-200 ALA is recommended in the summary of product characteristics for conventional red light PDT and is assumed to provide for enhanced ALA resorption and a better treatment response.<sup>10</sup> However, up to the present, controlled data on the impact of occlusion are lacking.

In the present intraindividual comparison study, we therefore assessed the efficacy and tolerability of occlusive versus non-occlusive BF-200 ALA PDT in patients with multiple AK on the face and bald scalp. Our data corroborate the assumption that occlusive application of BF-200 ALA improves the efficacy of PDT in

**TABLE 1** Patients' demographics and clinical characteristics

|                                | Number (percentage)        |                                |
|--------------------------------|----------------------------|--------------------------------|
| Enrolled patients              | 45 (100%)                  |                                |
| Drop-outs                      | 2 (4,4%)                   |                                |
| Mean age, yrs (range)          | 71 (54 - 87)               |                                |
| Male                           | 39 (86,7%)                 |                                |
| Female                         | 6 (13,3%)                  |                                |
|                                | occlusive PDT <sup>a</sup> | non-occlusive PDT <sup>a</sup> |
| Target lesions                 | 43 (100%)                  | 43 (100%)                      |
| Localization of target lesions |                            |                                |
| Bald scalp                     | 18 (42%)                   | 18 (42%)                       |
| Face                           | 25 (58%)                   | 25 (58%)                       |
| Total number of treated AK     | 265 (100%)                 | 250 (100%)                     |
| Localization of all treated AK |                            |                                |
| Bald scalp                     | 98 (37%)                   | 101 (40%)                      |
| Face                           | 11 167 (63%)               | 149 (60%)                      |

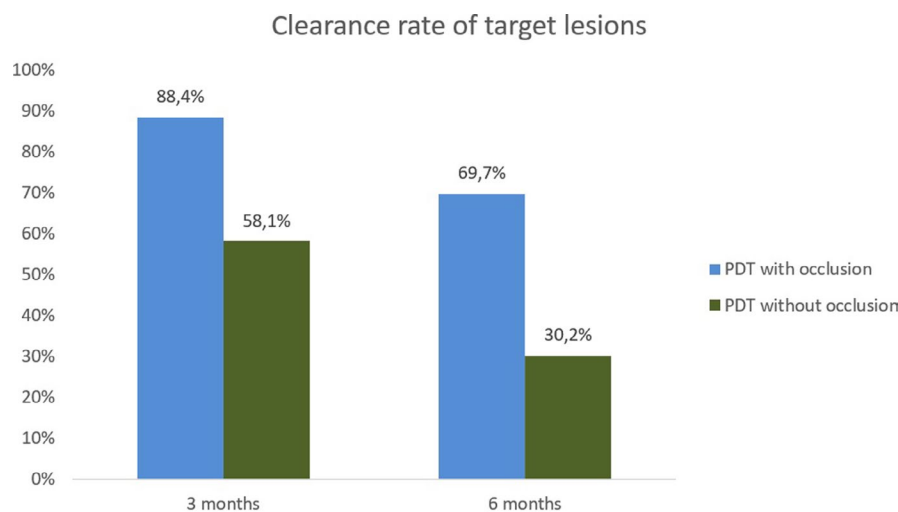
<sup>a</sup>Based on evaluable patients.

clearing AK. The clearance rate of target lesions and the total number of AK within predefined target areas were significantly higher with occlusive as compared to non-occlusive BF-200 ALA PDT (Figure 6).

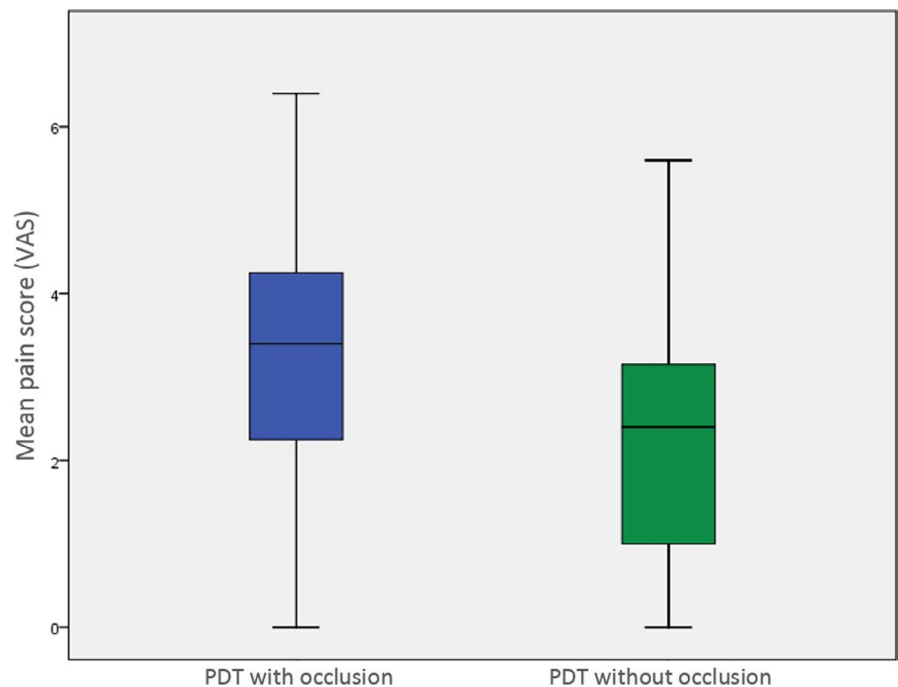
We are aware of only one further trial that investigated the impact of occlusion on the efficacy of PDT.<sup>10</sup> In that study occlusive versus non-occlusive application of a 20% topical ALA solution (Levulan Kerastick) followed by irradiation with 10 J/cm<sup>2</sup> of blue light was used to treat AK on the upper extremities. In agreement with our study, the clearance rate was significantly better for occlusive as compared to non-occlusive PDT (88.7% vs 70.0%;  $P < .0001$ ).<sup>10</sup>

The total clearance rate of 90,6% for occlusive application of BF-200 ALA as observed in our study compares well with two others studies on BF-200 ALA PDT for mild-to-moderate AK on the face and/or bald scalp that reported total clearance rates of 90.4% and 81%, respectively.<sup>6,8</sup>

The recurrence rate of the target lesions (21.1% vs 48%) and of total AK (20,4% vs. 49.3%) at 6 months after PDT tended to be lower after occlusion as compared to non-occlusion but the difference lacked statistical significance. An almost identical recurrence rate of

**FIGURE 2** Clearance rate of the target lesions at 3 mo (88.4% vs 58.1%;  $P < .001$ ) and 6 mo (76.7% vs 48.8%;  $P < .001$ ) after occlusive and non-occlusive PDT, respectively**FIGURE 3** Total clearance of AK within the target areas at 3 mo (94.0% vs 78.1%;  $P = .04$ ) and 6 mo (83.5% and 67.6%;  $P = .01$ ) after occlusive and non-occlusive PDT, respectively

**FIGURE 4** Boxplots showing the mean pain intensity during occlusive (3.3, min.=0, max = 6.4) and non-occlusive PDT (2.3, min.=0, max = 5.6;  $P < .001$ )



**FIGURE 5** More pronounced skin phototoxicity at 2 days after occlusive PDT on the right side of the forehead (A) as compared to non-occlusive PDT on the left side (B)



7% for total AK was reported in a randomized prospective multicenter study comparing PDT with BF-200 ALA against a registered methyl-5-aminolaevulinate cream in patients with multiple AK.<sup>11</sup> In the latter study, however, AK that were not cleared at 12 weeks after the first PDT received a second PDT whereas in our study only one PDT was performed.<sup>11</sup>

Occlusive application of BF-200 ALA was associated with a slight but significant increase in PDT-associated pain and phototoxicity. Of note, the mean VAS score of 3.3 for occlusive BF-200 ALA PDT as recorded in our study is lower than the respective values (mean VAS between 4.1 and 5.5) reported in other trials.<sup>6,9</sup> This is likely due to the fact that we employed continuous cold airflow during illumination as a pain-reducing measure. We have previously shown that this procedure is effective in decreasing the maximum pain intensity during PDT of AK (Silic et al, manuscript in preparation).

As far as the severity of the phototoxic reaction is concerned, it is difficult to compare our results to other studies due to different assessment methods. 96% of our patients experienced some phototoxicity which is similar to a rate of 98% found in another study.<sup>8</sup> In the vast majority of our patients (89%), skin phototoxicity was rated as mild to moderate.

We did not find any difference between occlusive and non-occlusive application of BF-200 with respect to the cosmetic outcome which overall was excellent. This is in line with the well-known fact that PDT in general provides for cosmetic results that are superior to those seen with other interventions for AK.<sup>12-15</sup>

In our study, we used a licensed 5-ALA nanoemulsion in combination with red light and exclusively treated AK located in the head region. Thus, our results might not apply to other topical photosensitizer formulations, other wavebands of photoactivating light or AK in anatomical regions different from those investigated in our study. In addition, the number of enrolled patients is relatively small. The conclusiveness of our study is, however, increased by the fact that we used an intraindividual left-right comparison approach that permitted us to exclude bias resulting from interindividual variabilities.

In conclusion, the data of our controlled study substantiate the notion that occlusive application of topical ALA has a significant impact on the efficacy of conventional red light PDT for AK. It is a simple and effective method to enhance clearance in AK patients treated with BF-200 ALA PDT. Although a slight increase of PDT-induced pain and phototoxicity was observed the treatment was in general well tolerated.



**FIGURE 6** Assessment of the patient shown in Figure 5 at 6 mo after PDT. The right side of the forehead shows complete clearance of all AK whereas on the left side two residual AK (marked with arrows) are still present after non-occlusive PDT

## ACKNOWLEDGEMENTS

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## CONFLICT OF INTEREST

None

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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