

Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a prospective, randomized, double-blind, placebo-controlled phase III study

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Summary

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Conflicts of interest

R.-M.S. and T.D. are consultants of the sponsoring company. G.P. and D.V. are employees of the company that was responsible for data management and statistical analysis. M.F., R.G. and H.L. are employees of the sponsoring company.

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Background Photodynamic therapy (PDT) with 5-aminolaevulinic acid (ALA) provides a therapeutic option for the treatment of actinic keratosis (AK). Different strategies are applied to overcome the chemical instability of ALA in solution and to improve skin penetration. A new stable nanoemulsion-based ALA formulation, BF-200 ALA, is currently in clinical development for PDT of AK.

Objectives To evaluate the efficacy and safety of PDT of AK with BF-200 ALA.

Methods The study was performed as a randomized, multicentre, double-blind, placebo-controlled, interindividual, two-armed trial with BF-200 ALA and placebo. A total of 122 patients with four to eight mild to moderate AK lesions on the face and/or the bald scalp were included in eight German study centres. The efficacy of BF-200 ALA after one and two PDT treatments was evaluated. BF-200 ALA was used in combination with two different light sources under illumination conditions defined by European competent authorities.

Results PDT with BF-200 ALA was superior to placebo PDT with respect to patient complete clearance rate (per-protocol group: 64% vs. 11%; $P < 0.0001$) and lesion complete clearance rate (per-protocol group: 81% vs. 22%) after the last PDT treatment. Statistically significant differences in the patient and lesion complete clearance rates and adverse effect profiles were observed for the two light sources, Aktelite[®] CL128 and PhotoDyn[®] 750, at both time points of assessment. The patient and lesion complete clearance rates after illumination with the Aktelite[®] CL128 were 96% and 99%, respectively.

Conclusions BF-200 ALA is a very effective new formulation for the treatment of AK with PDT. Marked differences between the efficacies and adverse effects were observed for the different light sources used. Thus, PDT efficacy is dependent both on the drug and on the characteristics of the light source and the illumination conditions used.

Actinic keratoses (AKs) are often a result of extensive sun exposure. They are classified as in situ squamous cell carcinomas (SCC).^{1,2} Current national and international guidelines recom-

mend the treatment of AKs in order to prevent their potential progression into SCC.³⁻⁵ Photodynamic therapy (PDT) of AKs with 5-aminolaevulinic acid (ALA) or its methylester (MAL)

are accepted treatment options for this disease. PDT is effective, comparatively fast and generates excellent cosmetic results.

One of the problems with the use of ALA formulations is the instability of the active compound in aqueous formulations. The use of a two-component system (Dusa Pharmaceuticals, Inc., Wilmington, MA, U.S.A.), the derivatization of the compound,⁶ the application of the compound as solid crystals in patches⁷ or the immediate use of freshly formulated ALA are strategies used to overcome the stability problem. A second drawback is the fact that ALA is a zwitterion (dipolar ion) at physiological pH with low lipid solubility and limited ability to penetrate the stratum corneum. One approach to overcome this problem involves more lipophilic ALA derivatives such as MAL.⁵

BF-200 ALA is a new, nanoemulsion-based formulation of 10% ALA in a gel matrix. The efficacy of nanoemulsion-based formulations containing 10% ALA has been demonstrated in the past for PDT of superficial basal cell carcinoma, condyloma and vulvar intraepithelial neoplasia.^{8–11} BF-200 ALA provides a solution for both major problems of conventional semisolid ALA formulations: (i) the nanoemulsion stabilizes the active ingredient ALA in solution and (ii) it improves its penetration into the skin¹² so that lower ALA concentrations are sufficient for a therapeutic effect. Based on previous unpublished clinical results, BF-200 ALA with a 10% concentration of ALA was selected for further development for the indication of AK.

Different light sources are accepted by European regulatory authorities for the illumination during PDT in combination with the registered drugs, as long as certain specifications concerning the light dose and the light spectrum are met. However, only a few standardized comparative studies have been published to date comparing light sources commonly used for PDT. Here we report the results of a phase III study with BF-200 ALA used in combination with two different light sources for PDT of AK.

Materials and methods

The study was performed as a confirmatory randomized, multi-centre, double-blind, placebo-controlled, interindividual, two-armed trial with BF-200 ALA and placebo in a ratio of 2 : 1.

The eight study centres involved included one university hospital, two dermatological clinical centres and five private dermatological practices. The study was approved by the responsible ethics committees and the competent authority (BfArM, Germany) prior to the start of the study and performed according to the German drug law, the guidelines of good clinical practice and the Declaration of Helsinki.

Study medication

The study medication was produced and released for the clinical trial according to good manufacturing practice and relevant regulations. Laminated aluminium tubes contained 2 g of either BF-200 ALA or a placebo gel whose optical appearance was identical.

Treatment protocol

The general treatment schedule was similar to the protocol described for MAL.¹³ PDT was performed in a double-blind manner with BF-200 ALA or its corresponding placebo formulation, which was indistinguishable by eye or feel. Crusts were carefully removed by mild curettage if necessary. All lesion surfaces were roughened and the skin was wiped with alcohol prior to drug application. After application the gel was allowed to dry for about 10 min in order to avoid sticking of the gel to the cover rather than the skin after drying. Thereafter, an occlusive, light-tight dressing was placed over the lesion. Illumination was performed 3 h after the application of the gel. It was planned in advance to involve centres using one of two light sources, Aktelite[®] CL128 (Photocure, Oslo, Norway) or PhotoDyn[®] 750 (Hydrosun Medizintechnik GmbH, Mühlheim, Germany), both widely used for PDT of AK in Europe, in order to reflect dermatological practice. The light sources were applied according to the manufacturers' instructions for PDT to ensure that the recommended light dose was applied. The Aktelite[®] CL128 was used in four centres which included 39.5% of the BF-200 ALA patients and 39% of the placebo patients. This lamp has a narrow emission spectrum between 590 and 670 nm with a peak wavelength near 630 nm and a half-width of approximately 20 nm. The irradiance varied between 50 and 70 mW cm⁻² at skin level, depending on the model and the distance to the skin (5–8 cm). The recommended light dose of 37 J cm⁻² was applied under the control of the timer in the lamp, which individually determines the illumination time, thereby considering the selected distance to the surface. The PhotoDyn[®] 750 is an incoherent broad-spectrum light source emitting light between 580 and 1400 nm. This lamp was used with the filter BTE595 eliminating light with wavelengths below 595 nm (irradiance 196 mW cm⁻²). This lamp was used in the other four centres for the treatment of 60.5% of BF-200 ALA and 61% of placebo patients. The light dose (170 J cm⁻²) recommended by the supplier was controlled by the distance (27 cm) and the irradiation time (15 min). The Aktelite[®] CL128 uses a ventilator as an internal cooling device. Twenty patients (15 treated with an Aktelite[®] CL128 and five with a Photodyn[®] 750) received further cooling measures such as sprayed water. Twelve weeks after a first PDT session, clearance of the AK lesions was assessed. All lesions not completely cleared were treated with a second PDT session. A final assessment of the lesion clearance was performed 12 weeks thereafter.

Randomization

A randomization list was generated using a validated SAS[®] programme (Focus CDD GmbH, Neuss, Germany) based on the random number function RANUNI for uniformly distributed variables. Random blocks for six patients were packed. Patient assignment to a group occurred according to the randomization list.

Study population

White male and female subjects, between 18 and 85 years of age, and diagnosed with at least four, but not more than eight, mild to moderate AK lesions (according to Olsen *et al.*¹⁴) on their face and/or on the scalp were included in the study. The size of each AK lesion was determined to be not < 0.5 cm and not > 1.5 cm in diameter. Adjacent AK lesions had to show a minimal distance of 1.0 cm from one another. A biopsy from one representative lesion per patient was taken to allow confirmation of the diagnosis by histopathology. Lesions and treated areas were documented with a standardized photodocumentation system. The pictures were reviewed by a second independent expert dermatologist. Exclusion criteria were all clinical conditions that could influence the study aims and intolerance to any ingredient of BF-200 ALA. Specifically excluded were patients with known hypersensitivity to ALA, subjects under immunosuppressive therapy, patients suffering from porphyria or showing hypersensitivity to porphyrins, patients receiving hypericin or systemically acting drugs with phototoxic or photoallergic potential, patients showing cornu cutaneum-like alterations (cutaneous horns) of the skin in the target area, and patients suffering from dermatoses. Topical treatments within the treatment area were not allowed 12 weeks before or during the study. Patients with treatments in the target area more than 12 weeks before the study were accepted. Therefore, it was possible that patients with previous PDT treatment failures of AK were included. Other topical treatments that may be able to affect the response to the study treatment were not allowed during the study. The use of substances with phototoxic or photoallergic potential was forbidden 8 weeks prior to and during PDT. Systemic treatments considered to have a possible impact on the outcome were not allowed for 1–6 months before (time frame depending on the substance, e.g. cytotoxic drugs, 6 months prior to PDT) and during the study.

Study plan

One week after PDT according to the protocol, patients were contacted by phone to inquire about possible adverse effects. Three weeks after the treatment, a first assessment of the lesion by the physician, and documentation of reported adverse effects was carried out. Treatment efficacy and cosmetic outcome were assessed by the investigator 12 weeks after PDT. In patients with remaining lesions, a second treatment was performed at this time point followed by assessments scheduled at intervals, as after the first treatment. In order to guarantee blinding, a second investigator or a delegated person performed the illumination and safety assessments during illumination.

Efficacy assessment

The clearance of individual lesions was assessed by visual inspection and by palpation and compared with the baseline 3

and 12 weeks after treatments. A second biopsy of a lesion defined and marked before the PDT treatment was taken during the end visit as an additional confirmation of the diagnosis. Patient complete clearance was defined as when all lesions were considered to be cleared both by the clinical and histological assessment.

Safety and tolerability assessment

Local adverse reactions at the application site during and after PDT were documented. The symptoms of pain, itching, burning, erythema, oedema and induration were classified, if present, into mild, moderate and severe cases as considered appropriate by the assessing physician or reporting patient. The distinction between the subjective sensations pain, burning and itching was made by the patient. Patients reported adverse events during the treatment, during their visits or in a telephone inquiry 1 week after each PDT session. Serious adverse events were documented and evaluated throughout the study. Patients were instructed to avoid intensive sunlight exposure for safety reasons for about 24 h after treatment and also not to expose themselves to intensive ultraviolet radiation during the course of the study.

Biometric analysis

The sample size was estimated based on a preliminary study with 28 patients treated with BF-200 ALA (10%) and 27 patients with the corresponding placebo. The primary endpoint, patient complete clearance rate, was defined as the number of subjects with complete remission of all AK lesions in the target area(s) as assessed 12 weeks after the last PDT session. The lesion complete clearance rate was assessed as a secondary endpoint. The clearance rates were calculated as the relative frequency separately for BF-200 ALA and placebo treatments. Testing was done to determine a statistically significant difference in the clearance rates between BF-200 ALA and placebo. This evaluation was performed on all subjects, independent of whether they received one or two PDT treatments. Calculations were performed separately both for the full analysis set (FAS) and the per-protocol population (PPP). A Cochran–Mantel–Haenszel test, accounting for centres as a stratifying variable, was used. The test was evaluated as a two-sided test at an α level of 0.05; 95% confidence intervals (CIs) according to the method of Pearson–Clopper were calculated for the clearance rates of each of the treatments. Analyses were performed with the whole patient set as well as the patient sets illuminated with different light sources.

The sample size was estimated based on the overall results of a preliminary study with 28 patients treated with BF-200 ALA (10%) and 27 patients with the corresponding placebo. The calculated sample size was expected to be sufficient for 80% power to show statistically significant superiority of BF-200 ALA over placebo, if the observed patient complete clearance rates were similar to those observed in the preceding study.

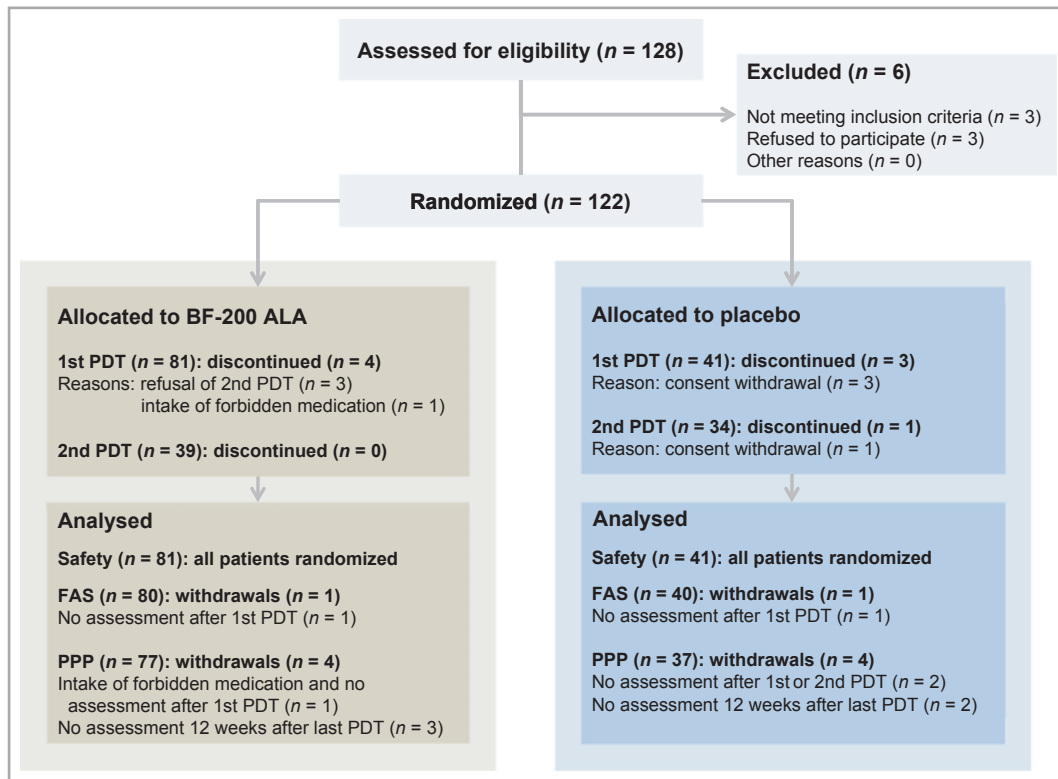


Fig 1. Flow chart for patient selection, describing the disposition of patients in the clinical study CT003. Calculations were performed both for the full analysis set (FAS) and the per-protocol population (PPP). PDT, photodynamic therapy.

Results

Patients

A total of 122 patients were randomized and treated with BF-200 ALA (81 subjects) or placebo (41 subjects). Treatment results were assessed 12 weeks after the first PDT session. Forty-two patients completed the study at this step (complete responders), six patients refused a second treatment and one patient was excluded due to a protocol violation. Seventy-three patients received a second treatment. One patient withdrew after the second PDT session. In total, 114 per-protocol patients completed the study. A flow chart of the disposition of patients is presented in Figure 1. Patient and lesion characteristics are summarized in Table 1. Results are shown for the PPP.

Efficacy

Patient complete clearance rate

The patient complete clearance rate 12 weeks after the last PDT session was 64% for BF-200 ALA and 11% for placebo. Forty-nine per cent of the BF-200 ALA-treated patients and 11% of the placebo patients were totally clear after the first treatment. Figure 2a shows the patient complete clearance rates together with the 95% CIs after one PDT and both PDT treatments. The difference between the two treatment groups

was statistically significant in all cases ($P < 0.0001$) both for the PPP and the FAS.

No significant difference was seen for the site (face/forehead vs. bald scalp) or the grade of the lesion (grade I vs. grade II according to Olsen *et al.*¹⁴).

Lesion complete clearance rate

The rates of AK lesions showing total clearance 12 weeks after one and two PDT treatments are presented in Figure 2b. At the end of the study, 353 of 434 lesions (81%) showed full remission after treatment with BF-200 ALA and 45 of 205 lesions (22%) were totally cleared after placebo treatment (PPP). Similar results were found for the FAS population (81% vs. 21%). The differences between the treatment groups were statistically significant ($P < 0.0001$) both for the PPP and the FAS; 95% CIs did not overlap.

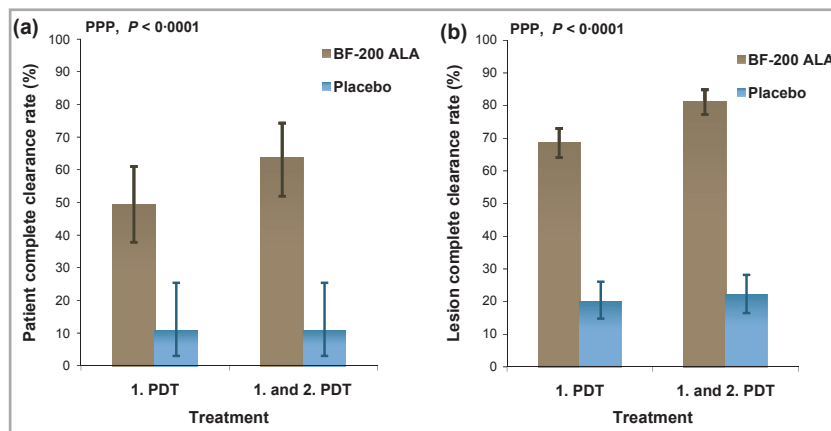
Light source effects

Differences were found in the patient complete clearance rates in relation to the irradiation source. In the BF-200 ALA group the patient complete clearance rates both after the first and after the last treatment were significantly higher in subjects who were irradiated with the Aktelite[®] CL128 device compared with the PhotoDyn[®] 750 device (Fig. 3a). After the last PDT session, 96% (27/28) efficacy was observed in the PPP [FAS (27/31) 87%] compared with subjects who were irradi-

Table 1 Summary of patient and actinic keratosis (AK) lesion characteristics before treatment (safety population)

	Study arm		
	BF-200 ALA (n = 81)	Placebo (n = 41)	Overall (n = 122)
Sex, n (%)			
Male	73 (90.1)	32 (78.0)	105 (86.1)
Female	8 (9.9)	9 (22.0)	17 (13.9)
Age (years)			
Mean \pm SD	70.4 \pm 5.1	70.6 \pm 6.6	70.5 \pm 5.6
Medium, range	58–82	57–85	57–85
Number of AK lesions per group	463	225	688
Mean number of lesions per patient	5.7	5.5	5.6
Severity grade, n (%) ^a			
Mild (slight palpability, grade I)	247 (53.3)	127 (56.4)	374 (54.4)
Moderate (moderately thick, grade II)	216 (46.7)	98 (43.6)	314 (45.6)
Fitzpatrick skin type, n (%)			
I	5 (6.2)	1 (2.4)	
II	42 (51.9)	29 (70.7)	
III	32 (39.5)	11 (26.8)	
IV	2 (2.5)	NA	
V–VI	NA	NA	
Localization, %			
Face and forehead	62.9	66.2	64.0
Bald scalp	37.1	33.8	36.0
Total lesion area (mm ²)	406.5 (176.8)	393.8 (192.4)	402.2 (181.5)

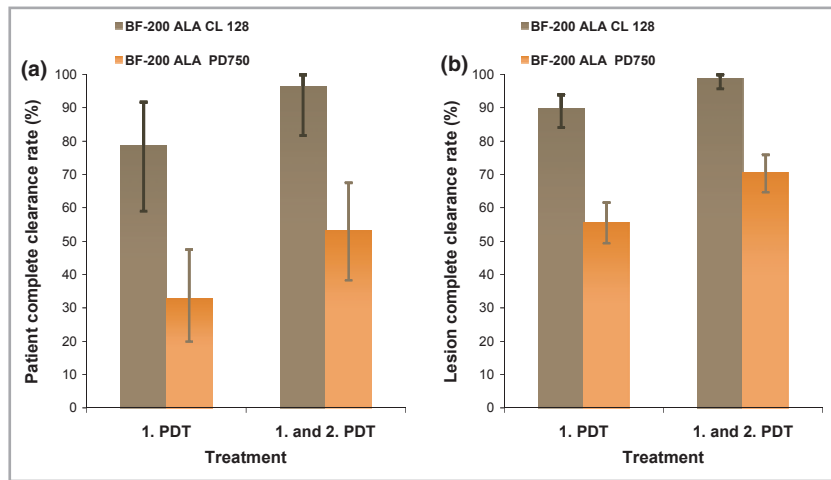
ALA, 5-Aminolaevulinic acid; NA, not applicable. ^aAccording to Olsen *et al.*, 1991.¹⁴

**Fig 2.** Patient and lesion complete clearance rates for the per-protocol population (PPP, overall) after photodynamic therapy (PDT) with BF-200 ALA as described in the text. The results for (a) patient and (b) lesion complete clearance for BF-200 ALA vs. placebo. ALA, 5-Aminolaevulinic acid.

ated with the PhotoDyn[®] 750 device [26/49 (53%) subjects in FAS and PPP, $P < 0.002$ and $P < 0.01$]. The 95% CI did not overlap (Fig. 3a), indicating a highly significant difference in the total patient clearance rates of the BF-200 ALA groups treated with the two light sources ($P < 0.0025$). In the placebo group, patient complete clearance rates were similar for both devices (PPP, 15% Aktelite[®] CL128 and 12% PhotoDyn[®] 750). Centre differences observed for the patient complete clearance rate can be attributed to the different irradiation sources used in the different centres. Three of the four centres using the Aktelite[®] CL128 showed a complete clearance rate of 89–100% at the end of the study whereas the centres using the PhotoDyn[®] 750 showed a patient complete clearance rate

of 33–67%. One centre using the Aktelite[®] CL128 had a patient complete clearance rate of only 40%, because in this centre two of five subjects in the BF-200 ALA group refused a required second PDT. One of the two patients withdrew from the study in view of the fact that only residues of one keratotic lesion remained, the other refused because of the side-effects of the treatment. With the exception of the efficacy differences due to light sources, no centre-specific differences were noticeable. Lesion complete clearance rates after use of the Aktelite[®] CL128 were 90% (PPP) and 88% (FAS) after the first PDT and 99% (PPP) and 96% (FAS) after the last PDT treatment. Corresponding lesion complete clearance rates after use of the PhotoDyn[®] 750 were 56% (after first PDT; FAS and PPP) and

Fig 3. Patient and lesion complete clearance rates by irradiation source. Patient and lesion complete clearance rates for the per-protocol population after photodynamic therapy (PDT) with BF-200 ALA as described in the text. Comparison of (a) the patient and (b) the lesion complete clearance rates achieved after use of individual irradiation sources (Aktilite® CL128 vs. Photodyn® 750). ALA, 5-Aminolaevulinic acid.



70% (after final PDT; FAS and PPP) (Figure 3b). Again, the differences between the two light sources were significant both after the first and the last time point of assessment.

Cosmetic outcome

Generally the cosmetic outcome, assessed by the investigator at the end of the study, was considered to be very good or good in 49% of the subjects in the BF-200 ALA group compared with 27% of the subjects in the corresponding placebo group (PPP).

Unsatisfactory/impaired outcome was judged for only 4% of the subjects in the BF-200 ALA group, but for 22% of the subjects in the placebo group. These findings were in agreement with the results of the skin quality assessment which showed an improvement of the skin quality in the BF-200 ALA group, especially for 'roughness, dryness, scaling' and 'hyperpigmentation detectable'. Less improvement was observed in the placebo group.

Safety and tolerability

No patients mentioned adverse effects, discomfort or pain from application of the gel prior to irradiation. Local adverse effects such as burning or itching were observed during or after the red light illumination. No such effects occurred during the application of the gel. There was no apparent relationship between the incidence and intensity of local adverse effects during PDT and the AK severity grade, the size of the lesion area or its location. However, a clear connection was apparent between both incidence and intensity of symptoms and the irradiation source. The incidence of pain, itching and burning was much higher in subjects irradiated with the Aktilite® CL128 (Table 2). For example, burning occurred in all subjects (100%) illuminated with the Aktilite® CL128 after the second PDT session. In contrast, 60% or fewer of the subjects who were illuminated with the Photodyn® 750 device reported this sensation. Additionally, symptoms of the highest intensity (severe) were mainly observed during or after the

irradiation with the Aktilite® CL128. Treatment with the Aktilite® on the face/forehead led to severe burning in eight subjects and four subjects reported severe pain, three subjects suffered from severe burning and severe pain during treatment on the bald scalp. Only two symptoms of severe intensity were observed during irradiation with the Photodyn® 750 device: itching on the face/forehead and burning on the bald scalp. Severe erythema and moderate oedema and induration only occurred in the Aktilite® subgroup.

Discussion

BF-200 ALA is a new gel formulation of ALA for PDT of AK with increased stability of the active compound due to the presence of a nanoemulsion. The gel can be applied easily to large areas with AK lesions and dries within a few minutes. In this study, the treated lesions were protected from light with an occlusive, light-tight cover but protection from light exposure may not be necessary for a successful and safe treatment as indicated by the treatment modalities commonly used in the U.S.A.¹⁵

The patient complete clearance rate for BF-200 ALA independent of the light source was 64%. The efficacy rate of 81% was observed for the lesion complete clearance rate. The very low corresponding placebo efficacy rates indicate that fully developed AK lesions were treated in this study and that BF-200 ALA is well suited for PDT of AK.

Similar overall efficacies were reported recently from PDT studies with an ALA solution,^{16,17} MAL^{18–20} and an adhesive ALA-patch.⁷ However, for a fair comparison of the results, two aspects need to be considered.

Firstly, high efficacies were achieved with BF-200 ALA despite the lower ALA concentration of 10% (ALA hydrochloride) in the formulation compared with registered products such as Levulan®/Kerastick®¹⁵ (20% ALA hydrochloride; Dusa Pharmaceuticals), Metvix® containing 16% MAL¹³ (21% MAL hydrochloride; Photocure) or formulations produced by pharmacy compounding, normally containing 20% ALA hydrochloride.^{21–23}

Table 2 Frequency of pain, itching and burning in the safety population during photodynamic therapy (PDT), separated by treatment area. The relative frequencies of the adverse events during and after the first and second PDT sessions are indicated by number and percentage of complaining subjects. Adverse events are shown independent of the light source and separated by light source

	Treatment group							
	BF-200 ALA (n = 81) n (%)				Placebo (n = 41) n (%)			
	Face/forehead		Bald scalp		Face/forehead		Bald scalp	
	1st PDT	2nd PDT	1st PDT	2nd PDT	1st PDT	2nd PDT	1st PDT	2nd PDT
Overall	n = 59	n = 25	n = 31	n = 18	n = 30	n = 25	n = 15	n = 12
Pain	35 (59.3)	6 (24.0)	12 (38.7)	4 (22.2)	2 (6.7)	1 (4.0)	1 (6.7)	–
Itching	17 (28.8)	1 (4.0)	5 (16.1)	2 (11.1)	–	–	–	–
Burning	48 (81.4)	14 (56.0)	23 (74.2)	12 (66.6)	7 (23.3)	1 (4.0)	2 (13.3)	1 (8.3)
Irradiation source								
Aktilite [®] CL128	n = 27	n = 4	n = 9	n = 3	n = 13	n = 9	n = 4	n = 4
Pain	23 (85.1)	2 (50.0)	8 (88.9)	2 (66.7)	–	–	–	–
Itching	11 (40.7)	1 (25.0)	3 (33.3)	1 (33.3)	–	–	–	–
Burning	26 (96.2)	4 (100)	9 (100)	3 (100)	4 (30.8)	1 (11.1)	–	–
PhotoDyn [®] 750	n = 32	n = 21	n = 22	n = 15	n = 17	n = 16	n = 11	n = 8
Pain	12 (37.5)	4 (19.0)	4 (18.2)	2 (13.3)	2 (11.8)	1 (6.3)	1 (9.1)	–
Itching	6 (18.7)	–	2 (9.1)	1 (6.7)	–	–	–	–
Burning	22 (68.8)	10 (47.7)	14 (63.6)	9 (60.0)	3 (17.6)	–	2 (18.2)	1 (12.5)

ALA, 5-Aminolaevulinic acid.

Secondly, the light source has a strong impact on the efficacy. The Aktilite[®] CL128 was the only or the predominantly used light source used in the cited studies performed with MAL or the ALA patch. This is important in view of the surprisingly high differences in patient and lesion complete clearance rates that were observed in this study with BF-200 ALA when the results were stratified by light source. Both light sources were used according to the manufacturers' recommendations. Illumination with the Aktilite[®] CL128 gave a markedly and significantly higher patient clearance rate of 96% compared with the PhotoDyn[®] 750 (53%). With Aktilite[®] CL128 illumination, none of the other PDT drugs reached efficacies similar to those seen with the combination of BF-200 ALA and the same light source. However, the lower efficacy of the PhotoDyn[®] 750 illumination regimen correlated with the incidence and intensity of adverse events, both of which were lower than after illumination with the Aktilite[®] CL128. With the latter light source, pain, burning and itching experienced by patients during the illumination and also side-effects such as erythema, oedema and induration reported after treatment were more abundant and more severe. The stronger side-effects observed for the Aktilite[®] CL128 may affect compliance by patients, in particular if used outside the controlled settings of a clinical study.

For alternative treatment options, a broad range of efficacies has been reported. However, patient complete clearance rates above 95% were rarely achieved in controlled AK studies.⁵ In the general medical literature, reported patient or lesion complete clearance rates vary widely for 5-fluorouracil (16–100%)^{24–26} and imiquimod (0–85%).^{24,27} A meta-analysis²⁸ reported average efficacy rates of 52% and 70%, respectively. Efficacy of cryotherapies (67–83%)^{20,24,29,30} was similar to that

reported for previous PDT studies.^{7,17–20} The clearance rates published for diclofenac range between 17% and 81%.^{31–35}

With 49% of the subjects in the BF-200 ALA group judged as very good/good, compared with 27% of the subjects in the corresponding placebo group, the cosmetic outcome is good, but lower than that described in other studies examining the outcome of PDT treatments. In those studies the cosmetic outcome was judged as good/very good in up to 98% of the patients.^{7,36} However, in these same studies the cosmetic outcome in placebo patients was judged as good/very good in up to 100% of the cases. Therefore, in the absence of direct comparator studies it is not possible to compare the cosmetic outcome in the present study with those of other published trials.

Taken together, the comparatively rapid treatment procedure, the high efficacy of the method and the generally excellent cosmetic results are strong arguments in favour of PDT. The very high patient clearance rate of 96% (placebo 15%) observed in this study after illumination with the Aktilite[®] CL128 indicates that BF-200 ALA is an exceptionally effective new drug for the PDT of AK.

What's already known about this topic?

- Photodynamic therapy with 5-aminolaevulinic acid (ALA) provides a therapeutic option for the treatment of actinic keratosis.
- Different strategies are applied to overcome the chemical instability of ALA in solution and to improve skin penetration.

What does this study add?

- This is the first pivotal phase III study with BF-200 ALA, a new stable nanoemulsion-based gel formulation of 5-aminolaevulinic acid (ALA) for photodynamic therapy (PDT) of actinic keratosis.
- A comparison was made of efficacy and adverse effects after use of PDT for actinic keratosis in combination with different light sources (illumination conditions).

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