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Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a multicentre, randomized, observer-blind phase III study in comparison with a registered methyl-5-aminolaevulinate cream and placebo

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Summary

Background Photodynamic therapy (PDT) with 5-aminolaevulinic acid (ALA) or its methylester [methyl-5-aminolaevulinate (MAL) or 5-amino-4-oxopentanoate] was recently ranked as first-line therapy for the treatment of actinic keratosis (AK) and is an accepted therapeutic option for the treatment of neoplastic skin diseases. BF-200 ALA (Biofrontera Bioscience GmbH, Leverkusen, Germany) is a gel formulation of ALA with nanoemulsion for the treatment of AK which overcomes previous problems of ALA instability and improves skin penetration.

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Conflicts of interest
R.-M.S. and T.D. are consultants of the sponsoring company. K.W.-P. and C.H. are employees of the company that was responsible for data management and statistical analyses. M.F., B.S. and H.L. are employees of the sponsoring company.

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Objectives To evaluate the efficacy and safety of PDT of AKs with BF-200 ALA in comparison with a registered MAL cream and with placebo.

Methods The study was performed as a randomized, multicentre, observer-blind, placebo-controlled, interindividual trial with BF-200 ALA, a registered MAL cream and placebo in a ratio of 3 : 3 : 1. Six hundred patients, each with four to eight mild to moderate AK lesions on the face and/or the bald scalp, were enrolled in 26 study centres in Germany, Austria and Switzerland. Patients received one PDT. If residual lesions remained at 3 months after treatment, PDT was repeated.

Results PDT with BF-200 ALA was superior to placebo PDT with respect to patient complete clearance rate (78·2% vs. 17·1%; $P < 0·0001$) and lesion complete clearance rate (90·4% vs. 37·1%) at 3 months after the last PDT. Moreover, superiority was demonstrated over the MAL cream regarding the primary endpoint patient complete clearance (78·2% vs. 64·2%; $P < 0·05$). Significant differences in the patient and lesion complete clearance rates and severity of treatment-related adverse events were observed for the narrow- and broad-spectrum light sources.

Conclusions BF-200 ALA is a very effective, well-tolerated new formulation for AK treatment with PDT and is superior to a registered MAL medication. Efficacies and adverse events vary greatly with the different light sources used.

The development of actinic keratoses (AKs) is considered the result of long-term exposure to ultraviolet (UV) radiation.[1] AKs are localized primarily on sun-exposed areas of the body and are classified as carcinoma *in situ* with potential progression to squamous cell carcinomas (SCCs).[2,3] As the estimates for transformation into SCC range from 5% to 20% within 10–25 years,[3–6] European guidelines strongly recommend the treatment of AKs in order to prevent their potential progression to SCC.[2,7,8] Photodynamic therapy (PDT) of AKs with 5-aminolaevulinic acid (ALA) or its methylester [methyl-5-aminolaevulinate (MAL), also known as 5-amino-4-oxopentanoate] is an accepted treatment option for this disease. Due to its efficacy and excellent cosmetic results, PDT is recommended as first-line therapy for AK treatment.[2]

ALA and MAL act as prodrugs penetrating the skin after topical administration and are metabolized to protoporphyrin IX (PpIX), a photosensitizer for PDT. PpIX is mainly located in the mitochondria and triggers the generation of reactive oxygen species upon activation by visible light. Due to the selective accumulation of PpIX in neoplastic cells the process selectively destroys tumour cells.[9]

BF-200 ALA (Biofrontera Bioscience GmbH, Leverkusen, Germany) is a new nanoemulsion-based gel formulation containing 7·8% ALA (10% ALA hydrochloride), which overcomes the drawbacks of previous ALA formulations by improving the stability of ALA in aqueous formulations and enhancing the penetration into the stratum corneum.[10] Based on these advantages, lower ALA concentrations are sufficient for a therapeutic effect. The high efficacy of BF-200 ALA was demonstrated in a recent phase III study.[11]

This study compares the efficacy and safety of BF-200 ALA in comparison with a registered cream containing 16% MAL and with placebo. As differences in efficacy and safety depending on the light source have been reported in an earlier phase III study with BF-200 ALA,[11] efficacy and safety obtained with narrow- and broad-spectrum light sources were also compared in this study.

Materials and methods

The study was performed as a confirmatory, randomized, multicentre, observer-blind, placebo-controlled, interindividual trial with BF-200 ALA, a registered MAL cream and placebo in a ratio of 3 : 3 : 1. The clinical trial was designed to demonstrate superiority to placebo and noninferiority to the MAL cream.

The 26 study centres involved included seven hospitals and 19 dermatological clinical centres or private dermatological practices. The study was approved by the responsible ethics committees and the competent authorities (BfArM, Germany; Swissmedic, Switzerland; BASG, Austria) and performed according to the National Drug Laws, the guidelines of Good Clinical Practice and the Declaration of Helsinki.

Study medication

BF-200 ALA gel contains 7·8% or 78 mg g^{-1} ALA (corresponding to 10% ALA hydrochloride). BF-200 ALA gel and placebo were produced and released according to Good Manufacturing Practice and relevant regulations. Laminated aluminium tubes contained 2 g of either BF-200 ALA or a placebo gel with identical appearance.

The comparator was a registered MAL cream (Metvix®; Galderma, Düsseldorf, Germany) containing 160 mg g^{-1} of MAL. MAL tubes were obtained from a pharmacy wholesaler.

Study plan

The treatment schedule and illumination conditions were identical to those described in the labelling for the registered MAL cream.[12] BF-200 ALA and placebo are gels and have a different consistency from the comparator. Therefore, to ensure an observer-blind conduct of the study, the application of study medication, illumination and safety assessments during illumination were done by one investigator. A second investigator was responsible for the patient's medical assessment before and after treatment. The investigational centres agreed that they would undertake all necessary efforts to maintain the observer-blind design. Adherence to the observer-blind design was monitored throughout the whole study. Crusts were carefully removed by mild curettage if necessary. Lesion surfaces were roughened and the skin was wiped with alcohol prior to drug application. After application of the gel an occlusive, light-tight dressing was placed over the lesion and illumination was performed 3 h later. The light sources included in the study are frequently used for PDT of AK in Europe, namely the Aktilite® CL 128 (Photocure, Oslo, Norway), Omnilux PDT™ (Photo Therapeutics Inc., Montgomeryville, PA, U.S.A.), PhotoDyn® 750/505 (Hydrosun Medizintechnik GmbH, Müllheim, Germany) and Waldmann® PDT 1200L (Waldmann Medizintechnik, Villingen-Schwenningen, Germany). They were used according to the manufacturers' instructions for PDT, such that the recommended light dose was applied. The Aktilite® CL 128 and Omnilux PDT™ have a narrow emission spectrum around 630 nm and a recommended light dose of 37 J cm^{-2}. The PhotoDyn® 750 or 505 is an incoherent broad-spectrum light source emitting light between 580 and 1400 nm with a recommended light dose of 170 J cm^{-2}. The light spectrum of the Waldmann® PDT 1200L ranges from 600 to 750 nm, and the recommended light dose is 100 J cm^{-2}. Fifteen centres used narrow-spectrum light sources (13 the Aktilite, two the Omnilux), and 11 centres performed PDT with broad-spectrum light sources (eight the PhotoDyn, three the Waldmann).

One week after PDT treatment patients were contacted by telephone to inquire about possible adverse events (AEs). Three weeks after the treatment, patients were examined by the physician and AEs were documented. Treatment efficacy and cosmetic outcome were assessed 12 weeks after PDT. In cases of remaining lesions, a second treatment was performed at this time point, followed by assessments scheduled at intervals as after the first treatment.

Randomization

The randomization list was generated centrally using Rando®, a validated program that automates the random assignment of treatments to randomization numbers (Accovion GmbH, Eschborn, Germany). The randomization schedule linked sequential numbers to treatment codes allocated at random with a 3 : 3 : 1 ratio. The randomization numbers were blocked. The block size was not revealed to the investigators. No disclosure of the randomization occurred during the study and all emergency envelopes remained concealed.

Study population

White male and female subjects, between 18 and 85 years of age, and diagnosed to have four to eight mild to moderate AK lesions (according to Olsen *et al.*[13]) in the face and/or on the scalp were included in the study. The diameter of each AK lesion was determined to be not less than 0·5 cm and not greater than 1·5 cm. Adjacent AK lesions had to show a minimal distance of 1·0 cm to one another. A biopsy from one representative lesion per patient was taken to allow confirmation of the diagnosis by histopathology prior to randomization. Exclusion criteria were clinical conditions such as porphyria and photodermatoses potentially influencing the aims of the study, and intolerance to any ingredient of BF-200 ALA or the MAL cream. Topical treatments within the treatment area were not allowed 12 weeks before or during the study. Other topical treatments possibly affecting 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 1–6 months before (timeframe depending on the substance, e.g. cytotoxic drugs 6 months prior to PDT) and during the study.

Efficacy assessment

Clearance of individual lesions was assessed by visual inspection and by palpation and compared with baseline 3 and 12 weeks after PDT. The primary endpoint, patient complete clearance, was defined as complete clearance of all lesions of a patient as determined by the clinical assessment. The rate of completely cleared lesions was calculated as a secondary endpoint. In addition, results obtained with different light sources, mild and moderate lesions, and lesions on the face and scalp were stratified with respect to complete patient response, total lesion clearance and AEs.

Safety and tolerability assessment

Local adverse reactions at the application site and discomfort during and after PDT were documented. A visual analogue score (VAS) showing an 11-point pain scale (from 'no pain' to 'pain as bad as you can imagine') was used to express the level of pain which the subjects experienced during PDT. According to Kasche *et al.*,[14] VAS values of 1–3 are interpreted as 'mild', 4–7 as 'moderate' and 8–10 as 'severe' pain. Zero represents no pain. The symptoms according to local skin reactions and discomfort were classified into mild, moderate and severe cases. Patients reported AEs during the treatment, during their visits or in a telephone inquiry 1 week after each PDT session. Serious AEs were documented and evaluated throughout the study. Patients were instructed to avoid intense

sunlight for 24 h after treatment and not to expose themselves to intense UV radiation during the course of the study.

Biometric analysis

Efficacy of treatments was tested either for superiority to placebo [two-sided at a significance level of 0·05 in the intent-to-treat (ITT) population] or for noninferiority to MAL applying a −15% margin [one-sided confidence interval (CI) at a significance level of 97·5% in the per-protocol population (PPP)]. Clearance rates were calculated separately for the BF-200 ALA, MAL and placebo groups. Next, it was calculated whether a statistically significant difference in the clearance rates existed between the three study arms. Following the hierarchical testing strategy, the second primary null hypothesis (inferiority to MAL) would only be tested if the first primary null hypothesis had been rejected and superiority over placebo established.

Results

Patients

Six hundred patients were enrolled, and 571 patients randomized and treated with BF-200 ALA (248 subjects), MAL (247 subjects) or placebo (76 subjects). Two hundred and fourteen patients were complete responders after the first PDT. Twenty-two subjects dropped out prematurely (one patient due to refusing a second treatment, two patients were withdrawn due to protocol violations, four patients due to AEs, and 15 patients dropped out for other reasons). Three hundred and forty-one (59·8%) patients received a second treatment. In total, 549 patients completed the study, and 539 subjects were included into the PPP. A flow chart of the patient disposition is presented in Figure 1. Patient and lesion characteristics are summarized in Table 1. Results are shown for the ITT population if not otherwise specified.

Efficacy

Patient complete clearance rates

The patient complete clearance rates 12 weeks after the last PDT were 78·2% for BF-200 ALA, 64·2% for MAL and 17·1% for placebo. Results obtained for the PPP provide similar numbers: 79·4% for BF-200 ALA, 65·3% for MAL and 20·0% for placebo. Significant superiority of BF-200 ALA over placebo ($P < 0·0001$) and noninferiority of BF-200 ALA to MAL were proven by statistical evaluation of the primary variable in both populations (ITT, PPP) which emphasizes the robustness of the

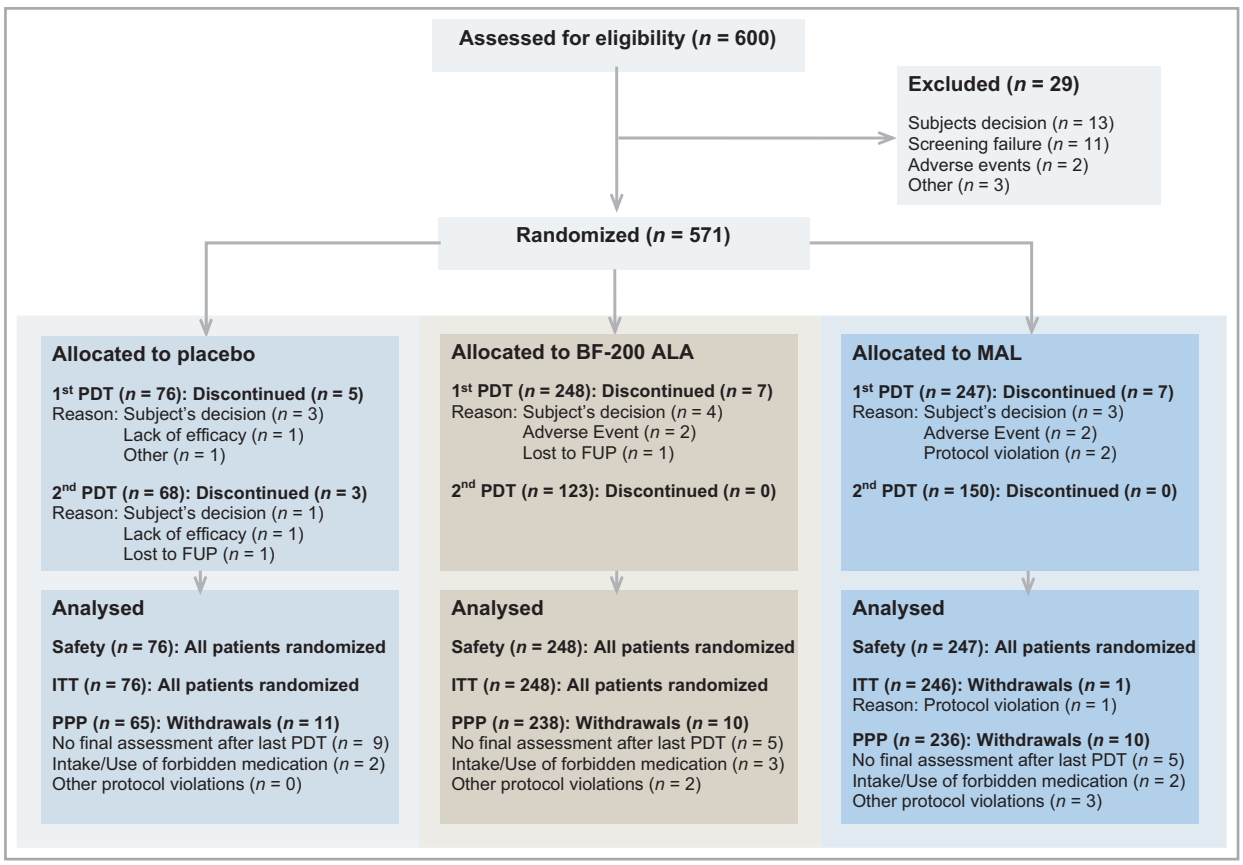

Fig 1. Flow chart for the disposition of patients. PDT, photodynamic therapy; FUP, follow-up; ALA, 5-aminolaevulinic acid; MAL, methyl-5-aminolaevulinate; ITT, intent-to-treat; PPP, per-protocol population.

Table 1 Summary of patient and actinic keratosis (AK) lesion characteristics before treatment (intent-to-treat population)

Study arm	BF-200 ALA (n = 248)	MAL (n = 246)	Placebo (n = 76)	Overall (n = 570)
Sex, n (%)				
Male	214 (86·3)	205 (83·3)	60 (78·9)	479 (84·0)
Female	34 (13·7)	41 (16·7)	16 (21·1)	91 (16·0)
Age (years)				
Mean ± SD	70·2 ± 7·18	71·0 ± 6·93	71·5 ± 6·68	70·7 ± 7·01
Median (range)	70·0 (39–87)	71·5 (44–85)	70·5 (51–84)	71·0 (39–87)
Number of AK lesions per group	1504	1557	490	3551
Number of lesions per patient, mean ± SD	6·1 ± 1·6	6·3 ± 1·5	6·4 ± 1·4	6·2 ± 1·5
Severity grade, n (%)				
Mild (slight palpability, grade I)	624 (41·5)	564 (36·2)	202 (41·2)	1390 (39·1)
Moderate (moderately thick, grade II)	880 (58·5)	991 (63·6)	288 (58·8)	2159 (60·8)
Severe (thick, grade III)	0	2 (0·1)	0	2 (< 0·1)
Fitzpatrick skin type, n (%)				
I	3 (1·2)	6 (2·4)	2 (2·6)	11 (1·9)
II	90 (36·3)	82 (33·3)	27 (35·5)	199 (34·9)
III	118 (47·6)	133 (54·1)	43 (56·6)	294 (51·6)
IV	35 (14·1)	23 (9·3)	4 (5·3)	62 (10·9)
V–VI	2 (0·8)	2 (0·8)	0	4 (0·7)
Localization, n (%)				
Face and forehead	964 (64·1)	990 (63·6)	279 (56·9)	2233 (62·9)
Bald scalp	540 (35·9)	567 (36·4)	211 (43·1)	1318 (37·1)
Total lesion area (mm^2), mean ± SD	478·3 ± 218·3	487·0 ± 215·28	461·1 ± 172·43	ND

ALA, 5-aminolaevulinic acid; MAL, methyl-5-aminolaevulinate; ND, not determined.

results. In addition, significant superiority of BF-200 ALA over MAL was proven as the error bars of the BF-200 ALA and MAL results were nonoverlapping and the difference of 0% was not included within the 97·5% CI (97·5% CI 6·0–∞; $P < 0·05$).

After the first PDT, total clearance was obtained in 48·4% of the BF-200 ALA-treated patients, 37·0% of the MAL-treated patients and 3·9% of the placebo patients. The difference between placebo and BF-200 ALA treatment groups was statistically significant ($P < 0·0001$). An 11·4% better efficacy was obtained in BF-200 ALA-treated subjects compared with MAL after one PDT. Figure 2a shows the patient complete clearance rates after one or two PDT treatments.

Both BF-200 ALA and MAL showed higher patient complete clearance rates at the face/forehead than the bald scalp. While with BF-200 ALA 81·9% of face/forehead lesions were completely cleared, 70·1% of lesions on the bald scalp were totally

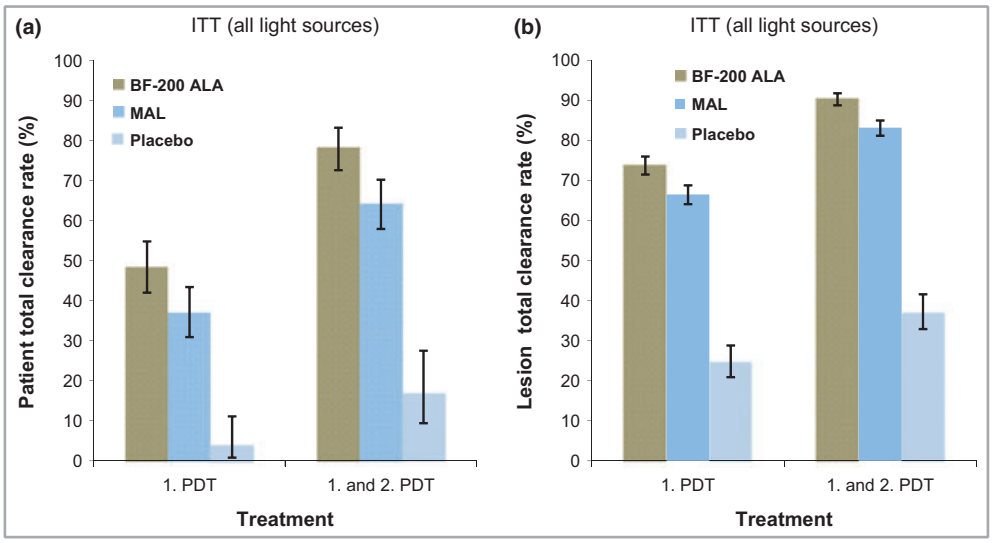

Fig 2. Patient (a) and lesion (b) complete clearance rates [intent-to-treat (ITT) population, all light sources] for BF-200 ALA vs. MAL and placebo. ALA, 5-aminolaevulinic acid; MAL, methyl-5-aminolaevulinate; PDT, photodynamic therapy. Error bars represent 95% confidence intervals.

cleared. With MAL, complete patient clearance was 77·5% and 39·7% for face/forehead and bald scalp, respectively. Patients with at least one Olsen grade II lesion displayed total clearance rates of 77·0% with BF-200 ALA and 58·5% with MAL. The 95% CIs did not overlap for bald scalp and grade II results, demonstrating significant differences between BF-200 ALA and MAL efficacies in these subgroups.

Lesion complete clearance rate

The rates of AK lesions showing total clearance 12 weeks after the last of one or two PDT treatments are presented in Figure 2b. At the end of the study, 1359 of 1504 lesions (90·4%) and 1295 of 1557 lesions (83·2%) showed full remission after treatment with BF-200 ALA or MAL, respectively, while only 182 of 490 lesions (37·1%) were totally cleared after placebo treatment. The differences between the treatment groups were statistically significant.

Analyses of the subgroups Olsen grade I vs. grade II, and target areas face/forehead vs. bald scalp revealed that complete lesion clearance rates were significantly higher with BF-200 ALA than with MAL or placebo.

Light source effects

In agreement with previous results,[11] differences were found in the patient complete clearance rates achieved with different irradiation sources. For BF-200 ALA and MAL (Fig. 3a), the rates were significantly higher in subjects who were irradiated with narrow-spectrum light sources (BF-200 ALA, 84·8%; MAL, 67·5%) than with broad-spectrum devices (BF-200 ALA, 71·5%; MAL, 61·3%). Complete clearance rates with placebo were higher with the broad-spectrum lamps (12·8% for narrow-spectrum lamps, 21·6% for broad-spectrum lamps).

Lesion complete clearance rates with narrow-spectrum lamps (Fig. 3b) were 77·1% (BF-200 ALA) and 73·0% (MAL) after the first PDT, and 93·6% (BF-200 ALA) and 89·3% (MAL) after one or two PDTs. With broad-spectrum devices, the rates were 69·7% and 59·1% after the first PDT (BF-200 ALA and MAL, respectively), and 86·3% and 76·3% after the final PDT (BF-200 ALA and MAL, respectively).

Similar findings were seen for the subgroups analysed. For example, complete patient clearance with BF-200 ALA was 94·5% for narrow-spectrum and 69·7% for broad-spectrum illumination of AK lesions in the face and forehead. BF-200 ALA-treated patients with at least one grade II lesion showed 83·2% total patient clearance with narrow-spectrum and 69·8% with broad-spectrum lamps. Corresponding values for MAL showed a similar trend but were generally lower. Values for face and forehead were 85·5% vs. 67·7%, and for patients with at least one grade II lesion 63·4% vs. 53·3% with narrow- and broad-spectrum illumination, respectively.

Cosmetic outcome

The cosmetic outcome, assessed at the last study visit, was considered as very good/good in 43·1% and 45·2% of BF-200 ALA- and MAL-treated subjects, respectively, compared with 36·4% in the corresponding placebo group. Unsatisfactory/impaired outcome was judged for 7·9% of the subjects in the BF-200 ALA group, 8·1% of the subjects in the MAL group and 18·2% of the placebo patients. These findings were confirmed by the results of the skin quality assessment where all treatment groups showed an improvement in skin quality. Most patients experienced an improvement in skin surface [40·0% and 46·4% in BF-200 ALA- and MAL-treated subjects, respectively, and to a lesser extent (27·3%) in the corresponding placebo subjects].

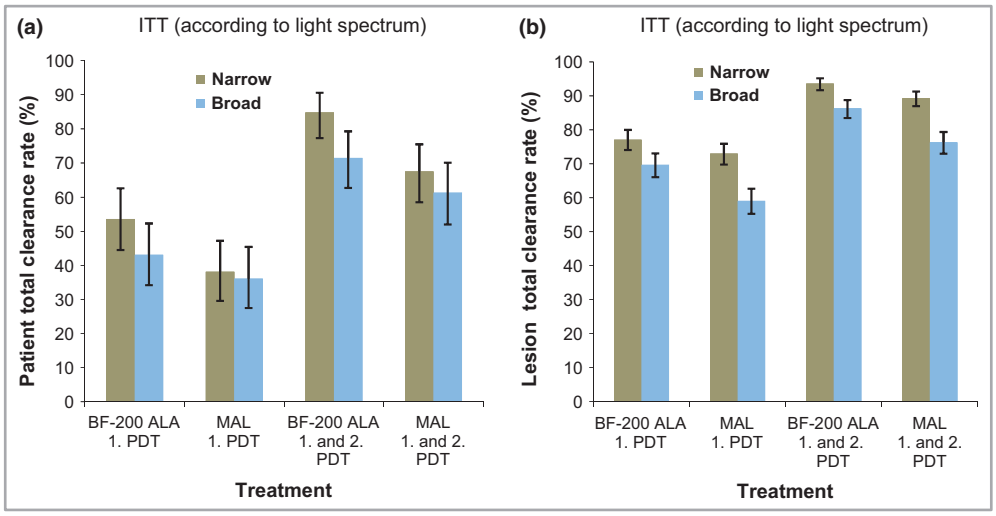

Fig 3. Patient (a) and lesion (b) complete clearance rates by irradiation source [intent-to-treat (ITT) population]: narrow-spectrum light sources, i.e. Aktilite® CL 128 or Omnilux PDT™, vs. broad-spectrum light sources, i.e. PhotoDyn® 750/505 or Waldmann® PDT 1200L. ALA, 5-aminolaevulinic acid; MAL, methyl-5-aminolaevulinate; PDT, photodynamic therapy. Error bars represent 95% confidence intervals.

Safety and tolerability

Almost all subjects reported AEs during the study. Most were consistent with the known safety profiles of BF-200 ALA and MAL and were experienced mainly as local skin reactions and discomfort in the treatment areas (Table 2). The overall percentage of treatment-emergent AEs was similar in the BF-200 ALA and MAL groups and was lower in the placebo group (96·4% of BF-200 ALA-treated subjects, 98·0% of subjects treated with MAL, and 72·4% of placebo subjects). Application site erythema, burning and pain represented the most common and most severe AEs (Tables 2 and 3). Incidences and severity of AEs increased in patients treated with narrow-spectrum devices compared with those illuminated with broad-spectrum light sources (Table 3).

Transient pain sensation was additionally assessed during PDT by VAS (11-point numeric rating scale) and showed similar values in BF-200 ALA- and MAL-treated subjects. Minor pain values were also reported for placebo patients (Table 4). Generally, AEs resolved within 5–7 days.

Incidence and severity of AEs decreased in re-treated patients during the second PDT compared with the first PDT irrespective of the treatment group.

No related serious AEs occurred. Two patients each in the BF-200 ALA and MAL groups discontinued PDT treatment due to AEs (one subject due to application site pain and nonserious application site burning; the three other subjects dropped out due to AEs considered as unrelated or unlikely to be related).

Discussion

In view of the increasing incidence of AK in fair-skinned subjects and the potential of AK to progress to SCC, PDT with ALA or its derivatives offers a highly effective and rapid therapy for this indication. ALA is a hydrophilic substance which is unstable in aqueous solutions and has a very limited ability to penetrate the stratum corneum. Therefore, the efficient topical administration of ALA is challenging.

Generally used medical preparations apply different approaches to address the stability problem. Either the final formulation is prepared shortly before use or, as with a recently approved ALA plaster, solid ALA is brought into intimate contact with the skin, or the somewhat more stable ester derivative (MAL) is used. However, these approaches do not optimize the skin penetration. Even the slightly more hydrophobic MAL does not display improved membrane penetration.[15] The oil-in-water nanoemulsion of BF-200 ALA both enhances the chemical stability of the active ingredient ALA and improves its skin and cell penetration. The better penetration into the epidermis was recently illustrated in pig skin

Table 2 Frequency of local skin reactions and discomfort in the safety population during and after the 1st and the 2nd photodynamic therapy (PDT) and with narrow- vs. broad-spectrum illumination

Most severe local skin reaction or discomfort (> 5%)	Treatment group								
	BF-200 ALA, %			MAL, %			Placebo, %		
	1st PDT	2nd PDT	Overall	1st PDT	2nd PDT	Overall	1st PDT	2nd PDT	Overall
Patients with at least one AE rated as local skin reaction	77·8	68·3	80·6	76·8	70·0	80·1	40·8	25·0	46·1
Application site erythema	75·0	65·9	78·2	75·2	68·7	78·5	36·8	23·5	40·8
Application site oedema	23·0	10·6	24·2	23·6	11·3	24·8	1·3	0	1·3
Application site exfoliation	14·5	16·3	17·7	13·8	15·3	17·1	5·3	2·9	6·6
Application site induration	8·5	4·1	8·9	8·5	3·3	8·5	0	0	0
Application site scab	7·7	4·9	10·1	6·1	10·0	10·6	1·3	2·9	2·6
Application site vesicles	7·3	1·6	8·1	8·1	3·3	9·3	1·3	0	1·3
Application site pruritus	4·8	2·4	5·6	2·0	1·3	2·8	0	0	0
By light spectrum									
Broad (PhotoDyn, Waldmann)	64·2	55·9	69·1	63·9	54·8	68·9	40·5	24·2	43·2
Narrow (Aktilite, Omnilux)	91·2	83·6	92·0	88·9	84·2	90·5	41·0	25·7	48·7
Patients with at least one AE rated as discomfort	87·1	75·6	89·1	90·7	82·7	93·5	39·5	14·7	40·8
Application site burning	81·5	68·3	85·9	85·4	73·3	89·8	28·9	13·2	31·6
Application site pain	67·3	50·4	69·4	67·9	60·7	72·8	21·1	10·3	25·0
Application site pruritus	16·5	9·8	19·4	17·1	11·3	20·7	5·3	2·9	6·6
Application site erythema	12·1	4·9	12·5	10·6	6·7	12·6	2·6	0	2·6
Application site oedema	6·9	2·4	7·7	7·7	2·7	8·1	0	0	0
Application site paraesthesia	6·0	4·9	6·5	6·1	4·7	7·3	2·6	0	2·6
By light spectrum									
Broad (PhotoDyn, Waldmann)	74·8	57·4	78·0	83·2	69·9	86·6	32·4	15·2	35·1
Narrow (Aktilite, Omnilux)	99·2	98·2	100	97·6	94·7	100	46·2	14·3	46·2

AE, adverse event; ALA, 5-aminolaevulinic acid; MAL, methyl-5-aminolaevulinate.

Table 3 Severe local skin reactions and discomfort in the safety population during photodynamic therapy (PDT). The list considers adverse events that occurred with narrow- or broad-spectrum illumination at a frequency of > 2 patients

Severe local skin reactions or discomfort (n > 2)	Treatment group								
	Placebo, %			BF-200 ALA, %			MAL, %		
	1st PDT	2nd PDT	Overall	1st PDT	2nd PDT	Overall	1st PDT	2nd PDT	Overall
Severe erythema									
Narrow	0	0	0	33·6	25·5	40·0	31·0	17·1	34·9
Broad	2·7	0	2·7	5·7	2·9	7·3	2·5	0	2·5
Severe oedema									
Narrow	0	0	0	1·6	0	1·6	6·3	0	6·3
Broad	0	0	0	0·8	0	0·8	0	0	0
Severe exfoliation									
Narrow	0	0	0	2·4	0	2·4	1·6	1·3	2·4
Broad	0	0	0	2·4	0	2·4	0	0	0
Severe scab									
Narrow	0	0	0	2·4	0	2·4	0	0	0
Broad	0	0	0	0·8	0	0·8	0	0	0
Severe induration									
Narrow	0	0	0	0	0	0	3·2	0	3·2
Broad	0	0	0	0	0	0	0	0	0
Severe burning									
Narrow	0	0	0	47·2	38·2	52·8	46·8	35·5	50·8
Broad	0	0	0	4·9	1·5	5·7	10·1	4·1	10·9
Severe pain									
Narrow	0	0	0	40·8	34·5	46·4	41·3	28·9	48·4
Broad	0	0	0	4·9	0	4·9	8·4	2·7	8·4
Severe paraesthesia									
Narrow	0	0	0	6·4	1·8	7·2	4·8	3·9	5·6
Broad	0	0	0	0	0	0	0	0	0

ALA, 5-aminolaevulinic acid; MAL, methyl-5-aminolaevulinate. Broad-spectrum lamps: PhotoDyn, Waldmann; narrow-spectrum lamps: Aktilite, Omnilux.

Table 4 Pain perception by visual analogue score (11-point numeric rating scale) during the first and the second photodynamic therapy (PDT), separated by target areas

	Treatment group					
	BF-200 ALA		MAL		Placebo	
	1st PDT	2nd PDT	1st PDT	2nd PDT	1st PDT	2nd PDT
Face and forehead	n = 181 4·1 ± 3·42[a]	n = 82 3·0 ± 3·34[a]	n = 188 4·3 ± 3·43	n = 98 3·0 ± 3·31	n = 55 0·4 ± 0·98	n = 45 0·3 ± 1·02
Bald scalp	n = 99 4·8 ± 3·61[a]	n = 51 3·3 ± 3·16[a]	n = 107 4·0 ± 3·58	n = 72 3·3 ± 3·01	n = 37 0·5 ± 1·12	n = 34 0·2 ± 1·04

ALA, 5-aminolaevulinic acid; MAL, methyl-5-aminolaevulinate. Data presented as mean ± SD. [a]No significant difference from MAL (Wilcoxon test, P > 0·05).

explants in a direct comparison of BF-200 ALA with the registered MAL cream.[10] Thus, BF-200 ALA provides a new gel formulation for ALA-PDT of AK with increased stability of the active ingredient and improved skin penetration.

High clinical efficacy of BF-200 ALA was recently shown in a prospective, placebo-controlled clinical phase III study in patients with AK.[11] The present study confirms the high efficacy and further demonstrates its superiority to the registered MAL product. The overall patient complete clearance rate for BF-200 ALA of 78·2% was statistically significantly better than for MAL (64·2%). Similarly, the lesion complete clearance rate of 90·4% for the BF-200 ALA group was clearly higher than the lesion efficacy achieved with MAL (83·2%).

The superiority over MAL is also reflected in the various subgroups analysed. In subgroups comprising more difficult to treat patients (e.g. patients with AK lesions on the bald scalp

or grade II lesions), the advantage of BF-200 ALA over MAL was even more pronounced than illustrated by the average of all patients. This may be explained by the better penetration of BF-200 ALA compared with the competitor product.[15] Consequently, the largest difference between BF-200 ALA and MAL was shown for the treatment of AK lesions on the bald scalp, namely 70·1% vs. 39·7%, respectively.

Efficacy rates for PDT with both BF-200 ALA and MAL were dependent on the light source used (Fig. 3). The results confirm previous findings of higher efficacy rates with narrow-spectrum light sources.[11] However, illumination with narrow-spectrum light sources also increased the amount and severity of AEs. Especially transient pain, burning, erythema and exfoliation were most pronounced in these patients and occurred with a similar frequency in patients treated with BF-200 ALA or MAL. Generally, drug-related AEs cleared within 1 week after PDT and were lower during the second PDT.

Efficacy results obtained with BF-200 ALA are at the upper end of overall efficacies reported recently from PDT studies with ALA or MAL.[16–21] Nevertheless, the concentration of the ALA prodrug in the BF-200 ALA gel is only half of that used in other products: BF-200 ALA contains 7·8% ALA (corresponding to 10% ALA hydrochloride) while the registered products Levulan®/Kerastick® (Dusa Pharmaceuticals, Wilmington, MA, U.S.A.)[22] use 20% ALA hydrochoride, and Metvix® 16% MAL (corresponding to 21% MAL hydrochloride).[12] Formulations produced by pharmacy compounding generally contain 20% ALA hydrochloride.[23–25] A marketing authorization has recently been granted to Alacare® (Medac, Hamburg, Germany), a 4 cm^2 plaster containing 8 mg solid ALA hydrochloride. Even though treatment with the plaster displayed good efficacy, its use is restricted to mild AKs.[21]

In the present study, skin protection was performed using an occlusive light-tight cover during the incubation period to fulfil requirements indicated for the use of the registered MAL cream. This measure may, however, not be necessary for a successful and safe treatment, as indicated by the treatment modalities commonly used in the U.S.A.[22]

In conclusion, the high patient and lesion clearance rates observed in this study with BF-200 ALA, in particular with narrow-spectrum light illumination, indicate that BF-200 ALA is an exceptionally effective, well-tolerated new drug for the PDT of AK. A direct comparison with the registered MAL cream demonstrated, furthermore, the strong and statistically significant superiority of BF-200 ALA over the MAL cream, without any significant change in the AE profile.

What's already known about this topic?

- Photodynamic therapy (PDT) with 5-aminolaevulinic acid (ALA) or its methylester [methyl-5-aminolaevulinate (MAL) or 5-amino-4-oxopentanoate] was recently ranked as first-line therapy for the treatment of actinic keratosis (AK) and is an accepted therapeutic option for the treatment of neoplastic skin diseases.
- BF-200 ALA is a new stable nanoemulsion-based gel formulation of ALA for PDT of AK which overcomes previous problems of ALA instability and improves skin penetration.

What does this study add?

- Pivotal phase III study with BF-200 ALA in comparison with a registered MAL cream and with placebo.
- Comparison of efficacy and adverse effects after use for PDT of AK in combination with different light sources (illumination conditions).

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