ORIGINAL ARTICLE

A randomized, intraindividual, non-inferiority, Phase III study comparing daylight photodynamic therapy with BF-200 ALA gel and MAL cream for the treatment of actinic keratosis

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Abstract

Background The most effective treatment modality for actinic keratosis (AK) is photodynamic therapy (PDT). Major obstacles of PDT are the need of a special illumination device and pain accompanying the illumination. These issues may be overcome by replacing an artificial high-power light source with natural daylight for more extended illumination at lower light doses.

Objective To determine whether BF-200 ALA (a nanoemulsion gel containing 7.8% 5-aminolaevulinic acid) is non-inferior to MAL (a cream containing 16% methyl-aminolaevulinate) in the treatment of mild-to-moderate AK with daylight PDT (dPDT). Non-inferiority of the primary efficacy variable (total lesion clearance rate per patient's side 12 weeks after PDT) is established if the mean response for BF-200 ALA is no worse than for MAL, within a statistical margin of $\Delta = -12.5\%$.

Methods The study was performed as an intraindividual comparison with 52 patients in seven centres in Germany and Spain. Each patient received one dPDT. Results include clinical endpoints as well as 1-year follow-up results.

Results Twelve weeks after a single dPDT, 79.8% of the AK lesions treated with BF-200 ALA gel and 76.5% of the lesions treated with MAL cream were completely cleared. The median of differences was 0.0 with a one-sided 97.5% CI of 0.0, establishing non-inferiority ($P < 0.0001$). Results for secondary efficacy parameters were in line with the primary outcome. Recurrence rates 1 year after the treatment were 19.9% for lesions treated with BF-200 ALA and 31.6% for lesions treated with MAL. Adverse reactions including pain were mostly mild and transient and identical to those previously described for dPDT.

Conclusion Daylight PDT of AK with BF-200 ALA is well-tolerated and non-inferior to MAL/dPDT. The study demonstrates a trend towards higher efficacies after 3 months and significantly lower recurrence rates after 1 year follow-up.

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Conflicts of interest

T.D. received clinical trial fees from Schulze und Böhm GmbH; has received lecture fees from Almirall, Biofrontera, Galderma, Leo, Meda, Riemser and Janssen; serves as a member of the advisory boards for Almirall, Biofrontera, Leo Pharma, Meda, Novartis, Riemser and Janssen; and has received unrestricted grants from Meda and Galderma. R.A. is a member of the advisory boards for Biofrontera and Leo Pharma and gives lectures for Biofrontera, Galderma, Meda, and Leo Pharma. E.H.-C. has served as a member of advisory boards for Pfizer

and Abbvie and has received lectured fees from Abbvie, Pfizer, Novartis, Leo Pharma, ISDIN, Lilly, Janssen and Celgene. R.B.-E. has served as a member of advisory boards for Pfizer, Abbvie and Galderma; he has received lectured fees from Abbvie, Pfizer, Novartis, Leo Pharma and MSD, and has received grants from Novartis, Pfizer, Abbvie, Janssen, Lilly, Cantabria and MSD. A.H., M.K. and B.S. are employees of the sponsoring company Biofrontera Bioscience GmbH and developed the study design together with the coordinating investigators. H.L. is CEO and Head of R & D of the sponsoring company Biofrontera Bioscience GmbH. He developed the study design together with his team and the coordinating investigators. S.P. has received lecture fees from Almirall, Bristol, ISDIN, Leo and Roche; serves as a member of the advisory boards for Almirall, Biofrontera, Leo Pharma, Meda, Merck and Novartis; and has received grants from Almirall, Cantabria, Glaxo Biomedicals, La Roche Posay, Meda, Merck, NewlinkGenetics and Roche. S.E.-B. and R.D. have no conflict of interest to declare.

Funding source

The study was sponsored by Biofrontera Bioscience GmbH.

Introduction

Photodynamic therapy (PDT) is a highly recommended therapeutic modality for the treatment of actinic keratosis (AK),[1] a potential precursor of squamous cell carcinoma caused by chronic skin exposure to ultraviolet light.[2] The advantages of PDT over various other therapies are the high treatment efficacy, the favourable cosmetic outcome and the short-time intervention. Moreover, its selectivity allows for the treatment of extended skin areas with field cancerization. However, the requirement of a specific illumination device and pain during illumination are major disadvantages of conventional PDT (cPDT).[3] To overcome this, recent studies focused on alternative posologies such as application of continuous daylight. While similar efficacy was observed for AK treatment with daylight PDT (dPDT) when compared with cPDT, the treatment was considerably less painful.[4–10] Thus, natural or simulated dPDT may greatly simplify the procedure and reduce PDT pain, without compromising efficacy.

BF-200 ALA is a topically applied nanoemulsion-based gel containing 7.8% 5-aminolaevulinic acid (ALA). Due to its rapid penetration,[11,12] the gel is well-suited for outdoor incubation. The present study compares BF-200 ALA with a cream containing 16% methyl-aminolaevulinate (MAL), which was already approved for the treatment of mild-to-moderate AK with dPDT. Both, ALA and MAL are prodrugs for the targeted photodestruction of neoplastic cells. They selectively induce accumulation of the photosensitizer protoporphyrin IX (PpIX) due to the cells' altered metabolism.[11,12] PpIX can be activated by the absorption of energy at several different wavelengths in the visible spectrum.

Studies on dPDT were previously conducted with both MAL cream and BF-200 ALA gel. In agreement with the superiority of BF-200 ALA shown in a pivotal trial comparing the two drugs for AK treatment with cPDT,[10] BF-200 ALA gel (Ameluz®) was found to be more effective than MAL cream in natural dPDT in a small single-centre study.[6,13] Additionally, BF-200 ALA was effective in indoor simulated dPDT.[5]

To compare BF-200 ALA gel and MAL cream in dPDT, a study was designed to prove the assumption that BF-200 ALA gel is non-inferior to MAL cream (with a non-inferiority margin of $\Delta = -12.5$). Meanwhile, BF-200 ALA was granted a label extension for the treatment of AK and field cancerization with dPDT in the EU.

Material and methods

The study was performed as a confirmatory, randomized, non-inferiority, Phase III trial using BF-200 ALA gel and MAL cream at a ratio of 1 : 1.

Seven study centres in Germany and Spain included university hospitals, dermatological clinical centres and private dermatological practices. The study was approved by the responsible ethics committees and the competent authorities prior to the start of the study and performed according to national drug laws, the guidelines of Good Clinical Practice and the Declaration of Helsinki (EudraCT number: 2015-004382-83). The study was sponsored by Biofrontera Bioscience GmbH. The study design was developed by the coordinating investigators in cooperation with the sponsor.

Investigational product

The investigational product (IP) was produced and released for the clinical study according to Good Manufacturing Practice and relevant regulations. Tubes with either BF-200 ALA gel (Ameluz®, Biofrontera, Leverkusen, Germany) or MAL cream (Metvix®/Metvixia®, Galderma, Düsseldorf, Germany) were used in their marketed 2 g formulations.

Study population

Male and female subjects (18–85 years of age) diagnosed with three to nine clinically confirmed AK target lesions of mild-to-moderate intensity (Olsen grade 1 or 2[14]) on each patient's side

EudraCT number: 2015-004382-83

were enrolled. Target lesions had to be within two comparable treatment areas located either on opposite sides of the face (excluding eyes, nostrils, ears and mouth) and/or the scalp. To ensure comparability, lesion numbers were not supposed to deviate by more than 50% between the two patient's sides.

Patients with porphyria, photodermatoses or intolerance to ingredients of BF-200 ALA gel or MAL cream were excluded. Treatments possibly affecting the response to the IPs and the dPDT were not allowed up to 6 months preceding the dPDT (timeframe depending on the substance) and during the study.

Randomization

The randomization schedule(s) was generated by FGK Clinical Research GmbH (Munich, Germany) using a validated program that automates the random assignment of the two patient sides to the IPs for the intraindividual contralateral comparison.

Treatment protocol

The study was conducted using an observer-blind design, as the IPs are distinct in the visual appearance of their formulations. The treatment regimen included one single dPDT. The clinical observation period lasted up to 12 weeks after the dPDT, followed by post-treatment observation for 9 months. Recurrence rates were assessed 1 year post-treatment.

Fifteen minutes prior to lesion pretreatment, a sunscreen without physical filters (ISDIN Fusion Gel, Barcelona, Spain) was applied to the sun exposed skin. After degreasing and carefully removing scabs, crusts and hyperkeratoses of AK lesions in the treatment areas, thin layers of the IPs were administered to the lesions on the respective patient's side such that AK lesions and surrounding 0.5–1.0 cm of healthy skin were covered. The IPs remained on the lesions throughout the entire illumination period. Daylight illumination started within 30 minutes after IP application and lasted for 2 continuous hours (Fig. 1). Daylight PDT was performed in full daylight during cloudy, cloudy to sunny or sunny weather conditions. On sunny days, patients were allowed to seek shelter in the shade if they felt uncomfortable in direct sunlight. Rainy periods or periods that the patient spent inside prolonged the outdoor exposure accordingly. The temperature was supposed to be ≥10°C, and overall weather conditions were to be reported for the start, after one hour, and at the end of the exposure, respectively. After the daylight illumination, remaining IPs were removed with 0.9% saline. Application site reactions and discomfort were documented.

Patients were contacted by phone 1 week after the dPDT session to inquire about any treatment-emergent adverse events (TEAEs). The efficacy of the treatment and further TEAEs were assessed by the investigator 4 and 12 weeks after dPDT. The clinical observation period ended 12 weeks after dPDT, at which time a 2-mm punch biopsy was taken from one target lesion on each patient's side that had been preselected at the screening visit. Patients were followed up for further 9 months.

Efficacy assessment

The primary efficacy parameter was the total lesion clearance rate in percentage per patient's side defined as the percentage of individual lesions cleared on the respective side of the patient 12 weeks after dPDT. AK lesions were considered 'cleared' (complete remission) if they disappeared completely, as assessed by visual inspection and palpitation (Olsen grade 0[14]). Subgroup analyses and analyses of secondary efficacy parameters (patient complete clearance per patient's side 12 weeks after dPDT, histological lesion response rate) were performed according to AK baseline characteristics and weather conditions during dPDT. Clinical recurrence was assessed up to 1 year after dPDT.

Cosmetic outcome was calculated according to skin quality parameters assessed by the investigators as described previously.[15] Patient satisfaction was assessed 12 weeks after dPDT using a 4-point scale from very good to impaired.

Safety and tolerability assessment

Treatment-emergent adverse events were defined as adverse events (AEs) with onset or worsening after treatment with the IPs. Pain during dPDT was assessed by the patient on an 11-point VAS scale ranging from 0 (no pain) to 10 (worst pain patient can imagine).

During follow-up (FU), any relevant local AE or condition that may impair a proper assessment of the recurrence rate of the treated AK lesions had to be documented.

Serious adverse events (SAEs) were evaluated throughout the complete study.

Statistical analysis

A sample size of 50 evaluable patients (intraindividual comparison) ensured a power of ≥ 90% to demonstrate a statistically significant non-inferiority in response rates. The primary null hypothesis was that the total lesion clearance rate in percentage per patient's side, assessed 12 weeks after treatment with BF-200 ALA/dPDT, is inferior compared to the corresponding total lesion clearance rate with MAL/dPDT, specified by a true inferiority of 0% within a non-inferiority margin of $\Delta = -12.5\%$. Non-inferiority of BF-200 ALA/dPDT in comparison with MAL/dPDT was established if the primary null hypothesis could be rejected for the per-protocol set (PPS). Secondary and safety variables were analysed descriptively and in an exploratory way.

Recurrence rates during FU were calculated for lesions or patients with complete response 12 weeks after dPDT and analysed *post hoc* using the Wilcoxon signed rank test for paired data and Fisher's exact test. Life tables were calculated for patients and lesions by multiplying the recurrence rate at FU (Pi) with the initial clearance rate (Pi*CR or Pi*RCL) as previously described.[16]

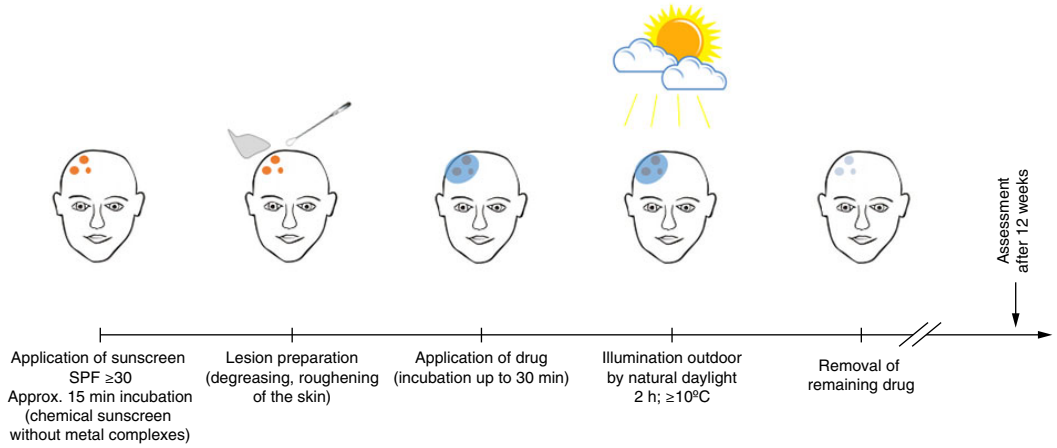

Figure 1 Treatment schedule of daylight PDT. Schematic illustration of the daylight PDT procedure. PDT, Photodynamic therapy; SPF, sun protection factor.

Results

Patients

The clinical observation period lasted from June 2016 to December 2016; 1-year FU was completed in September 2017. The intraindividual design provided equal numbers of patients in each arm. No patient prematurely discontinued the clinical part of the study. The disposition of patients is presented in Fig. 2. Patient and lesion characteristics are summarized in Table 1.

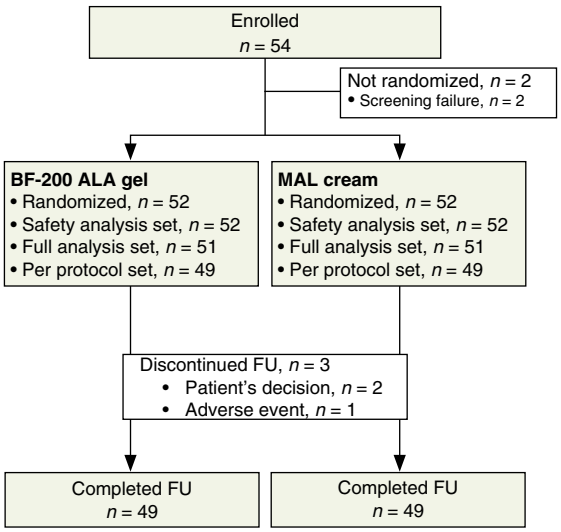

Figure 2 Flow chart of patient disposition. ALA: 5-aminolaevulinic acid; BF-200 ALA: nanoemulsion gel containing 7.8% ALA; MAL: methyl-aminolaevulinate (MAL cream formulation contains 16% MAL); numbers of patients are indicated.

Table 1 Baseline patient and AK lesion assessment

Variable	SAF *N* = 52	FAS *N* = 51	PPS *N* = 49
Sex, *n* (%)			
Male	50 (96.2)	49 (96.1)	47 (95.9)
Female	2 (3.8)	2 (3.9)	2 (4.1)
Age (years)			
Mean ± SD	72.2 ± 7.2	72.2 ± 7.3	72.6 ± 7.1
Fitzpatrick skin-type Score, *n* (%)			
I–III	48 (92.3)	47 (92.2)	45 (91.8)
IV–V	4 (7.7)	4 (7.8)	4 (8.2)
Variable; data for PPS	**BF-200 ALA gel**	**MAL cream**	
Number of target lesions per patient's side			
Mean ± SD	6.4 ± 2.2	6.4 ± 2.2	
Target lesion size, mm^2			
Mean ± SD	80.8 ± 35.2	77.6 ± 36.1	
Total area of target lesions, mm^2			
Mean ± SD	521.0 ± 264.6	439.9 ± 234.6	
Number of lesions by treatment area			
Total	316	312	
Face (%)	142 (44.9)	138 (44.2)	
Scalp (%)	174 (55.1)	174 (55.8)	
Number of lesion by severity grade†			
Mild (%)	154 (48.7)	154 (49.4)	
Moderate (%)	162 (51.3)	158 (50.6)	

†According to Olsen *et al.*[14]
AK, Actinic keratosis; FAS, full analysis set; *N*, number of patients in a treatment group; *n*, number of patients; PPS, per-protocol set; SAF, safety analysis set; SD, standard deviation.

Efficacy

Total lesion clearance rates At the end of the clinical observation period, 12 weeks after dPDT, 79.8 ± 23.6% of the BF-200

Table 2 Lesion clearance rates per patient's side 12 weeks after a single daylight PDT specified by baseline characteristics and environmental conditions during PDT

Lesion clearance rate in percentage at Week 12 post-PDT†,‡,§, LOCF		BF-200 ALA		MAL	
		n	%	*n*	%
Overall	Mean ± SD	49	79.8 ± 23.6	49	76.5 ± 26.5
	Median		87.5		83.3
By treatment area					
Face	Mean ± SD	20	85.2 ± 22.7	20	84.2 ± 19.8
	Median		100		94.4
Scalp	Mean ± SD	25	74.2 ± 24.9	25	67.5 ± 30.1
	Median		75.0		75.0
By maximum severity grade of AK lesions at baseline					
Mild	Mean ± SD	7	93.7 ± 16.8	7	91.2 ± 12.7
	Median		100		100
Moderate ¶	Mean ± SD	42	77.5 ± 23.9	42	74.1 ± 27.5
	Median		82.9		78.9
By minimum temperature during PDT					
≤20°C	Mean ± SD	25	80.1 ± 25.5	25	78.4 ± 27.7
	Median		87.5		87.5
>20°C	Mean ± SD	24	79.5 ± 21.8	24	74.6 ± 25.6
	Median		78.9		72.2
By worst weather condition during PDT					
Cloudy	Mean ± SD	14	80.1 ± 20.4	14	70.4 ± 32.9
	Median		86.6		81.7
Sunny/cloudy mixed	Mean ± SD	14	72.5 ± 32.5	14	73.5 ± 28.1
	Median		83.3		80.4
Sunny	Mean ± SD	21	84.5 ± 17.7	21	82.6 ± 19.9
	Median		100		100

†Total lesion clearance rate is defined as the percentage of completely cleared individual lesions (grade 0 according to Olsen criteria[14]) per patient's side.
‡Only subgroups with $n \geq 5$ are shown.
§Wilcoxon matched-pairs signed rank test.
¶Patients with at least one moderate lesion were categorized to moderate severity.
Data are presented for the per-protocol set.
LOCF, Last observation carried forward; *n*, number of patients; PDT, photodynamic therapy; SD, Standard deviation.

ALA-treated lesions were completely cleared, compared with 76.5 ± 26.5% on the MAL-treated sides, respectively (PPS; Table 2). The non-inferiority test revealed a median of differences (BF-200 ALA minus MAL) of 0.0 with a lower 97.5% confidence limit (CL) of 0.0 with the non-inferiority margin set at −12.5 (Fig. 3a). The *P*-value of the subordinate one-sided Wilcoxon signed rank test was $P < 0.0001$, confirming highly significant non-inferiority. The robustness of the result was confirmed by an identical statistical outcome of the full analysis set (FAS) analysis that displayed efficacies of 78.7 ± 25.8% for BF-200 ALA-treated sides and 75.0 ± 28.1% for MAL-treated sides, respectively.

With both IPs, the highest total lesion clearance rates were achieved for AKs in the face (85.2% for BF-200 ALA-treated sides and 84.2% for MAL-treated sides, respectively) and for treatment of patients with only mild AKs (93.7% for BF-200 ALA-treated sides and 91.2% for MAL-treated sides, respectively). For patients with at least one moderate AK (maximum severity grade moderate), lesion clearance rates per side were 77.5% for BF-200 ALA gel compared with 74.1% for MAL cream, respectively (Table 2). Calculating across all mild AKs treated with BF-200 ALA gel, 88.3% of the lesions were clinically cleared 12 weeks after dPDT, compared with 86.3% for MAL cream. For all moderate AK lesions, clearance rates were 68.5% and 67.1%, respectively.

The largest numerical differences between the IPs were observed for lesion clearance on the scalp and at cloudy weather. On the scalp, 74.2% of the lesions on the BF-200 ALA-treated sides were cleared 12 weeks after dPDT, compared with 67.5% on the MAL-treated sides, respectively. dPDT at cloudy weather resulted in 80.1% cleared lesions per patient's side for BF-200 ALA gel and 70.4% for MAL cream, respectively (Table 2). Medians of differences and corresponding 95% CIs of the subgroup analyses are displayed in Fig 3a–b. Please note that the CIs for differences between patient's sides with only mild lesions are extensive due to the small sample size in this subgroup ($n = 7$) making it difficult to draw a profound conclusion.

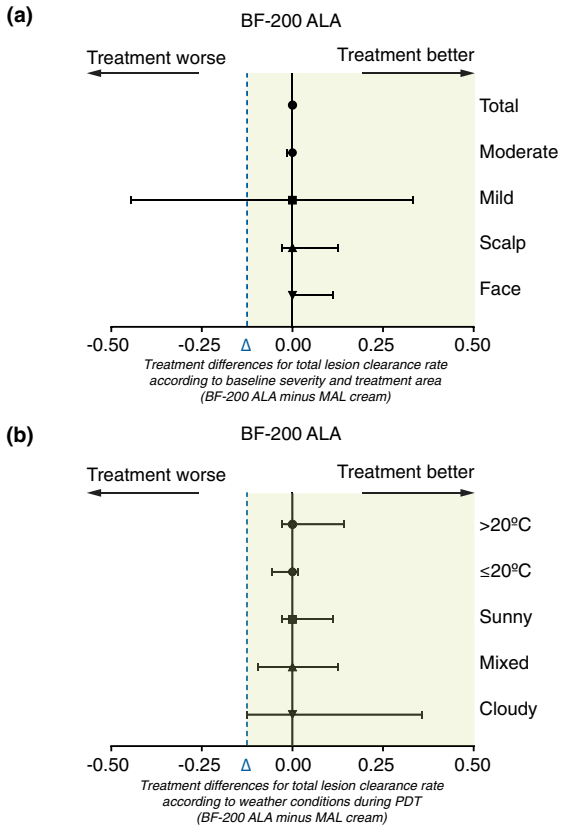

Figure 3 Treatment efficacy. Differences of total lesion clearance rates per patient's side, and subgroup analyses according to maximum baseline severity and treatment area are shown in (a), subgroup analyses according to weather conditions during dPDT in (b). A lesion was considered cleared 12 weeks after dPDT if it disappeared completely, as assessed by visual inspection and palpitation (Olsen grade 0[14]). Error bars represent two-sided 95% confidence intervals (CIs) of the median of differences between BF-200 ALA and MAL treatment. The blue dashed line at $\Delta = -12.5$ indicates the non-inferiority margin for the primary efficacy variable; the region to the right of $\Delta = -12.5$ indicates the zone of non-inferiority. Results are shown for the per-protocol set. Please note that the CIs for differences between patient's sides with only mild lesions are extensive due to the small sample size in this subgroup ($n = 7$) making it difficult to draw a profound conclusion.

Patient complete clearance Patient complete clearance rates, i.e. all lesions cleared at the respective patient's side, were 42.9% for BF-200 ALA compared with 38.8% for MAL, respectively (PPS). Subgroup analyses were consistent with this result, demonstrating slightly higher complete clearance rates for mild lesions and lesions in the face, and lower clearance rates for moderate lesions and lesions on the scalp, respectively.

Histologically cleared lesions For each patient, two lesions that were similar with respect to severity, size and location, one on each side, were selected prior to dPDT for biopsy taken at the last study visit 12 weeks after dPDT. Histopathological analyses according to Cockerell[17] and Röwert-Huber[18] agreed on a higher percentage of cleared lesions for BF-200 ALA gel (75.5%) compared with MAL cream (69.4%; $P = 0.2237$; PPS). All biopsies were also examined immunohistologically for p53 expression. While p53 expression was highly variable, the mean percentage of p53-positive cells after dPDT was lower for BF-200 ALA- than for MAL-treated lesions (33.9% vs. 40.5%, respectively; PPS).

Recurrence rates A Wilcoxon signed rank test showed significantly lower 1-year lesion recurrence rates for sides treated with BF-200 ALA gel (19.9%) compared with sides treated with MAL cream (31.6%; $P = 0.01$; PPS) (Table 3; Fig. 4a). Subgroups analyses revealed significantly lower recurrence rates for BF-200 ALA compared with MAL for patient with at least one moderate AK lesion at baseline (20.5% vs. 34.3%; $P = 0.009$) (Fig. 4b), for AKs on the scalp (23.4% vs. 43.7%; $P = 0.010$) (Fig. 4c), when treated at >20°C (18.6% vs. 36.1%; $P = 0.03$) (Fig. 4d), and during sunny weather (18.7% vs. 39.9%; $P = 0.002$) (Table 3; Fig. 4e). Of all mild AKs treated with BF-200 ALA gel that were cleared 12 weeks after dPDT, 17.7% were recurrent, compared with 19.3% of the MAL-treated lesions, respectively. For all moderate lesions, 22.1% of the BF-200 ALA-treated lesions recurred during FU compared with 36.4% of the lesions treated with MAL cream ($P = 0.03$, Fisher's exact test).

The significantly lower recurrence rates achieved with BF-200 ALA/dPDT are reflected in the 1-year estimated lesion-based clearance rates (P_i*RLC) that are in favour for BF-200 ALA (62.9%) compared with MAL/dPDT (56.6%). Scalp P_i*RLC values were 56.8% vs. 47.0%, and values for all moderate lesions were 53.1% vs. 43.4% for BF-200 ALA and MAL, respectively (Table 4).

Cosmetic outcome and patient satisfaction Cosmetic outcome was rated as very good or good for 40.7% and as unsatisfactory or impaired for 15.6% of the sides treated with BF-200 ALA gel and for 37.5% and 18.7% of the sides treated with MAL cream, respectively (PPS; patients with sum of all baseline skin quality assessments >0). Patient satisfaction regarding cosmetic outcome at Week 12 post-dPDT was very good, good or satisfactory for 91.8% of the patients for both BF-200 ALA/dPDT and MAL/dPDT. Most patients (94.1%) assessed the burden of the treatment as non-stressful (67.3%) or slightly stressful (26.5%).

Safety and tolerability

All adverse events were well-known transient application site reactions and discomforts reflecting the mode of action as listed in the summaries of product characteristics (SmPCs) for both medications. Application site erythema occurred on 73.1% of

Table 3 Lesion recurrence rates per patient's side 1 year after a single daylight PDT specified by baseline characteristics and environmental conditions during PDT

Lesion recurrence rate in percentage 1 year post-PDT†,‡		BF-200 ALA		MAL		Difference¶
		n	%	*n*	%	Median [95% CIs]
Overall	Mean ± SD	45	19.9 ± 24.1	44	31.6 ± 31.4	
	Median		16.7		25.0	0.1 [0; 0.2] *
By treatment area						
Face	Mean ± SD	19	20.1 ± 22.9	19	25.0 ± 29.0	
	Median	19	16.7	19	16.7	0 [−0.17; 0.2]
Scalp	Mean ± SD	22	23.4 ± 26.0	21	43.7 ± 31.0	
	Median	21	16.7	21	50.0	0.22 [0; 0.4] **
By maximum severity grade of AK lesions at baseline						
Mild	Mean ± SD	7	16.7 ± 16.7	7	17.5 ± 19.4	
	Median	7	16.7	7	16.7	0 [−0.33; 0.22]
Moderate¶	Mean ± SD	38	20.5 ± 25.3	37	34.3 ± 32.7	
	Median	37	16.7	37	33.3	0.1 [0; 0.25] **
By minimum temperature during PDT						
≤20°C	Mean ± SD	21	21.5 ± 26.5	21	26.8 ± 32.7	
	Median	21	16.7	21	16.7	0 [0; 0.2]
>20°C	Mean ± SD	24	18.6 ± 22.2	23	36.1 ± 30.1	
	Median	23	16.7	23	33.3	0.17 [0; 0.4] *
By worst weather condition during PDT						
Cloudy	Mean ± SD	11	15.9 ± 17.7	10	20.8 ± 21.8	
	Median	10	16.7	10	20.0	0.05 [−0.17; 0.2]
Sunny/cloudy mixed	Mean ± SD	13	25.4 ± 29.6	13	26.6 ± 33.8	
	Median	13	22.2	13	12.5	0 [−0.33; 0.25]
Sunny	Mean ± SD	21	18.7 ± 23.8	21	39.9 ± 32.7	
	Median	21	0.0	21	50.0	0.22 [0; 0.4] **

*$P \leq 0.05$; **$P \leq 0.01$.

†Lesion recurrence rate is defined as the percentage of completely cleared individual lesions (grade 0 according to Olsen criteria[14]) 12 weeks after daylight PDT per patient's side showing recurrence during follow-up.

‡Only subgroups with $n \geq 5$ are shown. §Wilcoxon matched-pairs signed rank test (unpaired data were not considered), two-sided, *post hoc*; median of differences with approx. 95% CIs.

¶Patients with at least one moderate lesion were categorized to moderate severity.

CIs, Confidence intervals; LOCF, last observation carried forward; *n*, number of patients; *P*, probability; PDT, Photodynamic therapy; SD, standard deviation. Data are presented for the follow-up per-protocol set.

BF-200 ALA-treated sides and 76.9% of MAL-treated sides. Application site pain was reported for 73.1% vs. 65.4%, application site pruritus for 50.0% vs. 51.9%, and application site scab for 36.5% vs. 32.7% of the BF-200 ALA- or MAL-treated sides, respectively. The majority of application site reactions were of mild or moderate intensity and resolved within 14 days. Adverse events of severe intensity were only reported for three patients for each IP (5.8%). Three patients experienced serious adverse events (SAEs) during FU that were not related to the study treatments; one of them discontinued the study due to the SAEs.

Pain intensity during PDT The mean maximal pain intensities during illumination on a scale from 0 (no pain) to 10 (worst pain) were 1.2 ± 2.1 (mean ± SD) for BF-200 ALA/dPDT and 1.1 ± 2.2 for MAL/dPDT, respectively. Pain intensities were 1.5 ± 2.6 for the face and 0.8 ± 1.5 for the scalp on BF-200 ALA-treated sides, and 1.5 ± 2.9 and 0.7 ± 1.2 on MAL-treated sides, respectively.

Discussion

Three Phase III studies have previously demonstrated high efficacy of cPDT with BF-200 ALA for the treatment of AK.[10,15,19] One of these studies compared BF-200 ALA and MAL and demonstrated significant superiority of BF-200 ALA gel over MAL cream.[10] Nevertheless, pain during cPDT remains a major obstacle for wider acceptance of PDT with either product.

In recent years, multiple clinical studies documented that PDT can be successfully performed with a 2-hour exposure to natural or simulated daylight,[4,6–8,20,21] and guidelines on dPDT were established.[22–25] The introduction of dPDT offered a concept to reduce pain and simplify the procedure while maintaining high efficacy.

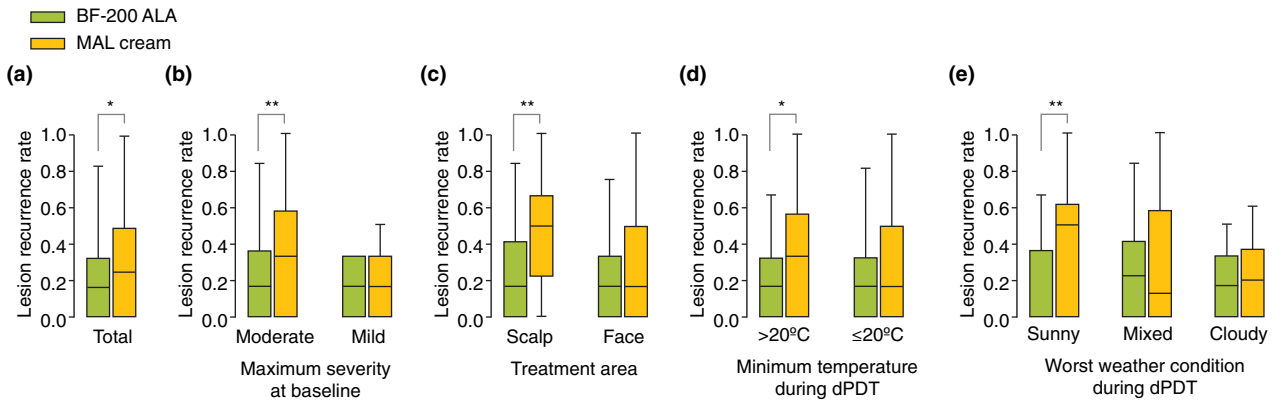

Figure 4 Recurrence rates. Overall lesion recurrence rates are shown in (a) followed by subgroup analyses according to baseline severity (b), treatment area (c), minimum temperature during dPDT (d), and worst weather conditions during dPDT (e). Recurrence rates during follow-up were calculated for lesions with a complete response 12 weeks after the dPDT and analysed *post hoc* using the Wilcoxon signed rank test for paired data. Boxplots indicate medians, and first and third quartiles. Error bars represent minimum and maximum. Results are shown for the per-protocol set. * $P \leq 0.05$; ** $P \leq 0.01$.

Table 4 Estimated lesion-based 1-year AK clearance rate related to number of lesions pretreatment specified by baseline characteristics and environmental conditions during daylight PDT

	BF-200 ALA gel				MAL cream			
	Cleared† *n*/*N* (%)	Recurrent‡ *n*/*N* (%)	P_i	P_i*RLC§	Cleared † *n*/*N* (%)	Recurrent‡ *n*/*N* (%)	P_i	P_i*RLC§
Overall	247/316 (78.16)	45/228 (19.74)	0.805	0.629	239/312 (76.60)	59/218 (27.06)	0.739	0.566
By treatment area								
Face	118/142 (83.10)	17/110 (15.45)	0.848	0.704	114/138 (82.61)	18/106 (16.98)	0.832	0.687
Scalp	129/174 (74.14)	28/118 (23.73)	0.766	0.568	125/174 (71.84)	41/112 (36.61)	0.655	0.470
By baseline severity								
Mild	136/154 (88.31)	22/124 (17.74)	0.829	0.732	133/154 (86.36)	23/119 (19.33)	0.815	0.704
Moderate	111/162 (68.52)	23/104 (22.12)	0.776	0.531	106/158 (67.07)	36/99 (36.36)	0.647	0.434
By minimum temperature during PDT								
≤20°C	141/178 (79.21)	22/122 (18.03)	0.824	0.653	136/171 (79.53)	24/115 (20.87)	0.806	0.641
>20°C	106/138 (76.81)	23/106 (21.70)	0.783	0.601	103/141 (73.05)	35/103 (33.98)	0.660	0.482
By worst weather condition during PDT								
Cloudy	69/88 (78.41)	8/50 (16.00)	0.845	0.663	64/88 (72.73)	8/42 (19.05)	0.842	0.603
Sunny/cloudy mixed	69/98 (70.41)	15/69 (21.74)	0.783	0.551	73/97 (75.26)	14/73 (19.18)	0.808	0.608
Sunny	109/130 (83.85)	22/109 (20.18)	0.798	0.669	103/127 (81.10)	37/103 (35.92)	0.641	0.520

†Total lesion clearance rate per IP is defined as the percentage of completely cleared individual lesions (grade 0 according to Olsen criteria 14) 12 weeks after daylight PDT. Data are presented for the per-protocol set.
‡Lesion recurrence rate per IP is defined as the percentage of completely cleared individual lesions (grade 0 according to Olsen criteria 14) 12 weeks after daylight PDT showing recurrence during follow-up. Data are presented for the follow-up per-protocol set. §Estimated lesionwise AK clearance rate at current visit (1 year after daylight PDT) related to number of lesions pretreatment. Data are presented for the per-protocol set.
IP, Investigational product; *N*, total number of lesions in a group; *n*, number of cleared or recurrent lesions; P_i, probability of remaining cleared up to current visit (1 year after daylight PDT); PDT, photodynamic therapy; RLC, rate of lesion clearance; SD, standard deviation.

Here, we present the first multicentric Phase III study comparing the efficacy of BF-200 ALA gel and MAL cream with dPDT in the treatment of AK. Our results show that a single PDT session with natural daylight achieved high clinical and histological clearance rates. In agreement with previous results in dPDT studies,[5–8] the mean pain score was reduced to between 0.7 and 1.5, while patients reported mean pain scores of >4 after cPDT.[7,8,10,15]

High clearance rates of mild AK lesions (88.3% for BF-200 ALA gel and 86.3% for MAL cream, respectively) were in line

with previously described lesion clearance rates for natural or simulated dPDT, ranging from 87% to 93% for BF-200 ALA gel[5,6] and from 74% to 90% for MAL cream,[6,7] respectively. Lesion clearance rates for moderate AKs were lower (68.5% for BF-200 ALA and 67.1% for MAL, respectively), also in agreement with previous dPDT trials.[26] The higher clearance rates of 82% after dPDT treatment with BF-200 ALA observed by Neittaanmäki *et al.*[6] may be due to a second treatment of moderate lesions in this study. For MAL, previously reported clearance rates for dPDT-treated moderate AKs ranged from 39% to 72%.[6,20,27]

During follow-up, the overall lesion recurrence was significantly different in favour of BF-200 ALA (19.9% vs. 31.6% for BF-200 ALA and MAL, respectively). 1-year recurrence rates were significantly better for BF-200 ALA (22.1% vs. 36.4%) for moderate lesions, in agreement with findings by Neittaanmäki *et al.*[13] Furthermore, the more difficult-to-treat lesions on the scalp displayed significantly lower recurrence rates for BF-200 ALA-treated sides compared with MAL-treated sides (23.4% vs. 43.7%, respectively).

During dPDT, environmental factors such as outdoor temperature and weather conditions may influence efficacy.[27] In the present study, dPDT was limited to an outdoor temperature of ≥10°C and was not performed on rainy days. While both drugs showed similar efficacy regarding temperature and weather conditions, recurrence rates were significantly lower for BF-200 ALA/dPDT during sunny weather and temperatures above 20°C, again demonstrating its more favourable long-term outcome.

For the primary endpoint and throughout all subgroups, the data show a trend towards higher clearance rates with BF-200 ALA gel compared with MAL cream. The current study was designed to demonstrate non-inferiority as relevant outcome for regulatory purposes, and not sufficiently powered to prove superiority. Nevertheless, the fact that numerically higher clinical and histological clearance rates after treatment and statistically significant lower 1-year recurrence rates were seen throughout most of the subgroups suggests that BF-200 ALA/dPDT is more effective than MAL/dPDT, as previously demonstrated for cPDT.[10]

In conclusion, this study reinforces the value of dPDT as an alternative approach for the treatment of mild-to-moderate AKs and shows that BF-200 ALA gel is at least as effective as MAL cream in dPDT, with overall significantly better long-term outcome. The combination of high response rates and low intensity of adverse events, in particular pain, may foster better acceptance of PDT by patients and physicians.

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