# A randomized, multinational, noninferiority, phase III trial to evaluate the safety and efficacy of BF-200 aminolaevulinic acid gel vs. methyl aminolaevulinate cream in the treatment of nonaggressive basal cell carcinoma with photodynamic therapy

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# A randomized, multi-national, non-inferiority, phase III trial to evaluate the safety and efficacy of BF-200 ALA gel versus MAL cream in the treatment of non-aggressive basal cell carcinoma with photodynamic therapy (PDT)

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## Topics

- To demonstrate non-inferiority of BF-200 ALA compared to MAL cream for the treatment of non-aggressive basal cell carcinoma (BCC) with PDT.
- To evaluate the safety related to BF-200 ALA for treatment of non-aggressive BCC with PDT.
- To evaluate the effect of PDT on different BCC subtypes.

## Key words

Basal cell carcinoma, 5-aminolaevulinic acid, methyl-aminolevulinate, photodynamic therapy, BF-RhodoLED

### Conflicts of interest

C.A.M. is a board member of Euro-PDT. He has been a member of advisory boards for Almirall, Biofrontera, Galderma, and Leo Pharma and has received speaker honoraria from Biofrontera and Galderma.
T.D. has received lecture fees from Almirall, Biofrontera, Galderma, Leo, Meda, Riemser, Janssen and is a member of advisory boards for Almirall, Biofrontera, Leo Pharma, Meda, Novartis, Riemser, Janssen and has received unrestricted grants from Meda and Galderma.
A.H. has received lecture fees from Almirall-Hermal.
U.R. has been a member of advisory boards for Almirall, Biofrontera, Galderma, and Leo Pharma; he has received speakers' honoraria from the aforementioned companies.
R.A. is a member of the advisory board for Biofrontera and holds lectures for Biofrontera, Galderma, and Leo Pharma.
M.U. is stakeholder in CMB Collegium Medicum Berlin GmbH; he received lecture fees from Almirall, Biofrontera, Galderma, Leo Pharma, Mavig GmbH, and Michelson Diagnostics.
S.I. has received travel expenses and honoraria from Galderma and Spirit HC.
R.O. is Vice Chairman of the BVDD-Regional Association North Rhine and Board Member for Germany in the EADV. He is member of advisory boards for Novartis, Leo Pharma, and in the past for Biofrontera; he has received speakers' honoraria from Aspen, Lilly, Novartis, and Biofrontera.
C.B. has been member of advisory boards for Almirall-Hermal, Biofrontera, Galderma, ISDIN, and Leo Pharma and has received speakers´ honoraria from Almirall-Hermal, Galderma, and Leo Pharma.
D.G. has been a member of the advisory board and received speakers' honoraria from Almirall, Allergan, Bayer, Galderma, Leo Pharma, Novartis, Meda, and l'Òreal.
H.J.S. is auditor of the German Cancer Society (DKG) for German skin cancer centres.
M.S. has received honoraria from Abbvie, Leo Pharma, Novartis, Janssen-Cilag, Lilly, Hexal, Celgene, Galderma, Böhringer Ingelheim, Almirall, Sanofi, Regeneron, Organobalance, Pfizer, GSK, Dr. Reddys, Mundipharma, and Medac.

H.S. has received lecture fees from Biofrontera and Galderma.
G.G. has been a member of advisory boards for Abbvie, Almirall, Leo Pharma, Meda, and Novartis and has received speakers' honoraria from Abbvie, Galderma, Leo Pharma, and Meda.
I.Z. is employee of Clinipace-Accovion GmbH, the company that was responsible as Clinical Research Organization for study conduct.
B.S., A.G., and H.L. are employees of the sponsoring company, Biofrontera Bioscience GmbH and developed the study design together with the coordinating investigators.
R.M.S. is Vice President of EURO-PDT. He has been member of advisory boards for Almirall, Biofrontera, Galderma, ISDIN, Leo Pharma, photonamic, and Pierre-Fabre; he has received speakers' honoraria.
R.D., P.R., S.K., S.E.B., H.M.O., V.J., H.K., and F.H. have no conflict of interest to declare.

## Funding source

The study was sponsored by Biofrontera Bioscience GmbH.

## What's already known about this topic?

- Photodynamic therapy (PDT) using BF-200 ALA gel is registered and highly effective in the treatment of mild to moderate actinic keratosis and field cancerisation. BF-200 ALA gel was recently approved for the treatment of superficial and/or nodular basal cell carcinoma unsuitable for surgical treatment.
- PDT using MAL cream is approved for the treatment of thin or non-hyperkeratotic and non-pigmented actinic keratoses, Bowen's disease, and superficial and nodular basal cell carcinomas (BCC) when other therapies are considered less appropriate.

## What does this study add?

- BF-200 ALA-PDT is confirmed to be significantly non-inferior to MAL-PDT for the treatment of non-aggressive BCC.
- Treatment-emergent adverse events were comparable between the two patient groups, with similar or slightly lower recurrence rates for BF-200 ALA gel compared to MAL cream after 12 months.

# Abstract

## Background

Basal cell carcinoma (BCC) represents the most common non-melanoma skin cancer worldwide affecting mainly adult, fair-skinned individuals. The WHO distinguishes aggressive and non-aggressive forms of which prototypical variants of the latter are primary nodular and superficial BCC.

## Objectives

To demonstrate non-inferiority of BF-200 ALA (a nanoemulsion gel containing 5-aminolaevulinic acid) compared to MAL (a cream containing methyl-aminolevulinate) in the treatment of non-aggressive BCC with photodynamic therapy (PDT). Non-inferiority of the primary efficacy variable (overall patient complete response 12 weeks after last PDT) would be declared if the mean response for BF-200 ALA was no worse than that for MAL, within a statistical margin of $\Delta$ = -15%.

## Patients/Methods

The study was a randomized, phase III trial performed in Germany and the UK with ongoing 5-year follow-up. Of 281 randomized patients, 138 were treated with BF-200 ALA, 143 with MAL. Patients received two PDT sessions one week apart. Remaining lesions 12 weeks after the second PDT were retreated. Illumination was performed with a red light source (635 nm, 37 J/cm$^2$). Results shown include clinical endpoints as well as patients' reassessment 12 months after the last PDT.

## Results

Of the BF-200 ALA-treated patients, 93.4% were complete responders compared to 91.8% in the MAL group. The difference of means was 1.6 with a one-sided 97.5% CI of -6.5, establishing non-inferiority ($p<0.0001$). Results for secondary efficacy parameters were in line with the primary outcome. Recurrence rates 12 months after the last treatment were $\leq$ 10%.

## Conclusions

Treatment of non-aggressive BCC with BF-200 ALA-PDT is highly effective and well tolerated with proven non-inferiority to MAL-PDT and demonstrates low recurrence rates after 1-year follow-up.

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# Introduction

Basal cell carcinoma (BCC) represents the most common type of non-melanoma skin cancer (NMSC) worldwide, affecting mainly adult (age ≥40), fair-skinned individuals [1,2]. Its incidence increases steadily and is currently estimated at 3-10% [1,3]. In the US, a 50% increase in males and a 20% increase in females was observed between two observational studies in 1977/78 and 1998/99, respectively [4]. In Europe, incidence rates increased 3-fold between 1997 and 2008 and rates are presumed to continue growing [5,6]. Worldwide, the highest incidences were reported for Australia showing a 4.4-fold increase in NMSC between 1985 and 2011 with higher rates in males and for BCCs, respectively [7]. The life time risk of developing BCC is estimated at ~30% which increases to ~40% within 3 years in patients with a prior BCC [2,6]. The aging population, higher awareness along with more frequent diagnosis of skin tumours, and changes in lifestyle are thought to contribute to the dramatically increasing numbers of patients and the associated increase in cost [6]. New therapeutic options are thus in the best interest of the general public [3].

Although invasive procedures are most widely used for the treatment of BCC, guideline recommendations are variable [5]. Cryosurgery has a weaker recommendation whereas surgical excision is usually the most appropriate treatment of BCC [1,5,8,9]. Nevertheless, alternative therapeutic concepts must be considered to overcome the drawbacks associated with physical measures, notably cosmetic outcome, functional impairments and/or the need for

reconstructive surgery after the treatment of multiple or larger lesions. This holds particularly true for locations in the face or on the neck, where at least 75% of all BCCs are located [3,6,10]. Among topical therapies, photodynamic therapy (PDT) is considered appropriate for the treatment of low-risk tumours, such as superficial (s)BCC and nodular (n)BCC, and for the treatment of large or multiple lesions [11-20]. The advantages of PDT include excellent compliance, and short treatment and down time, besides its high efficacy and superior cosmetic results.

BF-200 ALA is a topically applied nanoemulsion-based gel that contains 7.8% 5-aminolevulinic acid (ALA). The formulation improves ALA stability and enhances epidermal penetration compared to other formulations [21,22]. Thus, the concentration of the active substance could be significantly reduced. In the reported clinical study, BF-200 ALA was compared to a cream containing 16% methyl-aminolevulinic acid (MAL) using a non-inferiority trial design. MAL is approved for the treatment of sBCC and/or nBCC unsuitable for other available therapies due to possible treatment related morbidity and poor cosmetic outcome. Clinical studies comparing MAL with surgery or cryotherapy revealed lesion complete response rates for MAL ranging between 73% - 97%, always with superior cosmetic outcome [20,23-25]. Both, ALA and MAL are essential prodrugs for the targeted photo-destruction of neoplastic cells. They selectively induce accumulation of the photosensitive metabolite protoporphyrin IX (PpIX) due to these cells' altered metabolism. Illumination at an appropriate wavelength activates PpIX and leads to the specific destruction of tumour cells by reactive oxygen species [26-28].

A previous BCC study using a preliminary ALA nanoemulsion formulation showed a promising complete lesion response rate in superficial (s)BCC of 85% 6 months after a single PDT [29] confirming the results of the abovementioned studies. In order to compare BF-200 ALA gel and MAL cream in the treatment of non-aggressive BCC, a study based on the exception that BF-200 ALA gel is non-inferior to MAL cream (with a non-inferiority margin of $\Delta = -15$) was designed. Meanwhile, BF-200 ALA was granted a label extension for the treatment of superficial and nodular BCC in the EU.

# Material and Methods

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

The 24 study centres in Germany and UK included university hospitals, dermatological clinical centres and private dermatological practises. The study was approved by the responsible ethics committees and the competent authorities prior to the start of the study and performed according to the national drug laws, the guidelines of Good Clinical Practice and the Declaration of Helsinki (EudraCT number: 2013-003241-42). The study was sponsored by Biofrontera Bioscience GmbH. The study design was developed by the coordinating investigators in cooperation with the sponsor.

## Study medication and illumination

The study medication 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, Lausanne, Switzerland) were used in its marketed 2 g formulations. For

illumination, an LED light source (BF-RhodoLED®, Biofrontera, Leverkusen, Germany) producing red light at 635 ± 9 nm was used [30].

## Study population

Male and female subjects (>18 years of age) diagnosed with 1 to 3 non-aggressive BCC (0.5 - 2 cm in diameter) on the face/scalp, neck/trunk, or extremities were enrolled. A 3 mm punch biopsy taken at screening from each target lesion had to prove eligibility of non-aggressiveness and a thickness ≤ 2 mm by histological assessment.

Patients with porphyria and photodermatoses as well as any intolerance to ingredients of BF-200 ALA gel or MAL cream were excluded. Topical treatments possibly affecting the response to the study treatment were not allowed during the 12 weeks preceding the first PDT or during the study, with the exception of topical corticosteroids. Starting the use of substances with phototoxic or photoallergic potential was forbidden from 8 weeks prior to and during PDT. Patients exposed to these medications for longer than 8 weeks were allowed to participate if no phototoxic or photoallergic reactions were observed. Systemic treatments possibly impairing the outcome were not allowed 1 - 6 months before (timeframe depending on the substance) and during the study; patients were allowed to take up to 100 mg acetylsalicylic acid daily for preventive measures.

## Randomization

The randomization schedule(s) was generated by Accovion GmbH (Eschborn, Germany) using a validated program that automates the random assignment of treatments to randomization numbers. Randomization was performed with a block size of 6. Patient assignment to a group occurred according to the randomization schedule.

## Treatment protocol

The study was conducted using an observer-blind design, as the drug products display different consistencies in their formulation. The treatment regimen included one obligatory PDT cycle with two PDT sessions 1 week apart, and a second PDT cycle in case of remaining lesions 12 weeks after the first cycle. The clinical observation period lasted up to 12 weeks after the last PDT, followed by post-treatment observation for 57 months. Recurrence rates after 12 months post-treatment are included here; later time points will be reported separately.

After degreasing and carefully removing scabs, crusts, and exophytic tumour material, either BF-200 ALA gel or MAL cream was administered to the lesions at about 1 mm thickness. Subsequently, an occlusive light-tight dressing was placed over the target lesions for the entire incubation period (3 h ± 10 min). Thereafter, remnant gel or cream was wiped off and illumination of the target lesion(s) was immediately performed.

## Efficacy assessment

The clearance of individual lesions was assessed by visual inspection 4 and 12 weeks after treatments. The primary efficacy parameter was the overall patient complete response rate 12 weeks after the last PDT defined as the complete clearance of all treated lesions. Subgroup analyses and analyses of secondary efficacy parameters (lesion complete response 12 weeks

after the last PDT, patient complete response rate 12 weeks after PDT-2) were performed according to BCC baseline characteristics.

Cosmetic outcome was determined by the investigator according to skin quality parameters, as described by Reinhold *et al.* [30]. Patient satisfaction was assessed 12 weeks after the last PDT using a 4-point scale from very good to impaired.

### Safety and tolerability assessment

Local adverse reactions at the application site were documented during and after PDT. Symptoms were classified into mild, moderate, and severe. Ranking of the subjective sensations pain, burning and itching was done by the patient. Pain during PDT was assessed with a numeric rating pain scale (NRPS) ranging from 0 (no pain at all) to 10 (worst possible pain). For the overall adverse event (AE) assessment these data were transferred to a 4-point severity scale (0 = none, >0-3 = mild, 4-7 = moderate, 8-10 = severe). Treatment-emergent AEs (TEAEs) were defined as all AEs with onset or worsening after first treatment with randomized medication until the end of the clinical observation period. Serious adverse events (SAEs) were documented and evaluated throughout the study.

### Statistical analysis

The method of Farrington and Manning for testing non-inferiority of differences of proportions was used to test the primary hypothesis on a significance level of 2.5% (one-sided). A sample size of 115 evaluable patients per treatment group ensured a power of ≥90% for evaluation of the primary efficacy parameter, the overall patient complete response rate 12 weeks after the last PDT. This estimate was based on an expected response rate of 87% in each treatment arm and a non-inferiority margin of $\Delta = -15$. Analysis was performed on the per-protocol set; the full analysis set (FAS) was presented as supportive analyses. All other data were analysed descriptively and in an exploratory way.

Recurrence rates during FU were calculated for patients and for lesions with a complete response 12 weeks after the last PDT according to the primary and secondary efficacy variables. To determine the probability of remaining cleared up to a particular FU visit, 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 [31].

## Results

### Patients

The clinical observation period took place from Jan 2014 to Nov 2015; 1-year FU was completed in Aug 2016. Of 281 randomized patients (138 patients to BF-200 ALA gel and 143 patients to MAL cream), 19 patients prematurely discontinued the clinical part of the study. A flow chart of the disposition of patients is presented in Figure 1. All patients were Caucasian. Patient and lesion characteristics are summarized in Table 1.

## Efficacy

### *Overall Patient Complete Response Rate*

At 12 weeks after the last PDT, 93.4% (n=113) of patients in the BF-200 ALA group showed complete clearance of all BCC lesions compared to 91.8% (n=101) in the MAL group (Table 2). The non-inferiority test revealed a difference of means of 1.6 with a one-sided 97.5% CI of -6.5% ($p < 0.0001$), thus demonstrating statistical non-inferiority of BF-200 ALA gel compared to MAL cream for the primary efficacy parameter. The robustness of the results was confirmed by repeating the analyses on the FAS, which displayed a difference in efficacy of 5.2 (97.5% CI: -3.3; $p < 0.0001$) with 89.9% (n=124) of the patients in the BF-200 ALA group and 84.6% (n=121) in the MAL group showing complete clearance. More than half of the patients were already completely cleared 12 weeks after PDT-2 in both treatment arms: 57.9% in the BF-200 ALA group and 56.4% in the MAL group, respectively, with overlapping 95% CIs.

With respect to patients suffering from sBCC only, 94.7% in the BF-200 ALA, and 96.4% in the MAL group, respectively, showed complete clearance 12 weeks after the last treatment. Patients with nBCC only displayed clearance rates of 85.7% in the BF-200 ALA, and 76.2% in the MAL group, respectively (Table 2). Further subgroup analyses revealed clearance rates of 91.8% for the BF-200 ALA group and 92.6% for the MAL group with only 1 BCC lesion, whereas clearance rates for patients with 2 or more lesions were 100% and 87.5%, respectively. Differences between treatments are displayed in Figure 2.

One year after the last treatment (FU2) overall patient relapse occurred to a similar extent in both groups (8.4% for BF-200-ALA, 8.5% for MAL). Thus, of the full responders 12 weeks after the last PDT >91% remained fully cleared 12 months after PDT. In patients with sBCC only, the recurrence rate dropped to 6.9% for BF-200 ALA and to 8.0% for MAL, respectively. A larger difference was observed for patients with nBCC only, with 6.7% of the BF-200 ALA-, and 14.3% of the MAL-treated patients, respectively, relapsing within 12 months (Table 2).

Considering the still cleared patients at 1-year FU, the initial difference of 1.6% between both treatments was maintained due to the low recurrence rates. From the perspective of pre-treatment an overall patient clearance (Pi*CR) of 85.8% was calculated for the BF-200 ALA group compared to 84.4% for the MAL group. These values spread to 88.3% versus 89.0% for sBCC, and to 81.0% versus 66.3% for nBCC in the BF-200 ALA and MAL groups, respectively, at 1-year FU (Table 2).

### *Lesion Complete Response Rate*

The rate of completely cleared individual lesions assessed 12 weeks after the last PDT was 94.6% (n=148) in the BF-200 ALA, and 92.9% (n=127) in the MAL group. Subgroup analyses revealed numerical differences in lesion complete response rates when comparing BF-200 ALA with MAL treatment of sBCC (95.8% versus 96.9%), of nBCC (89.3% versus 78.6%), on face/scalp (82.4% versus 70.6%), on neck/trunk (97.9% versus 96.6%), and on extremities (91.2% versus 95.7%), respectively, but without statistical significance (Table 3). It is of note that there is some variation in the group sizes per treatment area as recruitment was not stratified for this parameter (Table 1).

From the cleared lesions observed during FU, 6.7% in the BF-200 ALA-, and 8.2% in the MAL group, respectively, relapsed within 12 months after the last PDT. Thus, of all lesions that had been clinically assessed as fully cleared after 3 months, 93.3% treated with BF-200 ALA and 91.8% treated with MAL were still clear at this time point. Regarding the sBCC

and nBCC lesions, 5.4% and 9.1% of lesions in the BF-200 ALA groups, respectively, and 7.9% and 10.0% in the MAL group, respectively, relapsed within 1 year after the last PDT. One-year recurrence rates for the different locations were 7.7% (face/scalp), 6.7% (neck/trunk), and 6.5% (extremities) in the BF-200 ALA group. The corresponding values in the MAL group were 18.2% (face/scalp), 7.6% (neck/trunk), and 5.0% (extremities) (Table 3).

Relative to the lesion number at baseline, the estimate for lesions to be cleared 1 year after the last treatment (Pi*RLC) was 88.4% in the BF-200 ALA, and 85.6% in the MAL group, respectively. For the main BCC subtypes, sBCC and nBCC, the estimates were 90.7% and 81.9% in the BF-200 ALA group compared to 89.5% and 71.3% in the MAL group, respectively. Thus, the initial proportion between the efficacies are maintained throughout the FU supporting an advantage for BF-200 ALA especially in nBCC treatment (Table 3).

***Cosmetic Outcome***

The overall cosmetic outcome was rated as very good or good by 60% of the patients treated with BF-200 ALA and by 48.6% of the patients treated with MAL (excluding those patients without skin quality impairment at baseline) 12 weeks after the last PDT (Table 4). The favourable assessment of very good or good increased during FU to 73.2% in BF-200 ALA-treated patients and to 68.4% in MAL-treated patients 1 year after the last PDT, respectively.

***Patient satisfaction***

The vast majority of patients in both groups rated their satisfaction as “very good or good” (87% of patients in the BF-200 ALA group and 86% of patients in the MAL group). This high satisfaction was maintained during the 1-year FU. 97.2% of BF-200 ALA-, and 99.0% of MAL-treated patients were still satisfied with PDT. No patient assessed the outcome as impaired at either time point.

## Safety and Tolerability

Frequencies and severity of TEAEs were within the range as expected with a BCC population of mainly elderly patients, the nature of the underlying disease, and the known safety profile of PDT with BF-200 ALA gel and MAL cream, which is related to the mode of action (Table 5). Frequencies were comparable between the groups and revealed no statistically significant differences. The most commonly reported TEAEs in both groups were local reactions at the application site (pain, erythema, pruritus, and oedema). The majority of related TEAEs were of mild to moderate intensity. Ten (3.6%) patients reported serious TEAEs during the clinical study part, which were all assessed as not related to study medication. Only four patients discontinued the study prematurely (Table 5). Local pain (NRPS) experienced during PDT was assessed for each PDT session and showed similar values for both treatments (Table 6).

# Discussion

Recent guidelines for BCC treatment discuss the choice of useful therapies based on the prognosis rather than on the clinical/histological subtype. For non-aggressive BCC displaying good to intermediate prognosis, PDT is regarded as a highly appropriate treatment option, providing high efficacy and favourable cosmetic outcome without significant functional constraints [5,8,9].

In the presented study, high overall response rates of >90% were obtained for both medications 12 weeks after the last PDT, with a patient complete response rate of 93.4% for BF-200 ALA versus 91.8% for MAL. Even after the first PDT cycle considerably more than 50% of the patients were clinically clear of BCC in both groups. Statistical analysis revealed that BF-200 ALA gel was non-inferior compared to the registered MAL cream.

The current study was designed to show non-inferiority of BF-200 ALA in comparison to MAL. However, superiority of BF-200 ALA had previously been demonstrated in a phase III trial treating actinic keratosis randomizing 571 patients [32]. In particular, the efficacy for thicker lesions or more difficult-to-treat lesions on the scalp was higher with BF-200 ALA [21,32]. In the present trial, similar findings were seen for nBCC lesions, for whom numerical higher proportion of response was revealed with BF-200 ALA (89.3%) than with MAL (78.6%) which was maintained during the 1-year FU period. Previous results reported by Rhodes *et al.* [23] showed high efficacies of MAL-PDT in the treatment of nBCC when compared to surgery (91% vs 96%, p=0.15). The differences for MAL may be due to different lesion preparations in the studies. Lower efficacy rates for nBCC were also described in the survey of Peng *et al.* [33] using extemporaneous ALA formulations. Based on 12 ALA-PDT studies with 208 lesions they achieved a weighted average complete response of 53%. The high efficacy observed for BF-200 ALA in the present study is presumed to be due to enhanced skin penetration of this formulation.

For sBCC lesions where skin penetration is less relevant, both medications displayed very similar efficacies (≥95%). These results exceed the weighted clearance rate of 87% calculated on the basis of 12 sBCC studies with 826 lesions treated with ALA-PDT [33]. Again, this may depend on the different formulations and treatment protocols [29]. In a previous study comparing MAL-PDT to surgery on sBCC, non-inferiority was demonstrated for MAL-PDT with clearance rates of 92.2% (MAL) vs 99.2% (surgery) [20]. A meta-analysis of 28 studies including various topical treatments resulted in clearance rates of 79% for MAL-PDT compared to 86.2% for imiquimod and indicated tumour free 1-year survival rates of 84% and 87.3%, respectively [11]. An additional study by Arits *et al.* [34] reported clearance rates for sBCC of 90.0% with imiquimod, 87.9% with 5-fluorouracil, and 84.2% with MAL after 3 months. In this study, only one PDT cycle was applied for MAL treatment, which is not in agreement with its label, while all other drugs were used according to their approved posology. However, after 12 months, the overall estimate of treatment success was calculated as 87.2%, 80.1%, and 72.5% for imiquimod, 5-fluorouracil, and MAL, respectively. In the present study, corresponding estimates were 88.3% for BF-200 ALA gel and 89.0% for MAL cream, respectively (Table 2). As patients will be followed-up for another 4 years, future recurrence rates will provide additional insight into the efficacy of BF-200 ALA-PDT.

Overall, high efficacy rates and low recurrence rates in the treatment of non-aggressive BCC, were achieved with BF-200 ALA- and MAL-PDT. The local adverse events observed in this study are well known for PDT and caused by the underlying mode of action. No difference in adverse events became apparent between both treatments. Several European guidelines have rated PDT in the categories Quality of Evidence: I, and Strength of Recommendation: A (for sBCC) or B (for nBCC) [5,8,35]. The present study reinforces the high ranking of PDT in the treatment of BCC. With BF-200 ALA, an excellent alternative for thin non-aggressive BCC is provided.

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# Figures and Tables

**Figure legends:**

**Figure 1: Flow chart of patient disposition in clinical study part**

*Initially, it was considered an exclusion criterion if – besides an eligible BCC – subjects had non-eligible BCC (all confirmed by biopsy), which resulted in a high amount of screening failures. In the course of the study, the protocol was amended such that individuals with at least one biopsy-proven, eligible BCC could be included if the distance to a non-eligible lesion was more than 10 cm. The protocol amendment was not expected to influence the composition of the enrolled patient population.

**Figure 2: Treatment efficacy**

Overall patient complete response rates and subgroup analyses for the per-protocol set. A patient was considered as complete responder if all treated lesions were cleared 12 weeks after the last PDT. Error bars represent one-sided 97.5% confidence intervals of the difference between BF-200 ALA and MAL treatment. The blue dashed line at -15 = Δ indicates the non-inferiority margin for the primary efficacy variable; the blue region to the right of -15 = Δ indicates the zone of non-inferiority.

**Table 1: Summary of patient and BCC lesion characteristics before treatment**

| Variable | MAL cream N=110 | BF-200 ALA gel N=121 |
|---|---|---|
| Sex, n (%) | | |
| Male | 55 (50.0) | 76 (62.8) |
| Female | 55 (50.0) | 45 (37.2) |
| Age (years) | | |
| Mean (SD) | 66.5 (11.53) | 67.3 (11.59) |
| Fitzpatrick Skin Type Score, n (%) | | |
| I-III | 98 (89.1) | 109 (90.1) |
| IV-VI | 12 (10.9) | 12 (9.9) |
| BCC lesions at baseline | 127 | 148 |
| BCC lesions at baseline per patient, Mean (SD) | 1.2 (0.39) | 1.2 (0.49) |
| No of BCC lesions at baseline per patient (%) | | |
| n = 1 | 94 (85.5) | 98 (81.0) |
| n ≥ 2 | 16 (14.5) | 23 (19.0) |
| BCC subtype*, n (%) | | |
| nBCC only | 21 (19.1) | 21 (17.4) |
| sBCC only | 83 (75.5) | 95 (78.5) |
| Others | 6 (5.5) | 5 (4.1) |
| Location of lesions, n (%) | | |
| Face/scalp[#] | 17 (13.6) | 17 (11.5) |
| Neck/trunk | 87 (68.5) | 97 (65.5) |
| Extremities | 23 (18.1) | 34 (23.0) |
| Thickness of BCC lesions overall (mm), Mean (SD) | 0.46 (0.36) | 0.41 (0.32) |

BCC: basal cell carcinoma; Max: maximum; Min: minimum; N: number of patients in a treatment group; n: number of patients, nBCC: nodular BCC; sBCC: superficial BCC, SD: standard deviation.

* Patient-based

[#] Only one lesion was located on the scalp.

Data presented for the per-protocol set.

**Table 2: Patient clearance and recurrence rates**

| | MAL cream | | | | BF-200 ALA gel | | | |
|---|---|---|---|---|---|---|---|---|
| **Subgroup/ Assessment time point after last PDT** | **Completely cleared n/N (%)** | **Recurrent n (%)** | **Pi [%]** | **Pi*CR [%]** | **Completely cleared n/N (%)** | **Recurrent n (%)** | **Pi [%]** | **Pi*CR [%]** |
| **Overall** | | | | | | | | |
| EOS (12 weeks) | 101/110 (91.8) | na | 100 | 91.8 | 113/121 (93.4) | na | 100 | 93.4 |
| 95% CI | 84.6 – 96.0 | | | | 87.0 – 96.9 | | | |
| FU2 (12 months) | 86/94* (91.5) | 8 (8.5) | 91.9 | 84.4 | 98/107* (91.6) | 9 (8.4) | 91.9 | 85.8 |
| 95% CI | 83.4 – 96.0 | 4.0 – 16.6 | | | 84.2 – 95.8 | 4.2 – 15.8 | | |
| **with sBCC only** | | | | | | | | |
| EOS (12 weeks) | 80/83 (96.4) | na | 100 | 96.4 | 90/95 (94.7) | na | 100 | 94.7 |
| 95% CI | 89.1 – 99.1 | | | | 87.6 – 98.0 | | | |
| FU2 (12 months) | 69/75* (92.0) | 6 (8.0) | 92.3 | 89.0 | 81/87* (93.1) | 6 (6.9) | 93.3 | 88.3 |
| 95% CI | 82.8 – 96.7 | 3.3 – 17.2 | | | 85.0 – 97.2 | 2.8 – 15.0 | | |
| **with nBCC only** | | | | | | | | |
| EOS (12 weeks) | 16/21 (76.2) | na | 100 | 76.2 | 18/21 (85.7) | na | 100 | 85.7 |
| 95% CI | 52.5 – 90.0 | | | | 62.6 – 96.2 | | | |
| FU2 (12 months) | 12/14* (85.7) | 2 (14.3) | 87.1 | 66.3 | 14/15* (93.3) | 1 (6.7) | 94.4 | 81.0 |
| 95% CI | 56.2 – 97.5 | 2.5 – 43.8 | | | 66.0 – 99.7 | 0.3 – 34.0 | | |

BCC: basal cell carcinoma; CI: confidence interval; EOS: end of clinical study, 12 weeks after last PDT; FU2: Follow-up 2, 12 months after last treatment; N: total number of patients with assessment; n: number of patients; na: not applicable; nBCC: nodular BCC; PDT: photodynamic therapy; Pi: Probability of patients remaining fully cleared until current visit (in percentage); Pi*CR: Estimated rate of patient clearance at current visit related to number of patients pre-treatment (in percentage); sBCC: superficial BCC.

* Complete responders 12 weeks after last PDT with data at 1 year follow-up

Data presented for the per-protocol set.

**Table 3: Lesion clearance and recurrence rates**

| | MAL cream | | | | BF-200 ALA gel | | | |
|---|---|---|---|---|---|---|---|---|
| **Subgroup/ Assessment time point after last PDT** | **Completely cleared n/N (%)** | **Recurrent n (%)** | **Pi (%)** | **Pi*RLC (%)** | **Completely cleared n/N (%)** | **Recurrent n (%)** | **Pi (%)** | **Pi*RLC (%)** |
| **Overall** | | | | | | | | |
| EOS (12 weeks) | 118/127 (92.9) | na | 100 | 92.9 | 140/148 (94.6) | na | 100 | 94.6 |
| 95% CI | 86.6 – 96.5 | | | | 89.3 – 97.5 | | | |
| FU2 (12 months) | 101/110* (91.8) | 9 (8.2) | 92.2 | 85.6 | 125/134* (93.3) | 9 (6.7) | 93.5 | 88.4 |
| 95% CI | 84.6 – 96.0 | 4.0 – 15.4 | | | 87.3 – 96.7 | 3.3 – 12.7 | | |
| **sBCC** | | | | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| EOS (12 weeks) | 95/98 (96.9) | na | 100 | 96.9 | 114/119 (95.8) | na | 100 | 95.8 |
| 95% CI | 90.7 – 99.2 | | | | 90.0 – 98.4 | | | |
| FU2 (12 months) | 82/89* (92.1) | 7 (7.9) | 92.4 | 89.5 | 105/111* (94.6) | 6 (5.4) | 94.7 | 90.7 |
| 95% CI | 83.9 – 96.5 | 3.5 – 16.1 | | | 88.1 – 97.6 | 2.2 – 11.9 | | |
| **nBCC** | | | | | | | | |
| EOS (12 weeks) | 22/28 (78.6) | na | 100 | 78.6 | 25/28 (89.3) | na | 100 | 89.3 |
| 95% CI | 58.5 – 91.0 | | | | 70.6 – 97.2 | | | |
| FU2 (12 months) | 18/20* (90.0) | 2 (10.0) | 90.7 | 71.3 | 20/22* (90.9) | 2 (9.1) | 91.7 | 81.9 |
| 95% CI | 66.9 – 98.2 | 1.8 – 33.1 | | | 69.4 – 98.4 | 1.6 – 30.6 | | |
| **BCC face/scalp[#]** | | | | | | | | |
| EOS (12 weeks) | 12/17 (70.6) | na | 100 | 70.6 | 14/17 (82.4) | na | 100 | 82.4 |
| 95% CI | 44.0 – 88.6 | | | | 55.8 – 95.3 | | | |
| FU2 (12 months) | 9/11* (81.8) | 2 (18.2) | 82.6 | 58.3 | 12/13* (92.3) | 1 (7.7) | 92.6 | 76.3 |
| 95% CI | 47.8 – 96.8 | 3.2 – 52.2 | | | 62.1 – 99.6 | 0.4 – 37.9 | | |
| **BCC neck/trunk** | | | | | | | | |
| EOS (12 weeks) | 84/87 (96.6) | na | 100 | 96.6 | 95/97 (97.9) | na | 100 | 97.9 |
| 95% CI | 89.5 – 99.1 | | | | 92.0 – 99.6 | | | |
| FU2 (12 months) | 73/79* (92.4) | 6 (7.6) | 92.7 | 89.5 | 84/90* (93.3) | 6 (6.7) | 93.6 | 91.7 |
| 95% CI | 83.6 – 96.9 | 3.1 – 16.4 | | | 85.5 – 97.3 | 2.7 – 14.5 | | |
| **BCC extremities** | | | | | | | | |
| EOS (12 weeks) | 22/23 (95.7) | na | 100 | 95.7 | 31/34 (91.2) | na | 100 | 91.2 |
| 95% CI | 76.0 – 99.8 | | | | 75.2 – 97.7 | | | |
| FU2 (12 months) | 19/20* (95.0) | 1 (5.0) | 95.3 | 91.2 | 29/31* (93.5) | 2 (6.5) | 93.5 | 85.3 |
| 95% CI | 73.1 – 99.7 | 0.3 – 26.9 | | | 77.2 – 98.9 | 1.1 – 22.8 | | |

BCC: basal cell carcinoma; CI: confidence interval; EOS: end of clinical study, 12 weeks after last PDT; FU2: Follow-up 2, 12 months after last treatment; N: total number of patients with assessment; n: number of patients; na: not applicable; nBCC: nodular BCC; PDT: photodynamic therapy; Pi: Probability of lesions remaining cleared up to current visit (in percentage); Pi*RLC: Estimated rate of lesion clearance at current visit related to number of lesions pre-treatment (in percentage); sBCC: superficial BCC.

* BCC lesions cleared 12 weeks after last PDT with data at 1 year follow-up

[#] Only one lesion was located on the scalp.

Data presented for the per-protocol set.

**Table 4: Cosmetic outcome 12 weeks after the last PDT and 1 year follow-up (patients with baseline evaluation "none"* were excluded)**

| | MAL cream n (%) | | BF-200 ALA gel n (%) | |
|---|---|---|---|---|
| | **EOS** | **1yFUP** | **EOS** | **1yFUP** |
| | **N=74*** | **N=57*#** | **N=70*** | **N=56*#** |
| **Very good,** n (%) | 16 (21.6) | 17 (29.8) | 28 (40.0) | 20 (35.7) |
| 95% CI | 13.2 – 33.0 | 18.8 – 43.6 | 28.7 – 52.4 | 23.7 – 49.7 |
| **Good,** n (%) | 20 (27.0) | 22 (38.6) | 14 (20.0) | 21 (37.5) |
| 95% CI | 17.7 – 38.8 | 26.3 – 52.4 | 11.7 – 31.6 | 25.2 – 51.5 |
| **Satisfactory,** n (%) | 24 (32.4) | 8 (14.0) | 16 (22.9) | 8 (14.3) |
| 95% CI | 22.3 – 44.4 | 6.7 – 26.3 | 14.0 – 34.7 | 6.8 – 26.8 |
| **Unsatisfactory,** n (%) | 9 (12.2) | 6 (10.5) | 8 (11.4) | 2 (3.6) |
| 95% CI | 6.1 – 22.3 | 4.4 – 22.2 | 5.4 – 21.8 | 0.6 – 13.4 |
| **Impaired,** n (%) | 5 (6.8) | 4 (7.0) | 4 (5.7) | 5 (8.9) |
| 95% CI | 2.5 – 15.7 | 2.3 – 17.8 | 1.8 – 14.7 | 3.3 – 20.4 |

1yFUP: follow-up 12 months after last PDT; CI: confidence interval; EOS: end of clinical study (12 weeks after last PDT); N: total number of patients with assessments at baseline and at respective follow-up visit; n: number of patients with respective improvement from baseline; PDT: photodynamic therapy.

Cosmetic outcome was calculated on the base of skin quality assessment [30]. Parameters (skin surface, pigmentation, degree of scarring, and atrophy) were rated on a 4-point scale from none to severe at baseline, at the end of the clinical observation period 12 weeks after the last PDT, and during follow-up (FU).

* Patients lacking compromised skin at baseline were excluded.

# Only complete responders are considered and patients with recurrent BCC lesions are excluded.

Data presented for the per-protocol set.

**Table 5 Overview of TEAEs**

| TEAE category | Number (%) of patients | | | |
|---|---|---|---|---|
| | MAL cream N=143 | | BF-200 ALA gel N=138 | |
| Patients with TEAEs | 143 | (100.0) | 138 | (100) |
| Patients with related[a] TEAEs | 143 | (100.0) | 138 | (100) |
| Patients with serious TEAEs | 7 | (4.9) | 3 | (2.2) |
| Patients with related[a] serious TEAEs | 0 | – | 0 | – |
| Patients with TEAEs leading to death | 1 | (0.7) | 0 | – |
| Patients with related[a] TEAEs leading to death | 0 | – | 0 | – |
| Patients with TEAEs leading to study withdrawal | 2 | (1.4) | 1 | (0.7) |
| Patients with related[a] TEAEs leading to study withdrawal | 1 | (0.7) | 1 | (0.7) |
| Patients with TEAEs rated as local skin reaction | 130 | (90.9) | 122 | (88.4) |
| Patients with related[a] TEAEs rated as local skin reaction | 130 | (90.9) | 121 | (87.7) |
| Patients with TEAEs rated as discomfort | 143 | (100.0) | 136 | (98.6) |
| Patients with related[a] TEAEs rated as discomfort | 143 | (100.0) | 136 | (98.6) |
| Patients with pain | 143 | (100.0) | 134 | (97.1) |
| Patients with pain considered related[a] to study treatment | 143 | (100.0) | 134 | (97.1) |

N= number of patients in a treatment group; TEAE= treatment emerged adverse event.

[a] Considered possibly, probably, or definitely related to study treatment.

Data comprised of TEAEs until 12 weeks after the last PDT.

Data presented for the safety population.

**Table 6: Maximal pain sensation during PDT**

| | | PDT-1 | PDT-2 | PDT-3 | PDT-4 |
|---|---|---|---|---|---|
| **MAL cream** | N | 143 | 142 | 61 | 60 |
| | Mean (SD) | 3.6 (2.22) | 4.1 (2.66) | 2.5 (2.23) | 2.9 (2.75) |
| **BF-200 ALA gel** | N | 138 | 138 | 54 | 55 |
| | Mean (SD) | 3.7 (2.42) | 4.5 (2.69) | 2.8 (2.55) | 3.9 (2.97) |

N= number of patients in a treatment group; PDT: photodynamic therapy; SD: Standard deviation.

Data present the means and SD of an 11-point numeric rating pain scale (NRPS) ranging from 0 (no pain at all) to 10 (worst possible pain) according to the patients assessment. In order to record pain experienced by the patients during the treatment, the PDT was to be started without measures to relieve pain. Potential pain management afterwards included physical cooling measures, reduction of light intensity to the expense of longer exposure times, or slight analgesia.

Data presented for the safety population.

Fig. 1

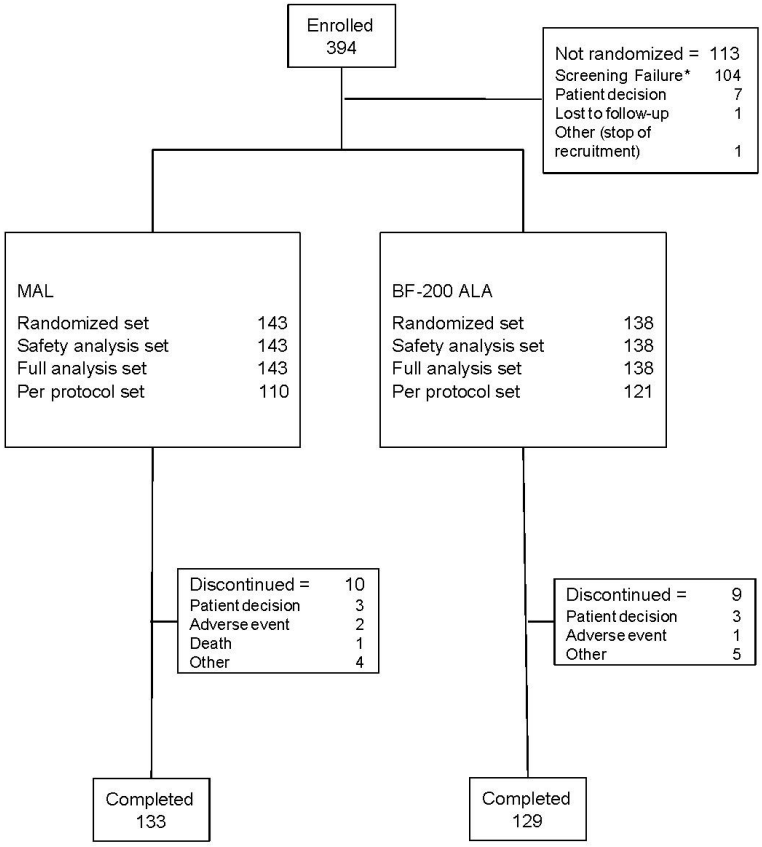

Fig . 2