

# 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\*

C.A. Morton,<sup>1</sup> R. Dominicus,<sup>2</sup> P. Radny,<sup>3</sup> T. Dirschka,<sup>4</sup> A. Hauschild,<sup>5</sup> U. Reinhold,<sup>6</sup> R. Aschoff,<sup>7</sup> M. Ulrich,<sup>8</sup> S. Keohane,<sup>9</sup> S. Ekanayake-Bohlig,<sup>10</sup> S. Ibbotson,<sup>11</sup> R. Ostendorf,<sup>12</sup> C. Berking,<sup>13</sup> D. Gröne,<sup>14</sup> H.J. Schulze,<sup>15</sup> H.M. Ockenfels,<sup>16</sup> V. Jasnoch,<sup>17</sup> H. Kurzen,<sup>18</sup> M. Sebastian,<sup>19</sup> H. Stege,<sup>20</sup> P. Staubach,<sup>21</sup> G. Gupta,<sup>22</sup> F. Hübinger,<sup>23</sup> I. Ziabreva,<sup>24</sup> B. Schmitz,<sup>25</sup> A. Gertzmann,<sup>25</sup> H. Lübbert<sup>25</sup> and R.-M. Szeimies<sup>26</sup>

<sup>1</sup>Dermatology Department, Stirling Community Hospital, NHS Forth Valley, Stirling, U.K.

<sup>2</sup>ProDerma, Dülmen, Germany

<sup>3</sup>Private Dermatological Practice, Friedrichshafen, Germany

<sup>4</sup>CentroDerm GmbH, Wuppertal, and Faculty of Health, University Witten/Herdecke, Witten, Germany

<sup>5</sup>Dermatologikum Kiel and Department of Dermatology, University Hospital Schleswig-Holstein (UKSH), Kiel, Germany

<sup>6</sup>Medical Centre Bonn, Bonn, Germany

<sup>7</sup>Department of Dermatology, University Hospital Carl Gustav Carus, Technical University Dresden, Dresden, Germany

<sup>8</sup>CMB Collegium Medicum Berlin GmbH, Berlin, Germany

<sup>9</sup>St Mary's Hospital, Portsmouth Dermatology Centre, NHS Trust, Portsmouth, U.K.

<sup>10</sup>MENSINGDERMA research GmbH, Hamburg, Germany

<sup>11</sup>Photobiology Unit, University of Dundee, Ninewells Hospital and Medical School, Dundee, U.K.

<sup>12</sup>ZENTderma, Mönchengladbach, Germany

<sup>13</sup>Department of Dermatology and Allergy, University Hospital Munich, Munich, Germany

<sup>14</sup>Dermatological Private Practice, Clinical Research and Laser Medicine, Berlin, Germany

<sup>15</sup>Specialist Hospital Hornheide, Department of Dermatology, Münster, Germany

<sup>16</sup>Dermatology and Allergy Practice at the Clinical Centre Hanau, Hanau, Germany

<sup>17</sup>Centre for Dermatology Vechta, Vechta, Germany

<sup>18</sup>Private Practice, Freising, Germany

<sup>19</sup>Private Practice, Mahlow, Germany

<sup>20</sup>Department of Dermatology, Clinical Centre Lippe GmbH Detmold, Detmold, Germany

<sup>21</sup>Department of Dermatology, University Hospital Johannes Gutenberg University Mainz, Clinical Research Center, Mainz, Germany

<sup>22</sup>Monklands Hospital, NHS Lanarkshire, Airdrie and University of Glasgow, Glasgow, U.K.

<sup>23</sup>Private Practice, Wuppertal, Germany

<sup>24</sup>Clinipace – Accovion GmbH, Eschborn, Germany

<sup>25</sup>Biofrontera Bioscience GmbH, Leverkusen, Germany

<sup>26</sup>Department of Dermatology and Allergy, Vest Clinic, Recklinghausen, Germany

## Summary

### Correspondence

Colin A. Morton.

E-mail: colin.morton@nhs.net

### Accepted for publication

4 February 2018

### Funding sources

The study was sponsored by Biofrontera Bioscience GmbH.

**Background** Basal cell carcinoma (BCC) represents the most common nonmelanoma skin cancer worldwide, affecting mainly adult, fair-skinned individuals. The World Health Organization distinguishes aggressive and nonaggressive forms, of which prototypical variants of the latter are primary nodular and superficial BCC. **Objectives** To demonstrate noninferiority of BF-200 ALA (a nanoemulsion gel containing 5-aminolaevulinic acid) compared with MAL (a cream containing methyl aminolaevulinate) in the treatment of nonaggressive BCC with photodynamic therapy (PDT). Noninferiority of the primary efficacy variable (overall patient complete response 12 weeks after last PDT) would be declared if the mean

**Conflicts of interest**

Conflicts of interest statements can be found in the Appendix.

\*Plain language summary available online

DOI 10.1111/bjd.16441

response for BF-200 ALA was no worse than that for MAL, within a statistical margin of  $\Delta = -15\%$ .

**Methods** The study was a randomized, phase III trial performed in Germany and the U.K. with ongoing 5-year follow-up. Of 281 randomized patients, 138 were treated with BF-200 ALA and 143 with MAL. Patients received two PDT sessions 1 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<sup>-2</sup>). The results shown include clinical end points and patients' reassessment 12 months after the last PDT. The study was registered with EudraCT (number 2013-003241-42).

**Results** Of the BF-200 ALA-treated patients, 93.4% were complete responders compared with 91.8% in the MAL group. The difference of means was 1.6, with a one-sided 97.5% confidence interval of -6.5, establishing noninferiority ( $P < 0.0001$ ). The 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 nonaggressive BCC with BF-200 ALA-PDT is highly effective and well tolerated with proven noninferiority to MAL-PDT. It demonstrates low recurrence rates after 1 year of follow-up.

**What's already known about this topic?**

- Photodynamic therapy (PDT) using BF-200 aminolaevulinic acid (ALA) gel is registered and highly effective in the treatment of mild-to-moderate actinic keratosis and field cancerization.
- BF-200 ALA gel was recently approved for the treatment of superficial and/or nodular basal cell carcinoma (BCC) unsuitable for surgical treatment.
- PDT using methyl aminolaevulinate (MAL) cream is approved for the treatment of thin or nonhyperkeratotic and nonpigmented actinic keratoses, Bowen disease, and superficial and nodular BCCs when other therapies are considered less appropriate.

**What does this study add?**

- BF-200 ALA-PDT is confirmed to be significantly noninferior to MAL-PDT for the treatment of nonaggressive 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 with MAL cream after 12 months.

Basal cell carcinoma (BCC) represents the most common type of nonmelanoma skin cancer (NMSC) worldwide, affecting mainly adult (age  $\geq 40$  years), fair-skinned individuals.<sup>1,2</sup> Its incidence is increasing steadily and is currently estimated at 3–10%.<sup>1,3</sup> In the U.S.A., a 50% increase in male patients and a 20% increase in female patients was observed between two observational studies in 1977–78 and 1998–99, respectively.<sup>4</sup> In Europe, incidence rates increased threefold between 1997 and 2008, and rates are presumed to continue growing.<sup>5,6</sup> Worldwide, the highest incidences were reported for Australia, showing a 4.4-fold increase in NMSC between 1985 and 2011, with higher rates in male patients and for BCCs.<sup>7</sup> The lifetime risk of developing BCC is estimated at around 30%, increasing to around 40% within 3 years in patients with a prior BCC.<sup>2,6</sup> The ageing population and 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.<sup>6</sup> New therapeutic options are thus in the best interest of the general public.<sup>3</sup>

Although invasive procedures are the most widely used for the treatment of BCC, guideline recommendations are variable.<sup>5</sup> Cryosurgery has a weaker recommendation, whereas surgical excision is usually the most appropriate treatment for BCC.<sup>1,5,8,9</sup> 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

$\geq 75\%$  of all BCCs are located.<sup>3,6,10</sup> 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.<sup>11–20</sup> 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-aminolaevulinic acid (ALA). The formulation improves the stability of ALA and enhances epidermal penetration compared with other formulations.<sup>21,22</sup> Thus, the concentration of the active substance could be significantly reduced. In the reported clinical study, BF-200 ALA was compared with a cream containing 16% methyl aminolaevulinic acid (MAL) using a noninferiority 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% and 97%, always with superior cosmetic outcome.<sup>20,23–25</sup> Both ALA and MAL are essential prodrugs for the targeted photodestruction 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.<sup>26–28</sup>

A previous study of BCC using a preliminary ALA nanoemulsion formulation showed a promising complete lesion response rate in sBCC of 85% 6 months after a single PDT treatment,<sup>29</sup> confirming the results of the above-mentioned studies. In order to compare BF-200 ALA gel and MAL cream in the treatment of nonaggressive BCC, a study based on the theory that BF-200 ALA gel is noninferior to MAL cream (with a noninferiority margin of  $\Delta = -15$ ) was designed. Meanwhile, BF-200 ALA was granted a label extension for the treatment of sBCC and nBCC in the European Union.

## Patients and methods

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

The 24 study centres in Germany and the U.K. included university hospitals, dermatological clinical centres and private dermatological practices. The study was approved by the responsible ethics committees and the appropriate authorities prior to the start of the study and was 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<sup>®</sup>; Biofrontera, Leverkusen, Germany) or MAL cream (Metvix<sup>®</sup> or Metvixia<sup>®</sup>; Galderma, Lausanne, Switzerland) were used in the marketed 2-g formulations. For illumination, a light-emitting diode source (BF-RhodoLED<sup>®</sup>; Biofrontera) producing red light at  $635 \pm 9$  nm was used.<sup>30</sup>

## Study population

Male and female patients (> 18 years of age) diagnosed with one to three nonaggressive BCCs (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 nonaggressiveness and a thickness  $\leq 2$  mm by histological assessment.

Patients with porphyria and photodermatoses, or any intolerance to the 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 > 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 (time frame depending on the substance) or during the study; patients were allowed to take up to 100 mg acetylsalicylic acid daily for preventive measures.

## Randomization

The randomization schedule 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 six. 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 performed immediately.

### 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 rate 12 weeks after the last PDT, patient complete response rate 12 weeks after the second PDT) were performed according to the baseline characteristics of the BCCs.

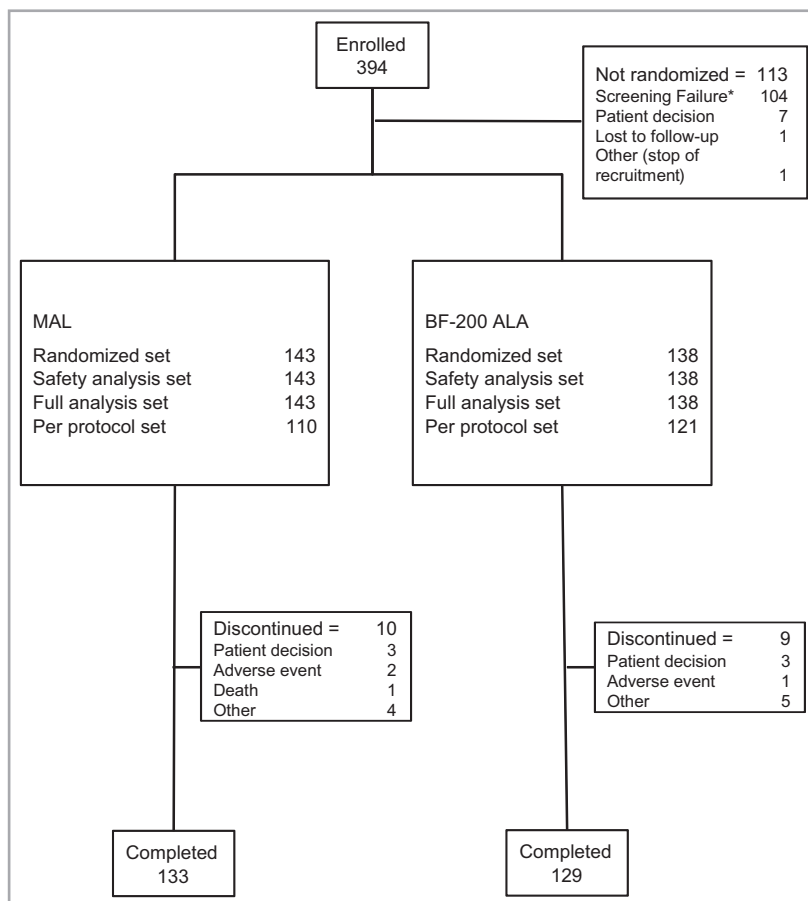
Cosmetic outcome was determined by the investigator according to skin-quality parameters, as described by Reinhold *et al.*<sup>30</sup> Patient satisfaction was assessed 12 weeks after the last PDT using a four-point scale from very good to impaired.

### Safety and tolerability assessment

Local adverse reactions at the application site were documented during and after PDT. Symptoms were classified as mild, moderate or severe. Ranking of the subjective sensations pain, burning and itching was done by the patient. Pain during PDT was assessed with a numerical rating pain scale 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 four-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 the first treatment with randomized medication until the end of the clinical observation period. Serious adverse events were documented and evaluated throughout the study.

### Statistical analysis

The method of Farrington and Manning for testing noninferiority 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, which was the overall patient complete response rate 12 weeks after the last PDT. This estimate was



**Fig 1.** Flowchart of patient disposition in the clinical part of the study. \*Initially it was considered an exclusion criterion if – besides an eligible basal cell carcinoma (BCC) – patients had noneligible 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 noneligible lesion was > 10 cm. The protocol amendment was not expected to influence the composition of the enrolled patient population. MAL, methyl aminolaevulinate; ALA, aminolaevulinic acid.

**Table 1** Summary of patient and basal cell carcinoma (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 $\pm$ SD	66.5 $\pm$ 11.5	67.3 $\pm$ 11.6
Fitzpatrick skin type, 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 $\pm$ SD	1.2 $\pm$ 0.39	1.2 $\pm$ 0.49
BCC lesions at baseline per patient, n (%)		
1	94 (85.5)	98 (81.0)
$\geq$ 2	16 (14.5)	23 (19.0)
BCC subtype, n (%) <sup>a</sup>		
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 <sup>b</sup>	17 (13.4)	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 $\pm$ SD	0.46 $\pm$ 0.36	0.41 $\pm$ 0.32

Data are presented for the per protocol set. MAL, methyl aminolaevulinate; ALA, aminolaevulinic acid; nBCC, nodular BCC; sBCC, superficial BCC. <sup>a</sup>Based on patients. <sup>b</sup>Only one lesion was located on the scalp.

based on an expected response rate of 87% in each treatment arm and a noninferiority margin of  $\Delta = -15$ . Analysis was performed on the per protocol set; the full analysis set was presented as supportive analysis. All other data were analysed descriptively and in an exploratory way.

Recurrence rates during follow-up 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 follow-up visit, life tables were calculated for patients and lesions by multiplying the recurrence rate at follow-up (Pi) by the initial clearance rate (Pi\*CR or Pi\*RCL), as described previously.<sup>31</sup>

## Results

### Patients

The clinical observation period took place between January 2014 and November 2015; 1-year follow-up was completed

in August 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 flowchart of the disposition of the patients is presented in Figure 1. All patients were white. The 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 with 91.8% (n = 101) in the MAL group (Table 2). The noninferiority test revealed a difference of means of 1.6 with a one-sided 97.5% confidence interval (CI) of  $-6.5\%$  ( $P < 0.001$ ), thus demonstrating statistical noninferiority of BF-200 ALA gel compared with MAL cream for the primary efficacy parameter. The robustness of the results was confirmed by repeating the analyses on the full analysis set, which displayed a difference in efficacy of 5.2 (one-sided 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 the second PDT session in both treatment arms: 57.9% in the BF-200 ALA group and 56.4% in the MAL group, with overlapping 95% CIs.

With respect to patients with sBCC only, 95% in the BF-200 ALA group and 96% in the MAL group showed complete clearance 12 weeks after the last treatment. Patients with only nBCC displayed clearance rates of 86% with BF-200 ALA and 76% with MAL (Table 2). Further subgroup analyses revealed clearance rates of 92% for BF-200 ALA and 93% for MAL in patients with only one BCC lesion, whereas clearance rates for patients with two or more lesions were 100% and 88%, respectively. Differences between treatments are displayed in Figure 2.

One year after the last treatment, 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 7% for BF-200 ALA and to 8% for MAL. A larger difference was observed for patients with nBCC only, with 7% of patients in the BF-200 ALA group and 14% in the MAL group relapsing within 12 months (Table 2).

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

Table 2 Patient clearance and recurrence rates

Subgroup and assessment time point after last PDT	MAL cream				BF-200 ALA gel			
	Completely cleared, n/N (%)	Recurrent, n (%)	Pi (%)	Pi*CR (%)	Completely cleared, n/N (%)	Recurrent, n (%)	Pi (%)	Pi*CR (%)
<b>Overall</b>								
EOS (12 weeks)	101/110 (91.8)	n.a.	100	91.8	113/121 (93.4)	n.a.	100	93.4
95% CI	84.6–96.0				87.0–96.9			
FU2 (12 months)	86/94 <sup>a</sup> (91.5)	8 (8.5)	91.9	84.4	98/107 <sup>a</sup> (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		
<b>With sBCC only</b>								
EOS (12 weeks)	80/83 (96)	n.a.	100	96.4	90/95 (95)	n.a.	100	94.7
95% CI	89.1–99.1				87.6–98.0			
FU2 (12 months)	69/75 <sup>a</sup> (92)	6 (8)	92.3	89.0	81/87 <sup>a</sup> (93)	6 (7)	93.3	88.3
95% CI	82.8–96.7	3.3–17.2			85.0–97.2	2.8–15.0		
<b>With nBCC only</b>								
EOS (12 weeks)	16/21 (76)	n.a.	100	76.2	18/21 (86)	n.a.	100	85.7
95% CI	52.5–90.0				62.6–96.2			
FU2 (12 months)	12/14 <sup>a</sup> (86)	2 (14)	87.1	66.3	14/15 <sup>a</sup> (93)	1 (7)	94.4	81.0
95% CI	56.2–97.5	2.5–43.8			66.0–99.7	0.3–34.0		

Data are presented for the per protocol set. ALA, aminolaevulinic acid; BCC, basal cell carcinoma; CI, confidence interval; EOS, end of clinical study (12 weeks after the last PDT); FU2, follow-up 2 (12 months after the last treatment); MAL, methyl aminolaevulinate; n.a., not applicable; nBCC, nodular BCC; PDT, photodynamic therapy; Pi, probability of patients remaining fully cleared until the current visit; Pi\*CR, estimated rate of patient clearance at the current visit relative to the number of patients pretreatment; sBCC, superficial BCC. <sup>a</sup>Complete responders 12 weeks after the last PDT with data at 1-year follow-up

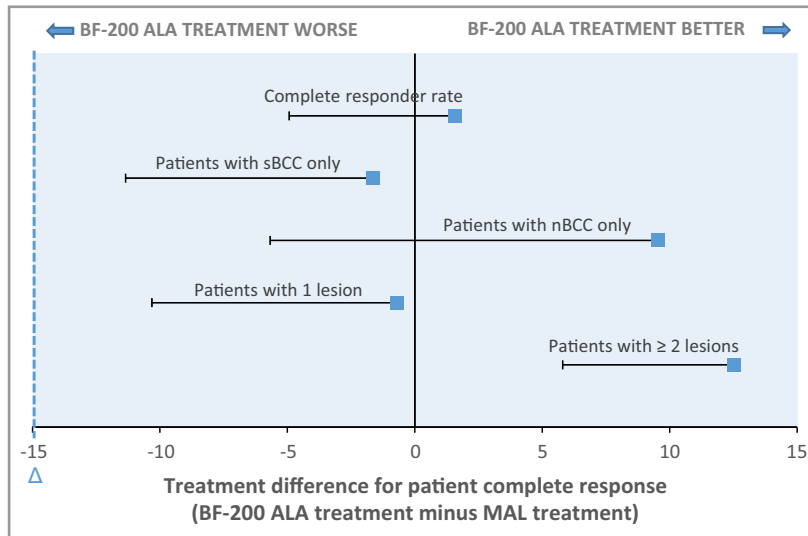


Fig 2. Treatment efficacy: overall patient complete response rate and subgroup analyses for the per protocol set. A patient was considered a complete responder if all treated lesions were cleared 12 weeks after the last session of photodynamic therapy. Error bars represent one-sided 97.5% confidence intervals of the difference between BF-200 aminolaevulinic acid (ALA) and methyl aminolaevulinate (MAL) treatment. The blue dashed line at  $\Delta = -15$  indicates the noninferiority margin for the primary efficacy variable; the blue region to the right of  $\Delta = -15$  indicates the zone of noninferiority. nBCC, nodular basal cell carcinoma; sBCC, superficial basal cell carcinoma.

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 group and 92.9% (n = 127) in the MAL group. Subgroup analyses revealed numerical differences in lesion complete response rates when comparing BF-200 ALA vs. MAL treatment of sBCC (96% vs. 97%), of nBCC (89% vs. 79%), on the face/scalp (82% vs. 71%), on the neck/trunk (98% vs. 97%) and on the extremities (91% vs. 96%), 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 follow-up, 6.7% in the BF-200 ALA group and 8.2% in the MAL group 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% and 9% of lesions, respectively, in the BF-200 ALA group, and 8% and 10%, respectively, in the MAL group relapsed within 1 year after the last PDT. One-year recurrence rates for the different locations were 8% (face/scalp), 7% (neck/trunk) and 6% (extremities) in the BF-200 ALA group. The corresponding values in the MAL group were 18%, 8% and 5%, respectively (Table 3).

Table 3 Lesion clearance and recurrence rates

Subgroup and assessment time point after last PDT	MAL cream				BF-200 ALA gel			
	Completely cleared, n/N (%)	Recurrent, n (%)	Pi (%)	Pi*RLC (%)	Completely cleared, n/N (%)	Recurrent, n (%)	Pi (%)	Pi*RLC (%)
Overall								
EOS	118/127 (92.9)	n.a.	100	92.9	140/148 (94.6)	n.a.	100	94.6
95% CI	86.6–96.5				89.3–97.5			
FU2	101/110 <sup>a</sup> (91.8)	9 (8.2)	92.2	85.6	125/134 <sup>a</sup> (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	95/98 (97)	n.a.	100	96.9	114/119 (96)	n.a.	100	95.8
95% CI	90.7–99.2				90.0–98.4			
FU2	82/89 <sup>a</sup> (92)	7 (8)	92.4	89.5	105/111 <sup>a</sup> (95)	6 (5)	94.7	90.7
95% CI	83.9–96.5	3.5–16.1			88.1–97.6	2.2–11.9		
nBCC								
EOS	22/28 (79)	n.a.	100	78.6	25/28 (89)	n.a.	100	89.3
95% CI	58.5–91.0				70.6–97.2			
FU2	18/20 <sup>a</sup> (90)	2 (10)	90.7	71.3	20/22 <sup>a</sup> (91)	2 (9)	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 <sup>b</sup>								
EOS	12/17 (71)	n.a.	100	70.6	14/17 (82)	n.a.	100	82.4
95% CI	44.0–88.6				55.8–95.3			
FU2	9/11 <sup>a</sup> (82)	2 (18)	82.6	58.3	12/13 <sup>a</sup> (92)	1 (8)	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	84/87 (97)	n.a.	100	96.6	95/97 (98)	n.a.	100	97.9
95% CI	89.5–99.1				92.0–99.6			
FU2	73/79 <sup>a</sup> (92)	6 (8)	92.7	89.5	84/90 <sup>a</sup> (93)	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	22/23 (96)	n.a.	100	95.7	31/34 (91)	n.a.	100	91.2
95% CI	76.0–99.8				75.2–97.7			
FU2	19/20 <sup>a</sup> (95)	1 (5)	95.3	91.2	29/31 <sup>a</sup> (94)	2 (6)	93.5	85.3
95% CI	73.1–99.7	0.3–26.9			77.2–98.9	1.1–22.8		

Data are presented for the per protocol set. ALA, aminolaevulinic acid; BCC, basal cell carcinoma; CI, confidence interval; EOS, end of clinical study (12 weeks after the last PDT); FU2, follow-up 2 (12 months after the last treatment); MAL, methyl aminolaevulinate; n.a., not applicable; nBCC, nodular BCC; PDT, photodynamic therapy; Pi, probability of lesions remaining cleared up to the current visit; Pi\*RLC, estimated rate of lesion clearance at the current visit relative to the number of lesions pretreatment; sBCC, superficial BCC. <sup>a</sup>BCC lesions cleared 12 weeks after the last PDT with data at 1-year follow-up. <sup>b</sup>Only one lesion was located on the scalp.

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 group and 85.6% in the MAL group. For the main BCC subtypes, sBCC and nBCC, the respective estimates were 90.7% and 81.9% in the BF-200 ALA group compared with 89.5% and 71.3% in the MAL group. Thus, the initial differences between the efficacies were maintained throughout follow-up, 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 49% 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 follow-up to 73% for BF-200 ALA and to 68% for MAL 1 year after the last PDT.

### 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% in the MAL group). This high satisfaction was maintained during the 1-year follow-up: 97% of BF-200 ALA- and 99% of MAL-treated patients were still satisfied with PDT. No patient assessed their satisfaction as impaired at either time point.

### Safety and tolerability

The frequencies and severities of TEAEs were within the ranges expected, given a population of mainly elderly patients,

**Table 4** Cosmetic outcome 12 weeks after the last photodynamic therapy (PDT) and 1-year follow-up

	MAL cream		BF-200 ALA gel	
	EOS (n = 74)	1y FU (n = 57) <sup>a</sup>	EOS (n = 70)	1 year (n = 56) <sup>a</sup>
Very good, n (%)	16 (22)	17 (30)	28 (40)	20 (36)
95% CI	13.2–33.0	18.8–43.6	28.7–52.4	23.7–49.7
Good, n (%)	20 (27)	22 (39)	14 (20)	21 (38)
95% CI	17.7–38.8	26.3–52.4	11.7–31.6	25.2–51.5
Satisfactory, n (%)	24 (32)	8 (14)	16 (23)	8 (14)
95% CI	22.3–44.4	6.7–26.3	14.0–34.7	6.8–26.8
Unsatisfactory, n (%)	9 (12)	6 (11)	8 (11)	2 (4)
95% CI	6.1–22.3	4.4–22.2	5.4–21.8	0.6–13.4
Impaired, n (%)	5 (7)	4 (7)	4 (6)	5 (9)
95% CI	2.5–15.7	2.3–17.8	1.8–14.7	3.3–20.4

Data are presented for the per protocol set. Patients lacking compromised skin at baseline were excluded. Cosmetic outcome was calculated on the basis of skin-quality assessment.<sup>30</sup> Parameters (skin surface, pigmentation, degree of scarring and atrophy) were rated on a four-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. 1y FU, follow-up 12 months after the last PDT; ALA, aminolaevulinic acid; CI, confidence interval; EOS, end of clinical study (12 weeks after the last PDT); MAL, methyl aminolaevulinate. <sup>a</sup>Only complete responders were considered and patients with recurrent basal cell carcinoma lesions were excluded.

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

**Table 5** Overview of treatment-emergent adverse events (TEAEs)

TEAE category	MAL cream (n = 143)	BF-200 ALA gel (n = 138)
Patients with TEAEs	143 (100)	138 (100)
Patients with related <sup>a</sup> TEAEs	143 (100)	138 (100)
Patients with serious TEAEs	7 (4.9)	3 (2.2)
Patients with related <sup>a</sup> serious TEAEs	0	0
Patients with TEAEs leading to death	1 (0.7)	0
Patients with related <sup>a</sup> TEAEs leading to death	0	0
Patients with TEAEs leading to study withdrawal	2 (1.4)	1 (0.7)
Patients with related <sup>a</sup> 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 <sup>a</sup> TEAEs rated as local skin reaction	130 (90.9)	121 (87.7)
Patients with TEAEs rated as discomfort	143 (100)	136 (98.6)
Patients with related <sup>a</sup> TEAEs rated as discomfort	143 (100)	136 (98.6)
Patients with pain	143 (100)	134 (97.1)
Patients with pain considered related <sup>a</sup> to study treatment	143 (100)	134 (97.1)

Values are the number (%) of patients. Data are presented for the safety population and comprise TEAEs until 12 weeks after the last photodynamic therapy. <sup>a</sup>Considered possibly, probably or definitely related to study treatment. MAL, methyl aminolaevulinate; ALA, aminolaevulinic acid.

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 part of the study, none of which was assessed as being related to the study medication. Only four patients discontinued the study prematurely (Table 5). Local pain experienced during PDT was assessed for each PDT session (on a numerical rating pain scale) 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 or histological subtype. For nonaggressive 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.<sup>5,8,9</sup>

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 vs. 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 noninferior to the registered MAL cream.

The current study was designed to show noninferiority of BF-200 ALA in comparison with MAL. However, superiority of BF-200 ALA had previously been demonstrated in a phase III trial treating actinic keratosis in 571 randomized patients.<sup>32</sup> In particular, the efficacy for thicker lesions or more difficult-to-treat lesions on the scalp was higher with BF-200 ALA.<sup>21,32</sup> In the present trial, similar findings were seen for nBCC



**Table 6** Maximal pain sensation during photodynamic therapy (PDT) by treatment

	PDT-1	PDT-2	PDT-3	PDT-4
MAL cream				
Patients	143	142	61	60
Mean $\pm$ SD	3.6 $\pm$ 2.2	4.1 $\pm$ 2.7	2.5 $\pm$ 2.2	2.9 $\pm$ 2.8
BF-200 ALA gel				
Patients	138	138	54	55
Mean $\pm$ SD	3.7 $\pm$ 2.4	4.5 $\pm$ 2.7	2.8 $\pm$ 2.6	3.9 $\pm$ 3.0

Data are presented for the safety population. The data are the mean  $\pm$  SD of an 11-point numerical rating pain scale ranging from 0 (no pain at all) to 10 (worst possible pain) according to the patient's assessment. In order to record pain experienced by the patients during treatment, the PDT was to be started without measures to relieve pain. Potential pain management afterwards included physical cooling measures, reduction of light intensity at the expense of longer exposure times, or slight analgesia. MAL, methyl aminolaevulinate; ALA, aminolaevulinic acid.

lesions, for which a higher proportion of response was revealed with BF-200 ALA (89%) than with MAL (79%); this was maintained during the 1-year follow-up period. Previous results reported by Rhodes *et al.*<sup>23</sup> showed high efficacies of MAL-PDT in the treatment of nBCC when compared with 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.*<sup>33</sup> using extemporaneous ALA formulations. Based on 12 ALA-PDT studies with 208 lesions there was 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 the enhanced skin penetration of this formulation.

For sBCC lesions, where skin penetration is less relevant, both medications displayed very similar efficacies ( $\geq 95\%$ ). These results exceed the weighted clearance rate of 87% calculated on the basis of 12 sBCC studies with 826 lesions treated with ALA-PDT.<sup>33</sup> Again, this may depend on the different formulations and treatment protocols.<sup>29</sup> In a previous study comparing MAL-PDT with surgery for sBCC, noninferiority was demonstrated for MAL-PDT with clearance rates of 92.2% (MAL) vs. 99.2% (surgery).<sup>20</sup> A meta-analysis of 28 studies including various topical treatments showed clearance rates of 79% for MAL-PDT compared with 86.2% for imiquimod, and indicated tumour-free 1-year survival rates of 84% and 87.3%, respectively.<sup>11</sup>

An additional study by Arits *et al.*<sup>34</sup> reported clearance rates for sBCC of 90.0% with imiquimod, 87.9% with 5-fluorouracil and 84.2% with MAL after 3 months. In that 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 estimates of treatment success were calculated as 87.2%, 80.1% and 72.5% for imiquimod, 5-fluorouracil and MAL, respectively. In the present study, the

corresponding estimates were 88.3% for BF-200 ALA gel and 89.0% for MAL cream (Table 2). As these 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 nonaggressive BCC were achieved with BF-200 ALA-PDT and MAL-PDT. The local adverse events observed in this study are well known for PDT and are caused by the underlying mode of action. No difference in adverse events became apparent between the 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).<sup>5,8,35</sup> 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.

## Acknowledgments

The authors are grateful to the staff of the participating clinical study centres for patient recruitment and treatment. We are also indebted to the patients involved in this trial. We gratefully acknowledge the assistance of Miriam Kremser and Ben Novak in the preparation of the manuscript and would like to thank the BCC project team at Accovion GmbH (Frankfurt, Germany), and Aylin Amrani-Hanchi and Anika Hunfeld at Biofrontera for excellent support during the clinical trial.

## References

- LeBoit PE, Burg G, Weedon D, Sarasin A, eds. *Pathology and Genetics of Skin Tumours. World Health Organization Classification of Tumours*. Lyon: IARC Press, 2006.
- Walling HW, Fosko SW, Geraminejad PA *et al.* Aggressive basal cell carcinoma: presentation, pathogenesis, and management. *Cancer Metastasis Rev* 2004; **23**:389–402.
- Trakatelli M, Ulrich C, del Marmol V *et al.* Epidemiology of non-melanoma skin cancer (NMSC) in Europe: accurate and comparable data are needed for effective public health monitoring and interventions. *Br J Dermatol* 2007; **156** (Suppl. 3):1–7.
- Athas WF, Hunt WC, Key CR. Changes in nonmelanoma skin cancer incidence between 1977–1978 and 1998–1999 in Northcentral New Mexico. *Cancer Epidemiol Biomarkers Prev* 2003; **12**:1105–8.
- Trakatelli M, Morton C, Nagore E *et al.* Update of the European guidelines for basal cell carcinoma management. *Eur J Dermatol* 2014; **24**:312–29.
- Flohil SC, de Vries E, Neumann HA *et al.* Incidence, prevalence and future trends of primary basal cell carcinoma in the Netherlands. *Acta Derm Venereol* 2011; **91**:24–30.
- Perera E, Gnaneswaran N, Staines C *et al.* Incidence and prevalence of non-melanoma skin cancer in Australia: a systematic review. *Australas J Dermatol* 2015; **56**:258–67.
- Telfer NR, Colver GB, Morton CA. Guidelines for the management of basal cell carcinoma. *Br J Dermatol* 2008; **159**:35–48.
- Dandurand M, Petit T, Martel P *et al.* Management of basal cell carcinoma in adults: clinical practice guidelines. *Eur J Dermatol* 2006; **16**:394–401.

- 10 Patel RV, Frankel A, Goldenberg G. An update on nonmelanoma skin cancer. *J Clin Aesthet Dermatol* 2011; **4**:20–7.
- 11 Roozeboom MH, Arits AH, Nelemans PJ, Kelleners-Smeets NW. Overall treatment success after treatment of primary superficial basal cell carcinoma: a systematic review and meta-analysis of randomized and non-randomized trials. *Br J Dermatol* 2012; **167**:733–56.
- 12 Morton CA, Whitehurst C, McColl JH *et al.* Photodynamic therapy for large or multiple patches of Bowen disease and basal cell carcinoma. *Arch Dermatol* 2001; **137**:319–24.
- 13 Blume JE, Oseroff AR. Aminolevulinic acid photodynamic therapy for skin cancers. *Dermatol Clin* 2007; **25**:5–14.
- 14 Roozeboom MH, Aardoom MA, Nelemans PJ *et al.* Fractionated 5-aminolevulinic acid photodynamic therapy after partial debulking versus surgical excision for nodular basal cell carcinoma: a randomized controlled trial with at least 5-year follow-up. *J Am Acad Dermatol* 2013; **69**:280–7.
- 15 Wang I, Bendsoe N, Klinteberg CA *et al.* Photodynamic therapy vs. cryosurgery of basal cell carcinomas: results of a phase III clinical trial. *Br J Dermatol* 2001; **144**:832–40.
- 16 Rhodes LE, de Rie MA, Leifsdottir R *et al.* Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy versus surgery for nodular basal cell carcinoma. *Arch Dermatol* 2007; **143**:1131–6.
- 17 Mosterd K, Thissen MR, Nelemans P *et al.* Fractionated 5-aminolevulinic acid-photodynamic therapy vs. surgical excision in the treatment of nodular basal cell carcinoma: results of a randomized controlled trial. *Br J Dermatol* 2008; **159**:864–70.
- 18 Kuijpers DJ, Thissen MR, Thissen CA, Neumann MH. Similar effectiveness of methyl aminolevulinate and 5-aminolevulinate in topical photodynamic therapy for nodular basal cell carcinoma. *J Drugs Dermatol* 2006; **5**:642–5.
- 19 Szeimies RM. Methyl aminolevulinate-photodynamic therapy for basal cell carcinoma. *Dermatol Clin* 2007; **25**:89–94.
- 20 Szeimies RM, Ibbotson S, Murrell DF *et al.* A clinical study comparing methyl aminolevulinate photodynamic therapy and surgery in small superficial basal cell carcinoma (8–20 mm), with a 12-month follow-up. *J Eur Acad Dermatol Venereol* 2008; **22**:1302–11.
- 21 Maisch T, Santarelli F, Schreml S *et al.* Fluorescence induction of protoporphyrin IX by a new 5-aminolevulinic acid nanoemulsion used for photodynamic therapy in a full-thickness *ex vivo* skin model. *Exp Dermatol* 2010; **19**:e302–5.
- 22 Schmitz L, Novak B, Hoeh AK *et al.* Epidermal penetration and protoporphyrin IX formation of two different 5-aminolevulinic acid formulations in *ex vivo* human skin. *Photodiagnosis Photodyn Ther* 2016; **14**:40–6.
- 23 Rhodes LE, de Rie M, Enstrom Y *et al.* Photodynamic therapy using topical methyl aminolevulinate versus surgery for nodular basal cell carcinoma: results of a multicenter randomized prospective trial. *Arch Dermatol* 2004; **140**:17–23.
- 24 Basset-Seguín N, Ibbotson SH, Emtestam L *et al.* Topical methyl aminolevulinate photodynamic therapy versus cryotherapy for superficial basal cell carcinoma: a 5 year randomized trial. *Eur J Dermatol* 2008; **18**:547–53.
- 25 Foley P. Clinical efficacy of methyl aminolevulinate (Metvix) photodynamic therapy. *J Dermatolog Treat* 2003; **14**(Suppl. 3):15–22.
- 26 Kennedy JC, Pottier RH, Pross DC. Photodynamic therapy with endogenous protoporphyrin IX: basic principles and present clinical experience. *J Photochem Photobiol B* 1990; **6**:143–8.
- 27 Schulten R, Novak B, Schmitz B, Lubbert H. Comparison of the uptake of 5-aminolevulinic acid and its methyl ester in keratinocytes and skin. *Naunyn Schmiedeberg Arch Pharmacol* 2012; **385**:969–79.
- 28 Agostinis P, Berg K, Cengel KA *et al.* Photodynamic therapy of cancer: an update. *CA Cancer J Clin* 2011; **61**:250–81.
- 29 Hurlimann AF, Hanggi G, Panizzon RG. Photodynamic therapy of superficial basal cell carcinomas using topical 5-aminolevulinic acid in a nanocolloid lotion. *Dermatology* 1998; **197**:248–54.
- 30 Reinhold U, Dirschka T, Ostendorf R *et al.* A randomized, double-blind, phase III, multicentre study to evaluate the safety and efficacy of BF-200 ALA (Ameluz<sup>®</sup>) vs. placebo in the field-directed treatment of mild-to-moderate actinic keratosis with photodynamic therapy (PDT) when using the BF-RhodoLED<sup>®</sup> lamp. *Br J Dermatol* 2016; **175**:696–705.
- 31 Dirschka T, Radny P, Dominicus R *et al.* Long-term (6 and 12 months) follow-up of two prospective, randomized, controlled phase III trials of photodynamic therapy with BF-200 ALA and methyl aminolevulinate for the treatment of actinic keratosis. *Br J Dermatol* 2013; **168**:825–36.
- 32 Dirschka T, Radny P, Dominicus R *et al.* 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-aminolevulinate cream and placebo. *Br J Dermatol* 2012; **166**:137–46.
- 33 Peng Q, Warloe T, Berg K *et al.* 5-Aminolevulinic acid-based photodynamic therapy. *Clinical research and future challenges. Cancer* 1997; **79**:2282–308.
- 34 Arits AH, Mosterd K, Essers BA *et al.* Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. *Lancet Oncol* 2013; **14**:647–54.
- 35 Morton CA, Szeimies RM, Sidoroff A, Braathen LR. European guidelines for topical photodynamic therapy part 1: treatment delivery and current indications – actinic keratoses, Bowen's disease, basal cell carcinoma. *J Eur Acad Dermatol Venereol* 2013; **27**:536–44.

## Appendix

### Conflicts of interest

C.A.M. is a board member of Euro-PDT; 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 Pharma, Meda, Riemser and Janssen; is a member of advisory boards for Almirall, Biofrontera, LEO Pharma, Meda, Novartis, Riemser and 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 and 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 a stakeholder in CMB Collegium Medicum Berlin GmbH and has 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 a member of advisory boards for Novartis and LEO Pharma, and was in the past for

Biofrontera; he has received speakers' honoraria from Aspen, Lilly, Novartis and Biofrontera. C.B. has been a 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 boards of and received speakers' honoraria from Almirall, Allergan, Bayer, Galderma, LEO Pharma, Novartis, Meda and l'Oréal. 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 an employee of Clinipace-Accovion

GmbH, the company that was responsible as the 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; has been a member of advisory boards for Almirall, Biofrontera, Galderma, ISDIN, LEO Pharma, photonamic GmbH and Pierre-Fabre; and 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 conflicts of interest to declare.

## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Video S1** Author video.

**Powerpoint S1** Journal Club Slide Set.