SYNOPSIS

Name of Sponsor: Biofrontera Bioscience GmbH	Individual Study Table Referring to Dossier Part	(For National Authority Use Only)
Name of Finished Product: BF-200 ALA (Ameluz)	Volume:	
Name of Active Ingredient: 5-Aminolevulinic acid hydrochloride	Report:	

Title of study:	A randomized, observer blind, multinational phase III study to evaluate the safety and efficacy of a nanoemulsion gel formulation BF-200 ALA, in comparison with Metvix® and placebo, for the treatment of actinic keratosis with photodynamic therapy. Study number: ALA-AK-CT002 (EudraCT no.: 2007-006854-24)
Investigator, study sites:	PD Dr med Thomas Dirschka, Wuppertal, Germany Multinational / 26 centers sites: Germany (23), Austria (2) and Switzerland (1)
Publications (references):	Dirschka T, Radny P, Dominicus R, Mensing H, Brüning H, Jenne L, Karl L, Sebastian M, Oster-Schmidt C, Klövekorn W, Reinhold U, Tanner M, Gröne D, Deichmann M, Simon M, Hübinger F, Hofbauer G, Krähn-Senftleben G, Borrosch F, Reich K, Berking C, Wolf P, Lehmann P, Moers-Carpi M, Hönigsmann H, Wernicke-Panten K, Helwig C, Foguet M, Schmitz B, Lübbert H, Szeimies RM; AK-CT002 Study Group. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a multicentre, randomized, observer-blind phase III study in comparison with a registered methyl-5-aminolaevulinate cream and placebo. Br J Dermatol. **2012** Jan;166(1):137-46.
Study duration and dates:	08 Apr 2008: First subject signed informed consent 21 Aug 2009: Last subject completed clinical part of study
Clinical phase:	III
Objectives:	Primary objective: To compare the efficacy of a nanoemulsion gel formulation containing 10% 5-aminolevulinic acid (ALA) as active ingredient (also referred to as BF-200 ALA) with the marketed product Metvix® and with placebo, for the treatment of actinic keratosis (AK) with photodynamic therapy (PDT). Secondary objectives: To evaluate the safety and secondary efficacy parameters related to BF-200 ALA gel for treatment of AK with PDT.
Methodology:	This was a randomized, observer blind, multinational, controlled parallel-group (3:3:1 ratio) study to compare the efficacy and safety of BF-200 ALA with the comparator Metvix® (methyl-[5-amino-4-oxopentanoat]) and placebo, for the treatment of AK with PDT. Each subject received only one of these treatments (BF-200 ALA, Metvix® or placebo) and interindividual comparisons were performed. For complete responders after one PDT (all lesions showing complete remission) the study consisted of a screening visit (Visit 1), pre-randomization period lasting up to 2 weeks, a randomization / treatment visit (Visit 2, PDT1), a phone contact one week after treatment, and two clinical visits (Visit 3, 3-4 weeks after PDT1 and Visit 4, 12 weeks after PDT1). The clearance of AK lesions was assessed 12 weeks after the first PDT. All lesions that were not completely cleared were treated with a second PDT (PDT2). Non-responders or partial responders (subjects still showing lesions in the target areas) at week 12 (Visit 4) were re-treated during Visit 4 (PDT2). They had a phone contact one week after re-treatment / PDT2 (at week 13) and two additional clinical visits (Visit 5, 3-4 weeks after PDT2 and Visit 6, 12 weeks after PDT2).

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	Subjects who were partial or non-responders 3 months after re-treatment received further treatment at the discretion of the investigator. For all subjects, two follow-up visits (6 months and 12 months after the last PDT) were scheduled which were to be analyzed and reported separately and were not part of the actual study. Amendment 1 (prior to the start of the study) was submitted following a request from the German Competent Authority, BfArM, and specified that a second, optional biopsy of actinic keratosis (AK) lesions could be performed at the end of the clinical part of the study (Visit 4 for complete responders, Visit 6 for re-treated subjects), at the discretion of the investigator. Amendment 2 (during the course of the study) was submitted to specify the handling of new lesions. If new AK lesions appeared within the treatment area during the study and the treating physician decided that immediate treatment was necessary, the subject was to be withdrawn from the study. Amendment 2 also modified the exclusion criteria related to concomitant treatments and medications. Whereas the original protocol specified the exclusion of subjects treated with hypericin or systemically-acting drugs with phototoxic or photoallergic potential, the use of phototoxic or photoallergic drugs within 8 weeks prior to the first PDT session was permitted if the patient did not show evidence of a phototoxic or photoallergic reaction. This was amended to allow the inclusion of subjects who received such treatments.
Number of subjects:	It was planned to conduct the study in 32 centers (23 in Germany, 4 in Austria, 4 in France and 1 in Switzerland). 616 subjects were to be randomized, with approximately 264 subjects in the BF-200 ALA group, 264 subjects in the Metvix® group, and 88 subjects in the placebo group (3:3:1 ratio). The sample size of 264 subjects in the BF-200 ALA group and 88 subjects in the placebo group permitted demonstration of the superiority over placebo with more than 90% power assuming response rates of 65% for BF-200 ALA and 40% for placebo. This sample size of 264 subjects per active treatment arm also allowed demonstration of non-inferiority of BF-200 ALA to Metvix® using a non-inferiority margin of -15% with at least 90% power assuming response rates of 70% for BF-200 ALA and Metvix® and 20% non-evaluable subjects.

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Inclusion criteria:

Main inclusion criteria:

- Written informed consent.
- Men and women between 18 and 85 years of age.
- 4-8 AK lesions of 0.5 to 1.5 cm diameter of mild to moderate intensity (Olsen grade 1 and 2) in the face and/or on the bald scalp. Lesions on the eyes, nostrils, ears and mouth were not considered for treatment during the planned study.
- Target AK lesions were to be discrete and quantifiable; adjacent AK lesions were to show a minimum distance of 1.0 cm from one another.
- Confirmation of AK by biopsy taken at screening.
- Free of significant physical abnormalities (e.g., tattoos, dermatoses) in the potential treatment region that could have caused difficulty with examination or final evaluation.
- Willingness to stop the use of moisturizers and any other topical treatments within the treatment region.
- Good general health condition.
- Healthy subjects and subjects with clinically stable medical conditions including, but not limited to the following diseases (controlled hypertension, diabetes mellitus type II, hypercholesterolemia, osteoarthritis) were permitted to be included in the study if the medication taken for the treatment of the disease did not match an exclusion criterion or was not specified as prohibited concomitant medication.
- No extensive sunbathing or solarium use during the trial.
- Negative pregnancy test at screening.
- Effective contraception in women of childbearing potential.

Exclusion criteria:

Main exclusion criteria:

- Known hypersensitivity to BF-200 ALA, MAL (methyl-aminolevulinic acid) and/or any of the ingredients of the formulations
- Clinically significant medical conditions (tumor disease etc.) making implementation of the protocol or interpretation of the study results difficult
- Presence of photodermatoses
- Presence of other tumors in the treatment areas within the last 4 weeks
- Start of treatment with phototoxic or photoallergic drugs within 8 weeks prior to screening
- Current treatment with immunosuppression therapy
- Hypersensitivity to porphyrins
- Presence of porphyria
- Presence of inherited or acquired coagulation defect
- Any topical treatment within the treatment area within 12 weeks before PDT1
- Topical treatment with ALA or MAL outside the treatment area during participation in the study

None of the specified systemic treatments within the designated period before PDT1

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Test product, dose and mode of administration, batch number:	The investigational products (IPs) were a nanoemulsion gel formulation of 10% 5-ALA hydrochloride (referred to as BF-200 ALA), placebo (the nanoemulsion gel vehicle without the active ingredient ALA), and the marketed product Metvix® (a cream). After thorough preparation of the lesions, including removal of all scabs, crusts and hyperkeratotic parts by curettage, the skin sites were to be cleaned with alcohol (ethanol or isopropanol).
Duration of treatment:	For each subject, one of these formulations was applied to the target AK lesions and covered with occlusive tape material for 3 hours. Thereafter, the remnants of these applied formulations were removed carefully and the PDT was administered. Subjects with non-responding AK lesions were re-treated with the same medication after 12 weeks.
Reference therapy, dose and mode of administration, batch number:	Placebo (the nanoemulsion gel vehicle without the active ingredient ALA), and marketed product Metvix® (a cream).
Efficacy data:	The primary efficacy variable was the overall subject complete response assessed 12 weeks after the last PDT. An overall complete responder was defined as a subject in whom all treated lesions were cleared after either the first PDT or re-treatment. The secondary efficacy analysis variables included (as stated in the statistical analysis plan [SAP]): • Subject complete response (complete clearance of all treated lesions) at each assessment. • Subject partial response (complete clearance of at least 75% of the treated lesions) at each assessment. • Lesion complete response (completely cleared individual lesions) at each assessment. • Reduction of total lesion area (summation of sizes of all treated lesions) per subject at each assessment. • The change in skin quality assessments compared to baseline assessed 12 weeks after PDT1 and 12 weeks after the last PDT. • The overall cosmetic outcome 12 weeks after the last PDT. For the follow-up period, the following variables were analyzed: • Subject recurrence rate defined as the number of subjects with completely cleared lesions 12 weeks after the last PDT with at least one recurrent lesion during follow-up. • Lesion recurrence rate defined as the number of lesions of complete responders 12 weeks after the last PDT showing recurrence during follow-up 1. For follow-up 2 it was defined as the number of complete responders after follow-up 1 showing recurrence during follow-up 2. If a patient received further AK therapy after the last PDT, but before the time point of derivation of the recurrent lesions rate, all of the patient's lesions were defined as recurrent. The results from the follow-up will be analyzed and reported separately and are not part of the actual study.

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Safety data:

The safety analysis variables included:

- Frequency and extent of treatment-emergent adverse events (TEAEs), including serious AEs (SAEs). TEAEs were defined as all AEs with onset or worsening after first treatment with randomized IP. At the follow-up visits any local AEs or conditions considered relevant for proper assessment of the recurrence rate of the treated AK lesions was documented, and SAEs that occurred after the End-of-study visit were also documented.
- Local skin reactions at the treatment area assessed by the investigators.
- Local discomfort and pain reported during illumination by the subjects.
- Vital signs data.
- Safety laboratory data.
- Data from the physical examinations.

Statistical methods:

The main statistical analysis was performed as soon as the 12-week post last PDT data were available for analysis. Additional data from the follow-up period (6 months or 12 months after the last PDT) will be analyzed and reported separately from the report of the treatment phase of the study.

Two primary hypotheses were tested using a hierarchical testing procedure as follows:

- The first primary null hypothesis was that the overall complete responder rate assessed 12 weeks after the last PDT for subjects treated with BF-200 ALA was equal to that of subjects treated with placebo. The first primary alternative hypothesis was that the overall complete subject responder rate assessed 12 weeks after the last PDT for subjects treated with BF-200 ALA was different from that for subjects treated with placebo. The superiority of BF-200 ALA over placebo was tested using a chi-square test with a two-sided significance level of 0.05. Superiority of BF-200 ALA over placebo was established if the first primary null hypothesis could be rejected.
- The second primary null hypothesis was that the overall subject complete responder rate assessed 12 weeks after the last PDT for subjects treated with BF-200 ALA was inferior compared to the corresponding responder rate for subjects treated with Metvix® as specified by a non-inferiority margin of $\Delta = 15\%$. The second primary alternative hypothesis was that the overall subject complete responder rate assessed 12 weeks after the last PDT for subjects treated with BF-200 ALA was non-inferior compared to the corresponding responder rate for subjects treated with Metvix® as specified by a non-inferiority margin of $\Delta = 15\%$. The difference in response rates, together with a 1-sided lower 97.5% confidence interval, was calculated to assess non-inferiority.
  Non-inferiority of BF-200 ALA to Metvix® was established if the second primary null hypothesis could be rejected.

Following the hierarchical testing strategy, the second primary null hypothesis was only planned to be tested if the first primary null hypothesis was rejected. Non-inferiority of BF-200 ALA to Metvix® is established if the second primary null hypothesis can be rejected. Both primary hypotheses were to be tested two-sided at a significance level of 0.05. The hierarchical testing procedure controls for type I error inflation due to multiple testing. Therefore, no adjustment of the significance level was necessary.

The first primary analysis was performed on the ITT population and the second primary analysis on the PP population.

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Interim analysis: No interim analysis was performed.		

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Results – Study subjects and conduct:

Number of subjects in the study populations

Population	No. (%) subjects			
	Placebo	**BF-200 ALA**	**Metvix®**	**Total**
Enrolled				600
Randomized	76 (100)	248 (100)	247 (100)	571 (100)
ITT population	76 (100)	248 (100)	246 (99.6)	570 (99.8)
Safety population	76 (100)	248 (100)	246 (99.6)	570 (99.8)
PP population	65 (85.5)	238 (96.0)	236 (95.5)	539 (94.4)

Although 616 subjects were planned to be randomized only 600 were enrolled. Recruitment was stopped, as the drop-out rate was much lower than the expected rate of 20%.
Of the 600 subjects enrolled, 571 were randomized, 570 included in the ITT/safety population and 539 in the PP population. Efficacy analysis is based on the ITT population (superiority of BF-200 ALA over placebo) and PP population (non-inferiority of BF-200 ALA to Metvix®) and safety analysis on the safety population.
22 randomized subjects prematurely discontinued the clinical part of the study, and 549 subjects completed the study (241 in the BF-200 ALA, 240 in the Metvix® and 68 in the placebo group). 31 subjects in the ITT population had major protocol violations, consequently 539 subjects were included in the PP population.
All subjects in the ITT population were Caucasian, 84.0% were men, 16.0% women and the mean age was 70.7 years. Most subjects (86.5%) were of skin type II or III (according to Fitzpatrick Skin Typing Score) and mean duration of AK was 3.9 years.
Most subjects had keratinocytic intraepithelial neoplasm (KIN) Grade II (73.3% subjects), 83.3% of the subjects had at least one lesion with a moderate Olsen severity grade, and the mean number of AK lesions at baseline per subject was 6.2. 74.4% of the subjects received treatment to Target Area A (face and forehead) alone or in combination with Target Area B, 42.8% to Target Area B (bald scalp) alone or in combination with Target Area A and 17.2% to Target Areas A and B.

The total number of AK lesions at baseline was 3551. Of the 3551 lesions, 2233 (62.9%) were in Target Area A and 1318 (37.1%) in Target Area B. The maximum Olsen Severity Grading was mild in 1390 lesions (983 [27.7%] in Target Area A and 407 [11.5%] in Target Area B), moderate in 2159 lesions (1248 [35.1%] and 911 [25.7%]) and severe in 2 lesions (both in Target Area A).
All 570 subjects in the ITT / safety population were exposed to PDT during PDT1 session (248 received BF-200 ALA, 246 Metvix® and 76 placebo). During PDT1, Target Area A only was illuminated in 326 (57.2%) subjects, Target Area B only in 146 (25.6%) subjects, and Target Areas A and B in 98 (17.2%) subjects.

341 subjects were exposed to a second PDT session (PDT2) 12 weeks after the first PDT (123 received BF-200 ALA, 150 received Metvix® and 68 received placebo) During PDT2, Target Area A only was illuminated in 184 (32.3%) subjects, Target Area B only in 114 (20.0%) subjects, and Target Areas A and B in 43 (7.5%) subjects.

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Number of subjects exposed to PDT1 and PDT2 by Target Area (safety population)

Population	No. (%) subjects			
	Placebo	**BF-200 ALA**	**Metvix®**	**Total**
PDT1	76 (100)	248 (100)	246 (100)	570 (100)
Target Area A only	39/76 (51.3)	149/248 (60.1)	138/246 (56.1)	326/570 (57.2)
Target Area B only	21/76 (27.6)	67/248 (27.0)	58/246 (23.6)	146/570 (25.6)
Target Areas A and B	16/76 (21.1)	32/248 (12.9)	50/246 (20.3)	98/570 (17.2)
PDT2	68/76 (89.5)	123/248 (49.6)	150/246 (61.0)	341/570 (59.8)
Target Area A only	34/76 (44.7)	72/248 (29.0)	78/246 (31.7)	184/570 (32.3)
Target Area B only	22/76 (28.9)	41/248 (16.5)	51/246 (20.7)	114/570 (20.0)
Target Areas A and B	12/76 (15.8)	10/248 (4.0)	21/246 (8.5)	43/570 (7.5)

Table 11.1.9.1

Results – Efficacy:

Topical application of BF-200 ALA with PDT was effective in the treatment of AK. The primary endpoint, overall subject complete response assessed 12 weeks after the last PDT, was statistically significantly higher with BF-200 ALA than placebo (78.2% vs 17.1%; difference between the two groups 61.1% points; p=0.0000) demonstrating superiority of BF-200 ALA to placebo (ITT population). In addition, BF-200 ALA was non-inferior to Metvix® in the complete response assessed 12 weeks after the last PDT (79.4% vs 65.3%; difference between the two groups 14.2% points; one-sided lower 97.5% CI of 6.0 i.e. > -15%; PP population). The robustness of these results was confirmed by analyzing the superiority of BF-200 ALA to placebo in the PP population and the non-inferiority of BF-200 ALA to Metvix® in the ITT population. In fact, significant superiority of BF-200 ALA over Metvix® was demonstrated because the 97.5% CI for the difference between the treatments did not include 0% (i.e. 97.5% CI: 6.0, infinity) which is equivalent to a significant test for superiority.
The superiority of BF-200 ALA to placebo (in terms of the subject complete response assessed 12 weeks after the last PDT) was reflected in subject complete response and partial response at all assessments. Non-inferiority of BF-200 ALA to Metvix® (in terms of the subject complete response assessed 12 weeks after the last PDT) was reflected in subject complete response and partial response at all assessment. Significant superiority of BF-200 ALA over Metvix® was also demonstrated in subject complete response at 3-4 weeks and 12 weeks after PDT1, 12 weeks after PDT2, and 3-4 weeks after last PDT. Significant superiority of BF-200 ALA over Metvix® was shown in the partial responder rates 12 weeks after the last PDT.

When AK lesions were located in both target areas (Target Area A [face] and Target Area B [bald scalp]), 78.1% of subjects treated with BF-200 ALA were complete responders 12 weeks after the last PDT, compared to 56.0% with Metvix® and 25.0% with placebo.

Both active treatments were more effective when AK lesions were located on the face only vs the bald scalp only: 81.9% vs 70.1% subjects with BF-200 ALA were complete responders 12 weeks after the last PDT and 77.5% vs 39.7% with Metvix® (compared to 10.3% vs 23.8% subjects with placebo). No females presented with lesions located on the scalp, consequently the efficacy of both active treatments was higher in females vs males: complete response rates 88.2 vs 76.6% with BF-200 ALA, 70.7% vs 62.9% with Metvix® (whereas the reverse was true for placebo: 0% vs 21.7%).

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Complete response rates 12 weeks after the last PDT were higher when PDT was performed with a narrow spectrum lamp (e.g. Omnilux or Aktilite) vs a broad spectrum lamp (e.g. Waldmann or Hydrosun PhotoDyn) in the BF-200 ALA group (84.8 vs 71.5% subjects) and Metvix® group (67.5 vs 61.3%). In comparison, more subjects treated with placebo responded to a broad than a narrow spectrum lamp (21.6 vs 12.8% subjects were complete responders 12 weeks after the last PDT). In the BF-200 ALA group, complete response rates 12 weeks after the last PDT were higher when PDT was performed with a narrow spectrum lamp (e.g. 82.0% subjects with the Aktilite lamp, 91.4% subjects with the Omnilux lamp); satisfying with the broad spectrum Waldmann lamp (86.7% subjects); and inferior with the Hydrosun Photodyn lamp (69.4% subjects). However, due to the small sample size of the Waldmann lamp subgroup, no definite conclusions regarding this subgroup could be drawn.

Complete responder rates 12 weeks after the last PDT showed that all three treatments (BF-200 ALA, Metvix® and placebo) were more effective in younger compared to older subjects (<=65 vs >65 years; i.e. 87.3% vs 75.6% with BF-200 ALA; 77.1% vs 61.1% with Metvix®; 18.2% vs 16.9% with placebo) and that BF-200 ALA and Metvix® were more effective in females compared to males (whereas placebo was ineffective in females). In younger subjects, older subjects, females and males, complete responder rates 12 weeks after the last PDT were consistently higher with BF-200 ALA than Metvix® or placebo.
In both active treatment groups and the placebo group, subjects presenting with Olsen Grade I AK lesions at baseline were more likely to be complete responders 12 weeks after the last PDT than subjects with Grade II lesions. For those with only Grade I lesions at baseline, the most effective treatment was Metvix® (92.7% subject were complete responders 12 weeks after the last PDT compared to 84.6% with BF-200 ALA and 21.4% with placebo).
However, for subjects with more severe lesions (Grade II) at baseline BF-200 ALA was more effective than Metvix® and placebo (77.0% subject were complete responders 12 weeks after the last PDT vs 58.5% and 16.1%, respectively). AK disease severity at baseline had a substantial effect on the efficacy of treatment. Treatment was more effective in subjects with <=5 lesions vs >=6 lesions at baseline in the BF-200 ALA group (83.0 vs 74.6% subjects were complete responders 12 weeks after the last PDT) and Metvix® group (74.2 vs 58.2%) but not in the placebo group (16.7 vs 17.2%). Comparable percentages of complete responders were achieved 12 weeks after the last PDT when comparing the AK lesion areas (<=400 mm² vs >400 mm²) at baseline for BF-200 ALA (81.5% vs 76.3%).
Fewer subjects with fair skin (Fitzpatrick type I – III) were complete responders 12 weeks after the last PDT compared to those with dark skin (type IV – V): 77.7 vs 81.1% subjects with BF-200 ALA, 63.8 vs 68.0% with Metvix® and 16.7 vs 25.0% with placebo. These findings suggest that subjects with fair skin tend to have more severe disease than those with darker skin.

In general, the results mentioned above were reflected in complete response rates 12 weeks after PDT1 and PDT2, although lower response rates were generally observed. The complete response rate in the active treatment groups increase as the time after PDT increases and as the number of PDTs increases.
At all assessments, complete lesion response rates were higher with BF-200 ALA than placebo or Metvix®.
In the illumination source subgroups (broad, narrow), complete lesion response rates were higher with BF 200 ALA than placebo at each assessment, and were higher (as a %) than Metvix® at all but 1 assessment (i.e. 3-4 weeks after PDT2 with the narrow illumination source).
In the AK baseline severity subgroups (Grade I, Grade II) and target area subgroups (A, B) complete lesion response rates (as a %) were higher with BF-200 ALA than placebo or Metvix® at all but 1 assessment (the exception was 3-4 weeks after PDT2 in Grade I severity).

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Results of the complete and partial responses at each assessment are consistent with the results of the primary efficacy variable. In addition, complete lesion response rates at the six assessments (3-4 and 12 weeks after PDT1, PDT2 and last PDT) were greater with BF-200 ALA than placebo or Metvix®, as was the mean percentage reduction in total lesion area per subject and this was reflected in the total lesion count.
Improvements in skin quality from baseline to 12 weeks after the last PDT occurred in all three treatment groups with subjects experiencing most improvements in skin surface (27.3% subjects with BF-200 ALA, 29.6% with Metvix® and 17.6% with placebo including the baseline evaluation "none"; and 40.0%, 46.4% and 27.3% subjects, respectively excluding the baseline evaluation "none").
Cosmetic outcome assessed 12 weeks after the last PDT (with baseline sum score 0 excluded) was judged as: very good or good in 43.1% subjects in the BF-200 ALA group, 45.2% in the Metvix® group and 36.4% in the placebo group; and unsatisfactory or impaired in 7.9%, 8.1% and 18.2% subjects, respectively.

Results – Safety:

Safety information contained in this report was collected up until and including 21 Aug 2009 (date that the last patient completed the clinical part of the study and entered the follow-up phase).
Overall, nearly all subjects reported TEAEs after treatment with BF-200 ALA (96.4% subjects) or Metvix® (98.0%) and almost three quarters after placebo (72.4%). In all treatment groups, TEAEs were most commonly reported in the system organ classes (SOCs) general disorders and administration site conditions (94.8%, 96.7% and 64.5% subjects, respectively) and skin and subcutaneous tissue disorders (17.3%, 14.2% and 13.2%, respectively). The most common TEAEs in all groups were application site irritation (88.3%, 90.2% and 32.9%, respectively), followed by application site erythema (79.8%, 80.9% and 40.8%) and application site pain (70.6%, 72.8% and 25.0%). In all subjects these three TEAEs were assessed by the investigator as related to treatment; and were also the most common severe TEAEs.

The overall incidence and intensity of local skin reactions occurring during PDT was higher in the BF-200 ALA and Metvix® groups compared to the placebo group. In all treatment groups the incidence and intensity of local skin reactions were lower during the second PDT compared to the first PDT. In Target Area A (face/forehead) and Target Area B (bald scalp) erythema was the most frequent skin reaction observed during PDT in all three treatment groups. The incidence and intensity of erythema was similar in the BF-200 ALA and Metvix® group during PDT1 and PDT2, and was much lower in the placebo group. Similarly in Target Area A and Target Area B the incidence and intensity of edema was similar in the BF-200 ALA and Metvix® group during PDT1 and PDT2, and was much lower in the placebo group. In Target Area A and Target Area B, induration was only reported in the BF-200 ALA and Metvix® groups, and was observed with a similar incidence in the two groups during both PDTs.
The overall incidence and intensity of discomfort (itching and burning) occurring during PDT was lower after the second PDT compared to the first PDT. The number of subjects reporting discomfort in Target Area A and Target Area B was similar in the BF-200 ALA and Metvix® groups during PDT1 and PDT2 and was lower in the placebo group.
In all treatment groups, the assessment of pain in Target Area A and Target Area B was generally worse during PDT1 than PDT2. The assessment of pain was similar in the BF-200 ALA and Metvix® groups during PDT1 and also during PDT2; and was lower in the placebo group. An illumination source with a narrow light spectrum was associated with worse pain than an illumination source with a broad light spectrum in the BF-200 ALA and Metvix® groups.
Overall frequencies of serious TEAEs were low and similar in the BF-200 ALA, Metvix® and placebo groups (4.4%, 4.1% and 3.9%, respectively). No related serious TEAEs were reported.

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No TEAEs resulting in death were reported during the clinical part of the study. To date (07 December 2009), during the follow-up part of the study one death was reported: Subject 102/06 in the Metvix® group died due to cardiac arrest. The investigator considered the event as unrelated to study treatment.
4 subjects discontinued study medication due to AEs. Two subjects discontinued treatment due to an AE after treatment with BF-200 ALA and PDT1: one subject due to severe pneumonia (considered unrelated to BF-200 ALA), and another due to application site pain and non-serious application site irritation (both severe and considered related to BF-200 ALA). Another two subjects discontinued treatment in the Metvix® group: one due to serious non-Hodgkin's lymphoma (severe), and another due to serious cerebrovascular accident (moderate). Both events were considered unlikely related or unrelated to study treatment.

No pregnancies were reported during the study.
Laboratory monitoring, vital signs and physical examination showed no clinically relevant changes.

Conclusions

- Topical application of BF-200 ALA with PDT was effective in the treatment of AK. In subjects with AK overall subject complete response with BF-200 ALA 12 weeks after the last PDT treatment was: superior to placebo (78.2% vs 17.1% subjects; p=0.0000; ITT population); and superior to Metvix® (79.4% vs 65.3% subjects; one-sided lower 97.5% CI of 6.0 [i.e. >-15%]; PP population). The robustness of these results was confirmed.
- Complete responder rates 12 weeks after the last PDT were comparable between the treatment groups for lesions on the face only (81.9% subjects with BF-200 ALA and 77.5% with Metvix®) but were quite different for the bald scalp only (70.1% and 39.7%, respectively). BF-200 ALA was more effective than Metvix® in subjects with more severe disease (Olsen grade II AK lesions) at baseline. Overall, the complete response rates 12 weeks after the last PDT with active treatment (BF-200 ALA, Metvix®) were higher if PDT was performed with a narrow spectrum lamp (i.e. Omnilux or Aktilite) compared to a broad spectrum lamp (i.e. Waldmann or Hydrosun PhotoDyn).
- In general, complete response rates were better after the second PDT than after the first PDT, thus a repetition of PDT treatment after 3 months is highly recommended.
- Improvements in skin quality from baseline to 12 weeks after the last PDT occurred with BF-200 ALA, Metvix® and placebo but were only fair. The cosmetic outcome (with baseline sum score 0 excluded), assessed 12 weeks after the last PDT, was considered as very good/good in 43.1% subjects in the BF 200 ALA group and 45.2% in the Metvix® group.
- Overall, BF-200 ALA was well tolerated. The safety profile was largely comparable to that previously observed / reported, and there were no new or unexpected safety findings. The most common TEAEs (also the most common related TEAEs and the most common severe TEAEs) affected the "application site" i.e. application site irritation, application site erythema and application site pain. Overall frequencies of serious TEAEs were low and no related serious TEAEs were reported. Local skin reactions were mainly of mild to moderate intensity. Pain and discomfort (itching and burning) during PDT in the face only or bald scalp only was worse during PDT1 than PDT2.

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