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, Double-Blind, Phase III Multi-Center Study Evaluating the Safety and Efficacy of BF-200 ALA versus Placebo in the Treatment of Actinic Keratosis (AK) when using Photodynamic Therapy (PDT) Study number: ALA-AK-CT003 (EudraCT-No.: 2007-003371-39)
Co-ordinating Investigator:	Prof. Dr. med. Rolf-Markus Szeimies Klinikum der Universität Regensburg Klinik und Poliklinik für Dermatologie Franz-Josef-Strauß-Allee 11 93053 Regensburg, Germany
Study center(s):	8 study centers in Germany.
Publications (references):	Szeimies RM, Radny P, Sebastian M, Borrosch F, Dirschka T, Krahn-Senftleben G, Reich K, Pabst, G, Voss D, Foguet M, Gahlmann R, Lubbert H, Reinhold, U. Photodynamic therapy with BF-200 ALA for the treatment of actinic keratosis: results of a prospective, randomized, double-blind, placebo-controlled phase III study. Br J Dermatol 2010; 163: 386-94
Period of study:	13 December 2007 to 01 October 2008
Clinical phase:	III
Objectives:	Evaluation of the efficacy of photodynamic therapy (PDT) with a topical nanoemulsion formulation of 5-aminolevulinic acid (BF-200 ALA) for actinic keratosis (AK) and demonstration of superiority of BF-200 ALA over placebo.
Methodology (design of study):	Randomized, double-blind, placebo-controlled, inter-individual, 2 armed, multi-center study using BF-200 ALA and placebo, with a verum/placebo ratio of 2:1. Each subject received one or two treatments for 4-8 AK lesions either with BF-200 ALA or placebo. 12 weeks after the first PDT the clearance of AK lesions was assessed. All lesions which were not completely cleared were treated with a second PDT. A final assessment of clearance took place after additional 12 weeks for those patients who were treated with a second PDT. After completion of the study subjects received conventional treatment for all AK lesions which were not completely cleared according to the investigator's decision.
Number of subjects:	120 subjects (80 subjects receiving BF-200 ALA and 40 subjects receiving placebo with a ratio of 2:1 of verum and placebo) were planned to be included in this study.

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Diagnosis and main criteria for inclusion:	White male and female subjects, between 18 and 85 years of age, and diagnosed to have at least 4 but not more than 8 lesions of AK in their face and/or on the scalp. The diameter of each AK lesion was to be not less than 0.5 cm and not greater than 1.5 cm. Adjacent AK lesions had to show a minimal distance of 1.0 cm to one another.
Test product, dose and mode of administration, batch number:	BF-200 ALA nanoemulsion gel, batch number: 81589G0001 (concentration: 10% ALA). Scabs, crusts, or hyperkeratosis were thoroughly removed from the AK-lesions. In addition, all lesion surfaces were abraded using a curette or scalpel blade avoiding bleeding and were cleaned with an ethanol-soaked cotton pad prior to drug application and incubation. One tube containing 2 g of test drug was dispensed for one PDT session, enough to cover up to 8 distinct AK lesions with a maximum diameter of 1.5 cm. After application, the gel was allowed to dry for approx. 10 min. Thereafter, an occlusive, light-tight dressing was placed over the lesions. After the incubation time of 3 h $\pm$ 10 min, the occlusion was removed and the remnant gel wiped off with a 0.9% saline solution immediately before illumination of the target area with a suitable red light source for 11-15 min.
Duration of treatment:	The subjects received one PDT including BF-200 ALA gel application and illumination on Day 0. A second treatment session with BF-200 ALA or placebo was performed if there were lesions which were not cleared 12 weeks after the first PDT. The treatment with either verum or placebo was the same in both treatment sessions.
Reference therapy, dose and mode of administration, batch number:	Placebo, identical to the test product but without ALA, served as reference therapy (batch number 81590G001). Administration and illumination were performed identically to the treatment with the test product.
Criteria of evaluation:	The schedule of evaluations after the first and second PDT treatment was the same. Subjects returned to the clinic after 3 weeks ($\pm$ 2 days) and 12 weeks ($\pm$ 4 days) after each PDT (first and second) for the monitoring of the clinical outcome and the healing process. The investigator clinically assessed the treated area for evidence of AK lesions and clinical symptoms. The clearance rate of AK lesions per subject was calculated 12 weeks after last PDT and the cosmetic outcome was assessed. The efficacy and safety of BF-200 ALA and placebo were assessed and documented throughout the study by the following: • Pre-treatment clinical examination of the lesions with photo

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documentation, biopsy of a representative AK lesion and graphic templates of the target area.

- Telephone contact with the subject 7 days after the treatment session.
- Review of local skin reactions at 3 and 12 weeks after treatment.
- Review of adverse events (AEs) and concomitant medications.
- 3 and 12 week post-treatment clinical examination and photo documentation of the treated area.
- General physical examination and vital signs; check of clinical chemistry and hematology parameters.
- Biopsy of a second representative AK lesion, which was defined at screening, 12 weeks after treatment with the last PDT.

For safety reasons, dip stick pregnancy tests for women of childbearing potential were performed.

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Study endpoints:	The primary endpoint was the AK clearance rate, defined as the number of subjects with complete remission of all AK lesions in the target area(s) assessed 12 weeks after the last PDT. The secondary endpoints were: • Proportion of AK lesions showing complete remission at week 12 after the last PDT, ie the lesion was completely cleared and no adherent scaling plaques of AK were visible any longer. • Reduction in total lesion area within the target treatment area per subject (face or bald scalp) at week 12 after the last PDT when compared to baseline. • Proportion of subjects with complete clearance after the first treatment, proportion of subjects with clearance of at least 75% of lesions after the first treatment and at 12 weeks after the last PDT treatment. • Change in skin quality assessment compared to baseline of all target lesions located within the target treatment area; • Local skin reactions at the target treatment area assessed by the investigator. • Overall cosmetic outcome at 12 weeks post-treatment. • Number of days with discomfort within 7 days after photodynamic treatment – based on phone contact. • Frequency and extent of AEs during illumination and throughout the study. • Frequency of abnormal vital signs at each clinical visit, and hematology and clinical chemistry parameters at baseline and at the end of the clinical trial.

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Statistical methods:	The analysis of the efficacy parameter was performed for the full analysis set (FAS) and the per-protocol (PP) population. The clearance rate was estimated as a relative frequency separately for BF-200 ALA and placebo treatments. Statistical evaluation was performed including all subjects, independent whether they received one or two PDTs. A Cochran-Mantel-Haenszel test, accounting for centers as stratifying variable, was used. The test was evaluated as two-sided test at an α-level of 0.05. Furthermore, 95% confidence intervals according to the method of Pearson-Clopper were calculated. Rates of lesion clearance (ie percent of lesions cleared) were estimated with 95% confidence intervals, giving each lesion the same weight. In addition, the lesion clearance was calculated using the weighting method for correlated binary data as described by Jung and Ahn. The reduction in total lesion area was compared between treatments by analysis of covariance, using the baseline measurement as covariate. For exploratory purposes the total lesion areas were also compared by nonparametric methods (Brunner, Domhof, Langer 2002). A factor for treatment, time and treatment vs time interaction was included into the nonparametric repeated measurements model based on rank statistics. The proportions of totally (complete vs incomplete) and partially (at least 75% vs $<$75%) cleared subjects were compared between treatments by Cochran-Mantel-Haenszel test accounting for centers as stratifying variable. The changes in skin quality assessment (per category) and the overall cosmetic outcome at 12 week post-treatment were evaluated by χ^2 test, independent of study centers. The evaluation of the other secondary endpoints (local skin reactions at the target treatment area assessed by the investigator, number of days with discomfort within 7 days after PDT, frequency and extent of AEs during illumination and throughout the study, frequency of abnormal vital signs, hematology and clinical chemistry parameters at baseline and at the end of the clinical trial) was performed using descriptive statistics. AEs were coded by MedDRA 11.1. Pre-study and concomitant medication data were coded according to the latest version of WHO-DD (version 10.0).

Summary and conclusions:
All included subjects were valid for the safety population. Two subjects were excluded from the full-analysis set (FAS) because they had no post-dose assessment of the clearance of AK lesions in the

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target area. Further six subjects had significant protocol deviations and were excluded from the per-protocol (PP) data set.

Table-Fehler! Kein Text mit angegebener Formatvorlage im Dokument.**-1: Subject disposition**

Population		**Treatment group**		
		BF-200 ALA	**Placebo**	**Overall**
Subjects treated	n	81	41	122
Safety population	N (%)	81 (100%)	41 (100%)	122 (100%)
Full analysis set	N (%)	80 (98.8%)	40 (97.6%)	120 (98.4%)
Per protocol set	N (%)	77 (95.1%)	37 (90.2%)	114 (93.4%)

The overall mean age was 70.5 years (70.4 years for the BF-200 ALA group and 70.6 years for the placebo group), mean height was 172.5 cm (173.4 and 170.6 cm, respectively), mean weight was 79.2 kg (79.6 and 78.3 kg, respectively) and mean BMI was 26.7 kg/cm^2 (26.5 and 27.0 kg/cm^2, respectively). The differences between the treatment groups were marginal. Mean duration of AK was 4.5 years (4.6 and 4.4 years, respectively).

Efficacy

At 12 weeks after treatment with either 1 or 2 PDTs (end of study), 66.3% of the subjects in the BF-200 ALA group showed a complete clearance of all AK lesions compared to only 12.5% of subjects in the placebo group (see Figure-1). The difference between the BF-200 ALA group and placebo was statistically significant ($P<0.0001$; Cochran-Mantel-Haenszel test stratified by center).

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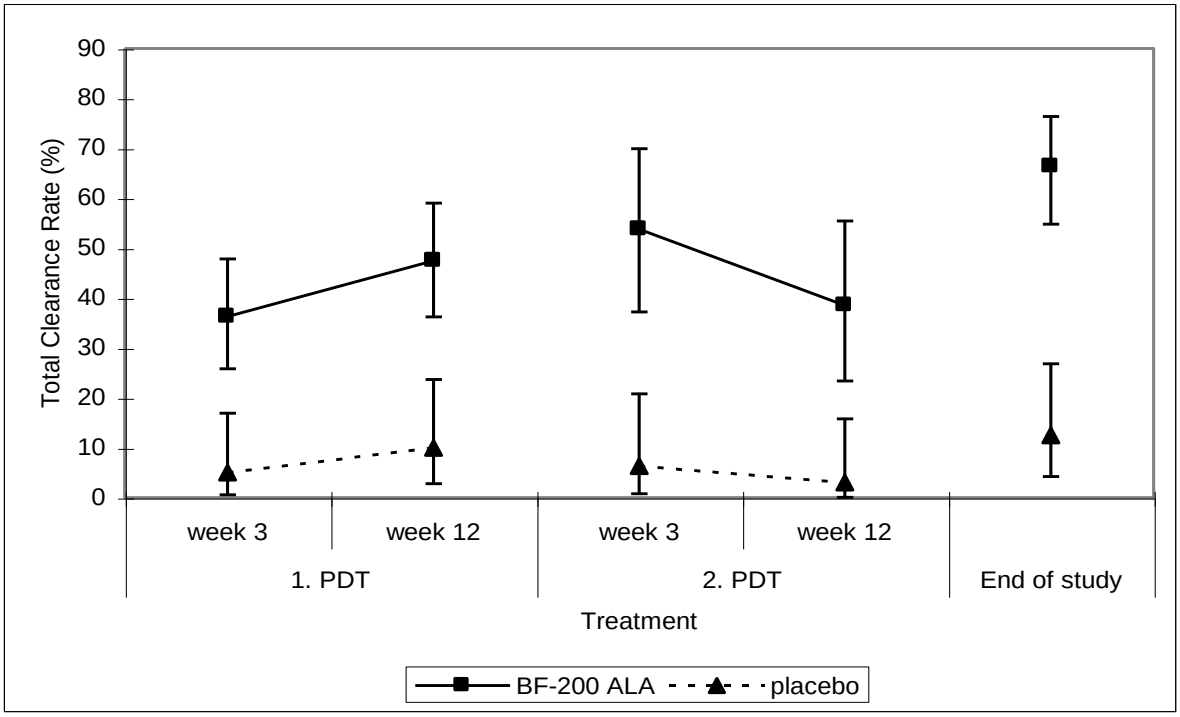
Figure-1: Total clearance rate and 95% CI for the clearance rate by week and treatment (FAS)



No apparent relationship between the clearance rate and the initial number of lesions, the area treated, gender or duration of AK history was observed.
For the following subgroups differences were seen, but the 95% confidence intervals (CIs) overlapped, indicating that the differences were not statistically significant: higher clearance rates were seen:

- In subjects with a baseline AK lesion severity grade according to Olsen at baseline of maximally grade I (78.9%) compared to subjects with maximally grade II severity (62.3%, at least 1 lesion of an individual subject was of grade II).
- In subjects aged 52 to 68 years (80.0%) compared to subjects 69 to 85 years of age (58.0%).
- In subjects with skin type II (75.6%) compared to subjects with skin type III (56.3%).

A clear relationship was seen between the clearance rate and the irradiation source, showing a higher clearance rate after irradiation with the Aktilite CL 128 device (87.1%) compared to the PhotoDyn 750 device (53.1%) in the BF-200 ALA group. The 95% CI did not overlap. No remarkable difference between the irradiation sources were observed in the placebo group.

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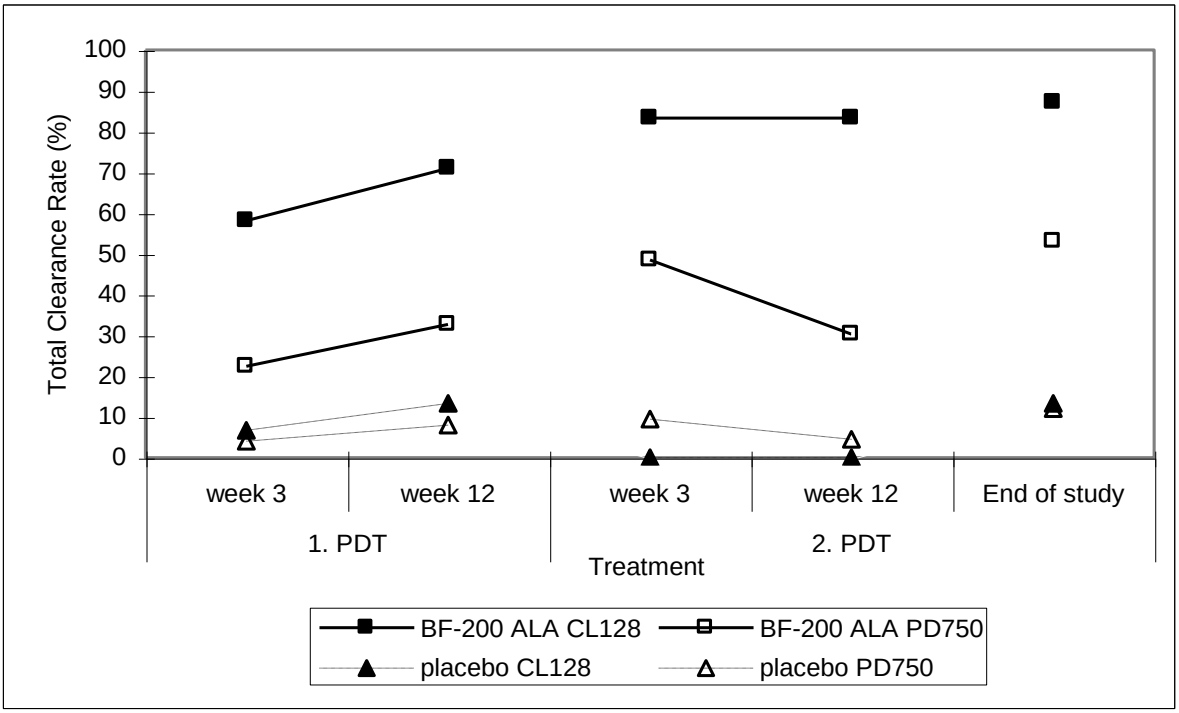
Figure-2: Total clearance rate and 95% CI for the clearance rate by irradiation source, week, and treatment; only BF-200 ALA group (FAS)



CL 128 = Aktilite CL 128, PD750 = PhotoDyn 750

The proportion of AK lesions showing complete remission at week 12 after the last PDT was statistically significantly higher in the BF-200 ALA group compared to placebo (81.1% of the lesions showed complete remission after treatment with BF-200 ALA and 20.9% were cleared after placebo treatment).

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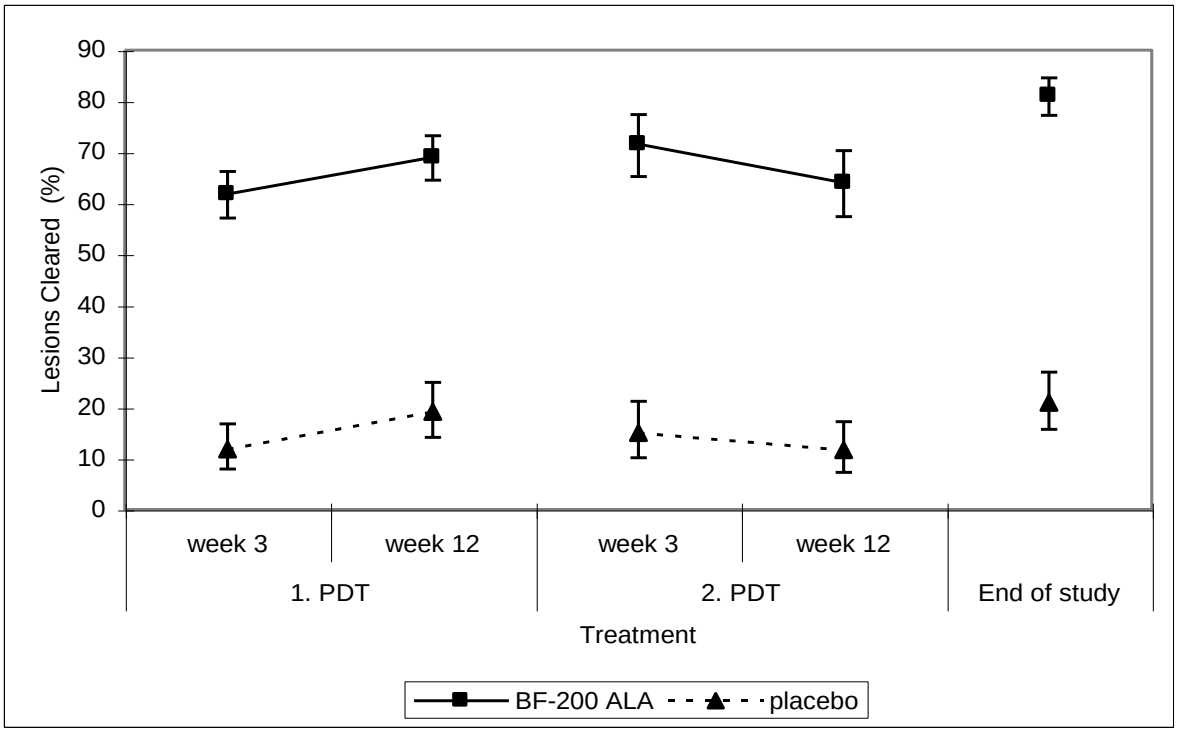
Figure-3: Number of AK lesions showing complete remission and 95% CI by week and treatment (FAS)



A relationship between the proportion of AK lesions showing complete remission and the irradiation source (in favor of Aktilite CL 128), AK baseline severity (in favor of grade I severity), age (in favor of subjects aged 52 to 68 years) and skin type (in favor of type II) was observed; for all group-comparisons the 95% CIs did not overlap, indicating significant differences between the subgroups.

The average number of lesions decreased after treatment with BF-200 ALA on the face and forehead from 4.9 lesions at baseline to 0.8 lesions at the end of the study and on the bald scalp from 5.5 lesions at baseline to 1.3 lesions at the end of the study. The corresponding means for the placebo group were: face and forehead - baseline 5.0 lesions, 4.2 lesions at the end of the study; bald scalp - baseline 5.1 lesions, 3.4 lesions at the end of the study.

Mean lesion size of the lesions on the face and forehead per subject was reduced from 70.8 mm^2 at baseline to 6.3 mm^2 at the end of the study in the BF-200 ALA group. On the bald scalp mean lesion size decreased from 71.3 mm^2 to 10.0 mm^2.

Until the end of the study the mean total lesion area within the target treatment area per subject decreased after treatment with BF-200 ALA by 360.2 mm^2 (from 403.8 mm^2 to 43.6 mm^2) and after treatment with placebo by 110.3 mm^2 (from 399.3 mm^2 to 289.2 mm^2). ANCOVA revealed that the difference between the treatment groups was statistically significant ($P<0.0001$).

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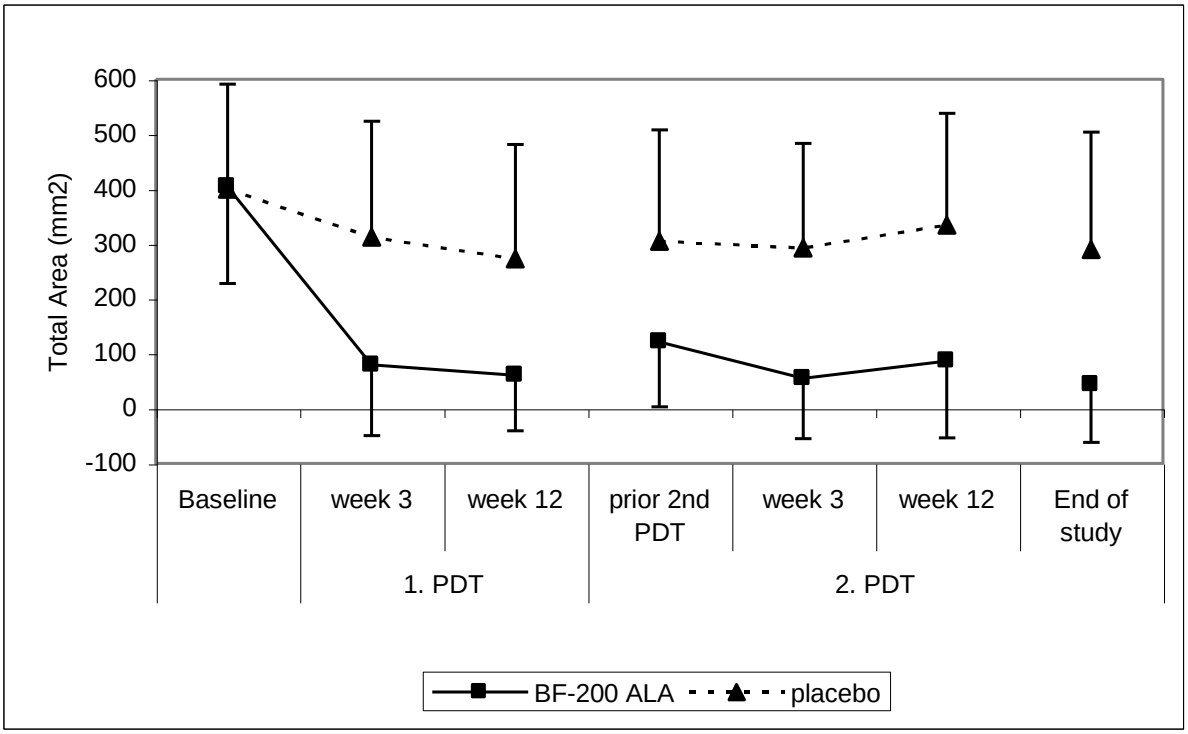
The mean reduction in the total lesion area was higher in subjects, when the Aktilite was used for irradiation (compared to PhotoDyn irradiation) and in subjects with skin type II (compared to those with skin type III). No remarkable differences were detected for analysis per number of lesions, AK severity grade at baseline, target area, age and duration of AK history.

Figure-4: Mean total lesion area (±SD) by week and treatment (FAS)



Already at 12 weeks after the first PDT 47.5% of the subjects in BF-200 ALA group but only 10.0% in the placebo group were totally cleared from AK lesions. At the same time 62.5% of the subjects in the BF-200 ALA group and 10.0% of subjects in the placebo group showed a 75% clearance, i.e. at least 75% of the lesions of a subject were cleared. The percentages of subjects totally cleared at 12 weeks after the first PDT and of those, who showed at least 75% clearance were statistically significantly higher in the BF-200 ALA group compared to placebo ($P<0.0001$, Cochran-Mantel-Haenszel test stratified by center). At the end of the study (i.e. after first or second PDT) 78.8% of the subjects in the BF-200 ALA group and 17.5% of the subjects in the placebo group showed at least a 75% clearance. Again the clearance rate was statistically significantly higher in the BF-200 ALA group ($P<0.0001$). At 12 weeks after the first PDT the percentage of subjects showing at least 75% clearance was higher in subjects irradiated with Aktilite CL 128 (87.1% in the BF-200 ALA group) compared to 46.9% of subjects irradiated with PhotoDyn 750. At the end of the study 96.8% of the subjects irradiated with Aktilite CL 128 showed at least 75% clearance compared to 67.3% of the subjects irradiated with PhotoDyn 750.

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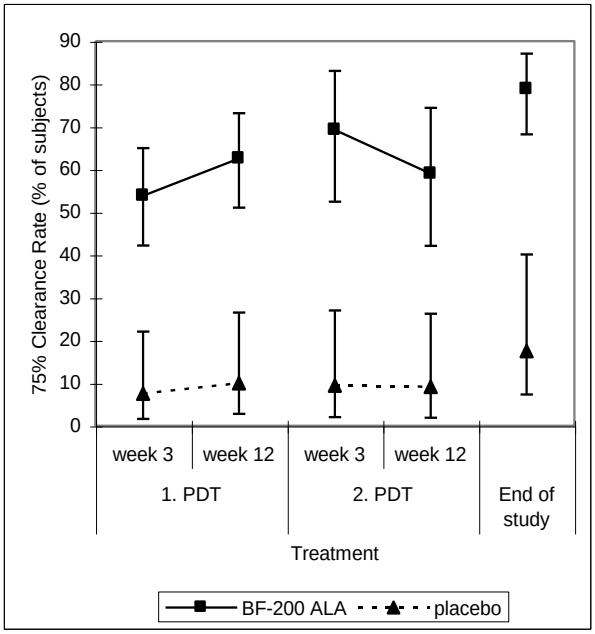
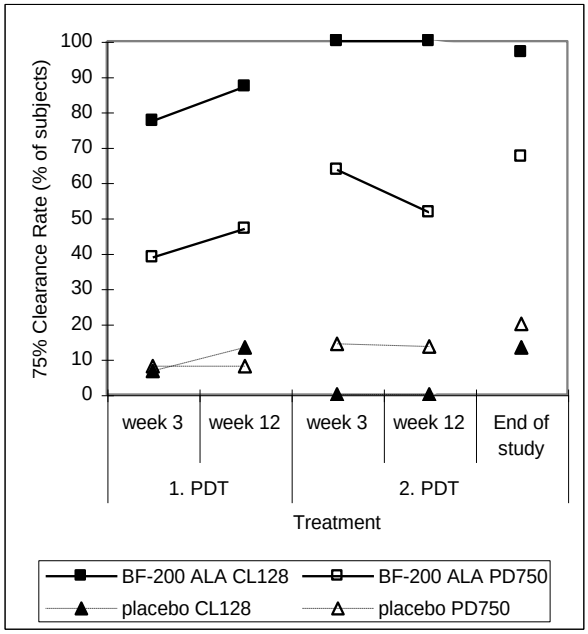
Figure-5: Percentage of subjects showing complete or at least 75% remission)

Overall (with 95% CI)



By irradiation source



CL 128 = Aktilite CL 128, PD750 = PhotoDyn 750

Cosmetic outcome

Skin quality improved during the course of the study in the BF-200 ALA group, especially for 'roughness, dryness, scalings' and 'hyperpigmentations' detectable (roughness improved in 41.3% of the subjects in the BF-200 ALA group and in 15.0% of the subjects in the placebo group; hyperpigmentation improved in 20.1% of the subjects in the BF-200 ALA group and in 17.5% of the subjects in the placebo group). For all other skin irritation parameters more than 80% of all subjects showed no changes from baseline to the end of the study.

The cosmetic outcome was assessed as very good or good in 47.6% of the subjects compared to 25.0% of subjects in the placebo group. An unsatisfactory or impaired cosmetic outcome was judged for 3.8% of the subjects in the BF-200 ALA group and in 22.5% of the subjects in the placebo group.

Safety

Application site disorders (mainly erythema, skin irritation, application site pain, application site edema and application site pruritus) were the most frequently reported AEs, experienced by 39.0% of the placebo treated subjects and 96.3% of the subjects treated with BF-200 ALA (see Table-Fehler**! Kein Text mit angegebener Formatvorlage im Dokument.**-2). Most AEs were considered as drug-related by the investigator. In most subjects application site disorders started on the day of PDT and resolved within a week.

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Table-Fehler! Kein Text mit angegebener Formatvorlage im Dokument.**-2: Summary of application site disorders**

Application site disorder	Treatment group			
	BF-200 ALA n=81 x (y, z%)		Placebo n=41 x (y, z%)	
	Overall	Starting during PDT	Overall	Starting during PDT
	x (y, z%)	x (y, z%)	x (y, z%)	x (y, z%)
Total	393* (78, 96.3)	373 (78,96.3)	40 (16, 39.0)	40 (16,39.0)
Application site discomfort	2 (1, 1.2)	-	-	-
Application site erythema	116 (72, 88.9)	115 (72,88.9)	22 (15, 36.6)	22 (15,36.6)
Application site induration	14 (12, 14.8)	14 (12,14.8)	-	-
Application site irritation	109 (70, 86.4)	104 (70,86.4)	11 (10, 24.4)	11 (10,24.4)
Application site edema	39 (32, 39.5)	38 (31,38.3)	1 (1, 2.4)	1 (1, 2.4)
Application site pain	62 (44, 54.3)	62 (44,54.3)	4 (4, 9.8)	4 (4, 9.8)
Application site pruritus	32 (27, 33.3)	30 (26,32.1)	-	-
Application site reaction	11 (9, 11.1)	9 (7, 8.6)	2 (2, 4.9)	2 (2, 4.9)
Application site scab	1 (1, 1.2)	1 (1, 1.2)	-	-
Application site vesicles	2 (1, 1.2)	-	-	-
Application site pustules [a]	5 (1, 1.2)	-	-	-

a 388 AEs coded under 'General disorders and administration site conditions', 5 AEs (Application site pustules) coded under 'Infections and infestations'.
x (y, z%): x = number of AEs; y = number of subjects with particular AE; z = percentage of subjects with particular AE who received respective treatment

Skin reactions immediately after the end of the irradiation were more frequently observed after BF-200 ALA treatment compared to placebo. Incidence and intensity of skin reactions were lower after the second PDT. Erythema was the most frequent skin reaction observed in 86.4% of the subjects in the BF-200 ALA group after the first PDT and in 59.0% of the subjects after the second PDT compared to 34.1% of the subjects in the placebo group after the first PDT and 20.6% of the subjects after the second PDT. Erythema was mainly of mild to moderate intensity. In the BF-200 ALA group mild to moderate edema was seen in 35.8% of the subjects after the first PDT and in 20.5% of the subjects after the second PDT. Edema of mild intensity was observed in one subject in the placebo group. Mild to moderate induration was observed in 14.8% of the subjects in the BF-200 ALA group after the first PDT and in 5.1% of the subjects after the second PDT. Induration was not observed after placebo treatment. The difference in the incidence of erythema, edema and induration between the BF-200 ALA and placebo groups was statistically significant. The incidence and the intensity of local skin reactions were higher in subjects irradiated with the Aktilite CL128 than in subjects irradiated with the PhotoDyn 750. Severe erythema, moderate edema and induration occurred after irradiation with Aktilite CL 128 only.

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Table-Fehler! Kein Text mit angegebener Formatvorlage im Dokument.**-3: Frequency of local skin reactions by lesion target area and treatment**

Skin reaction		Treatment group							
		BF-200 ALA n=81 n (%)				Placebo n=41 n (%)			
		Face / forehead		Bald scalp		Face / forehead		Bald scalp	
		1st PDT n=59	2nd PDT n=25	1st PDT n=31	2nd PDT n=18	1st PDT n=30	2nd PDT n=25	1st PDT n=15	2nd PDT n=12
Erythema	Mild	20 (33.9%)	12 (48.0%)	13 (41.9%)	8 (44.4%)	11 (36.7%)	4 (16.0%)	3 (20.0%)	3 (25.0%)
	Moderate	31 (52.5%)	3 (12.0%)	9 (29.0%)	3 (16.7%)	-	-	1 (6.7%)	-
	Severe	2 (3.4%) [a]	-	1 (3.2%)[a]	-	-	-	-	-
Edema	Mild	14 (23.7%)	4 (16.0%)	4 (12.9%)	3 (16.7%)	1 (3.3%)	-	-	-
	Moderate	8 (13.6%)[a]	-	3 (9.7%)*	1 (5.6%) [a]	-	-	-	-
Induration	Mild	8 (13.6%)	1 (4.0%)	2 (6.5%)	1 (5.6%)	-	-	-	-
	Moderate	-	-	2 (6.5%)[a]	-	-	-	-	-
Scaling/ Flaking	Mild	2 (3.4%)	-	-	-	-	-	-	-
	Severe	1 (1.7%)	-	-	-	-	-	-	-
Scabbing/ Crusting	Mild	1 (1.7%)	-	-	-	-	-	-	-
	Moderate	1 (1.7%)	-	-	-	-	-	-	-

a All irradiated with Aktilite CL 128

Discomfort during PDT was more frequently experienced by subjects in the BF-200 ALA group compared to subjects in the placebo group and incidence and intensity decreased during the second PDT. The most frequently reported symptom during PDT was burning, occurring in more than 75% of the subjects in the BF-200 ALA group during the first PDT and by about 50% of the subjects during the second PDT. Pain was experienced in this group by about 50% of the subjects and itching by about 25% of the subjects during the first PDT. There was a clear relation between the incidence and intensity of symptoms and the irradiation source. All 3 symptoms occurred in a higher incidence in subjects irradiated with the Aktilite CL 128. Moreover, symptoms of severe intensity were mainly observed during irradiation with the Aktilite CL 128. In most subjects discomfort resolved within 7 days after the first and second PDT, respectively.

2 subjects of the placebo group experienced an SAE (severe myocardial infarction, hospitalization due to a myositis). Both events were considered as not related to the study medication. Both events

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resolved completely.
Laboratory monitoring and vital signs showed no clinically relevant drug-related changes.

Conclusions

- Topical PDT with BF-200 ALA was highly effective with statistically significantly higher complete clearance rate of patients in the BF-200 ALA group compared to placebo at the end of the study, ie 12 weeks after first and second PDT, respectively.
- All secondary efficacy endpoints, like proportion of AK lesions showing complete remission, reduction of total lesion area within the target treatment area, the proportion of subjects with complete clearance after the first treatment, and the proportion of subjects with clearance of at least 75% of lesions after 1 or 2 PDTs confirmed the results of the primary endpoint. For all endpoints treatment with BF-200 ALA proved to be statistically significantly better than treatment with placebo.
- Efficacy was more pronounced in subjects irradiated with the Aktilite CL 128 device compared to subjects irradiated with the PhotoDyn 750 device.
- Overall, PDT with BF-200 ALA was well tolerated. Application site disorders, local skin reactions and subjective feeling of discomfort of the subjects were mainly of mild to moderate intensity and were tolerated by the subjects.
- Incidence and intensity of local skin reactions after PDT and discomfort during PDT was higher in subjects irradiated with the Aktilite CL 128 device compared to subjects receiving irradiation with the PhotoDyn 750, indicating that the inflammation induced by the photodynamic reaction after PDT with BF-200 ALA was more intensive with the Aktilite CL 128.

Date of report: May 6th, 2010