# Clinical trial results:
# A randomized, observer-blind, intra-individual phase III study to evaluate the safety and efficacy of BF 200 ALA (Ameluz®) in combination with daylight-PDT (photodynamic therapy) in comparison with Metvix® for the treatment of mild to moderate actinic keratosis

## Summary

| | |
|---|---|
| EudraCT number | 2015-004382-83 |
| Trial protocol | DE ES |
| Global end of trial date | 07 December 2016 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 11 November 2017 |
| First version publication date | 11 November 2017 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | ALA-AK-CT009 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Biofrontera Bioscience GmbH |
| Sponsor organisation address | Hemmelrather Weg 201, Leverkusen, Germany, 51377 |
| Public contact | Clinical Trial Department, Biofrontera Bioscience GmbH, +49 2148763210, ameluz@biofrontera.com |
| Scientific contact | Clinical Trial Department, Biofrontera Bioscience GmbH, +49 2148763210, ameluz@biofrontera.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 07 December 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 07 December 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 07 December 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to compare the efficacy and safety of BF-200 ALA treatment of mild to moderate AK with Metvix® when using daylight PDT.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 23 June 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Safety |
| Long term follow-up duration | 9 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | Germany: 48 |
| Worldwide total number of subjects | 54 |
| EEA total number of subjects | 54 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 6 |
| From 65 to 84 years | 47 |

| | |
|---|---|
| 85 years and over | 1 |

## Subject disposition

### Recruitment

Recruitment details:

Trial was conducted in Germany and Spain with total of 7 sites who recruited patients. Enrolment of patients started 23 June 2016.

### Pre-assignment

Screening details:

Of the 54 patients enrolled in this study, 52 patients were randomized. 2 patients enrolled were excluded before randomization due to screening failure (1 patient) and sponsor decision (1 patient).

### Period 1

| | |
|---|---|
| Period 1 title | clinical observation period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Investigator[1] |

Blinding implementation details:

To guarantee the blind status the first investigator performed the initial diagnosis and all assessments on visits following PDT, a second investigator or delegated person performed the PDT, including the application of the IMP, and conducted all safety evaluations and questionnaires at the PDT day. Both investigators (or investigator and delegated person) were bound to not exchange information.
The patients were strictly advised not to talk about the medication with the medical personnel.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | No |
| **Arm title** | BF-200 ALA |

Arm description:

BF-200 ALA containing 7.8% 5-aminolevulinic acid (5-ALA).
As this is an intra-individual study design BF-200 ALA (verum) and Metvix® (comparator) were compared in parallel intraindividually (1:1 ratio).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | BF-200 ALA |
| Investigational medicinal product code | |
| Other name | Ameluz® |
| Pharmaceutical forms | Gel |
| Routes of administration | Topical use |

Dosage and administration details:

This study was conducted using an intra-individual design, i.e. a split face design.
BF-200 ALA gel was administered to the selected target lesions of the assigned side of the face and scalp according to the randomization schedule. BF-200 ALA was to be applied to the selected target lesions covering the AK lesions and the surrounding 0.5-1.0 cm of normal skin with a thin film using gloveprotected fingertips or a spatula. Application near the eyes, nostrils, mouth, ears or mucosa was to be avoided (keep a distance of 1 cm).
No occlusive, light-tight dressing was applied as this is not necessary for daylight PDT. The gel should not be wiped off during the entire daylight PDT and remaining IMP was removed after completion of light exposure with a 0.9% saline solution.
For light exposure patients should go outside within 30 minutes after application of the study medicine and stay for 2 continuous hours in full daylight.

| | |
|---|---|
| **Arm title** | Metvix® |

Arm description:

Metvix® containing 16% methylaminolevulinate (MAL).
As this is an intra-individual study design BF-200 ALA (verum) and Metvix® (comparator) were compared in parallel intraindividually (1:1 ratio).

| | |
|---|---|
| Arm type | Active comparator |

| | |
|---|---|
| Investigational medicinal product name | Metvix® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Cream |
| Routes of administration | Topical use |

Dosage and administration details:

This study was conducted using an intra-individual design, i.e. a split face design.
Metvix® creme was administered to the selected target lesions of the assigned side of the face and scalp according to the randomization schedule. Metvix® creme was to be applied to the selected target lesions covering the AK lesions and the surrounding 0.5-1.0 cm of normal skin with a thin film using gloveprotected fingertips or a spatula. Application near the eyes, nostrils, mouth, ears or mucosa was to be avoided (keep a distance of 1 cm).
No occlusive, light-tight dressing was applied as this is not necessary for daylight PDT. The creme should not be wiped off during the entire daylight PDT and remaining IMP was removed after completion of light exposure with a 0.9% saline solution.
For light exposure patients should go outside within 30 minutes after application of the study medicine and stay for 2 continuous hours in full daylight.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: During this study, the investigator assessing efficacy after PDT was observer-blind. A second investigator or delegated person performed drug application and saftey evaluation. This was important since IMPs can be distinguished by their texture and consistency. IMPs have a comparable saftey profile.

| **Number of subjects in period 1** | BF-200 ALA | Metvix® |
|---|---|---|
| Started | 52 | 52 |
| Completed | 52 | 52 |

## Baseline characteristics

| Reporting groups[1] | |
|---|---|
| Reporting group title | clinical observation period |
| Reporting group description: - | |

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.
Justification: 54 patients were enrolled but only 52 patients were randomized. Due to non-randomized subjects, the number of enrolled subjects is not equal to the number of subjects in the clinical phase (subjects reported in the baseline period).

| Reporting group values | clinical observation period | Total | |
|---|---|---|---|
| Number of subjects | 52 | 52 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 6 | 6 | |
| From 65-84 years | 45 | 45 | |
| 85 years and over | 1 | 1 | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 72.2 | | |
| standard deviation | ± 7.2 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 2 | 2 | |
| Male | 50 | 50 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | BF-200 ALA |

Reporting group description:

BF-200 ALA containing 7.8% 5-aminolevulinic acid (5-ALA).
As this is an intra-individual study design BF-200 ALA (verum) and Metvix® (comparator) were compared in parallel intraindividually (1:1 ratio).

| | |
|---|---|
| Reporting group title | Metvix® |

Reporting group description:

Metvix® containing 16% methylaminolevulinate (MAL).
As this is an intra-individual study design BF-200 ALA (verum) and Metvix® (comparator) were compared in parallel intraindividually (1:1 ratio).

| | |
|---|---|
| Subject analysis set title | FAS - BF-200 ALA |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All patients randomized and treated at least with one assigned IMP (IMP application and illumination) after randomization. In accordance with the intent-to-treat (ITT) principle, the assignment of patients' sides to the treatment groups will be as randomized.

| | |
|---|---|
| Subject analysis set title | FAS - Metvix® |
| Subject analysis set type | Full analysis |

Subject analysis set description:

All patients randomized and treated at least with one assigned IMP (IMP application and illumination) after randomization. In accordance with the intent-to-treat (ITT) principle, the assignment of patients' sides to the treatment groups will be as randomized.

| | |
|---|---|
| Subject analysis set title | PPS - BF-200 ALA |
| Subject analysis set type | Per protocol |

Subject analysis set description:

All patients of the FAS without any major protocol deviations. Patients will be included in the PPS if they fulfil all of the following criteria:
• Treated with investigational products and PDT mode according to the randomization plan.
• All target lesions have grade 1 or 2 according to Olsen at baseline.
• The 2 patient's sides (R & L) are comparable and the number of AK lesions varies not more than 50%.
• At least one assessment of a patient's side after PDT is available.
• No forbidden concomitant medications or therapies.

| | |
|---|---|
| Subject analysis set title | PPS - Metvix® |
| Subject analysis set type | Per protocol |

Subject analysis set description:

All patients of the FAS without any major protocol deviations. Patients will be included in the PPS if they fulfil all of the following criteria:
• Treated with investigational products and PDT mode according to the randomization plan.
• All target lesions have grade 1 or 2 according to Olsen at baseline.
• The 2 patient's sides (R & L) are comparable and the number of AK lesions varies not more than 50%.
• At least one assessment of a patient's side after PDT is available.
• No forbidden concomitant medications or therapies.

| | |
|---|---|
| Subject analysis set title | BF-200 ALA - Treatment area Face |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with lesions in the treatment area Face only.

| | |
|---|---|
| Subject analysis set title | Metvix® - Treatment area Face |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with lesions in the treatment area Face only.

| | |
|---|---|
| Subject analysis set title | BF-200 ALA - Treatment area Scalp |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with lesions in the treatment area Scalp only.

| | |
|---|---|
| Subject analysis set title | Metvix® - Treatment area Scalp |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with lesions in the treatment area Scalp only.

| | |
|---|---|
| Subject analysis set title | BF-200 ALA - Mild AK lesion |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with maximum severity grade "mild" of AK lesions at baseline.

| | |
|---|---|
| Subject analysis set title | Metvix® - Mild AK lesion |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with maximum severity grade "mild" of AK lesions at baseline.

| | |
|---|---|
| Subject analysis set title | BF-200 ALA - Moderate AK lesion |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with maximum severity grade "moderate" of AK lesions at baseline.

| | |
|---|---|
| Subject analysis set title | Metvix® - Moderate AK lesion |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with maximum severity grade "moderate" of AK lesions at baseline.

| | |
|---|---|
| Subject analysis set title | BF-200 ALA - min temperature ≤20°C |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with  a minimum temperature during PDT ≤20°C.

| | |
|---|---|
| Subject analysis set title | Metvix® - min temperature ≤20°C |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with  a minimum temperature during PDT ≤20°C.

| | |
|---|---|
| Subject analysis set title | BF-200 ALA - min temperature >20°C |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with a minimum temperature during PDT >20°C.

| | |
|---|---|
| Subject analysis set title | Metvix® - min temperature >20°C |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with a minimum temperature during PDT >20°C

| | |
|---|---|
| Subject analysis set title | BF-200 ALA - Cloudy |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with the worst weather condition „cloudy“ during PDT.

| | |
|---|---|
| Subject analysis set title | Metvix® - Cloudy |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with the worst weather condition „cloudy“ during PDT.

| | |
|---|---|
| Subject analysis set title | BF-200 ALA - Sunny/cloudy mixed |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with the worst weather condition „sunny/cloudy mixed“ during PDT.

| | |
|---|---|
| Subject analysis set title | Metvix® - Sunny/cloudy mixed |
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with the worst weather condition „sunny/cloudy mixed“ during PDT.

| Subject analysis set title | BF-200 ALA - Sunny |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with the worst weather condition „sunny“ during PDT.

| Subject analysis set title | Metvix® - Sunny |
|---|---|
| Subject analysis set type | Full analysis |

Subject analysis set description:

Patients with the worst weather condition „sunny“ during PDT.

## Primary: Total lesion clearance rate in percent per patient’s side 12 weeks after PDT

| End point title | Total lesion clearance rate in percent per patient’s side 12 weeks after PDT |
|---|---|

End point description:

Total lesion clearance rate in percent per patient’s side is defined as the percentage of completely cleared individual lesions with complete remission on the respective side of the patient assessed 12 weeks after PDT (LOCF (last observation carried forward) post-PDT).

| End point type | Primary |
|---|---|

End point timeframe:

12 weeks after PDT

| End point values | FAS - BF-200 ALA | FAS - Metvix® | PPS - BF-200 ALA | PPS - Metvix® |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 51 | 51 | 49 | 49 |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 78.7 (± 25.8) | 75 (± 28.1) | 79.8 (± 23.6) | 76.5 (± 26.5) |

| End point values | BF-200 ALA - Treatment area Face | Metvix® - Treatment area Face | BF-200 ALA - Treatment area Scalp | Metvix® - Treatment area Scalp |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 20 | 20 | 27 | 27 |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 85.2 (± 22.7) | 84.2 (± 19.8) | 72.4 (± 28.4) | 65.4 (± 31.8) |

| End point values | BF-200 ALA - Mild AK lesion | Metvix® - Mild AK lesion | BF-200 ALA - Moderate AK lesion | Metvix® - Moderate AK lesion |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 7 | 7 | 44 | 44 |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 93.7 (± 16.8) | 91.2 (± 12.7) | 76.3 (± 26.3) | 72.5 (± 29.1) |

| End point values | BF-200 ALA - min temperature ≤20°C | Metvix® - min temperature ≤20°C | BF-200 ALA - min temperature >20°C | Metvix® - min temperature >20°C |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 27 | 27 | 24 | 24 |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 77.9 (± 29.3) | 75.4 (± 30.6) | 79.5 (± 21.8) | 74.6 (± 25.6) |

| End point values | BF-200 ALA - Cloudy | Metvix® - Cloudy | BF-200 ALA - Sunny/cloudy mixed | Metvix® - Sunny/cloudy mixed |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 15 | 15 | 15 | 15 |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 74.8 (± 28.6) | 65.7 (± 36.5) | 74.4 (± 32.1) | 73.7 (± 27.1) |

| End point values | BF-200 ALA - Sunny | Metvix® - Sunny | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 21 | 21 | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 84.5 (± 17.7) | 82.6 (± 19.9) | | |

## Statistical analyses

| Statistical analysis title | One-sided non-parametric CI (PPS) |
|---|---|

Statistical analysis description:

The primary analysis on non-inferiority was performed on PPS. The analysis using FAS was used to test robustness of data.
Evaluation of non-inferiority was primarily based on the non-parametric CIs; the one-sided Wilcoxon signed rank test is subordinate. This course of action was prespecified in case of non-normal distributed data.

| | |
|---|---|
| Comparison groups | PPS - BF-200 ALA v PPS - Metvix® |
| Number of subjects included in analysis | 98 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[1] |
| Parameter estimate | Median of differences |
| Point estimate | 0 |

| | |
|---|---|
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 1-sided |
| lower limit | 0 |

Notes:

[1] - Non-inferiority margin of Δ=-12.5% with a true inferiority of 0%

| **Statistical analysis title** | One-sided non-parametric CI (FAS) |
|---|---|

Statistical analysis description:

The primary analysis on non-inferiority was performed on PPS. The analysis using FAS was used to test robustness of data.
Evaluation of non-inferiority was primarily based on the non-parametric CIs; the one-sided Wilcoxon signed rank test is subordinate. This course of action was prespecified in case of non-normal distributed data.

| | |
|---|---|
| Comparison groups | FAS - BF-200 ALA v FAS - Metvix® |
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[2] |
| Parameter estimate | Median of differences |
| Point estimate | 0 |
| Confidence interval | |
| level | Other: 97.5 % |
| sides | 1-sided |
| lower limit | 0 |

Notes:

[2] - Non-inferiority margin of Δ=-12.5% with a true inferiority of 0%

| **Statistical analysis title** | One-sided Wilcoxon signed rank test (PPS) |
|---|---|

Statistical analysis description:

The primary analysis on non-inferiority was performed on PPS. The analysis using FAS was used to test robustness of data.
Evaluation of non-inferiority was primarily based on the non-parametric CIs; the one-sided Wilcoxon signed rank test is subordinate. This course of action was prespecified in case of non-normal distributed data.

| | |
|---|---|
| Comparison groups | PPS - BF-200 ALA v PPS - Metvix® |
| Number of subjects included in analysis | 98 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[3] |
| P-value | < 0.0001 |
| Method | Wilcoxon signed rank test |

Notes:

[3] - Non-inferiority margin of Δ=-12.5% with a true inferiority of 0%

| **Statistical analysis title** | One-sided Wilcoxon signed rank test (FAS) |
|---|---|

Statistical analysis description:

The primary analysis on non-inferiority was performed on PPS. The analysis using FAS was used to test robustness of data.
Evaluation of non-inferiority was primarily based on the non-parametric CIs; the one-sided Wilcoxon signed rank test is subordinate. This course of action was prespecified in case of non-normal distributed data.

| | |
|---|---|
| Comparison groups | FAS - BF-200 ALA v FAS - Metvix® |

| | |
|---|---|
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[4] |
| P-value | < 0.0001 |
| Method | Wilcoxon signed rank test |

Notes:

[4] - Non-inferiority margin of Δ=-12.5% with a true inferiority of 0%

## Secondary: Patient complete clearance per patient's side

| | |
|---|---|
| End point title | Patient complete clearance per patient's side |

End point description:

Patient complete clearance per patient's side, i.e. all lesions cleared at the respective patient's side 12 weeks after PDT (LOCF (last observation carried forward) post PDT).

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

12 weeks after PDT

| End point values | FAS - BF-200 ALA | FAS - Metvix® | BF-200 ALA - Treatment area Face | Metvix® - Treatment area Face |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 51 | 51 | 20 | 20 |
| Units: patients | 22 | 19 | 12 | 10 |

| End point values | BF-200 ALA - Treatment area Scalp | Metvix® - Treatment area Scalp | BF-200 ALA - Mild AK lesion | Metvix® - Mild AK lesion |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 27 | 27 | 7 | 7 |
| Units: patients | 9 | 7 | 6 | 4 |

| End point values | BF-200 ALA - Moderate AK lesion | Metvix® - Moderate AK lesion | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 44 | 44 | | |
| Units: patients | 16 | 15 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Reduction of total lesion area from baseline 12 weeks after PDT

| End point title | Reduction of total lesion area from baseline 12 weeks after PDT |
|---|---|

End point description:

Reduction of total lesion area (the size of all treated lesions added up) from baseline per patient 12 weeks after PDT (LOCF (last observation carried forward) post PDT) per patient's side.
Reduction of total lesion area is calculated as (post baseline lesion area - baseline lesion area) / baseline lesion area *100.

| End point type | Secondary |
|---|---|

End point timeframe:

12 weeks after PDT

| End point values | FAS - BF-200 ALA | FAS - Metvix® | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 51 | 51 | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | -89.3 (± 15.4) | -88.3 (± 19.3) | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Patient histologically confirmed response rate per patient's side 12 weeks after PDT according to Cockerell

| End point title | Patient histologically confirmed response rate per patient's side 12 weeks after PDT according to Cockerell |
|---|---|

End point description:

Patient histologically confirmed response rate per patient's side 12 weeks after PDT (LOCF (last observation carried forward) post PDT).
A patients' lesion was "not cleared", if the histopathological evaluation of the biopsy after Cockerell (KIN I, II,III; Cockerell, C.J. (2000) J Am.Acad.Dermatol, 42, 11-17.) was positive, and "cleared", if the biopsy was negative ("Histopathologically cleared"), irrespective of the investigator's clinical assessment. "Other" outcomes were reviewed during a data review meeting and assigned to "cleared" or "not cleared" accordingly. A missing biopsy resulted in a missing HC response.
Analysis according to Röwert-Huber (Rowert-Huber, J., Patel, M.J., Forschner, T., Ulrich, C., Eberle, J., Kerl, H., Sterry, W. & Stockfleth, E. (2007) Br J Dermatol, 156 Suppl 3, 8-12) showed identical results.

| End point type | Secondary |
|---|---|

End point timeframe:

12 weeks after PDT

| End point values | FAS - BF-200 ALA | FAS - Metvix® | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 51 | 51 | | |
| Units: Patients | 37 | 34 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: p53 expression per patient's side in one biopsiy taken 12 weeks after PDT

| End point title | p53 expression per patient's side in one biopsiy taken 12 weeks after PDT |
|---|---|

End point description:

p53 expression (% p53-positive cells) per patient's side in one biopsy on each side taken at the end-of-observerblind period.
An immunostaining was performed in order to evaluate and quantify p53 expression in biopsies of preselected lesions. Biopsies were taken 12 weeks after PDT. A missing biopsy resulted in a missing p53 result. The p53 reactivity was quantified by counting the percentage of positive nuclei from the region of highest reactivity and expressed as the average of the counted areas (p53 positive cells /all counted nuclei). A p53 score <10% was considered 'normal' or a 'complete response'.

| End point type | Secondary |
|---|---|

End point timeframe:

12 weeks after PDT

| End point values | FAS - BF-200 ALA | FAS - Metvix® | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 50 | 50 | | |
| Units: percent | | | | |
| arithmetic mean (standard deviation) | 34.3 (± 32.4) | 40.6 (± 31.3) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Overall cosmetic outcome 12 weeks after PDT per patient's side (with sum score >0 at baseline)

| End point title | Overall cosmetic outcome 12 weeks after PDT per patient's side (with sum score >0 at baseline) |
|---|---|

End point description:

Overall cosmetic outcome 12 weeks after PDT (LOCF (last observarion carried forward)) per patient's side (with sum score >0 at baseline).
The cosmetic outcome is calculated for each patient's side on the basis of the skin quality assessment and is calculated as follows: Very good: The sum of all ratings for each skin quality sign has improved by at least 2 points as compared to baseline. If at least one sign has worsened by one point, the sum score must have improved by at least 3 points; Good: Sum score has improved by at least 1 point; Satisfactory: Sum score is identical to the one at baseline; Unsatisfactory: Sum score has worsened by 1 point; Impaired: Sum score has worsened by at least 2 points.
LOCF is used to impute missing Week 12 data. If skin quality assessment is not assessed at Week 12

missing value will be imputed with the respective baseline value.

| End point type | Secondary |
|---|---|

End point timeframe:

12 weeks after PDT

| End point values | FAS - BF-200 ALA | FAS - Metvix® | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 34[5] | 34[6] | | |
| Units: percent | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Very good | 23.5 (9.27 to 37.79) | 23.5 (9.27 to 37.79) | | |
| Good | 17.6 (4.83 to 30.46) | 14.7 (2.8 to 26.61) | | |
| Satisfactory | 44.1 (27.43 to 60.81) | 44.1 (27.43 to 60.81) | | |

Notes:

[5] - please note that categories unsatisfactory and impaired are not reported due to patient number <5

[6] - please note that categories unsatisfactory and impaired are not reported due to patient number <5

### Statistical analyses

No statistical analyses for this end point

## Secondary: Patient's satisfaction on cosmetic outcome

| End point title | Patient's satisfaction on cosmetic outcome |
|---|---|

End point description:

Patient's satisfaction regarding overall cosmetic outcome 12 weeks after PDT.

| End point type | Secondary |
|---|---|

End point timeframe:

12 weeks after PDT

| End point values | FAS - BF-200 ALA | FAS - Metvix® | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 51 | 51 | | |
| Units: percent | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Very good | 23.5 (11.89 to 35.17) | 21.6 (10.28 to 32.86) | | |
| Good | 51 (37.26 to 64.7) | 45.1 (31.44 to 58.75) | | |
| Satisfactory | 15.7 (5.71 to 25.67) | 23.5 (11.89 to 35.17) | | |
| Unsatisfactory | 9.8 (1.64 to 17.97) | 9.8 (1.64 to 17.97) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Patient satisfaction regarding PDT treatment 12 weeks after PDT

| End point title | Patient satisfaction regarding PDT treatment 12 weeks after PDT |
|---|---|

End point description:

Patient satisfaction regarding PDT treatment at Week 12 (LOCF (last obsercation carried forward) post PDT).

| End point type | Secondary |
|---|---|

End point timeframe:

12 weeks after PDT

| End point values | FAS - BF-200 ALA | FAS - Metvix® | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 51 | 51 | | |
| Units: percent | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Patient would choose treatment again | 94.1 (87.66 to 100) | 96.1 (90.75 to 100) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Total lesion clearance rate per IMP 12 weeks after PDT

| End point title | Total lesion clearance rate per IMP 12 weeks after PDT |
|---|---|

End point description:

Total lesion clearance rate per IMP 12 weeks after PDT (LOCF (last observation carried forward)), expressed as number of completely cleared individual lesions.

| End point type | Secondary |
|---|---|

End point timeframe:

12 weeks after PDT

| End point values | FAS - BF-200 ALA | FAS - Metvix® | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 51[7] | 51[8] | | |
| Units: lesions | 256 | 246 | | |

Notes:

[7] - 51 patients with 330 lesions included in the study

[8] - 51 patients with 327 lesions included in the study

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of completely cleared individual lesions per patient's side 12 weeks after PDT

| End point title | Number of completely cleared individual lesions per patient's side 12 weeks after PDT |
|---|---|

End point description:

Number of completely cleared individual lesions per patient’s side 12 weeks after PDT (LOCF (last observation carried forward) post-PDT) compared to baseline.

| End point type | Secondary |
|---|---|

End point timeframe:

12 weeks after PDT

| End point values | FAS - BF-200 ALA | FAS - Metvix® | BF-200 ALA - Treatment area Face | Metvix® - Treatment area Face |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 51[9] | 51[10] | 20[11] | 20[12] |
| Units: lesions | | | | |
| arithmetic mean (standard deviation) | 5 (± 2.3) | 4.8 (± 2.5) | 5.4 (± 2.2) | 5.2 (± 2) |

Notes:

[9] - baseline values: 6.5 ± 2.2

[10] - baseline values: 6.4 ± 2.2

[11] - baseline values: 6.5 ± 2.3

[12] - baseline values: 6.4 ± 2.2

| End point values | BF-200 ALA - Treatment area Scalp | Metvix® - Treatment area Scalp | BF-200 ALA - Mild AK lesion | Metvix® - Mild AK lesion |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 27[13] | 27[14] | 38[15] | 39[16] |
| Units: lesions | | | | |
| arithmetic mean (standard deviation) | 4.4 (± 2.2) | 4.1 (± 2.6) | 3.7 (± 2) | 3.5 (± 2.3) |

Notes:

[13] - baseline values: 6.1 ± 2.2

[14] - baseline values: 6.1 ± 2.2

[15] - baseline values: 4.2 ± 2.1

[16] - baseline values: 4.2 ± 2.2

| End point values | BF-200 ALA - Moderate AK | Metvix® - Moderate AK | | |
|---|---|---|---|---|

| | lesion | lesion | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 43[17] | 43[18] | | |
| Units: lesions | | | | |
| arithmetic mean (standard deviation) | 2.7 (± 1.5) | 2.5 (± 1.5) | | |

Notes:

[17] - baseline values: 4.0 ± 2.1

[18] - baseline values: 3.8 ± 2.1

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

23 June 2016 (study initiation date) until 07 December 2016 (study completion date for observer blind part)

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | related to side treated with BF-200 ALA |
| Reporting group description: - | |
| Reporting group title | related to side treated with Metvix ® |
| Reporting group description: - | |
| Reporting group title | relation to side not applicable |

Reporting group description: -

| Serious adverse events | related to side treated with BF-200 ALA | related to side treated with Metvix ® | relation to side not applicable |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 52 (0.00%) | 0 / 52 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | related to side treated with BF-200 ALA | related to side treated with Metvix ® | relation to side not applicable |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 52 / 52 (100.00%) | 49 / 52 (94.23%) | 12 / 52 (23.08%) |
| General disorders and administration site conditions | | | |
| Application site discharge | | | |
| subjects affected / exposed | 10 / 52 (19.23%) | 6 / 52 (11.54%) | 0 / 52 (0.00%) |
| occurrences (all) | 10 | 6 | 0 |
| Application site erosion | | | |
| subjects affected / exposed | 3 / 52 (5.77%) | 1 / 52 (1.92%) | 0 / 52 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Application site erythema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 38 / 52 (73.08%) | 40 / 52 (76.92%) | 0 / 52 (0.00%) |
| occurrences (all) | 45 | 46 | 0 |
| Application site exfoliation | | | |
| subjects affected / exposed | 9 / 52 (17.31%) | 7 / 52 (13.46%) | 0 / 52 (0.00%) |
| occurrences (all) | 11 | 8 | 0 |
| Application site induration | | | |
| subjects affected / exposed | 8 / 52 (15.38%) | 6 / 52 (11.54%) | 0 / 52 (0.00%) |
| occurrences (all) | 8 | 6 | 0 |
| Application site oedema | | | |
| subjects affected / exposed | 7 / 52 (13.46%) | 6 / 52 (11.54%) | 0 / 52 (0.00%) |
| occurrences (all) | 7 | 6 | 0 |
| Application site pain | | | |
| subjects affected / exposed | 38 / 52 (73.08%) | 34 / 52 (65.38%) | 0 / 52 (0.00%) |
| occurrences (all) | 61 | 54 | 0 |
| Application site paraesthesia | | | |
| subjects affected / exposed | 6 / 52 (11.54%) | 4 / 52 (7.69%) | 0 / 52 (0.00%) |
| occurrences (all) | 6 | 5 | 0 |
| Application site pruritus | | | |
| subjects affected / exposed | 26 / 52 (50.00%) | 27 / 52 (51.92%) | 0 / 52 (0.00%) |
| occurrences (all) | 33 | 32 | 0 |
| Application site scab | | | |
| subjects affected / exposed | 19 / 52 (36.54%) | 17 / 52 (32.69%) | 0 / 52 (0.00%) |
| occurrences (all) | 22 | 19 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Actinic keratosis | | | |
| subjects affected / exposed | 4 / 52 (7.69%) | 3 / 52 (5.77%) | 1 / 52 (1.92%) |
| occurrences (all) | 5 | 5 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 0 / 52 (0.00%) | 3 / 52 (5.77%) |
| occurrences (all) | 0 | 0 | 3 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported