



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	Safety, Efficacy
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 safety evaluation. This was important since IMPs can be distinguished by their texture and consistency. IMPs have a comparable safety 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			
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			
Units: years			
arithmetic mean	72.2		
standard deviation	± 7.2	-	
Gender categorical			
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: <ul style="list-style-type: none">• 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: <ul style="list-style-type: none">• 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 $\leq 20^{\circ}\text{C}$
Subject analysis set type	Full analysis

Subject analysis set description:

Patients with a minimum temperature during PDT $\leq 20^{\circ}\text{C}$.

Subject analysis set title	Metvix® - min temperature $\leq 20^{\circ}\text{C}$
Subject analysis set type	Full analysis

Subject analysis set description:

Patients with a minimum temperature during PDT $\leq 20^{\circ}\text{C}$.

Subject analysis set title	BF-200 ALA - min temperature $> 20^{\circ}\text{C}$
Subject analysis set type	Full analysis

Subject analysis set description:

Patients with a minimum temperature during PDT $> 20^{\circ}\text{C}$.

Subject analysis set title	Metvix® - min temperature $> 20^{\circ}\text{C}$
Subject analysis set type	Full analysis

Subject analysis set description:

Patients with a minimum temperature during PDT $> 20^{\circ}\text{C}$

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 $\leq 20^{\circ}\text{C}$	Metvix® - min temperature $\leq 20^{\circ}\text{C}$	BF-200 ALA - min temperature $> 20^{\circ}\text{C}$	Metvix® - min temperature $> 20^{\circ}\text{C}$
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 (\pm 29.3)	75.4 (\pm 30.6)	79.5 (\pm 21.8)	74.6 (\pm 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 (\pm 28.6)	65.7 (\pm 36.5)	74.4 (\pm 32.1)	73.7 (\pm 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 (\pm 17.7)	82.6 (\pm 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 $\Delta = -12.5\%$ 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 $\Delta = -12.5\%$ 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 $\Delta = -12.5\%$ 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 $\Delta = -12.5\%$ 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., Forscher, 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 biopsy taken 12 weeks after PDT

End point title	p53 expression per patient's side in one biopsy 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 observation 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 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®		
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 (\pm 1.5)	2.5 (\pm 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