Clinical trial results:
A randomized, double-blind, intra-individual, multi-center Phase III study to evaluate the safety and efficacy of BF 200 ALA (Ameluz®) versus placebo in the treatment of mild to severe actinic keratosis on extremities, trunk/ neck with photodynamic therapy (PDT) when using the BF-RhodoLED® lamp

Summary

EudraCT number	2017-000486-72
Trial protocol	DE
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	03 July 2019
First version publication date	03 July 2019

Trial information

Trial identification

Sponsor protocol code	ALA-AK-CT010

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 Management, Biofrontera Bioscience GmbH, +49 2148763210, clintrialCT010@biofrontera.com
Scientific contact	Clinical Trial Management, Biofrontera Bioscience GmbH, +49 2148763210, clintrialCT010@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	Interim
Date of interim/final analysis	09 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 January 2019
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective: To compare the efficacy of BF-200 ALA (also referred to as Ameluz®) with placebo for treatment of mild to severe actinic keratosis (AK) located on extremities and trunk/neck with PDT when using the BF RhodoLED® lamp.

Secondary objective: To evaluate the safety and secondary efficacy parameters related to BF 200 ALA for treatment of AK on extremities and trunk/neck with PDT when using the BF-RhodoLED® lamp.

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	18 September 2017
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	Germany: 56
Worldwide total number of subjects	56
EEA total number of subjects	56

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)	10
From 65 to 84 years	45

85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Trial was conducted in Germany with a total of 6 sites that recruited subjects. Recruitment of subjects started on 18 September 2017.

Pre-assignment

Screening details:

Subjects were screened at Visit 1 for eligibility which was approx. 2 weeks prior to assignment to treatment (PDT-1).
Of the 56 subjects screened in the study, 50 subjects were randomized, and 48 subjects completed the study regularly.

Pre-assignment period milestones

Number of subjects started	56
Number of subjects completed	50

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal prior to treatment: 1
Reason: Number of subjects	Consent withdrawn by subject prior to treatment: 1
Reason: Number of subjects	Screening failure: 4

Period 1

Period 1 title	Clinical observation period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Although verum and placebo are indistinguishable by appearance, the intensity of adverse events (AEs) is likely to differ. To guarantee the blind status of the investigator assessing the efficacy of the treatment in this intra-individual study, PDT and all safety assessments were to be performed by a second investigator. Patients were to be instructed to report AEs during the illumination(s) and the coming days only to the second investigator.

Arms

Are arms mutually exclusive?	No
Arm title	BF-200 ALA (Verum)

Arm description:

A nanoemulsion containing 7.8% 5-aminolevulinic acid (5-ALA)

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

Dosage and administration details:

• BF-200 ALA gel (2g) was administered (about 1 mm thickness) according to randomization schedule, covering lesions and surroundings
• Treatment field on one side did not have to be continuous, but had to cover a total area of approx. 20 cm² and had to be within the 6x16 cm² illumination field to allow illumination in a single step

• Treatment field on each patient’s side could be located on all parts of extremities or trunk/neck, but treatment fields on both sides had to be located in comparable locations (treatment subareas)
• Treatment subareas included back of the hands, lower arms, upper arms, lower legs, upper legs, décolleté, neck or other comparable parts of the trunk
• Application near genitalia was to be avoided
• IMP dried for approx. 10 min
• Lesions were occluded with a light-tight dressing
• Subjects had to stay in a well-tempered environment during 3h incubation
• Dressing was removed; remnant gel wiped off
• Illumination with BF-RhodoLED®(10 min; 37 J/cm²)

Arm title	Placebo

Arm description:

A nanoemulsion formulation similar to BF-200 ALA but without the active ingredient ALA.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	Vehicle
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

• Placebo gel (2g) was administered (about 1 mm thickness) according to randomization schedule, covering lesions and surroundings
• Treatment field on one side did not have to be continuous, but had to cover a total area of approx. 20 cm² and had to be within the 6x16 cm² illumination field to allow illumination in a single step
• Treatment field on each patient’s side could be located on all parts of extremities or trunk/neck, but treatment fields on both sides had to be located in comparable locations (treatment subareas)
• Treatment subareas included back of the hands, lower arms, upper arms, lower legs, upper legs, décolleté, neck or other comparable parts of the trunk
• Application near genitalia was to be avoided
• IMP dried for approx. 10 min
• Lesions were occluded with a light-tight dressing
• Subjects had to stay in a well-tempered environment during 3h incubation
• Dressing was removed; remnant gel wiped off
• Illumination with BF-RhodoLED®(10 min; 37 J/cm²)

Number of subjects in period 1	BF-200 ALA (Verum)	Placebo
Started	50	50
Completed	48	48
Not completed	2	2
Consent withdrawn by subject	2	2

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: 56 patients were screened, but only 50 patients were randomized. Due to non-randomized subjects, the number of enrolled subjects is not equal to the number of subjects in the clinical observation period (subjects reported in baseline period).

Reporting group values	Clinical observation period	Total	
Number of subjects	50	50	
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)	10	10	
From 65-84 years	40	40	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	70.8		
standard deviation	± 8.3	-	
Gender categorical Units: Subjects			
Female	26	26	
Male	24	24	
Fitzpatrick skin type Units: Subjects			
Type I to III	48	48	
Type IV to VI	2	2	

End points

End points reporting groups

Reporting group title	BF-200 ALA (Verum)
Reporting group description:	
A nanoemulsion containing 7.8% 5-aminolevulinic acid (5-ALA)	
Reporting group title	Placebo
Reporting group description:	
A nanoemulsion formulation similar to BF-200 ALA but without the active ingredient ALA.	

Primary: Total lesion clearance rate in percent per patient’s side 12 weeks after last PDT (FAS)

End point title	Total lesion clearance rate in percent per patient’s side 12 weeks after last PDT (FAS)
End point description:	
Total lesion clearance rate in percent per patient’s side, defined as the percentage of individual lesions with complete remission on the respective side of the patient assessed 12 weeks after the last PDT. The full analysis set (FAS) consists of 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.	
End point type	Primary
End point timeframe:	
12 weeks after last PDT	

End point values	BF-200 ALA (Verum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: percent				
arithmetic mean (standard deviation)	86.0 (± 23.2)	32.9 (± 37.1)		

Statistical analyses

Statistical analysis title	One-sided Wilcoxon signed rank test (FAS)
Statistical analysis description:	
The Wilcoxon signed rank test (one-sided, alpha=0.025) was applied (using the location parameter mu0 of 0%). Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.	
Comparison groups	BF-200 ALA (Verum) v Placebo

Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	One-sided Wilcoxon signed rank test

Statistical analysis title	Non-parametric, one-sided 97.5% CI (FAS)

Statistical analysis description:

Additionally, a non-parametric, one-sided 97.5% confidence interval (CI) for the median difference in response rates rALA - rPla was calculated. If the lower bound of this CI is greater than 0, it indicates superiority of BF-200 ALA PDT to placebo PDT. The application of the non-parametric CI was subordinate.

Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.

Comparison groups	BF-200 ALA (Verum) v Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	60
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	33.3

Secondary: Patient complete clearance per patient’s side 12 weeks after the last PDT (FAS)

End point title	Patient complete clearance per patient’s side 12 weeks after the last PDT (FAS)

End point description:

Confirmatory hypothesis testing of secondary variables measured during the clinical study period was to be done only after the test of the primary efficacy variable was passed (superiority of BF-200 ALA PDT over placebo PDT confirmed for FAS), and was to be done strictly in the given order to ensure the family wise error rate. Confirmatory hypothesis testing in the pre-defined order would have stopped once the first non-significant test result had been obtained.

The first secondary efficacy variable in the hierarchic test procedure was the patient complete clearance per patient’s side, defined as the percentage of patients with all lesions cleared at the respective patient’s side.

The full analysis set (FAS) consists of 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 was as randomized.

End point type	Secondary

End point timeframe:

12 weeks after the last PDT

End point values	BF-200 ALA (Verum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: patients				
number (not applicable)	33	6		

Statistical analyses

Statistical analysis title	McNemar’s test (FAS)
Statistical analysis description:	
Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.	
Comparison groups	BF-200 ALA (Verum) v Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mcnemar

Secondary: Total lesion clearance rate of moderate (according to Olsen) lesions in percent per patient’s side 12 weeks after the last PDT (FAS)

End point title	Total lesion clearance rate of moderate (according to Olsen) lesions in percent per patient’s side 12 weeks after the last PDT (FAS)

End point description:

The second secondary efficacy variable in the hierarchic test procedure was the total lesion clearance rate of moderate lesions in percent per patient’s side, defined as the percentage of moderate lesions at baseline with complete remission on the respective side of the patient 12 weeks after the last PDT.

The full analysis set (FAS) consists of 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 was as randomized.

End point type	Secondary

End point timeframe:

12 weeks after the last PDT

End point values	BF-200 ALA (Verum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	44	43		
Units: percent				
arithmetic mean (standard deviation)	84.3 (± 28.6)	27.2 (± 36.5)		

Statistical analyses

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

Statistical analysis description:

Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.

Comparison groups	BF-200 ALA (Verum) v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	One-sided Wilcoxon signed rank test

Statistical analysis title	Non-parametric, one-sided 97.5% CI (FAS)

Statistical analysis description:

The application of the non-parametric CI was subordinate.

Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.

Comparison groups	BF-200 ALA (Verum) v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	75
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	33.3

Secondary: Total lesion clearance rate in percent per patient’s side in the treatment area extremities 12 weeks after the last PDT (FAS)

End point title	Total lesion clearance rate in percent per patient’s side in the treatment area extremities 12 weeks after the last PDT (FAS)

End point description:

The third secondary efficacy variable in the hierarchic test procedure was the total lesion clearance rate in percent per patient’s side in the treatment area extremities, defined as the percentage of individual lesions in the treatment area extremities with complete remission on the respective side of the patient.

The full analysis set (FAS) consists of 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 was as randomized.

End point type	Secondary

End point timeframe:

12 weeks after the last PDT

End point values	BF-200 ALA (Verum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: percent				
arithmetic mean (standard deviation)	83.5 (± 24.7)	27.1 (± 33.1)		

Statistical analyses

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

Statistical analysis description:

Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.

Comparison groups	BF-200 ALA (Verum) v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	One-sided Wilcoxon signed rank test

Statistical analysis title	Non-parametric, one-sided 97.5% CI (FAS)

Statistical analysis description:

The application of the non-parametric CI was subordinate.

Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.

Comparison groups	Placebo v BF-200 ALA (Verum)
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	66.7
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	35

Secondary: Total lesion clearance rate in percent per patient’s side in the treatment area trunk/neck 12 weeks after the last PDT (FAS)

End point title	Total lesion clearance rate in percent per patient’s side in the treatment area trunk/neck 12 weeks after the last PDT (FAS)

End point description:

The fourth secondary efficacy variable in the hierarchic test procedure was the total lesion clearance rate in percent per patient’s side in the treatment area trunk/neck, defined as the percentage of individual lesions in the treatment area trunk/neck with complete remission on the respective side of the patient.

The full analysis set (FAS) consists of 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 was as randomized.

End point type	Secondary

End point timeframe:

12 weeks after the last PDT

End point values	BF-200 ALA (Verum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: percent				
arithmetic mean (standard deviation)	96.0 (± 12.6)	55.5 (± 44.8)		

Statistical analyses

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

Statistical analysis description:

Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.

Comparison groups	Placebo v BF-200 ALA (Verum)
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0156
Method	One-sided Wilcoxon signed rank test

Statistical analysis title	Non-parametric, one-sided 97.5% CI (FAS)

Statistical analysis description:

The application of the non-parametric CI was subordinate.

Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.

Comparison groups	BF-200 ALA (Verum) v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	18.3
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0

Secondary: Histopathologically confirmed lesion response (HCR) rate 12 weeks after the last PDT per patient's side (FAS)

End point title	Histopathologically confirmed lesion response (HCR) rate 12 weeks after the last PDT per patient's side (FAS)

End point description:

The fifth secondary efficacy variable in the hierarchic test procedure was the histopathologically confirmed lesion response (HCR) rate per patient's side 12 weeks after the last PDT.

The full analysis set (FAS) consists of 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 was as randomized.

End point type	Secondary

End point timeframe:

12 weeks after the last PDT

End point values	BF-200 ALA (Verum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: patients				
number (not applicable)	40	30		

Statistical analyses

Statistical analysis title	McNemar's test (FAS)

Statistical analysis description:

Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.

Comparison groups	BF-200 ALA (Verum) v Placebo
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0032
Method	Mcnemar

Secondary: Total lesion clearance rate in percent per patient's side 12 weeks after PDT-1 (FAS)

End point title	Total lesion clearance rate in percent per patient's side 12 weeks after PDT-1 (FAS)

End point description:

The sixth secondary efficacy variable in the hierarchic test procedure was the total lesion clearance rate in percent per patient's side, defined as the percentage of individual lesions with complete remission on the respective side of the patient at Visit 4 (12 weeks after PDT-1), irrespective if patient received re-treatment or not.

The full analysis set (FAS) consists of 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 was as randomized.

End point type	Secondary

End point timeframe:

12 weeks after PDT-1

End point values	BF-200 ALA (Verum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: percent				
arithmetic mean (standard deviation)	67.5 (± 31.2)	27.6 (± 33.4)		

Statistical analyses

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

Statistical analysis description:

Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.

Comparison groups	Placebo v BF-200 ALA (Verum)
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	One-sided Wilcoxon signed rank test

Statistical analysis title	Non-parametric, one-sided 97.5% CI (FAS)

Statistical analysis description:

The application of the non-parametric CI was subordinate.

Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.

Comparison groups	BF-200 ALA (Verum) v Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	50
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	25

Secondary: Patient complete clearance per patient’s side, 12 weeks after PDT-1 (FAS)

End point title	Patient complete clearance per patient’s side, 12 weeks after PDT-1 (FAS)

End point description:

The seventh secondary efficacy variable in the hierarchic test procedure was the patient complete clearance per patient’s side, defined as the percentage of patients with all lesions cleared at the

respective patient’s side at Visit 4 (12 weeks after PDT-1), irrespective if patient received re-treatment or not.

The full analysis set (FAS) consists of 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 was as randomized.

End point type	Secondary

End point timeframe:

12 weeks after PDT-1

End point values	BF-200 ALA (Verum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: patients				
number (not applicable)	18	4		

Statistical analyses

Statistical analysis title	McNemar’s test (FAS)

Statistical analysis description:

Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.

Comparison groups	BF-200 ALA (Verum) v Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	Mcnemar

Secondary: The overall cosmetic outcome per patient’s side 12 weeks after the last PDT (FAS)

End point title	The overall cosmetic outcome per patient’s side 12 weeks after the last PDT (FAS)

End point description:

The eighth secondary efficacy variable in the hierarchic test procedure was the overall cosmetic outcome per patient's side 12 weeks after the last PDT as assessed by the investigator.

The full analysis set (FAS) consists of 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 was as randomized.

End point type	Secondary

End point timeframe:

12 weeks after the last PDT

End point values	BF-200 ALA (Verum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	49		
Units: patients				
number (not applicable)				
Very good	19	7		
Good	9	3		
Satisfactory	9	20		
Unsatisfactory	4	9		
Impaired	8	10		

Statistical analyses

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

Statistical analysis description:

A Wilcoxon signed rank test was applied to compare patient’s sides 12 weeks after the last PDT. Each 'very good' was counted as 0, each 'good' as 1, each 'satisfactory' as 2, each 'unsatisfactory' as 3, and each 'impaired' as 4.

Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.

Comparison groups	BF-200 ALA (Verum) v Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	One-sided Wilcoxon signed rank test

Statistical analysis title	Non-parametric, one-sided 97.5% CI (FAS)

Statistical analysis description:

The application of the non-parametric CI was subordinate.

Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.

Comparison groups	BF-200 ALA (Verum) v Placebo
Number of subjects included in analysis	98
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	0
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0

Other pre-specified: Lesion complete response per treatment arm (percentage of completely cleared individual lesions, in relation to number of lesions at baseline

[Visit 2]) assessed 12 weeks after the last PDT (FAS)

End point title	Lesion complete response per treatment arm (percentage of completely cleared individual lesions, in relation to number of lesions at baseline [Visit 2]) assessed 12 weeks after the last PDT (FAS)

End point description:

A tertiary efficacy variable was the lesion complete response per treatment arm (percentage of completely cleared individual lesions, in relation to number of lesions at baseline [Visit 2]) assessed 12 weeks after the last PDT.

The full analysis set (FAS) consists of 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 was as randomized.

To realistically reflect the result, the number of subjects (shown below) was replaced by the number of lesions for this analysis.

End point type	Other pre-specified

End point timeframe:

12 weeks after the last PDT

End point values	BF-200 ALA (Verum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[1]	49[2]		
Units: lesions				
number (not applicable)	219	88		

Notes:

[1] - This is the number of patients that received BF-200 ALA. They had 258 lesions in total.

[2] - This is the number of patients that received placebo. They had 268 lesions in total.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patient's satisfaction with treatment applied to his/her respective side (FAS)

End point title	Patient's satisfaction with treatment applied to his/her respective side (FAS)

End point description:

A tertiary efficacy variable was the patient's satisfaction with treatment applied to his/her respective side.

The full analysis set (FAS) consists of 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 was as randomized.

End point type	Other pre-specified

End point timeframe:

12 weeks after last PDT

End point values	BF-200 ALA (Verum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: patients				
number (not applicable)				
Patient would choose treatment again	38	32		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Application site pain during PDT-1 reported by the patients per patient’s side (SAF)

End point title	Application site pain during PDT-1 reported by the patients per patient’s side (SAF)

End point description:

Safety endpoint:
Patient's pain intensity during PDT is assessed at the end of each illumination period using a numeric rating pain scale ranging from no pain at all (0) to worst possible pain (10).
If the patient could not indicate the specific side of pain sensation, the worst pain experienced for patient’s both (left and right) side (and treatment areas) was documented equally.
One patient was treated incorrectly at PDT-2, but with the correct treatment at PDT-1. Within the Safety Analysis Set (SAF), this patient is allocated to BF-200 ALA for both sides.

End point type	Other pre-specified

End point timeframe:

During PDT-1

End point values	BF-200 ALA (Verum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50[3]	49		
Units: points				
arithmetic mean (standard deviation)	4.5 (± 3.2)	1.2 (± 2.5)		

Notes:

[3] - Subj. analysed: 51 (in SAF 1 pat. was allocated to verum for both sides -> incorrect IMP administr.)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Application site pain during PDT-2 reported by the patients per patient’s side (SAF)

End point title	Application site pain during PDT-2 reported by the patients per patient’s side (SAF)

End point description:

Safety endpoint:
Patient's pain intensity during PDT is assessed at the end of each illumination period using a numeric rating pain scale ranging from no pain at all (0) to worst possible pain (10).

If the patient could not indicate the specific side of pain sensation, the worst pain experienced for patient's both (left and right) side (and treatment areas) was documented equally.
One patient was treated incorrectly at PDT-2, but with the correct treatment at PDT-1. Within the Safety Analysis Set (SAF), this patient is allocated to BF-200 ALA for both sides.

End point type	Other pre-specified

End point timeframe:

During PDT-2

End point values	BF-200 ALA (Verum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	27		
Units: points				
arithmetic mean (standard deviation)	4.0 (± 3.4)	1.1 (± 2.2)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Total lesion clearance rate in percent per patient's side 12 weeks after last PDT (PPS)

End point title	Total lesion clearance rate in percent per patient's side 12 weeks after last PDT (PPS)

End point description:

Sensitivity analysis of primary endpoint.

Total lesion clearance rate in percent per patient's side, defined as the percentage of individual lesions with complete remission on the respective side of the patient assessed 12 weeks after the last PDT.

The per protocol set (PPS) consists of all patients of the FAS without any major protocol deviations. Patients will be included in the PPS if they fulfill all of the following criteria:
• Treated with investigational products and PDT mode according to the randomization plan.
• The 2 patient sides (R & L) are comparable and the number of AK lesions varies not more than 50%.
• At least one AK lesion assessment after the first, and if retreated after the second PDT, is available.
• No forbidden concomitant medications or therapies.

End point type	Other pre-specified

End point timeframe:

12 weeks after last PDT

End point values	BF-200 ALA (Verum)	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: percent				
arithmetic mean (standard deviation)	90.0 (± 20.0)	28.5 (± 36.7)		

Statistical analyses

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

Statistical analysis description:

The Wilcoxon signed rank test (one-sided, alpha=0.025) was applied (using the location parameter mu0 of 0%).

Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.

Comparison groups	BF-200 ALA (Verum) v Placebo
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	One-sided Wilcoxon signed rank test

Statistical analysis title	Non-parametric, one-sided 97.5% CI (PPS)

Statistical analysis description:

Additionally, a non-parametric, one-sided 97.5% confidence interval (CI) for the median difference in response rates rALA - rPla was calculated. If the lower bound of this CI is greater than 0, it indicates superiority of BF-200 ALA PDT to placebo PDT. The application of the non-parametric CI was subordinate.

Due to the intra-individual design, the number of subjects reflects the number of subjects' sides.

Comparison groups	Placebo v BF-200 ALA (Verum)
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Median difference (final values)
Point estimate	66.7
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	50

Adverse events

Adverse events information

Timeframe for reporting adverse events:

18 September 2017 (study initiation date/first patient signed informed consent) until 09 January 2019 (study completion date for observer blind part).

Adverse event reporting additional description:

TEAEs (treatment emergent adverse events) are defined as all AEs or SAEs with time of onset or worsening on or after the time of first IMP application. All safety analyses are based on the safety analysis set, which consists of all subjects treated at least with one IMP application. The assignment of subjects' sides was as actually treated.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	TEAEs related to side treated with BF-200 ALA
Reporting group description: -	
Reporting group title	TEAEs related to side treated with Placebo
Reporting group description: -	
Reporting group title	TEAEs with relation to side not applicable
Reporting group description: -	
Reporting group title	TEAEs with relation to side unknown

Reporting group description: -

Serious adverse events	TEAEs related to side treated with BF-200 ALA	TEAEs related to side treated with Placebo	TEAEs with relation to side not applicable
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 50 (4.00%)	0 / 50 (0.00%)	2 / 50 (4.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	TEAEs with relation to side unknown		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Humerus fracture			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Actinic keratosis			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	TEAEs related to side treated with BF-200 ALA	TEAEs related to side treated with Placebo	TEAEs with relation to side not applicable
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 50 (100.00%)	23 / 50 (46.00%)	11 / 50 (22.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 50 (2.00%)	1 / 50 (2.00%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Application site erosion			
subjects affected / exposed	2 / 50 (4.00%)	2 / 50 (4.00%)	0 / 50 (0.00%)
occurrences (all)	2	2	0
Application site erythema			
subjects affected / exposed	45 / 50 (90.00%)	7 / 50 (14.00%)	0 / 50 (0.00%)
occurrences (all)	71	9	0
Application site exfoliation			
subjects affected / exposed	12 / 50 (24.00%)	2 / 50 (4.00%)	0 / 50 (0.00%)
occurrences (all)	14	2	0
Application site induration			
subjects affected / exposed	3 / 50 (6.00%)	2 / 50 (4.00%)	0 / 50 (0.00%)
occurrences (all)	3	2	0
Application site oedema			

subjects affected / exposed	16 / 50 (32.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences (all)	21	0	0
Application site pain			
subjects affected / exposed	50 / 50 (100.00%)	20 / 50 (40.00%)	0 / 50 (0.00%)
occurrences (all)	148	47	0
Application site paraesthesia			
subjects affected / exposed	1 / 50 (2.00%)	2 / 50 (4.00%)	0 / 50 (0.00%)
occurrences (all)	1	2	0
Application site pruritus			
subjects affected / exposed	24 / 50 (48.00%)	9 / 50 (18.00%)	0 / 50 (0.00%)
occurrences (all)	37	13	0
Application site scab			
subjects affected / exposed	15 / 50 (30.00%)	2 / 50 (4.00%)	0 / 50 (0.00%)
occurrences (all)	21	3	0
Application site vesicles			
subjects affected / exposed	9 / 50 (18.00%)	3 / 50 (6.00%)	0 / 50 (0.00%)
occurrences (all)	15	3	0
Pain			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Swelling			
subjects affected / exposed	1 / 50 (2.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Eczema eyelids			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 50 (2.00%)	1 / 50 (2.00%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			

Nasopharyngitis			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	7 / 50 (14.00%)
occurrences (all)	0	0	7
Urinary tract infection			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2

Non-serious adverse events	TEAEs with relation to side unknown		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 50 (6.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Application site erosion			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Application site erythema			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Application site exfoliation			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Application site induration			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Application site oedema			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Application site pain			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		
Application site paraesthesia			
subjects affected / exposed	0 / 50 (0.00%)		
occurrences (all)	0		

Application site pruritus subjects affected / exposed occurrences (all) Application site scab subjects affected / exposed occurrences (all) Application site vesicles subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Swelling subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0 0 / 50 (0.00%) 0 0 / 50 (0.00%) 0 0 / 50 (0.00%) 0 1 / 50 (2.00%) 1		
Eye disorders Eczema eyelids subjects affected / exposed occurrences (all)	2 / 50 (4.00%) 2		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Skin and subcutaneous tissue disorders Actinic keratosis subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	0 / 50 (0.00%) 0 0 / 50 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 July 2017	Substantial Protocol Amendment resulting in Clinical Study Protocol (CSP) 2.0 dated 20-Jul-2017 to further define the extent of adverse events that had to be documented during the follow-up period. Approved by German Competent Authority (CA) on 28-Jul-2017. Recruitment of patients started after the approval of CSP V2.0 by CA and Ethics Committee.
06 August 2018	Substantial Protocol Amendment resulting in CSP 3.0 dated 23-Jul-2018 to change the order of two secondary endpoints. Approved by German Competent Authority on 06-Aug-2018.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported