Clinical trial results:
A randomized, double-blind, phase III multi-center study to evaluate the safety and efficacy of BF-200 ALA (Ameluz®) versus placebo in the field-directed treatment of mild to moderate actinic keratosis with photodynamic therapy (PDT) when using BF-RhodoLED®

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2013-002510-12
Trial protocol	DE
Global end of trial date	15 August 2014

Results information

Result version number	v1 (current)
This version publication date	17 July 2016
First version publication date	17 July 2016

Trial information

Trial identification

Sponsor protocol code	ALA-AK-CT007

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 2148763226, ameluz@biofrontera.com
Scientific contact	Clinical Trial Department, Biofrontera Bioscience GmbH, +49 2148763226, 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	03 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 August 2014
Global end of trial reached?	Yes
Global end of trial date	15 August 2014
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 of BF-200 ALA (Ameluz) with placebo, for the field-directed treatment of mild to moderate AK with PDT when using the BF RhodoLED® lamp.

Protection of trial subjects:

- During PDT, i.e. during illumination the patient wore suitably protective goggles
- Pain prevention (if the pain was regarded as unbearable by the patient):
* Cooling with an air stream or with nebulized water
* Short interruption of the illumination to inject a local fast-acting anesthetic such as xylocaine
* After PDT the treated areas could be cooled with wet or refrigerated compresses
* Analgesic treatment with paracetamol or metamizol
- Non- or partial responders received treatment of new or recurrent lesions with conventional therapy at the discretion of the investigator after the end of the observer-blind part

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 October 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 94
Worldwide total number of subjects	94
EEA total number of subjects	94

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)	15
From 65 to 84 years	79
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Trial was conducted in Germany with 7 study sites (Bonn, Dresden, Munich, Wuppertal, Mönchengladbach, Cologne, and Recklinghausen) who recruited patients.

Pre-assignment

Screening details:

94 patients were screened, 87 patients were randomized (55 patients to BF-200 ALA and 32 patients to placebo) and treated. 7 patients were screening failures: 3 withdrew consent, 2 did not meet the in-/exclusion criteria, and 2 failed for other reasons (recruitment stop).

Pre-assignment period milestones

Number of subjects started	94
Number of subjects completed	87

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 3
Reason: Number of subjects	Recruitment stop: 2
Reason: Number of subjects	Did not meet in-/exclusion criteria: 2

Period 1

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

Blinding implementation details:

- Verum and placebo are indistiguishable.
- To guarantee the blind status of the investigator assessing efficacy after each PDT session, a second investigator or delegated person performes the PDT and conducts all safety evaluations during the PDT and the telephone call 1 week after PDT (observer-blind design).
- The randomization schedule and the allocation to treatment groups will not be known to the investigator and the sponsor until completion of the study, except in case of an emergency.

Arms

Are arms mutually exclusive?	Yes
Arm title	Verum

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Ameluz 78 mg/g gel
Investigational medicinal product code	BF-200 ALA
Other name	5-aminolevulinic acid nanoemulsion
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

After lesion preparation, the entire content of 1 tube of verum was applied to the treatment fields identified for this study at screening. The verum was applied to the entire field(s) covering a size of approx. 20 cm² with a film of about 1 mm thickness. Application near the eyes, nostrils, mouth, ears, or mucosa was to be avoided (by a distance of 1 cm). After application, the IMP was allowed to dry for approx. 10 minutes before an occlusive light-tight dressing was placed over the treatment site. Following incubation of 3 hours (+/- 10 minutes) the dressing was removed and the remnant gel wiped off with a 0.9% saline solution. Thereafter illumination was performed using BF-RhodoLED lamp (635

nm) applying a total light dose of 37 J/cm² (per treated field). During illumination, the lamp was fixed at a distance of 5 to 8 cm from the skin surface as indicated in the user manual.
This treatment was performed once and repeated after 12 weeks if no complete response was observed.

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Gel
Routes of administration	Topical use

Dosage and administration details:

After lesion preparation, the entire content of 1 tube of placebo was applied to the treatment fields identified for this study at screening. The placebo was applied to the entire field(s) covering a size of approx. 20 cm² with a film of about 1 mm thickness. Application near the eyes, nostrils, mouth, ears, or mucosa was to be avoided (by a distance of 1 cm). After application, the IMP was allowed to dry for approx. 10 minutes before an occlusive light-tight dressing was placed over the treatment site.
Following incubation of 3 hours (+/- 10 minutes) the dressing was removed and the remnant gel wiped off with a 0.9% saline solution. Thereafter illumination was performed using BF-RhodoLED lamp (635 nm) applying a total light dose of 37 J/cm² (per treated field). During illumination, the lamp was fixed at a distance of 5 to 8 cm from the skin surface as indicated in the user manual.
This treatment was performed once and repeated after 12 weeks if no complete response was observed.

Number of subjects in period 1[1]	Verum	Placebo
Started	55	32
Completed	54	26
Not completed	1	6
Consent withdrawn by subject	-	5
Lost to follow-up	1	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 94 subjects were screened but only 87 subjects entered the baseline period. The other 7 subjects were screening failures. Thus the subject numbers of the baseline period and the worldwide number of subjects are not equal.

Baseline characteristics

Reporting groups	
Reporting group title	Observer blind part
Reporting group description:	
Full Analysis set	

Reporting group values	Observer blind part	Total	
Number of subjects	87	87	
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)	13	13	
From 65-84 years	74	74	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	71.6		
full range (min-max)	51 to 84	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	79	79	
Race Units: Subjects			
White	87	87	
Ethnicity Units: Subjects			
Not Hispanic or Latino	87	87	
Fitzpatrick skin type Units: Subjects			
Type I	1	1	
Type II	40	40	
Type III	38	38	
Type IV	7	7	
Type V to VI	1	1	
History of AK therapy Units: Subjects			
No previous therapy	10	10	
Non-surgical therapy	33	33	
Surgical therapy	2	2	
Non-surgical and surgical therapy	42	42	

Histological confirmation of AK diagnosis by KIN grade Units: Subjects			
KIN I	16	16	
KIN II	70	70	
KIN III	1	1	
Location of AK lesions			
Treatment areas are defined as follows: - Treatment area A: face and forehead - Treatment area B: bals scalp			
Units: Subjects			
Treatment area A	49	49	
Treatment area B	36	36	
Treatment area A and B	2	2	
Maximum Olsen severity grading Units: Subjects			
Mild	17	17	
Moderate	70	70	
Severe	0	0	
Weight Units: kg			
arithmetic mean	82.7		
standard deviation	± 11.41	-	
Height Units: cm			
arithmetic mean	175.3		
standard deviation	± 7.94	-	
Body mass index Units: kg/m^2			
arithmetic mean	26.9		
standard deviation	± 3.07	-	
Years since first diagnosis of AK Units: years			
arithmetic mean	5.6		
standard deviation	± 3.95	-	
AK lesions at baseline per patient Units: number			
arithmetic mean	5.4		
standard deviation	± 1.05	-	

End points

End points reporting groups

Reporting group title	Verum
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Verum Per Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

All patients of the FAS without any major protocol deviations. Patients were included in the PP population if they fulfilled all of the following
criteria:
- Treated with the study medication according to the randomization plan.
- All target lesions were grade I or II according to Olsen criteria at baseline.
- AK confirmed by biopsy of a representative lesion taken at screening.
- At least one AK lesion assessment was available, i.e. after PDT-1 or if retreated, after PDT-2.
- Evaluation of the second biopsy at the end-of-study visit that did not result in a diagnosis of BCC or SCC.
- No concomitant medications or therapies that might have an impact on the efficacy or safety analyses. The terms were identified during the blind data review meeting before database closure.
- Treatment with BF-RhodoLED lamp.

Subject analysis set title	Placebo Per Protocol Set
Subject analysis set type	Per protocol

Subject analysis set description:

All patients of the FAS without any major protocol deviations. Patients were included in the PP population if they fulfilled all of the following
criteria:
- Treated with the study medication according to the randomization plan.
- All target lesions were grade I or II according to Olsen criteria at baseline.
- AK confirmed by biopsy of a representative lesion taken at screening.
- At least one AK lesion assessment was available, i.e. after PDT-1 or if retreated, after PDT-2.
- Evaluation of the second biopsy at the end-of-study visit that did not result in a diagnosis of BCC or SCC.
- No concomitant medications or therapies that might have an impact on the efficacy or safety analyses. The terms were identified during the blind data review meeting before database closure.
- Treatment with BF-RhodoLED lamp.

Subject analysis set title	Verum: Maximum AK severity at baseline: Grade I
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with AK severity according to Olsen Grade I (mild) treated with verum

Subject analysis set title	Placebo: Maximum AK severity at baseline: Grade I
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with AK severity according to Olsen Grade I (mild) treated with placebo

Subject analysis set title	Verum: Maximum AK severity at baseline: Grade II
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with AK severity according to Olsen Grade II (moderate) treated with verum

Subject analysis set title	Placebo: Maximum AK severity at baseline: Grade II
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with AK severity according to Olsen Grade II (moderate) treated with placebo

Subject analysis set title	Verum: Age >65 years
Subject analysis set type	Sub-group analysis

Subject analysis set description:
Patients >65 years treated with verum

Subject analysis set title	Placebo: Age >65 years
Subject analysis set type	Sub-group analysis

Subject analysis set description:
Patients > 65 years treated with placebo

Subject analysis set title	Verum: Age ≤65 years
Subject analysis set type	Sub-group analysis

Subject analysis set description:
Patients ≤65 years treated with verum

Subject analysis set title	Placebo: Age ≤65 years
Subject analysis set type	Sub-group analysis

Subject analysis set description:
Patients ≤65 years treated with placebo

Subject analysis set title	Verum: Sex: male
Subject analysis set type	Sub-group analysis

Subject analysis set description:
Male patients treated with verum

Subject analysis set title	Placebo: Sex: male
Subject analysis set type	Sub-group analysis

Subject analysis set description:
Male patients treated with placebo

Subject analysis set title	Verum: Sex: female
Subject analysis set type	Sub-group analysis

Subject analysis set description:
Female patients treated with verum

Subject analysis set title	Placebo: Sex: female
Subject analysis set type	Sub-group analysis

Subject analysis set description:
Female patients treated with placebo

Subject analysis set title	Verum: Skin type group: I to III
Subject analysis set type	Sub-group analysis

Subject analysis set description:
Patients with Fitzpatrick Skin Type I to III treated with verum

Subject analysis set title	Placebo: Skin type group: I to III
Subject analysis set type	Sub-group analysis

Subject analysis set description:
Patients with Fitzpatrick Skin Type I to III treated with placebo

Subject analysis set title	Verum: Skin type group: IV or more
Subject analysis set type	Sub-group analysis

Subject analysis set description:
Patients with Fitzpatrick Skin Type IV or more treated with verum

Subject analysis set title	Placebo: Skin type group: IV or more
Subject analysis set type	Sub-group analysis

Subject analysis set description:
Patients with Fitzpatrick Skin Type IV or more treated with placebo

Subject analysis set title	Verum: Skin type: Type I
Subject analysis set type	Sub-group analysis

Subject analysis set description:
Patients with Fitzpatrick Skin Type I treated with verum

Subject analysis set title	Placebo: Skin type: Type I
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with Fitzpatrick Skin Type I treated with placebo
no patients had Fitzpatrick skin type I, however it is impossible to enter "number of subjects in subject analysis set" = 0, therefore 1 is entered but incorrect!

Subject analysis set title	Verum: Skin type: Type II
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with Fitzpatrick Skin Type II treated with verum

Subject analysis set title	Placebo: Skin type: Type II
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with Fitzpatrick Skin Type II treated with placebo

Subject analysis set title	Verum: Skin type: Type III
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with Fitzpatrick Skin Type III treated with verum

Subject analysis set title	Placebo: Skin type: Type III
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with Fitzpatrick Skin Type III treated with placebo

Subject analysis set title	Verum: Treatment area: A
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with treatment area A (face and forehead) treated with verum

Subject analysis set title	Placebo: Treatment area: A
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with treatment area A (face and forehead) treated with placebo

Subject analysis set title	Verum: Treatment area: B
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with treatment area B (bald scalp) treated with verum

Subject analysis set title	Placebo: Treatment area: B
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with treatment area B (bald scalp) treated with placebo

Subject analysis set title	Verum: Treatment area: A and B
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with treatment area A and B (face and forehead plus bald scalp) treated with verum

Subject analysis set title	Placebo: Treatment area: A and B
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with treatment area A and B (face and forehead plus bald scalp) treated with placebo

Subject analysis set title	Verum: Number of AK lesions at baseline: up to 5
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with up to 5 AK lesions at baseline treated with verum

Subject analysis set title	Placebo: Number of AK lesions at baseline: up to 5
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with up to 5 AK lesions at baseline treated with placebo

Subject analysis set title	Verum: Number of AK lesions at baseline: 6 or more
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with 6 or more AK lesions at baseline treated with verum	
Subject analysis set title	Placebo: Number of AK lesions at baseline: 6 or more
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with 6 or more AK lesions at baseline treated with placebo	
Subject analysis set title	Verum: AK lesion area: ≤400mm^2
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with AK lesion area ≤400mm^2 treated with verum	
Subject analysis set title	Placebo: AK lesion area: ≤400mm^2
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with AK lesion area ≤400mm^2 treated with placebo	
Subject analysis set title	Verum: AK lesion area: >400mm^2
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with AK lesion area >400mm^2 treated with verum	
Subject analysis set title	Placebo: AK lesion area: >400mm^2
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with AK lesion area >400mm^2 treated with placebo	
Subject analysis set title	Verum: AK history: Naive
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients without AK history treated with verum	
Subject analysis set title	Placebo: AK history: Naive
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients without AK history treated with placebo	
Subject analysis set title	Verum: AK history: Non-naive
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with AK history treated with verum	
Subject analysis set title	Placebo: AK history: Non-naive
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Patients with AK history treated with placebo	
Subject analysis set title	Verum: patients with sum score at baseline of 0 to 3
Subject analysis set type	Full analysis
Subject analysis set description:	
Verum: patients with sum score at baseline of 0 to 3	
Subject analysis set title	Placebo: patients with sum score at baseline of 0 to 3
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo: patients with sum score at baseline of 0 to 3	
Subject analysis set title	Verum: patients with sum score at baseline of 1 to 3
Subject analysis set type	Full analysis
Subject analysis set description:	
Verum: patients with sum score at baseline of 1 to 3 (0 excluded)	

Subject analysis set title	Placebo: patients with sum score at baseline of 1 to 3
Subject analysis set type	Full analysis

Subject analysis set description:

Placebo: patients with sum score at baseline of 1 to 3 (0 excluded)

Primary: Overall patient complete response 12 weeks after the last PDT

End point title	Overall patient complete response 12 weeks after the last PDT

End point description:

All efficacy variables were evaluated for the FAS. The primary efficacy variable was also analyzed for the PP population. All subgroup analyses were carried out for the FAS. Data for size and grade of AK lesions were analyzed using the last observation carried forward (LOCF) approach, affecting the response rates evaluation.
Due to the small amount of missing data in the study, which did not have any relevant impact on primary results, sensitivity analyses for missing data were not performed.
The primary efficacy variable was the overall patient complete response 12 weeks after the last PDT. An overall complete responder was defined as a patient in whom all treated AK lesions were cleared (Olsen score of 0) after the last PDT, i.e. after PDT 1 or after PDT 2 if re-treatment was performed.

End point type	Primary

End point timeframe:

12 weeks after PDT 1 or 12 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum	Placebo	Verum Per Protocol Set	Placebo Per Protocol Set
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	55	32	50	27
Units: percent				
arithmetic mean (confidence interval 95%)	90.9 (80 to 97)	21.9 (9.3 to 40)	90 (78.2 to 96.7)	25.9 (11.1 to 46.3)

Statistical analyses

Statistical analysis title	Superiority of verum to placebo (FAS)

Statistical analysis description:

Primary null hypothesis (H01, two-sided): overall CR-rate assessed 12 weeks after last PDT for patients treated with BF-200 ALA is equal to that of patients treated with placebo. Primary alternate hypothesis (H11, two-sided): overall CR-rate assessed 12 weeks after last PDT for patients treated with BF-200 ALA is not equal to the response rate for patients treated with placebo.
CR: complete responder
A missing 12-week assessment was imputed by the preceeding 4-week assessment (LOCF approach)

Comparison groups	Verum v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	69

Confidence interval	
level	95 %
sides	2-sided
lower limit	52.8
upper limit	85.2

Statistical analysis title	Superiority of verum to placebo (PP)

Statistical analysis description:

Primary null hypothesis (H01, two-sided): overall CR-rate assessed 12 weeks after last PDT for patients treated with BF-200 ALA is equal to that of patients treated with placebo. Primary alternate hypothesis (H11, two-sided): overall CR-rate assessed 12 weeks after last PDT for patients treated with BF-200 ALA is not equal to the response rate for patients treated with placebo.
CR: complete responder
A missing 12-week assessment was imputed by the preceeding 4-week assessment (LOCF approach)

Comparison groups	Verum Per Protocol Set v Placebo Per Protocol Set
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	64.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	45.6
upper limit	82.6

Primary: Overall patient complete response 12 weeks after the last PDT (by subgroups)

End point title	Overall patient complete response 12 weeks after the last PDT (by subgroups)

End point description:

All subgroup analyses were carried out for the FAS.
Data for size and grade of AK lesions were analyzed using the last observation carried forward (LOCF) approach, affecting the response rates evaluation.
Due to the small amount of missing data in the study, which did not have any relevant impact on primary results, sensitivity analyses for missing data were not performed.
The primary efficacy variable was the overall patient complete response 12 weeks after the last PDT. An overall complete responder was defined as a patient in whom all treated AK lesions were cleared (Olsen score of 0) after the last PDT, i.e. after PDT 1 or after PDT 2 if re-treatment was performed.

End point type	Primary

End point timeframe:

12 weeks after PDT 1 or 12 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum: Maximum AK severity at baseline: Grade I	Placebo: Maximum AK severity at baseline: Grade I	Verum: Maximum AK severity at baseline: Grade II	Placebo: Maximum AK severity at baseline: Grade II
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	7	45	25
Units: percent				
arithmetic mean (confidence interval 95%)	100 (69.2 to 100)	71.4 (29 to 96.3)	88.9 (75.9 to 96.3)	8 (1 to 26)

End point values	Verum: Age >65 years	Placebo: Age >65 years	Verum: Age ≤65 years	Placebo: Age ≤65 years
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	46	26	9	6
Units: percent				
arithmetic mean (confidence interval 95%)	91.3 (79.2 to 97.6)	23.1 (9 to 43.6)	88.9 (51.8 to 99.7)	16.7 (0.4 to 64.1)

End point values	Verum: Sex: male	Placebo: Sex: male	Verum: Sex: female	Placebo: Sex: female
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	50	29	5	3
Units: percent				
arithmetic mean (confidence interval 95%)	90 (78.2 to 96.7)	24.1 (10.3 to 43.5)	100 (47.8 to 100)	0 (0 to 70.8)

End point values	Verum: Skin type group: I to III	Placebo: Skin type group: I to III	Verum: Skin type group: IV or more	Placebo: Skin type group: IV or more
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	48	31	7	1
Units: percent				
arithmetic mean (confidence interval 95%)	93.8 (82.8 to 98.7)	22.6 (9.6 to 41.1)	71.4 (29 to 96.3)	0 (0 to 97.5)

End point values	Verum: Skin type: Type I	Placebo: Skin type: Type I	Verum: Skin type: Type II	Placebo: Skin type: Type II
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1	0[1]	28	12
Units: percent				
arithmetic mean (confidence interval 95%)	100 (2.5 to 100)	(to)	89.3 (71.8 to 97.7)	50 (21.1 to 78.9)

Notes:

[1] - no patient with skin type I was treated with placebo

End point values	Verum: Skin type: Type III	Placebo: Skin type: Type III	Verum: Treatment area: A	Placebo: Treatment area: A
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	19	19	32	17
Units: percent				
arithmetic mean (confidence interval 95%)	100 (82.4 to 100)	5.3 (0.1 to 26)	96.9 (83.8 to 99.9)	35.3 (14.2 to 61.7)

End point values	Verum: Treatment area: B	Placebo: Treatment area: B	Verum: Treatment area: A and B	Placebo: Treatment area: A and B
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	14	1	1
Units: percent				
arithmetic mean (confidence interval 95%)	81.8 (59.7 to 94.8)	7.1 (0.2 to 33.9)	100 (2.5 to 100)	0 (0 to 97.5)

End point values	Verum: Number of AK lesions at baseline: up to 5	Placebo: Number of AK lesions at baseline: up to 5	Verum: Number of AK lesions at baseline: 6 or more	Placebo: Number of AK lesions at baseline: 6 or more
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	32	18	23	14
Units: percent				
arithmetic mean (confidence interval 95%)	90.6 (75 to 98)	27.8 (9.7 to 53.5)	91.3 (72 to 98.9)	14.3 (1.8 to 42.8)

End point values	Verum: AK lesion area: ≤400mm^2	Placebo: AK lesion area: ≤400mm^2	Verum: AK lesion area: >400mm^2	Placebo: AK lesion area: >400mm^2
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	44	26	11	6
Units: percent				
arithmetic mean (confidence interval 95%)	88.6 (75.4 to 96.2)	23.1 (9 to 43.6)	100 (71.5 to 100)	16.7 (0.4 to 64.1)

End point values	Verum: AK history: Naive	Placebo: AK history: Naive	Verum: AK history: Non-naive	Placebo: AK history: Non-naive
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	8	2	47	30

Units: percent				
arithmetic mean (confidence interval 95%)	100 (63.1 to 100)	0 (0 to 84.2)	89.4 (76.9 to 96.5)	23.3 (9.9 to 42.3)

Statistical analyses

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: Maximum AK severity at baseline: Grade I v Placebo: Maximum AK severity at baseline: Grade I
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1544
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	28.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.9
upper limit	62

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: Maximum AK severity at baseline: Grade II v Placebo: Maximum AK severity at baseline: Grade II
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	80.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	66.8
upper limit	94.9

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: Age >65 years v Placebo: Age >65 years

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	68.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	50.1
upper limit	86.4

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: Age ≤65 years v Placebo: Age ≤65 years
Number of subjects included in analysis	15
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.011
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	72.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	36
upper limit	100

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: Sex: male v Placebo: Sex: male
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	65.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	48.2
upper limit	83.5

Statistical analysis title	Superiority of verum to placebo (FAS)

Comparison groups	Verum: Sex: female v Placebo: Sex: female
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0179
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	100
Confidence interval	
level	95 %
sides	2-sided
lower limit	100
upper limit	100

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: Skin type group: I to III v Placebo: Skin type group: I to III
Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	71.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	54.9
upper limit	87.4

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: Skin type group: IV or more v Placebo: Skin type group: IV or more
Number of subjects included in analysis	8
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.375
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	71.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	38
upper limit	100

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: Skin type: Type II v Placebo: Skin type: Type II
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0122
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	39.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.8
upper limit	69.8

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: Skin type: Type III v Placebo: Skin type: Type III
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	94.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	84.7
upper limit	100

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: Treatment area: A v Placebo: Treatment area: A
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	61.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	38.1
upper limit	85.1

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: Treatment area: B v Placebo: Treatment area: B
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	74.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	53.7
upper limit	95.7

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: Treatment area: A and B v Placebo: Treatment area: A and B
Number of subjects included in analysis	2
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	100
Confidence interval	
level	95 %
sides	2-sided
lower limit	100
upper limit	100

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: Number of AK lesions at baseline: up to 5 v Placebo: Number of AK lesions at baseline: up to 5

Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	62.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	39.8
upper limit	85.9

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: Number of AK lesions at baseline: 6 or more v Placebo: Number of AK lesions at baseline: 6 or more
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	77
Confidence interval	
level	95 %
sides	2-sided
lower limit	55.4
upper limit	98.7

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: AK lesion area: ≤400mm^2 v Placebo: AK lesion area: ≤400mm^2
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	65.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	46.8
upper limit	84.3

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: AK lesion area: >400mm^2 v Placebo: AK lesion area: >400mm^2
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	83.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	53.8
upper limit	100

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: AK history: Naive v Placebo: AK history: Naive
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0222
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	100
Confidence interval	
level	95 %
sides	2-sided
lower limit	100
upper limit	100

Statistical analysis title	Superiority of verum to placebo (FAS)
Comparison groups	Verum: AK history: Non-naive v Placebo: AK history: Non-naive
Number of subjects included in analysis	77
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	66
Confidence interval	
level	95 %
sides	2-sided
lower limit	48.5
upper limit	83.5

Secondary: Patient histopathological confirmed response rate

End point title	Patient histopathological confirmed response rate

End point description:

For the secondary confirmatory analysis, several superiority hypotheses were tested within a pre-defined hierarchic multiple testing procedure as described in the SAP.
The key secondary efficacy variables were tested strictly in a pre-defined order to ensure the FWER and the testing procedure had to be stopped once the first non-significant test was obtained.
The results of the confirmatory analysis are presented in the order pre-defined by the confirmatory testing procedure.
Assessments of HCR rates were based on the results from the biopsy taken 12 weeks after the last PDT from a representative AK lesion selected at screening. If the biopsy result for a patient revealed a residual AK, the patient was considered "not cleared" for the analysis irrespectively of the investigator's clinical assessment.

End point type	Secondary

End point timeframe:

12 weeks after PDT 1 or 12 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	27		
Units: percent				
arithmetic mean (confidence interval 95%)	77.8 (64.4 to 88)	22.2 (8.6 to 42.3)		

Statistical analyses

Statistical analysis title	Patient histopathological confirmed response rate
Comparison groups	Verum v Placebo
Number of subjects included in analysis	81
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	55.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	36.3
upper limit	74.8

Secondary: Patient complete response 12 weeks after PDT 1

End point title	Patient complete response 12 weeks after PDT 1

End point description:

The second key secondary efficacy variable in the hierarchic test procedure was the patient complete response (complete clearance of all treated AK lesions) assessed at 12 weeks after PDT 1.

End point type	Secondary

End point timeframe:

12 weeks after PDT 1

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	32		
Units: percent				
arithmetic mean (confidence interval 95%)	61.8 (47.7 to 74.6)	9.4 (2 to 25)		

Statistical analyses

Statistical analysis title	Patient complete response 12 weeks after PDT 1
Comparison groups	Verum v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	52.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	36.1
upper limit	68.8

Secondary: Lesion complete response 12 weeks after last PDT

End point title	Lesion complete response 12 weeks after last PDT

End point description:

The third key secondary efficacy variable in the hierarchic test procedure was the lesion complete response (completely cleared individual AK lesions) assessed at 12 weeks after last PDT.

Please take into consideration:
VERUM: number of subjects: 55 and number of lesions: 298
PLACEBO: number of subjects: 32 and number of lesions 173
To realistically reflect the result, the number of subjects (shown below) should be the number of lesions for this analysis, however, this is not possible to enter into the system.

End point type	Secondary

End point timeframe:

12 weeks after PDT 1 or 12 weeks after PDT 2 which might have been necessary because not all lesions

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[2]	32[3]		
Units: percent				
arithmetic mean (confidence interval 95%)	94.3 (91 to 96.6)	32.9 (26 to 40.5)		

Notes:

[2] - Not subjects but number of lesions were analyzed (no. of lesions = 298)

[3] - Not subjects but number of lesions were analyzed (no. of lesions = 173)

Statistical analyses

Statistical analysis title	Lesion complete response 12 weeks after last PDT
Comparison groups	Verum v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	61.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	53.9
upper limit	68.8

Secondary: Patient partial response 12 weeks after last PDT

End point title	Patient partial response 12 weeks after last PDT

End point description:

The fourth key secondary efficacy variable in the hierarchic test procedure was the patient partial response (defined as complete clearance of at least 75% of treated AK lesions) assessed at 12 weeks after last PDT.

End point type	Secondary

End point timeframe:

12 weeks after PDT 1 or 12 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	32		
Units: percent				
arithmetic mean (confidence interval 95%)	94.5 (84.9 to 98.9)	25 (11.5 to 43.4)		

Statistical analyses

Statistical analysis title	Patient partial response 12 weeks after last PDT
Comparison groups	Verum v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Fisher exact
Parameter estimate	Mean difference (final values)
Point estimate	69.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	53.4
upper limit	85.7

Secondary: Reduction of total lesion area 12 weeks after last PDT

End point title	Reduction of total lesion area 12 weeks after last PDT

End point description:

The fifth key secondary efficacy variable in the hierarchic test procedure was the reduction from baseline in the total lesion area per patient assessed at 12 weeks after last PDT.

End point type	Secondary

End point timeframe:

12 weeks after PDT 1 or 12 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	32		
Units: percent				
arithmetic mean (standard deviation)	-98.2 (± 9.65)	-45.5 (± 42.96)		

Statistical analyses

Statistical analysis title	Reduct. total lesion area 12 weeks after last PDT
Comparison groups	Verum v Placebo
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANCOVA

Secondary: Overall cosmetic outcome 12 weeks after last PDT

End point title	Overall cosmetic outcome 12 weeks after last PDT

End point description:

The sixth key secondary efficacy variable in the hierarchic test procedure was the overall cosmetic outcome 12 weeks after last PDT.

End point type	Secondary

End point timeframe:

12 weeks after PDT 1 or 12 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum: patients with sum score at baseline of 0 to 3	Placebo: patients with sum score at baseline of 0 to 3	Verum: patients with sum score at baseline of 1 to 3	Placebo: patients with sum score at baseline of 1 to 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	29	48	26
Units: percent				
arithmetic mean (confidence interval 95%)				
Very good	35.2 (22.7 to 49.4)	17.2 (5.8 to 35.8)	39.6 (25.8 to 54.7)	19.2 (6.6 to 39.4)
Good	24.1 (13.5 to 37.6)	13.8 (3.9 to 31.7)	27.1 (15.3 to 41.8)	15.4 (4.4 to 34.9)
Satisfactory	24.1 (13.5 to 37.6)	20.7 (8 to 39.7)	22.9 (12 to 37.3)	23.1 (9 to 43.6)
Unsatisfactory	11.1 (4.2 to 22.6)	27.6 (12.7 to 47.2)	6.3 (1.3 to 17.2)	26.9 (11.6 to 47.8)
Impaired	5.6 (1.2 to 15.4)	20.7 (8 to 39.7)	4.2 (0.5 to 14.3)	15.4 (4.4 to 34.9)

Statistical analyses

Statistical analysis title	Overall cosmetic outcome 12 weeks after last PDT

Statistical analysis description:

Overall cosmetic outcome 12 weeks after last PDT for patients with sum score at baseline of 0 to 3

Comparison groups	Placebo: patients with sum score at baseline of 0 to 3 v Verum:

	patients with sum score at baseline of 0 to 3
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0033
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Probabilistic index
Point estimate	0.689
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.558
upper limit	0.82

Statistical analysis title	Overall cosmetic outcome 12 weeks after last PDT
Statistical analysis description:	
Overall cosmetic outcome 12 weeks after last PDT for patients with sum score at baseline of 1 to 3 (0 excluded)	
Comparison groups	Verum: patients with sum score at baseline of 1 to 3 v Placebo: patients with sum score at baseline of 1 to 3
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0032
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Probabilistic index
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.562
upper limit	0.839

Other pre-specified: Patient complete response 3-4 weeks after PDT 1	
End point title	Patient complete response 3-4 weeks after PDT 1
End point description:	
A tertiary efficacy variable was the patient complete response (complete clearance of all treated AK lesions) assessed 3-4 weeks after PDT-1	
End point type	Other pre-specified
End point timeframe:	
3-4 weeks after PDT	

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	32		
Units: percent				
arithmetic mean (confidence interval 95%)	52.7 (38.3 to 66.3)	6.3 (0.8 to 20.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patient complete response 3-4 weeks after PDT 2

End point title	Patient complete response 3-4 weeks after PDT 2

End point description:

A tertiary efficacy variable was the patient complete response (complete clearance of all treated AK lesions) assessed 3-4 weeks after PDT-2.

End point type	Other pre-specified

End point timeframe:

3-4 weeks after PDT 2

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	29		
Units: percent				
arithmetic mean (confidence interval 95%)	76.2 (52.8 to 91.8)	6.9 (0.8 to 22.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patient complete response 12 weeks after PDT 2

End point title	Patient complete response 12 weeks after PDT 2

End point description:

A tertiary efficacy variable was the patient complete response (complete clearance of all treated AK lesions) assessed and 12 weeks after PDT-2.

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 2

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	29		
Units: percent				
arithmetic mean (confidence interval 95%)	76.2 (52.8 to 91.8)	13.8 (3.9 to 31.7)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patient complete response 3-4 weeks after last PDT

End point title	Patient complete response 3-4 weeks after last PDT

End point description:

A tertiary efficacy variable was the patient complete response (complete clearance of all treated AK lesions) assessed 3-4 weeks after last PDT.

End point type	Other pre-specified

End point timeframe:

3-4 weeks after PDT 1 or 3-4 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	32		
Units: percent				
arithmetic mean (confidence interval 95%)	74.5 (61 to 85.3)	9.4 (2 to 25)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patient partial response 3-4 weeks after PDT 1

End point title	Patient partial response 3-4 weeks after PDT 1

End point description:

A tertiary efficacy variable was the patient partial response (defined as complete clearance of at least 75% of treated AK lesions) assessed 3-4 weeks after PDT-1.

End point type	Other pre-specified

End point timeframe:

3-4 weeks after PDT 1

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	32		
Units: percent				
arithmetic mean (confidence interval 95%)	63.6 (49.6 to 76.2)	9.4 (2 to 25)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patient partial response 12 weeks after PDT 1

End point title	Patient partial response 12 weeks after PDT 1

End point description:

A tertiary efficacy variable was the patient partial response (defined as complete clearance of at least 75% of treated AK lesions) assessed 12 weeks after PDT-1.

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 1

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	32		
Units: percent				
arithmetic mean (confidence interval 95%)	76.4 (63 to 86.8)	12.5 (3.5 to 29)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patient partial response 3-4 weeks after PDT 2

End point title	Patient partial response 3-4 weeks after PDT 2

End point description:

A tertiary efficacy variable was the patient partial response (defined as complete clearance of at least 75% of treated AK lesions) assessed 3-4 weeks after PDT-2.

End point type	Other pre-specified

End point timeframe:

3-4 weeks after PDT 2

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	29		
Units: percent				
arithmetic mean (confidence interval 95%)	90.5 (69.6 to 98.8)	13.8 (3.9 to 31.7)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patient partial response 12 weeks after PDT 2

End point title	Patient partial response 12 weeks after PDT 2

End point description:

A tertiary efficacy variable was the patient partial response (defined as complete clearance of at least 75% of treated AK lesions) assessed 12 weeks after PDT-2.

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 2

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	29		
Units: percent				
arithmetic mean (confidence interval 95%)	85.7 (63.7 to 97)	17.2 (5.8 to 35.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patient partial response 3-4 weeks after last PDT

End point title	Patient partial response 3-4 weeks after last PDT

End point description:

A tertiary efficacy variable was the patient partial response (defined as complete clearance of at least 75% of treated AK lesions) assessed 3-4 weeks after last PDT.

End point type	Other pre-specified

End point timeframe:

3-4 weeks after PDT 1 or or 3-4 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	32		
Units: percent				
arithmetic mean (confidence interval 95%)	81.8 (69.1 to 90.9)	18.8 (7.2 to 36.4)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Lesion complete response 3-4 weeks after PDT 1

End point title	Lesion complete response 3-4 weeks after PDT 1

End point description:

A tertiary efficacy variable was the lesion complete response (completely cleared individual AK lesions) assessed 3-4 weeks after PDT-1.

Please take into consideration:
VERUM: number of subjects: 55 and number of lesions: 298
PLACEBO: number of subjects: 32 and number of lesions 173
To realistically reflect the result, the number of subjects (shown below) should be the number of lesions for this analysis, however, this is not possible to enter into the system.

End point type	Other pre-specified

End point timeframe:

3-4 weeks after PDT 1

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[4]	32[5]		
Units: percent				
arithmetic mean (confidence interval 95%)	68.5 (62.8 to 73.7)	15 (10.1 to 21.2)		

Notes:

[4] - Not subjects but number of lesions were analyzed (no. of lesions = 298)

[5] - Not subjects but number of lesions were analyzed (no. of lesions = 173)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Lesion complete response 12 weeks after PDT 1

End point title	Lesion complete response 12 weeks after PDT 1

End point description:

A tertiary efficacy variable was the lesion complete response (completely cleared individual AK lesions) assessed 12 weeks after PDT-1.

Please take into consideration:
VERUM: number of subjects: 55 and number of lesions: 298
PLACEBO: number of subjects: 32 and number of lesions 173
To realistically reflect the result, the number of subjects (shown below) should be the number of lesions

for this analysis, however, this is not possible to enter into the system.

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 1

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[6]	32[7]		
Units: percent				
arithmetic mean (confidence interval 95%)	84.2 (79.6 to 88.2)	22 (16 to 28.9)		

Notes:

[6] - Not subjects but number of lesions were analyzed (no. of lesions = 298)

[7] - Not subjects but number of lesions were analyzed (no. of lesions = 173)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Lesion complete response 3-4 weeks after PDT 2

End point title	Lesion complete response 3-4 weeks after PDT 2

End point description:

A tertiary efficacy variable was the lesion complete response (completely cleared individual AK lesions) assessed 3-4 weeks after PDT-2.

Please take into consideration:
VERUM: number of subjects: 21 and number of lesions: 47
PLACEBO: number of subjects: 29 and number of lesions 135
To realistically reflect the result, the number of subjects (shown below) should be the number of lesions for this analysis, however, this is not possible to enter into the system.

End point type	Other pre-specified

End point timeframe:

3-4 weeks after PDT 2

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[8]	29[9]		
Units: percent				
arithmetic mean (confidence interval 95%)	66 (50.7 to 79.1)	8.1 (4.1 to 14.1)		

Notes:

[8] - Not subjects but number of lesions were analyzed (no. of lesions = 47)

[9] - Not subjects but number of lesions were analyzed (no. of lesions = 135)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Lesion complete response 12 weeks after PDT 2

End point title	Lesion complete response 12 weeks after PDT 2

End point description:

A tertiary efficacy variable was the lesion complete response (completely cleared individual AK lesions) assessed 12 weeks after PDT-2.

Please take into consideration:
VERUM: number of subjects: 21 and number of lesions: 47
PLACEBO: number of subjects: 29 and number of lesions 135
To realistically reflect the result, the number of subjects (shown below) should be the number of lesions for this analysis, however, this is not possible to enter into the system.

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 2

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21[10]	29[11]		
Units: percent				
arithmetic mean (confidence interval 95%)	66 (50.7 to 79.1)	16.3 (10.5 to 23.6)		

Notes:

[10] - Not subjects but number of lesions were analyzed (no. of lesions = 47)

[11] - Not subjects but number of lesions were analyzed (no. of lesions = 135)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Lesion complete response 3-4 weeks after last PDT

End point title	Lesion complete response 3-4 weeks after last PDT

End point description:

A tertiary efficacy variable was the lesion complete response (completely cleared individual AK lesions) assessed 3-4 weeks after last PDT.

Please take into consideration:
VERUM: number of subjects: 55 and number of lesions: 298
PLACEBO: number of subjects: 32 and number of lesions 173
To realistically reflect the result, the number of subjects (shown below) should be the number of lesions for this analysis, however, this is not possible to enter into the system.

End point type	Other pre-specified

End point timeframe:

3-4 weeks after PDT 1 or 3-4 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55[12]	32[13]		
Units: percent				
arithmetic mean (confidence interval 95%)	80.9 (75.9 to 85.2)	21.4 (15.5 to 28.3)		

Notes:

[12] - Not subjects but number of lesions were analyzed (no. of lesions = 298)

[13] - Not subjects but number of lesions were analyzed (no. of lesions = 173)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Reduction of total lesion area 3-4 weeks after PDT 1 compared to baseline

End point title	Reduction of total lesion area 3-4 weeks after PDT 1 compared to baseline

End point description:

A tertiary efficacy variable was the reduction from baseline in total lesion area per patient assessed 3-4 weeks after PDT-1.

End point type	Other pre-specified

End point timeframe:

3-4 weeks after PDT 1

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	32		
Units: percent				
arithmetic mean (standard deviation)	-75.3 (± 37.65)	-27.7 (± 35.14)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Reduction of total lesion area 12 weeks after PDT 1 compared to baseline

End point title	Reduction of total lesion area 12 weeks after PDT 1 compared to baseline

End point description:

A tertiary efficacy variable was the reduction from baseline in total lesion area per patient assessed 12 weeks after PDT-1.

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 1

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	32		
Units: percent				
arithmetic mean (standard deviation)	-91.1 (± 19.48)	-34.3 (± 38.34)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Reduction of total lesion area 3-4 weeks after PDT 2 compared to baseline

End point title	Reduction of total lesion area 3-4 weeks after PDT 2 compared to baseline

End point description:

A tertiary efficacy variable was the reduction from baseline in total lesion area per patient assessed 3-4 weeks after PDT-2.

End point type	Other pre-specified

End point timeframe:

3-4 weeks after PDT 2

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	24		
Units: percent				
arithmetic mean (standard deviation)	-94.6 (± 15.09)	-30.3 (± 51.15)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Reduction of total lesion area 12 weeks after PDT 2 compared to baseline

End point title	Reduction of total lesion area 12 weeks after PDT 2 compared to baseline

End point description:

A tertiary efficacy variable was the reduction from baseline in total lesion area per patient assessed 12 weeks after PDT-2.

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 2

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	24		
Units: percent				
arithmetic mean (standard deviation)	-95.3 (± 15.41)	-44.9 (± 42.74)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Reduction of total lesion area 3-4 weeks after last PDT compared to baseline

End point title	Reduction of total lesion area 3-4 weeks after last PDT compared to baseline

End point description:

A tertiary efficacy variable was the reduction from baseline in total lesion area per patient assessed 3-4 weeks after last PDT.

End point type	Other pre-specified

End point timeframe:

3-4 weeks after PDT 1 or 3-4 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	32		
Units: percent				
arithmetic mean (standard deviation)	-88.2 (± 28.44)	-32.4 (± 48.45)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: New lesions in the treated field 12 weeks after PDT 2

End point title	New lesions in the treated field 12 weeks after PDT 2

End point description:

A tertiary efficacy variable was the number of new lesions in the treated field(s) 12 weeks after PDT-2.

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 2

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	29		
Units: subjects	0	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: New lesions in the treated fields 12 weeks after last PDT

End point title	New lesions in the treated fields 12 weeks after last PDT

End point description:

A tertiary efficacy variable was the number of new lesions in the treated field(s) 12 weeks after the last PDT.

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 1 or 12 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	32		
Units: subjects	0	1		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in skin quality assessments compared to baseline 12 weeks after last PDT

End point title	Change in skin quality assessments compared to baseline 12 weeks after last PDT

End point description:

Improvements in skin quality - parameter = Skin surface - 12 weeks after the last PDT compared to baseline (with the exclusion of patients who had no problems at baseline, thus making an improvement impossible).

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 1 or 12 weeks after PDT 2 which might have been necessary because not all lesions

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	25		
Units: percent				
arithmetic mean (confidence interval 95%)	69.6 (54.2 to 82.3)	32 (14.9 to 53.5)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in skin quality assessments compared to baseline 12 weeks after last PDT

End point title	Change in skin quality assessments compared to baseline 12 weeks after last PDT

End point description:

Improvements in skin quality - parameter = Hyperpigmentation - 12 weeks after the last PDT compared to baseline (with the exclusion of patients who had no problems at baseline, thus making an improvement impossible).

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 1 or 12 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	20		
Units: percent				
arithmetic mean (confidence interval 95%)	43.8 (26.4 to 62.3)	25 (8.7 to 49.1)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in skin quality assessments compared to baseline 12 weeks after last PDT

End point title	Change in skin quality assessments compared to baseline 12 weeks after last PDT

End point description:

Improvements in skin quality - parameter = Hypopigmentation - 12 weeks after the last PDT compared

to baseline (with the exclusion of patients who had no problems at baseline, thus making an improvement impossible).

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 1 or 12 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	13		
Units: percent				
arithmetic mean (confidence interval 95%)	44 (24.4 to 65.1)	15.4 (1.9 to 45.4)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in skin quality assessments compared to baseline 12 weeks after last PDT

End point title	Change in skin quality assessments compared to baseline 12 weeks after last PDT

End point description:

Improvements in skin quality - parameter = Mottled or irregular pigmentation - 12 weeks after the last PDT compared to baseline (with the exclusion of patients who had no problems at baseline, thus making an improvement impossible).

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 1 or 12 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	15		
Units: percent				
arithmetic mean (confidence interval 95%)	50 (29.9 to 70.1)	33.3 (11.8 to 61.6)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in skin quality assessments compared to baseline 12

weeks after last PDT

End point title	Change in skin quality assessments compared to baseline 12 weeks after last PDT

End point description:

Improvements in skin quality - parameter = Degree of scarring - 12 weeks after the last PDT compared to baseline (with the exclusion of patients who had no problems at baseline, thus making an improvement impossible).

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 1 or 12 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	8		
Units: percent				
arithmetic mean (confidence interval 95%)	35.7 (12.8 to 64.9)	12.5 (0.3 to 52.7)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change in skin quality assessments compared to baseline 12 weeks after last PDT

End point title	Change in skin quality assessments compared to baseline 12 weeks after last PDT

End point description:

Improvements in skin quality - parameter = Atrophy - 12 weeks after the last PDT compared to baseline (with the exclusion of patients who had no problems at baseline, thus making an improvement impossible).

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 1 or 12 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	9		
Units: percent				
arithmetic mean (confidence interval 95%)	47.1 (23 to 72.2)	0 (0 to 33.6)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Cosmetic outcome 12 weeks after last PDT

End point title	Cosmetic outcome 12 weeks after last PDT

End point description:

Very good and good cosmetic outcomes 12 weeks after last PDT

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 1 or 12 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum: patients with sum score at baseline of 0 to 3	Placebo: patients with sum score at baseline of 0 to 3	Verum: patients with sum score at baseline of 1 to 3	Placebo: patients with sum score at baseline of 1 to 3
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	54	29	48	26
Units: percent				
arithmetic mean (confidence interval 95%)	59.3 (45 to 72.4)	31 (15.3 to 50.8)	66.7 (51.6 to 79.6)	34.6 (17.2 to 55.7)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Patient satisfaction

End point title	Patient satisfaction

End point description:

Patient satisfaction was assessed at 12 weeks after last PDT (PDT-1 or PDT-2) using a 5-point scale of 0 to 4, where 0= very good, 1=good, 2=satisfactory, 3=unsatisfactory, and 4=impaired.

End point type	Other pre-specified

End point timeframe:

12 weeks after PDT 1 or 12 weeks after PDT 2 which might have been necessary because not all lesions were cleared after the first PDT

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	29		
Units: percent				
arithmetic mean (confidence interval 95%)				
Very good	27.8 (16.5 to 41.6)	6.9 (0.8 to 22.8)		

Good	63 (48.7 to 75.7)	37.9 (20.7 to 57.7)		
Satisfactory	7.4 (2.1 to 17.9)	17.2 (5.8 to 35.8)		
Unsatisfactory	1.9 (0 to 9.9)	37.9 (20.7 to 57.7)		
Impaired	0 (0 to 6.6)	0 (0 to 11.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

04-Oct-2013 (first patient signed informed consent) until 03-Sep-2014 (data base lock)

Adverse event reporting additional description:

AEs expected to occur as local discomfort were reported via patient questionnaires, local skin reaktions expected to occur were to be assessed by the assigned study team, any other AEs were to be reported by the patient or according to the assessment of the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Verum
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Verum	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 55 (3.64%)	0 / 32 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Femoral neck fracture			
subjects affected / exposed	1 / 55 (1.82%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 55 (1.82%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 55 (1.82%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	1 / 55 (1.82%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Verum	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 55 (100.00%)	22 / 32 (68.75%)	
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	53 / 55 (96.36%)	16 / 32 (50.00%)	
occurrences (all)	162	30	
Application site erythema			
subjects affected / exposed	51 / 55 (92.73%)	11 / 32 (34.38%)	
occurrences (all)	76	14	
Application site pruritus			
subjects affected / exposed	21 / 55 (38.18%)	9 / 32 (28.13%)	
occurrences (all)	25	10	
Application site scab			
subjects affected / exposed	20 / 55 (36.36%)	1 / 32 (3.13%)	
occurrences (all)	26	1	
Application site exfoliation			
subjects affected / exposed	17 / 55 (30.91%)	1 / 32 (3.13%)	
occurrences (all)	21	1	
Application site oedema			
subjects affected / exposed	12 / 55 (21.82%)	1 / 32 (3.13%)	
occurrences (all)	14	1	
Application site vesicles			
subjects affected / exposed	6 / 55 (10.91%)	0 / 32 (0.00%)	
occurrences (all)	6	0	
Application site discomfort			

subjects affected / exposed	5 / 55 (9.09%)	0 / 32 (0.00%)	
occurrences (all)	7	0	
Application site discharge			
subjects affected / exposed	3 / 55 (5.45%)	0 / 32 (0.00%)	
occurrences (all)	5	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 55 (10.91%)	0 / 32 (0.00%)	
occurrences (all)	7	0	

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