Clinical trial results:
The influence of occlusive application of 5-aminolaevulinic acid (ALA) on the efficacy of photodynamic therapy for actinic keratosis

Summary

EudraCT number	2014-003331-18
Trial protocol	AT
Global end of trial date	18 October 2016

Results information

Result version number	v1 (current)
This version publication date	23 September 2020
First version publication date	23 September 2020
Summary attachment (see zip file)	Paper (Meierhofer paper 21.03.20at.docx)

Trial information

Trial identification

Sponsor protocol code	PDTBG2

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Medizinische Universität Wien, Univ. Klinik für Dermatologie
Sponsor organisation address	Spitalgasse 23, Vienna, Austria, 1090
Public contact	Univ. Klinik für Dermatologie, Medizinische Universität Wien, Univ. Klinik für Dermatologie, +43 14040077020, sonja.radakovic@meduniwien.ac.at
Scientific contact	Univ. Klinik für Dermatologie, Medizinische Universität Wien, Univ. Klinik für Dermatologie, +43 14040077020, sonja.radakovic@meduniwien.ac.at

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 December 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The influence of occlusive application of 5-aminolaevulinic acid on the efficacy of photodynamic therapy in patients with actinic keratosis

Protection of trial subjects:

Pain was reduced during PDT by using a cooling airflow of –30° (Criojet, Air Mini, Linde Gas Therapeutics GmbH, Germany) and a fan integrated into the lamp. After PDT a cooled water gel (Avène Thermal Spring Water Gel, Pierre Fabre, France) was applied.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 45
Worldwide total number of subjects	45
EEA total number of subjects	45

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	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were asked at the dermatology departement of medical university vienna during routinely examinations if they want to take part in the presented study.
Patients were given written and verbal information on the nature of the study and signed informed consent was obtained before their enrolment.

Pre-assignment

Screening details:

45 patients with Fitzpatrick skin phototype I-III and mild-to-moderate AK (grade I-II according to Olsen et al.) on the scalp or face were enrolled. AK were diagnosed clinically. The size of the AK lesions ranged between 0.5 and 1.5 cm in diameter. Exclusion criteria were an age under 18 or over 90 years, hypersensitivity to ALA, porphyria, chroni

Pre-assignment period milestones

Number of subjects started	45
Intermediate milestone: Number of subjects	signed informed consent: 45
Number of subjects completed	45

Period 1

Period 1 title	Occlusive PDT treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

In all patients two target areas were randomly assigned to PDT with either occlusive or non-occlusive application of BF-200 ALA within a 1-week interval. Concealed randomization was done using Randomizer, a web-based program for prospective studies. Every patient was undergoing both treatments and thus served as his own control.

Arms

Are arms mutually exclusive?	No
Arm title	Occlusive PDT treatement

Arm description:

For occlusive treatment BF-200 ALA was applied in a thickness of 1 mm on the target area including a 5 mm margin of surrounding skin and allowed to dry for 10 minutes. The target area was then covered with an adhesive transparent dressing (Suprasorb®, Lohmann & Rauscher, Austria). After an incubation period of 3 hours during which the patients remained within the hospital all remnants of BF-200 ALA were removed with a 0.9% saline solution and illumination was performed with red light (635±9 nm; BF-RhodoLED©, Biofrontera Pharma GmbH, Leverkusen, Germany) at an irradiance of 62 mW/cm2 and a dose of 37 J/cm².

Arm type	Active comparator
Investigational medicinal product name	Adhesive transparent dressing (Suprasorb®, Lohmann & Rauscher, Austria)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous powder
Routes of administration	Cutaneous use

Dosage and administration details:

adhesive transparent dressing (Suprasorb®, Lohmann & Rauscher, Austria)

Arm title	Non occlusive PDT treatment

Arm description:
Treatment of the second target area was performed 2 – 7 days later in exactly the same way with the only exception that no occlusion was used after the application of BF-200 ALA

Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Occlusive PDT treatement	Non occlusive PDT treatment
Started	45	45
Occlusive PDT treatment	45	45
Completed	45	45

Baseline characteristics

Reporting groups	
Reporting group title	Occlusive PDT treatment

Reporting group description: -

Reporting group values	Occlusive PDT treatment	Total	
Number of subjects	45	45	
Age categorical			
Adults (18-90 years)			
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)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Adults (18-90 years)	45	45	
Gender categorical Units: Subjects			
Female	0	0	
Male	0	0	
not available	45	45	

End points

End points reporting groups

Reporting group title	Occlusive PDT treatement

Reporting group description:

For occlusive treatment BF-200 ALA was applied in a thickness of 1 mm on the target area including a 5 mm margin of surrounding skin and allowed to dry for 10 minutes. The target area was then covered with an adhesive transparent dressing (Suprasorb®, Lohmann & Rauscher, Austria). After an incubation period of 3 hours during which the patients remained within the hospital all remnants of BF-200 ALA were removed with a 0.9% saline solution and illumination was performed with red light (635±9 nm; BF-RhodoLED©, Biofrontera Pharma GmbH, Leverkusen, Germany) at an irradiance of 62 mW/cm2 and a dose of 37 J/cm².

Reporting group title	Non occlusive PDT treatment

Reporting group description:

Treatment of the second target area was performed 2 – 7 days later in exactly the same way with the only exception that no occlusion was used after the application of BF-200 ALA

Primary: complete clearance rate of the target lesion

End point title	complete clearance rate of the target lesion

End point description:

complete clearance rate of the target lesion (number of cleared target AK divided by the number of target AK at baseline x 100)

End point type	Primary

End point timeframe:

3 months after PDT

End point values	Occlusive PDT treatement	Non occlusive PDT treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: 43	38	25		

Attachments (see zip file)	Table 1 - clearance rate of target lesions 300dpi.jpg

Statistical analyses

Statistical analysis title	McNemar-test

Statistical analysis description:

Based on data in the literature a clearance rate of 85% was assumed for occlusive PTD and a 20 percent point decrease in efficacy as compared to occlusive application of ALA for non-occlusive PDT. According to these assumptions a sample size of 45 patients including a drop-out rate of 10% was calculated to ensure a power of 80% according to a one-sided McNemar-test. Target lesions were classified as completely cleared (yes/no)

Comparison groups	Occlusive PDT treatement v Non occlusive PDT treatment

Number of subjects included in analysis	86
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.001 [1]
Method	Mcnemar

Notes:

[1] - The clearance rate of the evaluable target lesions at 3 months after PDT was 88.4% (38/43) for occlusive BF-200 ALA PDT as compared to 58.1% (25/43) for non-occlusive PDT (Figure 2). The difference between the two mode of applications was highly sign

Secondary: total clearance rate of all AK in the target areas

End point title	total clearance rate of all AK in the target areas

End point description:

total clearance rate of all AK in the target areas (number of cleared AK within the target areas divided by the number of AK at baseline x 100)

End point type	Secondary

End point timeframe:

3 months after PDT

End point values	Occlusive PDT treatement	Non occlusive PDT treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: 265	240	176		

Attachments (see zip file)	Figure 3 - TCR 300dpi.jpg

Statistical analyses

Statistical analysis title	paired t-test

Statistical analysis description:

Total clearance rate of all AK lesions within the target areas at 3 months after PDT are presented in Figure 3. 90,6% (240/265) of the lesions treated with occlusive PDT and 70.4% (176/250) of AK treated with non-occlusive PDT showed complete clearance (p = 0.04).

Comparison groups	Occlusive PDT treatement v Non occlusive PDT treatment
Number of subjects included in analysis	86
Analysis specification	Post-hoc
Analysis type	superiority[2]
P-value	= 0.04 [3]
Method	t-test, 2-sided

Notes:

[2] - total clearance rate (complete clearance of all AK within the target areas) was analysed using a paired t-test

[3] - 90,6% (240/265) of the lesions treated with occlusive PDT and 70.4% (176/250) of AK treated with non-occlusive PDT showed complete clearance (p = 0.04)

Secondary: recurrence rate of target AK

End point title	recurrence rate of target AK

End point description:

recurrence rate of target AK (number of recurring target AK divided by the number of target AK at baseline x 100)

End point type	Secondary

End point timeframe:

6 months after PDT

End point values	Occlusive PDT treatement	Non occlusive PDT treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	38	25		
Units: 38	8	12		

Statistical analyses

Statistical analysis title	paired t-test

Statistical analysis description:

paired t-test

Comparison groups	Occlusive PDT treatement v Non occlusive PDT treatment
Number of subjects included in analysis	63
Analysis specification	Post-hoc
Analysis type	superiority[4]
P-value	= 0.016 [5]
Method	t-test, 2-sided

Notes:

[4] - The recurrence rate of all treated AK within the target areas was assessed using a paired t-test

[5] - 21.1% (8/38) for occlusive PDT and 48% (12/25) for non-occlusive PDT (p = 0.016). The difference was statistically significant

Secondary: recurrence rate of total AK

End point title	recurrence rate of total AK

End point description:

recurrence rate of total AK (number of recurrent AK divided by the number of all AK at baseline x 100)

End point type	Secondary

End point timeframe:

6 months after PDT

End point values	Occlusive PDT treatement	Non occlusive PDT treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: 240	49	87		

Statistical analyses

Statistical analysis title	paired t-test
Comparison groups	Occlusive PDT treatement v Non occlusive PDT treatment
Number of subjects included in analysis	86
Analysis specification	Post-hoc
Analysis type	superiority[6]
P-value	= 0.003 [7]
Method	t-test, 2-sided

Notes:

[6] - The recurrence rate of all treated AK within the target areas was assessed using a paired t-test

[7] - The recurrence rate within the target areas at 6 months after PDT was 20,4% (49/240) for occlusive PDT as compared to 49.4% (87/176) for non-occlusive PDT (p = 0.003)

Secondary: new AK in the target areas

End point title	new AK in the target areas

End point description:

new AK in the target areas measured 6 months after PDT

End point type	Secondary

End point timeframe:

6 months after PDT

End point values	Occlusive PDT treatement	Non occlusive PDT treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: 40	1	6		

Statistical analyses

Statistical analysis title	paired t-test
Comparison groups	Occlusive PDT treatement v Non occlusive PDT treatment
Number of subjects included in analysis	86
Analysis specification	Post-hoc
Analysis type	superiority[8]
P-value	= 0.63 [9]
Method	t-test, 2-sided

Notes:

[8] - One single new AK occurred in the target areas treated with occlusive PDT as compared to 6 AK after non-occlusive PDT. This difference was not statistically significant (p=0.63).

[9] - One single new AK occurred in the target areas treated with occlusive PDT as compared to 6 AK after non-occlusive PDT. This difference was not statistically significant (p=0.63).

Secondary: treatment-associated pain

End point title	treatment-associated pain

End point description:

treatment-associated pain that was evaluated on a visual analogue scale (VAS; range between 0 (no pain to 10 (unbearable pain)

End point type	Secondary

End point timeframe:
during PDT

End point values	Occlusive PDT treatement	Non occlusive PDT treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: VAS 0-10				
arithmetic mean (full range (min-max))	3.3 (0 to 10)	2.3 (0 to 100)		

Statistical analyses

Statistical analysis title	paired t-test

Statistical analysis description:

Pain intensity (arithmetic mean of all values obtained) and the severity of the phototoxic reaction (arithmetic mean of all summary scores) were analysed by means of paired t-test

Comparison groups	Occlusive PDT treatement v Non occlusive PDT treatment
Number of subjects included in analysis	86
Analysis specification	Post-hoc
Analysis type	superiority[10]
P-value	< 0.001 [11]
Method	t-test, 2-sided

Notes:

[10] - Pain intensity (arithmetic mean of all values obtained) and the severity of the phototoxic reaction (arithmetic mean of all summary scores) were analysed by means of paired t-test
[11] - The mean pain score during illumination after occlusive PDT was 3.3 (min. 0, max. 6.4) as compared to 2.3 (min. 0, max. 5.6) for non-occlusive PDT (p < 0.001)

Secondary: severity of the phototoxic skin reaction

End point title	severity of the phototoxic skin reaction

End point description:

severity of the phototoxic skin reaction (sum score of erythema, oedema and blistering each graded between 0 – 4; 0 = absent, 1 = slight, 2 = moderate, 3 = strong, 4 = very strong)

End point type	Secondary

End point timeframe:

2 and 7 days after PDT

End point values	Occlusive PDT treatement	Non occlusive PDT treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: 0-4				
arithmetic mean (full range (min-max))	2.8 (0 to 4)	2.1 (0 to 4)		

Statistical analyses

Statistical analysis title	paired t-test

Statistical analysis description:

The mean phototoxicity 7 days after PDT was 2.8 and 2.1 ($p < 0.001$)

Comparison groups	Occlusive PDT treatement v Non occlusive PDT treatment
Number of subjects included in analysis	86
Analysis specification	Post-hoc
Analysis type	superiority[12]
P-value	< 0.001 [13]
Method	t-test, 2-sided

Notes:

[12] - Pain intensity (arithmetic mean of all values obtained) and the severity of the phototoxic reaction (arithmetic mean of all summary scores) were analysed by means of paired t-test
[13] - The mean phototoxicity score 7 days after PDT was 2.8 and 2.1 ($p < 0.001$)

Secondary: cosmetic outcome

End point title	cosmetic outcome

End point description:

cosmetic outcome which was graded as excellent (absence of erythema and/or hypo-/hyperpigmentation and/or scarring), moderate (slight erythema and/or hypo-/hyperpigmentation and/or scarring) and poor (substantial erythema and/or hypo-/hyperpigmentation and/or scarring)

End point type	Secondary

End point timeframe:

6 months after PDT

End point values	Occlusive PDT treatement	Non occlusive PDT treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: 0-3				
arithmetic mean (full range (min-max))	00 (0 to 3)	0 (0 to 3)		

Statistical analyses

Statistical analysis title	McNemar-Bowker test

Statistical analysis description:

The difference in cosmetic outcome was tested using the McNemar-Bowker test

Comparison groups	Occlusive PDT treatement v Non occlusive PDT treatment

Number of subjects included in analysis	86
Analysis specification	Post-hoc
Analysis type	superiority[14]
P-value	= 0.508 [15]
Method	Mcnemar

Notes:

[14] - The difference in cosmetic outcome was tested using the McNemar-Bowker test

[15] - The overall cosmetic outcome was rated excellent for both methods without a significant difference between the two treatments (p = 0.508).

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
During the study (reporting until 6 months after PDT)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	intolerable pain

Reporting group description:

Out of all 45 enrolled patients two were excluded from the final analysis, one due to intolerable pain during PDT necessitating early termination of illumination and the other because of using imiquimod for treating a basal cell carcinoma adjacent to the target area subsequently to PDT

Serious adverse events	intolerable pain		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 43 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	intolerable pain		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 43 (2.33%)		
Skin and subcutaneous tissue disorders			
intolerable pain	Additional description: Out of all 45 enrolled patients two were excluded from the final analysis, one due to intolerable pain during PDT necessitating early termination of illumination		
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		

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