



## 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,<br>Univ. Klinik für Dermatologie, +43 14040077020,<br>sonja.radakovic@meduniwien.ac.at |
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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:

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**Results analysis stage**

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|  |                  |
|--|------------------|
| 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:

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**General information about the trial**

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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:

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**Population of trial subjects**

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**Subjects enrolled per country**

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

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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 department 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                      |
| <b>Arm title</b>             | Occlusive PDT treatment |

#### 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/cm<sup>2</sup> and a dose of 37 J/cm<sup>2</sup>.

|  |   |
|--|---|
| 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)

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Non occlusive PDT treatment |
|------------------|-----------------------------|

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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

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|          |                 |
|----------|-----------------|
| Arm type | No intervention |
|----------|-----------------|

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|   |  |
|---|--|
| No investigational medicinal product assigned in this arm |  |
|---|--|

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| <b>Number of subjects in period 1</b> | Occlusive PDT<br>treatment | Non occlusive PDT<br>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 treatment     |
| Reporting group description:<br>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/cm <sup>2</sup> and a dose of 37 J/cm <sup>2</sup> . |                             |
| Reporting group title  | Non occlusive PDT treatment |
| Reporting group description:<br>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:<br>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:<br>3 months after PDT  |  |

| End point values            | Occlusive PDT treatment | 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:<br>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 treatment v Non occlusive PDT treatment |

|   |                        |
|---|------------------------|
| Number of subjects included in analysis | 86                     |
| Analysis specification                  | Post-hoc               |
| Analysis type                           | superiority            |
| P-value                                 | < 0.001 <sup>[1]</sup> |
| 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:<br>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:<br>3 months after PDT  |  |

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

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Attachments (see zip file)</b> | Figure 3 - TCR 300dpi.jpg |
|-----------------------------------|---------------------------|

### Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | paired t-test   |
| Statistical analysis description:<br>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 treatment v Non occlusive PDT treatment |
| Number of subjects included in analysis   | 86  |
| Analysis specification  | Post-hoc  |
| Analysis type   | superiority <sup>[2]</sup>                            |
| P-value   | = 0.04 <sup>[3]</sup>                                 |
| 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 treatment | 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 treatment v Non occlusive PDT treatment

Number of subjects included in analysis 63

Analysis specification Post-hoc

Analysis type superiority<sup>[4]</sup>

P-value = 0.016 <sup>[5]</sup>

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 treatment | Non occlusive PDT treatment |  |  |
|-----------------------------|-------------------------|-----------------------------|--|--|
| Subject group type          | Reporting group         | Reporting group             |  |  |
| Number of subjects analysed | 43                      | 43                          |  |  |
| Units: 240                  | 49                      | 87                          |  |  |



## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | paired t-test   |
| Comparison groups                       | Occlusive PDT treatment v Non occlusive PDT treatment |
| Number of subjects included in analysis | 86  |
| Analysis specification                  | Post-hoc  |
| Analysis type                           | superiority <sup>[6]</sup>                            |
| P-value                                 | = 0.003 <sup>[7]</sup>                                |
| 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:<br>new AK in the target areas measured 6 months after PDT |                            |
| End point type   | Secondary                  |
| End point timeframe:<br>6 months after PDT                                       |                            |

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

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>       | paired t-test   |
| Comparison groups                       | Occlusive PDT treatment v Non occlusive PDT treatment |
| Number of subjects included in analysis | 86  |
| Analysis specification                  | Post-hoc  |
| Analysis type                           | superiority <sup>[8]</sup>                            |
| P-value                                 | = 0.63 <sup>[9]</sup>                                 |
| 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:<br>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 treatment | 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:<br>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 treatment v Non occlusive PDT treatment |
| Number of subjects included in analysis  | 86  |
| Analysis specification   | Post-hoc  |
| Analysis type  | superiority <sup>[10]</sup>                           |
| P-value  | < 0.001 <sup>[11]</sup>                               |
| 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:<br>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:<br>2 and 7 days after PDT   |  |

| End point values                       | Occlusive PDT treatment | 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

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | paired t-test   |
| Statistical analysis description:<br>The mean phototoxicity 7 days after PDT was 2.8 and 2.1 ( $p < 0.001$ ) |   |
| Comparison groups  | Occlusive PDT treatment v Non occlusive PDT treatment |
| Number of subjects included in analysis  | 86  |
| Analysis specification   | Post-hoc  |
| Analysis type  | superiority <sup>[12]</sup>                           |
| P-value  | $< 0.001$ <sup>[13]</sup>                             |
| 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:<br>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:<br>6 months after PDT  |                  |

| End point values                       | Occlusive PDT treatment | 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

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | McNemar-Bowker test                                   |
| Statistical analysis description:<br>The difference in cosmetic outcome was tested using the McNemar-Bowker test |   |
| Comparison groups  | Occlusive PDT treatment v Non occlusive PDT treatment |

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 86                          |
| Analysis specification                  | Post-hoc                    |
| Analysis type                           | superiority <sup>[14]</sup> |
| P-value                                 | = 0.508 <sup>[15]</sup>     |
| 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

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported