BF-200 ALA for the photodynamic treatment of non-aggressive basal cell carcinoma: Results of a phase III comparator trial

Authors: C. A. Werfel, R. H. Sperneth, R. Dominis, T. Wende, S. D. Nielsen, B. Schmidt, H. Lübbert*

Institutes: Department of Dermatology, Stirling Community Hospital, NHS Forth Valley, UK
Department of Dermatology and Allergology, Westfälische Wilhelms-University, Münster, Germany
Department of Dermatology, Clinic of Internal Medicine, University of Münster, Germany
Department of Dermatology and Allergology, Westfälische Wilhelms-University, Münster, Germany
Department of Dermatology, University of Bonn, Bonn, Germany
Biofrentera Biscay Labor GmbH, Biscay, Spain

Introduction
Basal cell carcinoma (BCC) represents the most common type of non-melanoma skin cancer (NMSC) worldwide, showing dramatically increasing incidence rates. Surgical excision is the most appropriate treatment of BCC. Nevertheless, alternative therapeutic concepts might be considered to overcome drawbacks associated with surgical treatment, particularly cosmetic outcome, inoperable tumor size, the need for reconstructive surgery after treatment of multiple or larger tumors or treatment related morbidity.

Photodynamic therapy (PDT) is characterized by short treatment and down time, excellent patient compliance, high efficacy rates and remarkable cosmetic results. PDT using methylaminolevulinate (MAL) (brand name: ALA) is highly effective in the treatment of small to moderate actinic keratosis on the face and scalp and of field carcinoma in adults [1-3].

This study (ALA-BCC-T008) was conducted to demonstrate the non-inferiority of BF-200 ALA compared to MAL (a cream containing 8% methylaminolevulinate) in the treatment of thin non-aggressive basal cell carcinoma (BCC) using PDT. Based on this trial, BF-200 ALA was recently approved in the EU for the treatment of superficial and/or nodular BCC, unsuitable for surgical treatment.

Trial protocol - ALA-BCC-T008

Medication
- BF-200 ALA contains 7.5% 5-aminolevulinate free ALA equivalent to 10% ALA hydrochloride
- MAL contains 16.8% methylaminolevulinate (MAL) equivalent to 23.3% MAL hydrochloride

Patients
- This double-blind, placebo-controlled, level I trial with an ongoing 5-year follow-up was conducted in 26 centers in Germany and the UK
- Male and female subjects aged 30-70 years of age diagnosed with 5-10 non-aggressive BCC on the facial skin, neck, trunk, and/or extremities were enrolled
- A total of 280 BCC patients were included and randomized in two study arms, 139 treated with BF-200 ALA and 141 with MAL
- All patients were Caucasian and the mean age was 63.4 (range: 55-75 years; 63% male; 37% female) (population)
- 10% of the patients (PPP) belonged to Fitzpatrick Skin Type I and II

Treatment procedure
- Histopathological confirmation of non-aggressiveness and a thickness ≤ 2 mm was performed according to WHO guidelines
- All lesions' surfaces were scraped gently using a curette or scalpel blade to get rid of exposed tumor material
- Two PDT sessions each week apart (PDT cycle) were performed using a 5-6mJ per spot laser (650-nm light, spot size up to 25 mm, 5-10J in) 3 times after drug application
- In case of remaining lesions twelve weeks after the first PDT cycle, patients were retreated with another cycle (2nd PDT cycle)

Endpoints and follow-up
- Two main endpoints comprised patient and lesion complete clearance of weeks after the last PDT
- Follow-up analysis was performed at 0, 2, 8, 24, 36 and 60 months

Patient disposition and lesion characteristics - ALA-BCC-T008

A. Patient disposition

<table>
<thead>
<tr>
<th>Variable</th>
<th>BF-200 ALA</th>
<th>MAL</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCC lesions at baseline</td>
<td>246</td>
<td>128</td>
<td>374</td>
</tr>
<tr>
<td>BCC lesions at per patient, mean (SD)</td>
<td>12 (4)</td>
<td>12 (4)</td>
<td>12 (4)</td>
</tr>
<tr>
<td>BCC category, % (N)</td>
<td>481 (33)</td>
<td>432 (30)</td>
<td>481 (33)</td>
</tr>
<tr>
<td>nBCC only</td>
<td>213 (15)</td>
<td>213 (15)</td>
<td>213 (15)</td>
</tr>
<tr>
<td>nBCC only</td>
<td>195 (15)</td>
<td>195 (15)</td>
<td>195 (15)</td>
</tr>
<tr>
<td>Others</td>
<td>51 (3.5)</td>
<td>51 (3.5)</td>
<td>51 (3.5)</td>
</tr>
<tr>
<td>Facial</td>
<td>31 (12)</td>
<td>31 (12)</td>
<td>31 (12)</td>
</tr>
<tr>
<td>Head/Neck</td>
<td>20 (7.8)</td>
<td>20 (7.8)</td>
<td>20 (7.8)</td>
</tr>
<tr>
<td>Extremities</td>
<td>24 (9)</td>
<td>24 (9)</td>
<td>24 (9)</td>
</tr>
<tr>
<td>Thickness of BCC (mm, median (range))</td>
<td>4.6 (1, 32)</td>
<td>4.6 (1, 32)</td>
<td>4.6 (1, 32)</td>
</tr>
</tbody>
</table>

B. BCC lesion characteristics before treatment

References

Figure 1: Time to complete elimination 12 weeks after the last PDT. The Kaplan-Meier estimate of time to complete regression of all lesions after the last PDT is shown for BF-200 ALA and MAL. ALA = methylaminolevulinate; BF-200 ALA = ALA 200 mg cream; MAL = methylaminolevulinate cream. The curves are compared using a log-rank test.

PDT with BF-200 ALA results in a predominantly very good and good cosmetic outcome 12 weeks after the last PDT.

CONCLUSION
In the present phase III study, PDT of non-aggressive BCC was performed using BF-200 ALA cream compared to MAL cream.

- BF-200 ALA shows a trend towards higher efficacy than MAL in the treatment of non-aggressive BCC
- High statistical significance for non-inferiority of BF-200 ALA (major statistical endpoint)
- Thicker and nodular BCC respond better to BF-200 ALA than MAL.
- Treatment emergence adverse events were comparable between the two treatment groups

C. Improvement of non-damaged skin

- High lesion complete clearance rates were achieved in lesions with a baseline thickness of 8.0 ± 0.0 mm
- More than 90% of initially cleared lesions were still cleared 12 months after the last treatment
- All subgroup analyses revealed non-inferiority of BF-200 ALA