Photodynamic therapy for actinic keratosis and field cancerization using BF-200 ALA: Results of pivotal Phase III trials and follow-up

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Introduction

BF-200 ALA is a gel containing 7.8% 5-aminolevulinic acid in a nanoscale lipid vesicle formulation. It is approved under the brand name of Ameluz® for lesion and field-directed treatment of mild to moderate AK on the face and scalp in the USA and Europe, and in the EU also for field cancerization and superficial and nodular BCC.The concept of field cancerization (introduced by Slaughter in the early 50s) is defined as the presence of one or more areas with genetically altered epidermal cells including visible and non- visible lesions (subclinical lesions). These lesions have a monoclonal origin and do not show invasive or metastatic patterns. To fully attend field cancerization in AK treatment, a field-directed, selective approach like photodynamic therapy (PDT)is recommended.

We herein report the results of 3 phase III trials to assess clinical efficacy and safety of BF-200 ALA in a total of 780 patients with 4-8 mild to moderate lesions of actinic keratosis. Two studies investigated the efficacy of lesion-directed PDT with BF-200 ALA, while a third study employed field treatment to address whole cancerized fields of AK. All studies used red light sources for illumination, including LED narrow spectrum lamps (~635 nm).

Trial protocols - Actinic Keratosis

Medication

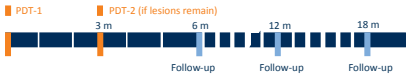
- BF-200 ALA contains 7.8% 5-aminolevulinic free acid (ALA) equivalent to 10% ALA hydrochloride
- MAL contains 16.8% methyl-aminolevulinate (MAL) equivalent to 21.3% MAL hydrochloride
- Placebo to BF-200 ALA gel

Patients & treatment procedure

- Three pivotal studies were conducted in centers in Germany, Switzerland and Austria to demonstrate efficacy and safety of BF-200 ALA
- BF-200 ALA-PDT was applied to a total of 780 patients (BF-200 ALA: 384 patients, MAL: 247 patients, vehicle: 149 patients) with 4-8 mild to moderate AK lesions,
- encompassing 87 patients enrolled in a randomized, double-blind trial comparing BF-200 ALA (55 patients) and vehicle (32 patients) on entire treatment fields (field cancerization) of max. 20 cm^2
- The illumination session was performed 3 h after drug application with narrow-spectrum LED (~630 nm) or incoherent broad-spectrum light sources (~570-670 nm)
- In case of remaining lesions after 1st PDT, a second treatment was performed after three months

Endpoints

- Primary endpoint: patient complete response 12 weeks after last PDT
- Secondary endpoint. lesion complete response 12 weeks after last PDT



Results

Placebo-controlled phase III trial for AK

Placebo-controlled, multicentric study on 122 patients using Aktilite® CL128 (narrow spectrum) and PhotoDyn® 750 (broad spectrum) (ALA-AK-CT003)

Treatment group	BF-200 ALA		Placebo
Efficacy	LED narrow-band lamp	Broad-spectrum lamp	
Patient complete response [%] (PP)*	96.4	53.1	10.8
Lesion complete response [%] (PP)	98.8	70.5	22
Safety	**LED narrow-band lamp**	**Broad-spectrum lamp**	
Severe erythema [%] Moderate edema [%] Moderate induration [%]	9.3 32 22.2	0 0 0	0 0 0
Pain [%] (light to severe)	72.7	22	4.3

*Primary clinical endpoint: patient complete clearance 12 weeks after last PDT

- BF-200 ALA reaches high clinical efficacies (significantly superior to placebo)
- Highest efficacies are reached in combination with a LED light source
- These very high efficacies (up to 96% patient complete clearance) correlate with increased side effects

Comparator-controlled phase III trial for AK

Three-arm multicentric study with BF-200 ALA (Ameluz®), MAL (Metvix®), and Placebo (3:3:1) on 570 patients using Aktilite® CL128, Omnilux PDT™ (both LED), PhotoDyn®750, and Waldmann® PDT 1200 (both broad-spectrum) (ALA-AK-CT002)

Primary clinical endpoint: patient complete clearance 12 weeks after last PDT

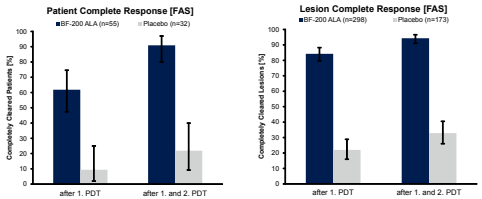
Treatment group (FAS)	BF-200 ALA	MAL	Placebo
Patient complete response [%], all light sources*	78.2	64.2	17
Patient complete response [%], LED light source§	84.8	67.5	13
Patient complete response [%], broad-spectrum light source	71.5	61.3	22
Lesion complete response [%], LED light source*	93.6	89.3	32.5
Lesion complete response [%], broad-spectrum light source§	86.3	76.3	42.8
P_{ICR} CR [%]†	53	41	---

*For the primary endpoint, patient complete clearance, BF-200 ALA was significantly superior with 78.2% over MAL (64.2%) and placebo (17%) (p<0.05 and p<0.0001).
BBF-200 ALA was significantly superior with 84.8% over MAL (67.5%) and placebo (12.8%) (p<0.0013 and p<0.0001).
§BF-200 ALA was significantly superior with 93.6% over MAL (89.3%) and placebo (32.5%) (p<0.004 and p<0.0001).
§BF-200 ALA was significantly superior with 86.3% over MAL (76.3%) and placebo (42.8%) (p<0.0003 and p<0.0001).
†Probability for a pre-therapy patient to remain cleared 12 months after the last treatment (PICR), LED light sources.

- BF-200 ALA showed significantly higher patient complete clearance rates compared to MAL and placebo
- LED light sources revealed the highest efficacies for PDT with BF-200 ALA
- Despite its higher efficacy, BF-200 ALA does not lead to an enhanced side effect profile
- Cosmetic outcome is judged as excellent

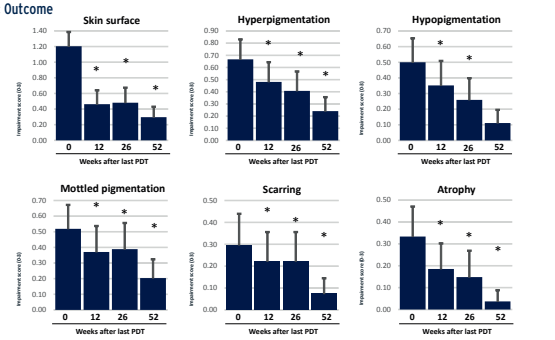
Placebo-controlled phase III trial for AK field treatment (with the red light source BF-RhodoLED®)

A. Clinical Efficacy



- Over 60% of the patients were completely cleared after only one field-directed PDT
- Over 90% patient complete response was reached with a maximum of two PDTs (primary endpoint 12 weeks after the last PDT)
- Long-term patient complete clearance rates for BF-200 ALA were 75.5% and 63.3% after 6 and 12 months after the last PDT, respectively
- No new safety issues became apparent with field treatment

B. Cosmetic Outcome



Impairment score: 0 - none, 1 - mild, 2 - moderate, 3 - severe (Data are mean ± 95% CI); *p<0.05, versus score at 0 weeks (baseline) after last PDT (paired T-test)

- Field treatment with BF-200 ALA allows quantification of the skin rejuvenation effect of PDT
- Impairment and long-term improvement was quantified by physicians
- A continued improvement was demonstrated 12 months after PDT with BF-200 ALA and red light

Conclusions

- BF-200 ALA gel constitutes a stabilized and penetration-enhancing formulation for use in PDT
- Clinical phase III trials revealed a high and sustainable efficacy of BF-200 ALA for AK treatment significantly higher than for MAL
- BF-200 ALA is approved for lesion- and field-directed treatment of AK
- PDT with BF-200 ALA significantly improves sund-induced skin impairment, resulting in an excellent cosmetic outcome

The presented phase III trials demonstrate very high efficacy for both AK and field cancerization and an excellent safety and cosmetic outcome.

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