Daylight photodynamic therapy of Actinic Keratosis with BF-200 ALA compared to MAL

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Introduction

Topical photodynamic therapy (PDT) is a non-invasive treatment option for skin diseases such as non-melanoma skin cancer. In general, there are three requirements for PDT: a photosensitizer, molecular oxygen and light of a specific wavelength. Commonly, dermatological PDT is based on the topical application of a prodrug to the skin, which is then converted by the cells, especially by neoplastic cells, into the actual photosensitizer. The activation of this photosensitizer by light induces the formation of reactive oxygen species (ROS). If a sufficient amount of ROS is obtained, cell death is induced. One extensively studied prodrug is 5-aminolevulinic acid (ALA), an endogenous precursor for the heme biosynthesis, which is converted into the photosensitizer protoporphyrine IX (PpIX). In contrast to conventional PDT (c-PDT) with light of a certain wavelength to specifically excite one absorption peak of PpIX, daylight-PDT (DL-PDT) takes advantage of the natural visual spectrum of light which contains the necessary wavelengths to excite several PpIX peaks. Furthermore, the protocol is altered regarding incubation time. While during c-PDT a high amount of PpIX accumulates and is excited within short time, DL-PDT relies on the constant production and excitation of PpIX molecules within 2 h. A strong advantage of DL-PDT lies in the reduced intensity of pain during treatment[1,2].

BF-200 ALA (Ameluz®) is a gel containing 7.8% 5-aminolevulinic acid in a nanoscale lipid vesicle formulation. Following development for topical use in photodynamic therapy by Biofrontera, it obtained EU- and US-wide approval for the lesion- and field-directed treatment of mild and moderate actinic keratosis (AK). Additionally, EU-wide approval for the treatment of certain types of basal cell carcinoma (BCC) was recently granted.

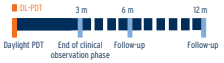
Objective

This study was conducted to demonstrate the non-inferiority of the efficacy, safety, and cosmetic outcome of BF-200 ALA (a nanoemulsion formulation containing 7.8% 5-aminolevulinic acid, FDA approved under the brand name Ameluz®) compared to MAL in the treatment of mild to moderate AK in a daylight-mediated photodynamic therapy (PDT) setting.

Trial protocol - Daylight-mediated photodynamic therapy for Actinic Keratosis

Medication

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



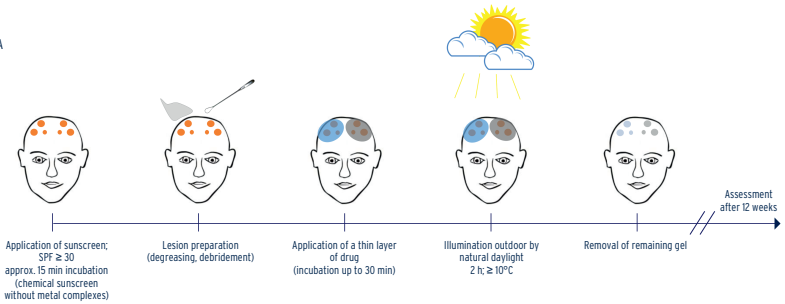
Patients & treatment procedure

- Randomized, observer-blind, intra-individual phase III trial with a 1-year follow-up was performed in 7 centers in Germany and Spain
- 52 patients with clinically mild to moderate AK lesions on face and scalp were treated after randomization
- After application of a thin layer of drug, a single two hours illumination by natural daylight was performed (figure 1 A)
- Follow-up 6 and 12 months

Endpoints

- Primary efficacy variable is the total lesion clearance rate in percent per patient's side assessed 12 weeks after PDT
- Different characteristics of lesions, temperature and weather conditions were included as secondary endpoints

A



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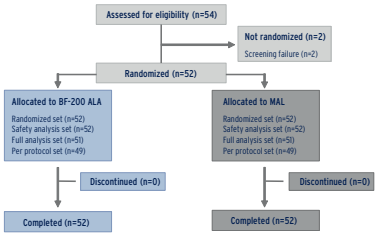

C

Variable	BF-200 ALA	MAL	Total
Total number of lesions	334	332	666
Number of target lesions per patient side			
Mean ± SD	6.4 ± 2.2	6.4 ± 2.2	12.8 ± 4.2
Median (Range)	6.5 (3-9)	7.0 (3-9)	13.0 (6-18)
Lesion location, n (%)			
Face	142 (21.3)	138 (20.7)	280 (42.0)
Scalp	192 (28.8)	194 (29.1)	386 (58.0)
Lesion severity, n (%)			
Mild	163 (24.5)	165 (24.8)	330 (49.5)
Moderate	171 (25.7)	190 (28.5)	336 (50.5)
Target lesion size, mm²			
Mean ± SD	81.4 ± 35.3	78.2 ± 36.0	79.8 ± 35.7
Median	72.0	72.0	72.0
Range	25 to 225	25 to 225	25 to 225

Figure 1: A) Schematic overview of the DL-mediated PDT workflow (ALA-AK-CT009 study). B) Flow chart of patient disposition: 54 patients were enrolled, 52 patients were randomized for an intra-individual study on DL-mediated PDT with BF-200 ALA and MAL. C) Summary of AK baseline characteristics (on a lesion basis)

Results- Daylight-mediated PDT for AK[8]

Table 1: Endpoints and subgroup analyses of the single daylight PDT treatment on 52 patients with BF-200 ALA and MAL (ALA-AK-CT009)

Endpoints and subgroup analyses		BF-200 ALA	MAL
Primary endpoint	**complete lesion clearance rate** (clinically confirmed; PPS)	**79.8%**	**76.5%**
Secondary endpoint	**complete lesion clearance rate** (histologically confirmed; FAS)	**72.5%**	**66.7%**
Subgroup analyses (of primary endpoint)	**lesion response rates** (FAS)		
	• face	85%	84%
	• bald scalp	72%	65%
	• moderate AKs	76%	73%
	• mild AKs	94%	91%
	• ≤ 5 AKs	83%	81%
	• > 5 AKs	77%	72%
	• < 65 years old	83%	74%
	• treatment during cloudy weather	75%	66%
	• treatment during sunny weather	85%	83%

FAS, full analysis set; PPS, per protocol set

- The assessment 12 weeks after a single PDT revealed a complete lesion clearance rate of 80% of AKs treated with BF-200 ALA gel and 77% of AKs treated with MAL cream, demonstrating a non-inferiority with a high level of significance (table 1).
- Subgroup analyses revealed mild AK lesions to be the most responsive, with complete lesion clearance of 94% for BF-200 ALA and 91% for MAL, respectively.
- Differences among both treatment sides were observed during cloudy weather with a complete lesion clearance rate of 75% for the BF-200 ALA-treated side and 66% for the MAL-treated side.
- No differences have been observed regarding treatment emergent adverse events which occurred in all patients treated.
- The assessment of pain intensity during daylight PDT, recorded by the patient via 11-point VAS (visual analogue scale), revealed similar pain

		Pain intensity[a]		
		BF-200 ALA	MAL	Total[#]
Overall	n	52	52	104
	Mean ± SD	1.2 ± 2.1	1.1 ± 2.2	1.1 ± 2.1
Face	n	24	24	48
	Mean ± SD	1.5 ± 2.6	1.5 ± 2.9	1.5 ± 2.7
Scalp	n	32	32	64
	Mean ± SD	0.8 ± 1.5	0.7 ± 1.2	0.7 ± 1.3

Table 2: Pain intensity analysis regarding DL-PDT treatment on 52 patients with BF-200 ALA and MAL.[a] Pain scale ranging from no pain at all (0) to worst possible pain (10); #Total considered total treatments (2 per patient); Data presented for SAF (safety analysis set).

Conclusions

What is known about the topic?

- DL-PDT has recently been shown to be an efficient and nearly painfree protocol for AK
- BF-200 nanoemulsion stabilizes ALA and enhances its penetration through the stratum corneum for use in PDT
- BF-200 ALA has already shown excellent therapeutic results in c-PDT of BCC and AK (lesion and field-directed treatment)[3-7]

What does this study add?

Daylight-mediated PDT of Actinic Keratosis with BF-200 ALA is:

- Highly effective even under cloudy weather conditions
- Well tolerated with a reduced level of pain compared to c-PDT
- Significantly non-inferior to MAL

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