30 January 2020
EMA/143592/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ameluz

International non-proprietary name: 5-aminolevulinic acid

Procedure No. EMEA/H/C/002204/II/0039/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE adverse event

AK actinic keratosis

ALA or 5-ALA 5-aminolaevulinic acid hydrochloride

ALT alanine aminotransferase (SGPT)

AMG Arzneimittelgesetz (German drug law)

AP alkaline phosphatase

AST aspartate aminotransferase (SGOT)

ß-HCG β human chorionic gonadotropin

BCC basal cell carcinoma

BF-200 nanoemulsion BF-200

BF-200 ALA drug product with nanoemulsion BF-200 and 10% ALA HCl, if not otherwise indicated

BLLQ below the lower limit of quantification

Cm centimeter(s)

Cmax maximal concentration

CSR clinical study report

DNA deoxyribonucleic acid

EDTA ethylenediaminetetraacetic acid

FAS full analysis set

FDA United States Food and Drug Administration

G gram(s)

GCP good clinical practice

H hour(s)

HCl hydrochloric acid

Hg mercury

IMP investigational medicinal product(s)

ISE integrated summary of effectiveness

ITT intent-to-treat

J Joule

LDH lactate dehydrogenase

LLOQ lower limit of quantification

LOCF last observation carried forward

MAL methyl-aminolaevulinate

MedDRA Medical Dictionary for Regulatory Activities

Mg milligram(s)

mL milliliter(s)

mm millimeter(s)

nBCC nodular basal cell carcinoma

ng nanogram

nm nanometer

NMSC non-melanoma skin cancer

PDT photodynamic therapy

PK pharmacokinetics

PI prescribing information

PpIX protoporphyrin IX

PP Per protocol

PPS Per protocol set

PT preferred term

RBC red blood cells

ROS reactive oxygen species

SAE serious adverse event

SAF Safety analysis set

SAP statistical analysis plan

sBCC superficial basal cell carcinoma

SCC squamous cell carcinoma

SOC(s) system organ class(es)

TEAE treatment-emergent adverse event

UV ultraviolet

WBC white blood cells / leukocytes

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Biofrontera Bioscience GmbH submitted to the European Medicines Agency on 28 August 2019 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Extension of indication to include the treatment of mild to severe actinic keratosis on extremities, trunk and neck for Ameluz; as a consequence, sections 4.1, 4.8 and 5.1 of the SmPC and the Package Leaflet are updated accordingly. In addition, section 5.1 of the SmPC is updated based on follow-up data from study ALA-AK-CT009, a randomised, observer-blind, intra-individual phase III study to evaluate the safety and efficacy of Ameluz (5-aminolevulinic acid) in combination with daylight PDT (photodynamic therapy) in comparison with methyl-5-aminolevulinate for the treatment of mild to moderate actinic keratosis.

The group of variations requested amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/157/2009 on (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Janet Koenig Co-Rapporteur: Peter Kiely

Timetable	Actual dates
Submission date	28 August 2019
Start of procedure:	14 September 2019
Rapporteur's preliminary assessment report circulated on	7 November 2019
CoRapporteur's preliminary assessment report circulated on	8 November 2019
CHMP members comments	2 December 2019
Joint Rapporteur's updated assessment report circulated on	6 December 2019
Request for supplementary information and extension of timetable adopted by the CHMP on:	12 December 2019
MAH's responses submitted to the CHMP on:	20 December 2020
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	16 January 2020
CHMP members comments	20 January 2020
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	22 January 2020
CHMP opinion:	30 January 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Actinic keratosis (AK) is a skin lesion induced by ultraviolet light and is considered an in-situ squamous cell carcinoma of the skin. AK may progress to invasive squamous cell carcinoma. It is by far the most common lesion with malignant potential to arise in the skin.

Epidemiology and risk factors

AK is mostly seen in fair-skinned persons on skin areas that have had long-term sun exposure. Epidemiological data show a high occurrence rate of AK. Regions with higher exposure to ultraviolet light have a higher prevalence of AK. In Europe, a prevalence of 15% in men and 6% in women has been documented. Over the age of 70 years, 34% of men and 18% of women were found to have AK. The USA show prevalences between 11 to 26% and in Australia, the country with the highest skin cancer rate in the world, the prevalence of actinic keratosis among adults older than 40 years has been

reported to range from 40 to 60%. Current national and international guidelines recommend the treatment of AKs in order to prevent their potential progression into SCC.

2.1.2. About the product

Ameluz (5-aminolaevulinic acid) gel had been approved in the EU on 14 December 2011.

The current indications of Ameluz (gel) are:

- Treatment of actinic keratosis of mild to moderate severity on the face and scalp (Olsen grade 1 to 2; see section 5.1) and of field cancerization in adults

- Treatment of superficial and/or nodular basal cell carcinoma unsuitable for surgical treatment due to possible treatment-related morbidity and/or poor cosmetic outcome in adults.

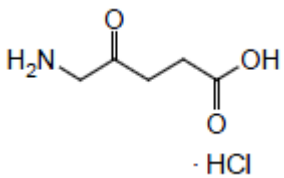
Pharmaceutical information:

BF-200 ALA 10% (Ameluz) is a non-sterile, topical formulation of 10% 5-aminolevulinic acid hydrochloride in a gel-matrix with nanoemulsion. BF-200 ALA 10% contains 10% ALA as hydrochloride salt, equaling 7.8% of the free acid.

BF-200 ALA 10% is used in combination with photodynamic therapy (PDT) using a red-light lamp or daylight.

Chemical structure:

The chemical structure of 5-aminolevulinic acid is:



5-aminolevulinic acid (ALA) is a delta-amino acid and occurs as an endogenous molecule of the heme biosynthesis pathway in almost every cell in humans, animals and plants. The hydrochloride salt is used as drug substance in the investigational and the to-be-marketed formulations.

ALA functions as a pro-drug and is metabolized to the photoactive substance protoporphyrin IX (PpIX) in mitochondria, which are therefore the major sites of ROS-induced damage. PpIX is a natural metabolite of ALA within the heme pathway.

Pharmacological class:

BF-200 ALA 10% (with 5-aminolevulinic acid hydrochloride as active ingredient) belongs to the class of medications called "photodynamic therapy photosensitizers".

Mode of action:

Photodynamic therapy (PDT) requires 3 components: (1) a photosensitizer, (2) light with a sufficient amount of energy at a suitable spectrum of wavelengths, and (3) oxygen. In PDT light energy is transferred through the photosensitizer to oxygen, leading to the formation of reactive oxygen species (ROS). ROS oxidize cell membranes and other cellular compounds, causing necrosis or apoptosis of targeted cells.

Dosage form, route of administration, and dosing regimen:

BF-200 ALA 10% gel is a white to yellowish gel for topical use delivered in a 2 g aluminum tube sufficient for the treatment of a total area of 20 cm².

Photodynamic therapy for actinic keratosis with BF-200 ALA 10% gel is indicated for the treatment of single lesions or of an entire field affected by multiple lesions (field cancerization).

Treated lesions that have not completely resolved after 3 months shall be retreated with BF-200 ALA 10% gel.

For treatment of basal cell carcinoma, two sessions of photodynamic therapy shall be administered with an interval of about one week between sessions for one or multiple lesions. Basal cell carcinoma lesions shall be evaluated three months after treatment. Treated lesions that have not completely resolved after 3 months shall be retreated.

Two different sources of illumination for PDT are available:

- Illumination with a lamp (medical device) as a red light source for the treatment of AK, field cancerization and BCC: The entire treatment area, for both AK and BCC, shall be illuminated with a red light source, either with a narrow spectrum around 630 nm and a light dose of approximately 37 J/cm2 or a broader and continuous spectrum in the range between 570 and 670 nm with a light dose between 75 and 200 J/cm2.

- Daylight illumination as a source of light for PDT in combination with BF-200 ALA is approved for the treatment of AK and field cancerization. Daylight PDT comprises application of BF-200 ALA to mild to moderate AK lesions or fields, followed by 30 minutes incubation time and 2 hours exposure to full daylight.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Since the active substance 5-aminolevulinic acid is an amino acid and an intermediate in basic biochemical pathways, an environmental risk assessment is not deemed necessary. This is supported by the guideline on the environmental risk assessment where it is stated that amino acids are exempted from the requirement for a detailed environmental risk assessment as they are unlikely to result in significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

- Tabular overview of clinical studies

Study Number, Location	Study Objective - Main inclusion criteria	Study design	IMPs (PDT lamp)	Duration of Treatment and follow-up	N Randomized / Planned
ALA-AK-CT010 - Germany -6 centers Follow-up is ongoing	The primary objective of the study was to compare the efficacy of BF-200 ALA with placebo for the treatment of mild to severe AK located on extremities and trunk/neck with PDT. For study inclusion, patients had to have 4 to 10 clinically confirmed AK target lesions of mild to severe intensity [d] within each of 2 comparable treatment fields either on opposite sides of extremities and/or the trunk/neck.	Phase III, randomized, double-blind, intra-individual, multicenter study.	- BF-200 ALA 10% - Placebo/ vehicle BF-RhodoLED lamp (635 nm).	Up to two PDTs. Twelve weeks after the first PDT, non-responders or partial responders were to be retreated. Follow-up visits are scheduled 6 and 12 months after last PDT.	50 / 52
ALA-AK-CT009 -Germany, Spain -7 centers 23 Jan 2016 – 19 Sep 2017 Completed	The primary objective of the study is to compare the efficacy and safety of BF-200 ALA treatment of mild to moderate AK with MAL (Metvix) when using daylight PDT. For study inclusion, patients had to have 3 to 9 clinically confirmed AK target lesions of mild to moderate intensity on each side of the face or bald scalp. The numbers of lesions on both sides should not vary by more than 50%.	Phase III, randomized, observer-blind, intra-individual study.	- BF-200 ALA - MAL cream (Daylight illumination)	Single PDT. Follow up was at 6 and 12 months after PDT.	52 / 50

ALA: 5-aminolevulinic acid; AK: actinic keratosis; BF-200 ALA: a nanoemulsion-based formulation of 10% ALA hydrochloride in a gel matrix (7.8% ALA free acid). ISAB: Independent Safety Advisory Board; MAL: methyl aminolevulinate; PDT: photodynamic therapy; PpIX: protoporphyrin IX; IMP: investigational medicinal product

a AK grade I and II according to Olsen et al. Dermatol 1991; 24: 738-743

b The Waldmann lamp (600 - 750 nm) was also recommended in the ALA-AK-CT003 protocol but it was not used during the study.

c The adaptive design of ALA-AK-CT001 was planned as 2 parts: the first to evaluate 3 different ALA dose strengths (1%, 3% and 10%) vs. vehicle,; and the second as a confirmatory study to compare one to two ALA dose strengths vs. vehicle (this second part was not performed).

d AK grade I to III according to Olsen et al. Dermatol 1991; 24: 738-743

2.4. Clinical efficacy

2.4.1. Main study

ALA-AK-CT010: A randomized, double-blind, intra-individual, multi-center phase III study to evaluate the safety and efficacy of BF-200 ALA (Ameluz) versus placebo in the treatment of mild to severe actinic keratosis on extremities, trunk/ neck with photodynamic therapy (PDT) when using the BF-RhodoLED lamp.

Methods

Randomized, multi-center, double-blind, intra-individual Phase III study (n= 50 patients, intra-individual comparison). Depending on the response one or two PDTs were done.

The study was conducted in 6 centres in Germany.

The study was divided into 2 parts, the clinical observation period (screening, PDT-1, PDT-2, if applicable, and the 12 weeks following the last PDT), and the follow-up visits (approximately 6 and 12 months after last PDT, respectively).

Patients were screened for the study on Visit 1; randomization and PDT with red light were performed on Visit 2. BF-200 ALA and placebo gel were randomized to the respective sides of the patient's extremities and/or trunk/neck (1:1 ratio). Each patient received one entire tube of test product and placebo gel (2 g each) per treatment. The amount of each BF-200 ALA and placebo tube is sufficient to cover one treatment field (continuous field or discontinuous field with several patches) totalling approximately 20 cm^2.

At baseline (Visit 2), 4 (Visit 3) and 12 weeks (Visit 4) after PDT, the target lesions were assessed (location/ side, number of lesions per side, size and severity of lesions). 12 weeks after PDT-1 final assessment of complete response was done. In case of non- or partial response PDT-2 was done.

These patients with remaining lesions on both sides 12 weeks after PDT-1 were re-treated with a second PDT (PDT-2). Their lesions were further assessed 4 weeks (Visit 5) and 12 weeks (Visit 6) after PDT-2.

Additionally, all patients were followed up for one year after their last PDT with 2 visits (6 and 12 months after last PDT) to assess recurrence of AK lesions. Skin quality was assessed at baseline, 12 weeks after the last PDT (Visit 4 or Visit 6) and at both follow-up visits.

Cosmetic outcome compared to baseline was calculated based on skin quality assessments. Patient's satisfaction regarding cosmetic outcome and PDT treatment were recorded 12 weeks after the last PDT and at the follow-up visits after 6 and 12 months. Mandatory biopsies of target lesions preselected at Visit 1 were taken for histopathological examination in a central accredited laboratory 12 weeks after the last PDT.

Optional biopsies were taken at the discretion of the investigator. Recurrent lesions had to be documented during FU.

At the time of the PDT, the treatment area was assessed for local skin reaction during PDT, local discomfort during PDT, and assessment of pain during PDT.

Adverse events (AEs), including new lesions, serious adverse events (SAEs) and local skin reactions were assessed at the time of the PDT, and 1, 4 and 12 weeks post-PDT. During FU (6 and 12 months post-PDT), any relevant local AEs including new AKs or non-melanoma skin cancer (NMSC) or melanoma, or conditions that may have had impaired a proper assessment of the recurrence rate of the treated AK lesions as well as any SAE that had occurred since the end of the clinical observation period had to be documented.

Non-responders or partial responders 12 weeks after PDT (end of clinical observation period), i.e. patients with remaining (non-responding) lesions at Week 12, could receive further treatment at the discretion of the investigator.

Study participants

Main inclusion Criteria:

- Males or females between 18 and 85 years of age (inclusive).
- Presence of 4 to 10 clinically confirmed AK target lesions of mild to severe severity according to Olsen (Olsen et al. 1991) on one treatment field (continuously or in several patches) totalling about 20 cm^2 per comparable patient's side. Treatment fields could be located either on opposite sides of the extremities and/or the trunk/neck, but treatment fields on both sides of a patient had to be in comparable subareas within the same treatment area (e.g. both treatment fields on hands or upper arms or lower arms or upper legs or lower legs or décolleté or back, but not for instance hand on one side of the body and arm on the other). A treatment field could be continuous or consist of several patches. The number of lesions per patient's side were not to vary by more than 50% between the two sides for each patient and should be comparable regarding AK severity. AK lesions had to be discrete and measurable; the diameter of each AK lesion had to be between 0.3 cm and 1.5 cm. The size of each baseline AK lesion was determined by measuring the two largest perpendicular diameters. Lesions included in the study should be entirely located within the treatment fields, leaving a distance of $\geq$ 0.5 cm between the lesion margin and the treatment field border. At least one of the lesions on each side with a diameter of $\geq$ 0.5 cm was to be selected for 2 mm punch biopsies to be taken 12 weeks after the last PDT.
- Willingness to undergo a 2 mm punch biopsy on each side at the end-of-study visit 12 weeks after the last PDT.
- Free of significant physical abnormalities (e.g. tattoos, dermatoses) in the potential treatment fields that may complicate examinations or final evaluations.
- Willingness to stop the use of moisturizers and any other non-medical topical treatments within the treatment fields within 24 h prior to the next clinical visit.
- Accept to abstain from extensive sunbathing and the use of a solarium during the period of the clinical visits. Patients experiencing sunburn within the treatment fields cannot be randomized before they have fully recovered.
- Good general health and/or stable health condition, as confirmed by a physical examination and medical history.
- Healthy patients and patients with clinically stable medical conditions.

- Women of childbearing potential can participate in this study only if they have a negative serum pregnancy test at screening and are willing to use a highly effective method of contraception.

Main exclusion Criteria:

- History of hypersensitivity to 5-ALA or any ingredient of BF-200 ALA.
- Presence of porphyria.
- Hypersensitivity to porphyrins.
- Presence of photodermatosis.
- Start of intake of medication with hypericin or systemically-acting drugs with phototoxic or photoallergic potential.

Treatments

Test product: Ameluz (gel), BF-200 ALA: BF-200 nanoemulsion containing 7.8% 5-aminolevulinic acid (5-ALA) as hydrochloride, with preservatives (sodium benzoate) and xanthan gum as the gel base.

Control product: Placebo (gel): Nanoemulsion without active ingredient, with preservatives (sodium benzoate) and xanthan gum as the gel base.

The study has been designed as an intra-individual comparison, and the treatments were equally randomized to the respective sides of the patient's extremities and/or trunk/neck (1:1 ratio). Depending on the response the patients received one or two PDTs. Each patient received one entire tube of each investigational medicinal product (IMP) (2 g). The amount of each BF-200 ALA and placebo tube is sufficient to cover one treatment field (continuous field or discontinuous field with several patches) totaling approximately 20 cm2. The IPs were only applied by study personnel.

Duration of therapy:

The IPs were applied topically once (single application each) on the day of Photodynamic Therapy (PDT-1 and PDT-2, if applicable) depending on the AK lesion assessment 12 weeks after PDT-1.

Patients with remaining lesions on both sides 12 weeks after PDT-1 were retreated with a second PDT (PDT-2). The duration of the clinical observation period was approx. 14 weeks for patients receiving one PDT and approx. 26 weeks for patients receiving two PDTs.

On the day of PDT the skin was exposed to Ameluz resp. placebo gel for a mean of 185 minutes (range 177 to 200 minutes). Illumination with the BF-RhodoLED lamp was done for 10 minutes. The illumination time was automatically calculated, so that a total light does of 37J/cm² (per treatment field) was achieved.

Objectives

The primary objective of the study 010 was to compare the efficacy and safety of BF-200 ALA (Ameluz) with placebo for the treatment of mild to severe actinic keratosis (AK) located on extremities and trunk/ neck with PDT when using the BF-RhodoLED lamp.

Outcomes/endpoints

Primary efficacy variable:

Total lesion clearance rate in percent per patient's side, defined as the percentage of individual lesions with complete remission on the respective side of the patient assessed 12 weeks after the last PDT.

Secondary efficacy variables (12 weeks after the last PDT unless otherwise stated; with hierarchical testing):

-Patient complete clearance

-Total lesion clearance rate of moderate (according to Olsen) lesions in percent

-Total lesion clearance rate in percent in the treatment area extremities

-Total lesion clearance rate in percent in the treatment area trunk/neck-

-Histopathologically confirmed lesion response (HCR) rate

-Total lesion clearance rate in percent 12 weeks after PDT-1

-Patient complete clearance 12 weeks after PDT-1

-Overall cosmetic outcome as assessed by the investigator.

Safety variables include frequency and extent of TEAEs including SAEs, application site skin reactions, application site discomfort and pain during PDT, and documentation of new lesions, as well as safety laboratory data and physical assessments at Visit 1 and Visit 4 or Visit 6, if retreated. Vital sign measurements were performed at all clinical visits.

Sample size

An overall sample size of 52 patients was calculated considering:

- the study was to be conducted as split-body treatments in a ratio of 1:1.
- the treatment fields had to be comparable, and number of lesions were not allowed to differ more than 50% between patient's sides.
- A sample size of 44 patients (BF-200 ALA PDT vs. placebo PDT, ratio 1:1 split-body design)with a correlation between items of BF-200 ALA PDT and placebo PDT of 0.2 would ensure a power of 90% of a Wilcoxon rank sum test, one-sided, with a significance level of 0.025 to demonstrate a statistically significant superiority in response rates between patient' s sides treated with BF-200 ALA PDT versus placebo PDT in the FAS.
- The additional N=8 patients were to be enrolled (screened but without screening failures) to ensure a) a sufficient number of patients in subgroups Olsen grade and treatment area, b) a sufficient number of patients in the per protocol analysis set, and c) to consider for possible diverging effects in treatment areas, for which actual efficacy results especially for area trunk/neck are not published.

In total, 56 patients enrolled (with screening failures) of which 50 were the randomized set and the safety analysis set (SAF), with 49 as full analysis set (FAS), and 43 per protocol set (PPS).

Randomisation

As the study has been designed as an intra-individual comparison, the treatments were equally randomized to the respective sides of the patient's extremities and/or trunk/neck in a 1:1ratio. Each patient received one entire tube (2 g) of each BF-200 ALA and placebo gel, each tube sufficient to

cover one treatment field (continuous field or discontinuous field with several patches) totaling approximately 20 cm2.

Blinding (masking)

The study was a double-blind design.

Statistical methods

Statistical analyses were performed as soon as the 12 weeks after the last PDT data and histopathological assessments were available for analysis. Data from the FU period (6 months or 12 months after the last PDT) will be analyzed and reported separately, as the study is currently ongoing.

The primary null hypothesis (H01, one-sided) was that the total lesion clearance rate in percent per patient's side, assessed 12 weeks after the last PDT, on the patient's side treated with BF-200 ALA was not superior to the corresponding patient's side treated with placebo. The primary alternative hypothesis (H11, one-sided) was that the total lesion clearance rate in percent per patient's side assessed 12 weeks after the last PDT for the patient's side treated with BF-200 ALA was superior to the corresponding patient's side treated with placebo.

A Wilcoxon signed rank test was used to test the primary hypothesis on a significance level of 2.5% (alpha=0.025). The primary analysis was performed on the FAS.

Confirmatory hypothesis testing of secondary variables was to be done only if the test of the primary efficacy variable was passed (superiority of BF-200 ALA over placebo confirmed) and was to be done strictly in the given order to ensure the family-wise error rate (FWER). For secondary endpoint analyses, also a significance level of 2.5% (alpha=0.025) was applied.

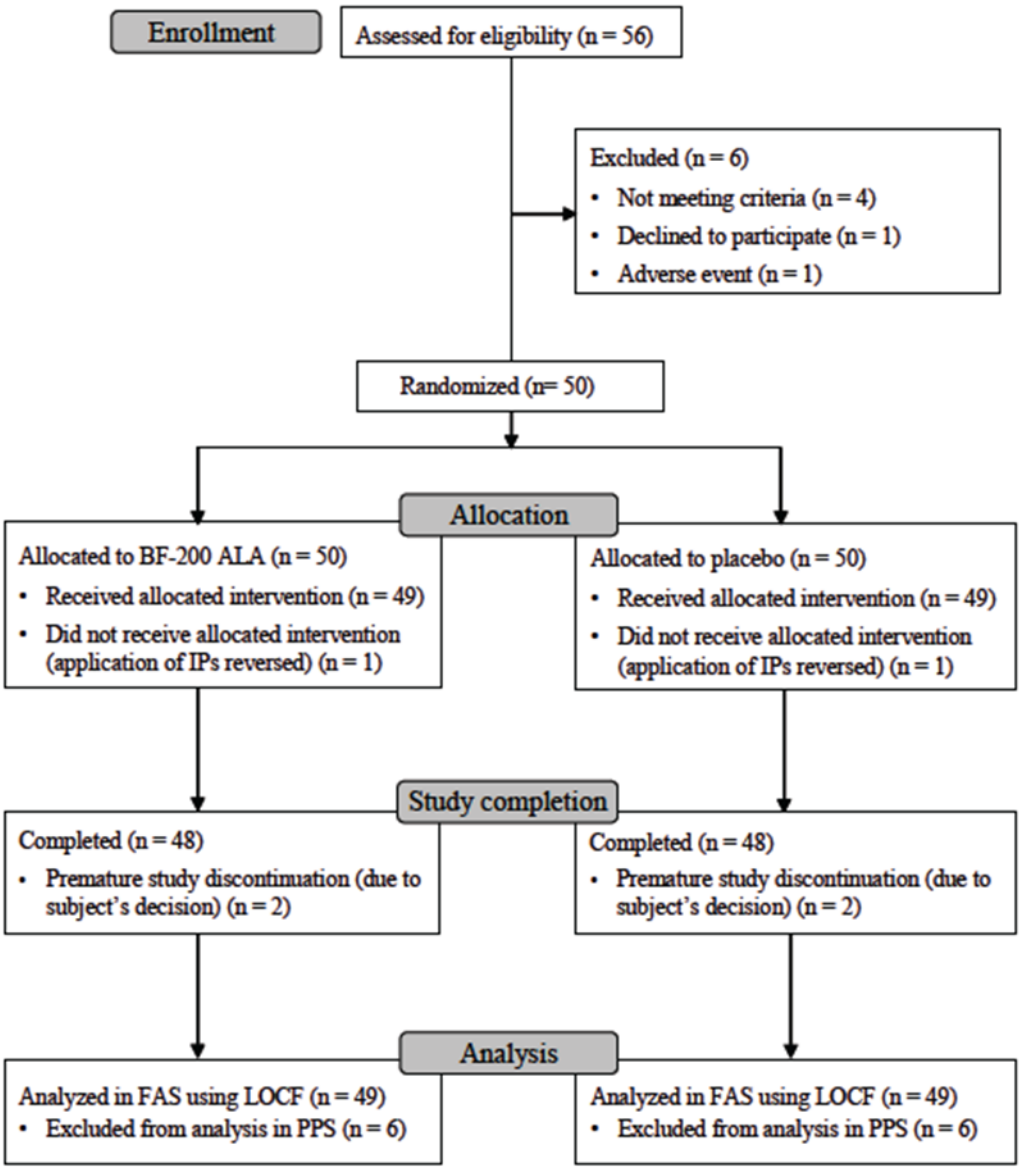
Tertiary efficacy endpoints were to be analyzed descriptively and in an exploratory way. All efficacy analyses were performed on the FAS and were repeated, in the sense of sensitivity analyses, for the PPS.

Missing values for the efficacy endpoints were imputed by the last preceding non-missing assessment, if applicable, using a last observation carried forward (LOCF) approach (FAS).

Results

Participant flow

Figure 1: Patient disposition, study ALA-AK-CT010



Recruitment

The study period was from 18-Sep-2017 (first patient in) to 09-Jan-2019 (last patient completed clinical observation period).

Conduct of the study

The Clinical Study Protocol dated 12-Apr-2017 was amended three times: substantial Protocol Amendment 1 resulting in CSP 2.0 dated 20-Jul-2017 to further define the extent of AEs that had to be documented during the FU period; non-substantial Protocol Amendment 2 resulting in CSP 2.1 dated

31-Jan-2018 to adapt the number of study sites and study timelines; substantial Protocol Amendment 3 resulting in CSP 3.0 dated 23-Jul-2018 to change the order of two secondary endpoints. There were no substantive changes to the clinical conduct of the study.

One patient was excluded from the FAS and PPS because the application of IPs was reversed at PDT-1. Within the SAF, this patient was assigned to the treatment groups as actually treated.

Six patients were excluded from the PPS (alone) because of major protocol deviations:

• Two patients had a biopsy of a lesion not meeting inclusion criteria (too small).

• Two patients discontinued their study participation before their last Visit, thus no final efficacy assessment was performed.

• One patient was not treated as randomized at PDT-2; application of IPs was reversed.

• One patient had a biopsy of a lesion not meeting inclusion criteria (too small), and the treatment field did not meet inclusion criterium 3: all lesions of the side fit into the illumination area of 6 x16 cm, but the surrounding margin did not fit into the illumination area.

All further protocol deviations were minor.

Baseline data

Table 2: Patient demographics, SAF, FAS and PPS

			SAF N=50	FAS N=49	PPS N=43
Sex	n (%)	Female	26 (52.0)	26 (53.1)	21 (48.8)
		Male	24 (48.0)	23 (46.9)	22 (51.2)
Age, years	Mean ± SD		70.8 ± 8.3	70.9 ± 8.4	71.1 ± 8.2
	Range		54 to 84	54 to 84	54 to 84
Age group	n (%)	<65	10 (20.0)	10 (20.4)	9 (20.9)
		≥65	40 (80.0)	39 (79.6)	34 (79.1)
		65 to 74	24 (48.0)	23 (46.9)	20 (46.5)
		≥75	16 (32.0)	16 (32.7)	14 (32.6)
Race	n (%)	White	50 (100)	49 (100)	43 (100)
Ethnicity	n (%)	Not Hispanic or Latino	50 (100)	49 (100)	43 (100)
Skin type Fitzpatrick	n (%)	I-III	48 (96.0)	47 (95.9)	42 (97.7)
		IV-VI	2 (4.0)	2 (4.1)	1 (2.3)

FAS: full analysis set; N: number of patients; PPS: per protocol set; SAF: safety analysis set

Table 3: Summary of target AK lesion baseline characteristics, on a patient and on a lesion basis for FAS and PPS

FAS			BF-200 ALA N=49	Placebo N=49
Number of target lesions per patient		Mean ± SD	5.3 ± 1.1	5.5 ± 1.2
		Median	5.0	5.0
Total area of target lesions per patient's side, mm^2		Mean ± SD	254.3 ± 125.5	262.0 ± 124.0
		Median	247.0	248.0
Number of target lesions		Total	258	268
Lesion location	Extremities	n (%)	210 (81.4)	218 (81.3)
	Trunk/Neck		48 (18.6)	50 (18.7)
Lesion severity	Mild		93 (36.0)	109 (40.7)
	Moderate		158 (61.2)	152 (56.7)
	Severe		7 (2.7)	7 (2.6)
PPS			**N=43**	**N=43**
Number of target lesions per patient		Mean ± SD	5.3 ± 1.1	5.4 ± 1.3
		Median	5.0	5.0
Total area of target lesions per patient's side, mm^2		Mean ± SD	264.2 ± 122.4	271.8 ± 120.9
		Median	255.0	259.0
Number of target lesions		Total	226	234
Lesion location	Extremities	n (%)	183 (81.0)	191 (81.6)
	Trunk/Neck		43 (19.0)	43 (18.4)
Lesion severity	Mild		90 (39.4)	101 (43.2)
	Moderate		131 (58.0)	129 (55.1)
	Severe		5 (2.2)	4 (1.7)

FAS: full analysis set; n: number of lesions per subgroup; N: number of patients; PPS: per protocol set
* relative to total number of target AK lesions (sum of both sides)

Numbers analysed

50 patients were in the safety analysis set (SAF), 49 patients in the full analysis set (FAS), and 43 patients in the per protocol set (PPS).

Outcomes and estimation

The primary endpoint – the total lesion clearance rate in percent of AK on extremities and/or trunk/neck per patient's side 12 weeks after the last PDT – was 86.0% ± 23.2% for BF-200 ALA and 32.9% ± 37.1% for placebo (FAS, LOCF).

The median of differences (BF-200 ALA *minus* placebo) was 60.0 [lower 97.5% confidence limit (CL) 33.3] ($p<0.0001$, one-sided Wilcoxon signed rank test), thus, demonstrating superiority of BF-200 ALA over placebo. The robustness of this result was confirmed by the PPS analysis (table 4).

Table 4: Primary efficacy variable for study ALA-AK-CT010

Primary efficacy variable		BF-200 ALA	Placebo	p-value
Total lesion clearance rate in percent per patient's side 12 weeks after the last PDT (FAS)	Mean ± SD	86.0 ± 23.2	32.9 ± 37.1	<0.0001 [a]
Total lesion clearance rate in percent per patient's side 12 weeks after the last PDT (PPS)	Mean ± SD	90.0 ± 19.5	28.5 ± 36.7	<0.0001 [a]

[a] One-sided Wilcoxon signed rank test; Last observation carried forward (LOCF) was used. FAS: full analysis set; p-value: probability value; PDT: photodynamic therapy; PPS: per protocol set; SD: standard deviation.

The results for all secondary efficacy variables tested in the hierarchical test procedure are summarized in the table below.

Table 5: Secondary efficacy variables for study ALA-AK-CT010

Secondary efficacy variables; FAS		BF-200 ALA	Placebo	p-value
Patient complete clearance per patient's side 12 weeks after the last PDT	n/N (%)	33/49 (67.3)	6/49 (12.2)	<0.0001 [a]
Total lesion clearance rate of moderate (according to Olsen) lesions in percent per patient's side 12 weeks after the last PDT	Mean ± SD	84.3 ± 28.6	27.2 ± 36.5	<0.0001 [b]
Total lesion clearance rate in percent per patient's side in the treatment area extremities 12 weeks after the last PDT	Mean ± SD	83.5 ± 24.7	27.1 ± 33.1	<0.0001 [b]
Total lesion clearance rate in percent per patient's side in the treatment area trunk/neck 12 weeks after the last PDT	Mean ± SD	96.0 ± 12.6	55.5 ± 44.8	0.0156 [b]
Histopathologically confirmed lesion response (HCR) rate 12 weeks after the last PDT per patient's side	n/N (%)	40/47 (85.1)	30/47 (63.8)	0.0032 [a]
Total lesion clearance rate in percent per patient's side 12 weeks after PDT-1	Mean ± SD	67.5 ± 31.2	27.6 ± 33.4	<0.0001 [b]
Patient complete clearance per patient's side, 12 weeks after PDT-1	n/N (%)	18/49 (36.7)	4/49 (8.2)	0.0003 [a]
The overall cosmetic outcome per patient's side 12 weeks after the last PDT as assessed by the investigator	Very good; n (%)	19 (38.8)	7 (14.3)	<0.0001 [b]
	Good	9 (18.4)	3 (6.1)	
	Satisfactory	9 (18.4)	20 (40.8)	
	Unsatisfactory	4 (8.2)	9 (18.4)	
	Impaired	8 (16.3)	10 (20.4)	

[a] McNemar test; [b] One-sided Wilcoxon signed rank test; Last observation carried forward (LOCF) was used.

FAS: full analysis set; N: number of patients' sides with data; n: number of patients' sides with response/with outcome; p-value: probability value; PDT: photodynamic therapy; SD: standard deviation.

The proportion of patients with improvement in skin quality due to treatment with BF-200 ALA ranged from 38.1% (hypopigmentation) to 69.2% of patients (skin surface) and for placebo from 13.8% (mottled pigmentation) to 35.7% (atrophy) [considering patients with skin quality of at least mild impairment at baseline].

More patients were more satisfied by the BF-200 ALA treatment than by the placebo treatment: 38 (82.6%) patients would choose the BF-200 ALA treatment again versus 32 (69.6%) patients for the placebo treatment.

A majority of patients was satisfied by the cosmetic outcome of the BF-200 ALA treatment: 38 (80.9%) patients rated their satisfaction as 'very good' or 'good' and only 6 (12.8%) patients were unsatisfied with their cosmetic outcome. For the placebo treatment, 'very good' or 'good' satisfaction with cosmetic outcome was reported by 23 (48.9%) patients and more than one third (19 [40.4%] patients) were unsatisfied by the treatment. One patient (2.1%) each rated the cosmetic outcome for BF-200 ALA and placebo as 'impaired'.

Ancillary analyses

Subgroup Analyses of Primary Efficacy Endpoint

Subgroup analyses by sex, age group, severity, and Fitzpatrick skin type category were exploratory and showed consistent results to the primary analysis for both analysis sets, FAS and PPS. Results for the FAS are summarized in the below table.

Table 6: Total lesion clearance rate per patient's side 12 weeks after the last PDT by demographic and baseline characteristics – FAS, LOCF

		BF-200 ALA		Placebo		p-value[a]
		n	Mean ± SD (%)	n	Mean ± SD (%)	
By sex	Male	23	87.4 ± 20.3	23	39.2 ± 40.2	< 0.0001
	Female	26	84.8 ± 25.8	26	27.3 ± 34.0	< 0.0001
By age group, years	<65	10	78.5 ± 24.7	10	31.7 ± 35.2	0.0078
	65-74	23	85.9 ± 25.2	23	32.0± 38.9	< 0.0001
	≥75	16	90.8 ± 19.0	16	34.9 ± 38.0	0.0008
By baseline severity	Mild	32	88.3 ± 28.0	36	37.3 ± 43.3	< 0.0001
	Severe	7	71.4 ± 48.8	7	42.9 ± 53.5	0.5000
By Fitzpatrick skin type	I-III	47	86.5 ± 23.0	47	33.2 ± 37.5	< 0.0001
	IV-VI	2	75.0 ± 35.4	2	25.0 ± 35.4	0.5000

FAS: full analysis set; LOCF: last observation carried forward; n: number of patients' sides per subgroup; SD: standard deviation

[a] One-sided Wilcoxon signed rank test

The total lesion clearance is defined as the percentage of individual lesions with complete remission on the respective side of the patient.

Tertiary Efficacy Endpoints and Subgroup Analyses

All tertiary efficacy endpoints were analyzed descriptively and in an exploratory way.

- **Total Lesion Clearance Rate in Percent per Patient's Side 12 Weeks After PDT-1 Stratified by Olsen Grade and Treatment Area**

The total lesion clearance rate in percent per patient's side 12 weeks after PDT-1, defined as the percentage of individual lesions with complete remission on the respective side of the patient (secondary endpoint) is further stratified by Olsen grade and by treatment area as part of the tertiary efficacy analyses. Results for the FAS are summarized in table 7.

Table 7: Total lesion clearance rate per patient's side 12 weeks after PDT-1 by baseline characteristics – FAS, LOCF

		BF-200 ALA		Placebo		p-value[a]
		n	Mean ± SD (%)	n	Mean ± SD (%)	
By baseline severity	Mild	32	73.7 ± 34.5	36	27.1 ± 36.7	< 0.0001
	Moderate	44	65.5 ± 36.4	43	22.6 ± 32.1	< 0.0001
	Severe	7	42.9 ± 53.5	7	42.9 ± 53.5	0.2500
By treatment area	Extremities	39	65.6 ± 31.0	39	24.3 ± 30.8	< 0.0001
	Trunk/neck	10	75.0 ± 32.1	10	40.4 ± 41.4	0.0391

FAS: full analysis set; LOCF: last observation carried forward; n: number of patients' sides per subgroup; SD: standard deviation
The total lesion clearance is defined as the percentage of individual lesions with complete remission on the respective side of the patient.

[a] One-sided Wilcoxon signed rank test

- **Clinical Versus Histopathological Assessment of Lesion Clearance**

To evaluate the correspondence between clinical and histopathological assessment, the percentage of lesions assessed as fully cleared by the investigator 12 weeks after the last PDT but not fully cleared according to histopathology and the percentage of lesions assessed as not cleared by the investigator 12 weeks after the last PDT but fully cleared according to histopathology were analyzed. Most of the BF-200 ALA-treated biopsied lesions were clinically cleared according to the investigator as well as histopathologically cleared whereas a smaller number of placebo-treated biopsied lesions was both, clinically and histopathologically cleared (70.2% versus 19.1%). Only one (2.1%) of the BF-200 ALA-treated lesions, but 36.2% of the placebo-treated lesions were neither clinically nor histopathologically cleared. Results are summarized below.

Clinical versus histopathological assessment of biopsied lesions 12 weeks after the last PDT – FAS:

		Lesions assessed as fully cleared by the investigator			
N = 47		BF-200 ALA		Placebo	
n (%)		Yes	No	Yes	No
Lesions cleared according to histopathology	Yes	33 (70.2)	7 (14.9)	9 (19.1)	21 (44.7)
	No	6 (12.8)	1 (2.1)	0 (0.0)	17 (36.2)

FAS: full analysis set; N: number of biopsied lesions; n: number of biopsied lesions per assessment group
Only preselected lesions assessed by the investigator (according to Olsen) and with histopathological evaluation (according to Cockerell) are considered.

- **Change in Skin Quality Assessments Per Patient's Side**

Skin quality parameters (including skin surface, hyperpigmentation, hypopigmentation, mottled or irregular pigmentation, degree of scarring, and atrophy) were assessed by the investigator at baseline and 12 weeks after the last PDT using a 4-point scale, where 0=none, 1=mild, 2=moderate, 3=severe.

The changes in skin quality assessments from baseline to 12 weeks after the last PDT are summarized by skin quality parameter and severity for both treatment groups in Table 8. The overall cosmetic outcome (secondary endpoint no.7, see e.g. "*Summary of main studies*", below) is based on these assessments.

Table 8: Change in skin quality per patient's side from baseline to 12 weeks after the last PDT – FAS, LOCF

		12 weeks after the last PDT							
n (%)		BF-200 ALA				Placebo			
Skin category	Baseline	None	Mild	Mod.	Severe	None	Mild	Mod.	Severe
Skin surface	None	9 (18.4)	0	0	0	8 (16.3)	1 (2.0)	0	0
	Mild	15 (30.6)	10 (20.4)	1 (2.0)	0	7 (14.3)	16 (32.7)	3 (6.1)	1 (2.0)
	Mod.	8 (16.3)	4 (8.2)	2 (4.1)	0	0	3 (6.1)	10 (20.4)	0
	Severe	0	0	0	0	0	0	0	0
Hyper-pigmen-tation	None	9 (18.4)	5 (10.2)	1 (2.0)	0	7 (14.3)	7 (14.3)	1 (2.0)	0
	Mild	4 (8.2)	16 (32.7)	1 (2.0)	0	3 (6.1)	16 (32.7)	2 (4.1)	1 (2.0)
	Mod.	4 (8.2)	8 (16.3)	1 (2.0)	0	0	4 (8.2)	8 (16.3)	0
	Severe	0	0	0	0	0	0	0	0
Hypo-pigmen-tation	None	17 (34.7)	10 (20.4)	0 (0)	0	16 (32.7)	11 (22.4)	0	0
	Mild	2 (4.1)	10 (20.4)	1 (2.0)	0	1 (2.0)	10 (20.4)	1 (2.0)	0
	Mod.	2 (4.1)	4 (8.2)	3 (6.1)	0	0	2 (4.1)	8 (16.3)	0
	Severe	0	0	0	0	0	0	0	0
Mottled pigmen-tation	None	13 (26.5)	6 (12.2)	0	0	13 (26.5)	6 (12.2)	0	0
	Mild	8 (16.3)	13 (26.5)	1 (2.0)	0	3 (6.1)	18 (36.7)	1 (2.0)	0
	Mod.	1 (2.0)	6 (12.2)	1 (2.0)	0	1 (2.0)	0	7 (14.3)	0
	Severe	0	0	0	0	0	0	0	0
Scarring	None	41 (83.7)	2 (4.1)	0	0	39 (79.6)	3 (6.1)	0	0
	Mild	3 (6.1)	2 (4.1)	0	0	2 (4.1)	5 (10.2)	0	0
	Mod.	0	0	1 (2.0)	0	0	0	0	0
	Severe	0	0	0	0	0	0	0	0
Atrophy	None	32 (65.3)	3 (6.1)	0	0	32 (65.3)	3 (6.1)	0	0
	Mild	5 (10.2)	6 (12.2)	0	0	4 (8.2)	6 (12.2)	1 (2.0)	0
	Mod.	0	3 (6.1)	0	0	0	1 (2.0)	2 (4.1)	0
	Severe	0	0	0	0	0	0	0	0

FAS: full analysis set; LOCF: last observation carried forward; Mod.: moderate; n: number of patients' sides per category and severity

'Mild', 'Moderate', and 'Severe' assess the impairment in skin quality and do not refer to AK lesions.

- **Patient's Satisfaction**

Patient satisfaction with cosmetic outcome at 12 weeks after the last PDT was assessed using a 5-point scale of 0 to 4, where 0= very good, 1=good, 2=satisfactory, 3=unsatisfactory, and 4=impaired. Results by treatment are summarized in Table 9.

Table 9: Patient's satisfaction with cosmetic outcome on his/her respective side 12 weeks after the last PDT – FAS, PPS

	FAS (N = 47)		PPS (N = 43)	
n (%)	BF-200 ALA	Placebo	BF-200 ALA	Placebo
Very good	21 (44.7)	13 (27.7)	19 (44.2)	11 (25.6)
Good	17 (36.2)	10 (21.3)	16 (37.2)	10 (23.3)
Satisfactory	2 (4.3)	4 (8.5)	2 (4.7)	4 (9.3)
Unsatisfactory	6 (12.8)	19 (40.4)	5 (11.6)	17 (39.5)
Impaired	1 (2.1)	1 (2.1)	1 (2.3)	1 (2.3)

FAS: full analysis set; n: number of patients' sides per subgroup; PPS: per protocol set

Summary of main study

The following table summarises the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10. Summary of Efficacy for study ALA-AK-CT010

Title: A randomized, double-blind, intra-individual, multi-center Phase III study to evaluate the safety and efficacy of BF-200 ALA (Ameluz®) versus placebo in the treatment of mild to severe actinic keratosis on extremities, trunk/ neck with photodynamic therapy (PDT) when using the BF-RhodoLED® lamp		
Study identifier	**Sponsor's study number: ALA-AK-CT010** EudraCT number: 2017-000486-72	
Design	Randomised, double-blind, intra-individual comparison (test product vs. placebo), multi-center study	
	Duration of main phase:	The duration of the clinical observation period was approx. 14 weeks for patients receiving one PDT and approx. 26 weeks for patients receiving two PDTs.
	Duration of Run-in phase:	not applicable
	Duration of Follow up phase:	1 year after last PDT
Hypothesis	Superiority: Superiority of the total lesion clearance rate in percent per patient's side assessed 12 weeks after the last PDT for the patient's side treated with BF-200 ALA compared to the corresponding patient's side treated with placebo.	
Treatments groups (intra-individual comparison)	Test product	**Ameluz (gel)** [5-aminolevulinic acid], number randomized= 50
	Placebo	**Placebo (gel)**, without active ingredient, number randomized = 50

Endpoints and definitions	Primary endpoint	TLC	Total lesion clearance rate in percent per patient's side, defined as the percentage of individual lesions with complete remission on the respective side of the patient assessed 12 weeks after the last PDT.
	Secondary endpoints	hierarchical testing	12 weeks after last PDT: -Patient complete clearance, -Total lesion clearance rate of moderate (according to Olsen) lesions in percent -Total lesion clearance rate in percent in the treatment area extremities, -Total lesion clearance rate in percent in the treatment area trunk/neck -Histopathologically confirmed lesion response (HCR) rate -Total lesion clearance rate in percent 12 weeks after PDT-1 -Patient complete clearance 12 weeks after PDT-1 -Overall cosmetic outcome as assessed by the investigator.

	Tertiary endpoints		12 weeks after last PDT: -Lesion complete response per treatment arm -Total lesion clearance rate in percent per patient's side 12 weeks after PDT-1 stratified by Olsen grade -Total lesion clearance rate in percent per patient's side 12 weeks after PDT-1 stratified by treatment area (extremities, trunk/neck) -Reduction of total lesion area per patient's side -Lesion complete response per treatment arm assessed 12 weeks after PDT-1 -Percentage of lesions assessed as fully cleared by investigator but not fully cleared according to histopathology -Percentage of lesions assessed as not cleared by investigator but fully cleared according to histopathology -Change in skin quality assessments per patient's side compared to baseline -Patient's satisfaction with treatment applied to his/ her respective side -Patient's satisfaction with cosmetic outcome on his/ her respective side.
Database lock	13 March 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent-to-treat principle, assignment of patients' sides to the treatment groups as randomized. 12 weeks after the last PDT FAS population		
Descriptive statistics and estimate variability	Treatment group	**Ameluz (gel)**	**Placebo (gel)**
	Number of subject	N=50	N= 50

	Primary endpoint Total Lesion Clearance Rate**,** TLC (%)	86.0	32.9
	SD	23.2	37.1
	Secondary endpoints **1)** Patient complete clearance (%)	67.3	12.2
	2) TLC moderate lesions (%) SD	84.3 28.6	27.2 36.5
	3) TLC extremities (%)	83.5	27.1
	SD	24.7	33.1
	4) TLC trunk/neck (%)	96.0	55.5
	SD	12.6	44.8
	5) Histopath. Confirmed Lesion Response, HCR (%) trunk/neck (%)	85.1	63.8
	6) TLC after PDT-1 (%)	67.5	27.6
	SD	31.2	33.4
	7) Overall Cosmetic Outcome "very good or good" (%)	47.2	20.4

Effect estimate per comparison	**Primary endpoint**	Comparison groups	**Ameluz - placebo**

	TLC	Median of differences	60
		One-sided non parametric Confidence Interval, Lower 97.5% Limit	33.3
		P-value one-sided Wilcoxon signed rank test	<0.0001
	Secondary endpoints **2)** TLC moderate lesions	Comparison groups	**Ameluz - placebo**
		Median of differences	75.0
		One-sided non parametric Confidence Interval , Lower 97.5% Limit	33.3
		P-value one-sided Wilcoxon signed rank test	<0.0001
	3) TLC extremities	Median of differences	66.7
		One-sided non parametric CI, Lower 97.5% Limit	35.0
		P-value one-sided Wilcoxon signed rank test	<0.0001
	4) TLC trunk/neck	Median of differences	18.3
		One-sided non para-metric CI, Lower 97.5% Limit	0.0
		P-value one-sided Wilcoxon signed rank test	<0.0001
	6) TLC after PDT-1	Median of differences	50.0
		One-sided non para-metric CI, Lower 97.5% Limit	25.0
		P-value one-sided Wilcoxon signed rank test	<0.0001

Analysis performed across trials (pooled analyses and meta-analysis)

In order to compare the efficacy of Ameluz/red-light PDT in study ALA-AK-CT010 (AK in extremities and/or trunk/neck) a pooled analysis of previously submitted phase III studies (study ALA-AK-CT002, ALA-AK-CT003 and ALA-AK-CT007) in AK in the face and/or scalp were presented. These 3 studies included a placebo (vehicle control) as comparator arm and had the same main inclusion criteria. In all studies, up to two PDTs were applied. All three studies used the same primary endpoint, i.e. percentage of patients for whom all treated AK lesions were completely cleared 12 weeks after the last PDT. The main differences of these studies are that in study 007 a field-directed treatment of AK was applied, and in studies 002 and 003, different sources of red-light (narrow resp. broad spectrum lamps) were applied. Separate analysis of the different light sources revealed, that narrow spectrum lamps (e.g. BF-RhodolLED) was more efficacious compared to broad-spectrum lamps. Table 11 presents the pooled efficacy results of the studies 002, 003 and 007 (face and/or scalp).

Table 11: Rate of patient complete response 12 weeks after last PDT, ISE, FAS

		Vehicle (N= 148)			BF-200 ALA (N=383)			Difference [95% CI]	P value [a]
		N	n	%	N	n	%		
Step I [b]	Overall	148	25	16.9	383	297	77.5	60.7 (53.3; 68.0)	<0.0001
Step II [b]	All narrow spectrum lamps, pooled [c]	86	14	16.3	211	183	86.7	70.5 (61.4; 79.5)	<0.0001
Step III [b]	All broad spectrum lamps, pooled [c]	62	11	17.7	172	114	66.3	48.5 (36.7; 60.4)	<0.0001
Step IV [b]	Narrow spectrum, by type of lamp								
	BF-RhodoLED	32	7	21.9	53	48	90.6	68.7 (52.3; 85.0)	<0.0001
	Aktilite	43	4	9.3	122	102	83.6	74.3 (63.4; 85.2)	<0.0001
	Omnilux	11	3	27.3	35	32	91.4	64.2 (36.3; 92.1)	<0.0001

n (%): number (%) of patients; %: percent of patients

[a] Fisher's exact test

[b] The tests were done in a hierarchical manner, proceeding with Step II, only after the difference at Step I showed statistical significance; with Step III, only after the treatment difference at Step II showed statistical significance; with Step IV, only after the treatment difference at Step III showed statistical significance.

[c] If the lamp type was changed within a patient from PDT1 to PDT2, the patient was excluded from the subgroup analyses on lamp type for complete response.

Study ALA-AK-CT009 (follow-up)

Follow-up data of ALA-AK-CT009 (Phase III – reference therapy-controlled study): A randomized, observer-blind, intra-individual phase III study to evaluate the safety and efficacy of BF-200 ALA (Ameluz) in combination with daylight PDT (photodynamic therapy) in comparison with Metvix for the treatment of mild to moderate actinic keratosis.

This was a study on face/scalp that was included within variation EMEA/H/C/2204/II/0027/G (daylight therapy of AK was approved based on this study).

Within the current application the MAH submitted an "Addendum to Clinical Study Report", dated 26 September 2018, covering the follow-up period of study ALA-AK-CT009.

Randomized, multi-center, double-blind, intra-individual Phase III study (n= 50 patients, intra-individual comparison). One single PDT was done.

3 centers in Spain, 4 centers in Germany.

Study 009 was divided into 2 parts, the clinical observation period (screening, PDT and the 12 weeks following the PDT), and the follow-up visits (approximately 6 and 12 months after the single PDT, respectively).

Patients were screened for the study on Visit 1; randomization and PDT were performed on Visit 2. The overall ratio for BF-200 ALA (gel)/daylight and Metvix (cream)/daylight was 1:1. Test product and active comparator were randomized to the respective sides of the patient's face and/or scalp (intra-individual comparison).

Identically to study 010, at baseline (Visit 2), 4 (Visit 3) and 12 weeks (Visit 4) after PDT, the target lesions were assessed (location/ side, number of lesions per side, size and severity of lesions).

Also identical to study 010, mandatory biopsies of target lesions preselected at Visit 1 were taken for histopathological examination in a central accredited laboratory 12 weeks after the PDT.

All patients were followed up for one year after their PDT with 2 visits (6 and 12 months after PDT) to assess recurrence of AK lesions. Timing of assessment of skin quality, cosmetic outcome, patient's satisfaction (via a questionnaire) and AE was nearly identical to study 010.

Skin quality, cosmetic outcome and patient's satisfaction were recorded 12 weeks after the single PDT and at the follow-up visits after 6 and 12 months. Moreover, patient's satisfaction was recorded the day of PDT, one week after PTD.

During FU (6 and 12 months post-PDT), any relevant local AEs including new AKs or non-melanoma skin cancer (NMSC) or melanoma, or conditions that may have had impaired a proper assessment of the recurrence rate of the treated AK lesions as well as any SAE that had occurred since the end of the clinical observation period had to be documented.

Study participants

Patient's age identical to study 010 (18 to 85 years). 3 to 9 clinically confirmed AK target lesions of only mild to moderate intensity, i.e. AK grade 1 or 2 according to Olsen *et al.* (1991), within each of two comparable treatment areas located either on opposite sides of the face and/or the scalp, i.e. right and left side of the face/scalp. Identical to study 010 the number of lesions per patient's side were not to vary by more than 50% between the two sides for each patient. AK lesions had to be discrete and measurable; the diameter of each AK lesion had to be between 0.5 cm and 1.5 cm. The treatment area per side included a margin of about 0.5-1.0 cm surrounding each lesion. The size of each baseline AK lesion was determined by measuring the two largest perpendicular diameters.

Treatments

Test product: Ameluz (gel), BF-200 ALA

Control product: Metvix (cream), containing 160 mg/g of methyl-5-aminolevulinate (MAL) as hydrochloride equivalent to 16.0% of MAL. The excipients include cetostearyl alcohol (40 mg/g), methyl parahydroxybenzoate (E 218; 2 mg/g), propyl parahydroxybenzoate (E 216; 1 mg/g) and arachis oil (30 mg/g).

Intra-individual comparison. Application to right resp. left side of face and/or scalp. The patients in this study received one single daylight PDT. 12 weeks after PDT the response was evaluated.

The follow-up of this study was identical to study 010. During the 1-year FU no investigational treatment was applied.

Objectives

The primary objective of the study 009 was to compare the efficacy and safety of BF-200 ALA (Ameluz®) treatment of mild to moderate actinic keratosis (AK) with Metvix when using daylight PDT.

The current application for variation refers to the 1-year follow-up period of this study only. Amongst others, the lesion recurrence rate is reported.

Outcomes/endpoints

Efficacy:

For the FU, the following efficacy variables were analyzed:

- Lesion recurrence defined as the number of completely cleared individual lesions 12 weeks after the PDT according to the dedicated patient's side showing recurrence during follow-up
- Patient recurrence per patient's side defined as the number of patients with all lesions on a specific side completely cleared 12 weeks after the PDT with at least one recurrent lesion during follow-up
- Change in skin quality assessments compared to baseline assessed on follow-up visits per patient's side
- Overall cosmetic outcome on follow-up visits per patient's side
- Patient's satisfaction on follow-up visits regarding PDT treatment, in general and according to the dedicated patient's site, and cosmetic outcome (per patient's side)

Safety:

For the FU, the following safety variables were analyzed:

- Any relevant local AEs or conditions that may impair a proper assessment of the recurrence rate of the treated AK lesions as well as any SAE that have occurred since the end of the clinical observation period
- New lesions (AK, NMSC, melanoma) on follow-up visits per patient's side

Data assigned to the clinical observation period of the study that were documented during FU (e.g. an AE reported during FU with start of onset during observation period) were listed separately and not used for descriptive analysis of FU data. AEs assigned to the clinical observation period but changed after data base lock for the clinical observation period were also listed separately.

Sample size

Planned:

50 (enrolment); 44 (evaluable without major protocol deviation)

Analyzed:

Clinical observation period (PTD-1 + PTD 2): 54 screened (enrolled) patients; 52 randomized; 52 safety analysis set (SAF), 51 full analysis set (FAS), 49 per protocol set (PPS).

All 52 randomized patients entered the FU period.

Follow-up period: 49 completed FU, 3 patients discontinued FU; 52 SAF-FUP, 47 FAS-FUP, 46 PPS-FUP

Randomisation

Intra-individual comparison; BF-200 ALA (gel)/daylight and Metvix® (cream)/daylight were randomized to the respective sides of the patient's face and/or scalp with a ratio 1.1

Blinding (masking)

Observer-blind

Statistical methods

Follow-up efficacy variables

FU efficacy variables were analyzed descriptively and in an exploratory way with both sets, the FAS-FUP and the PPS-FUP. Continuous data in the FU were summarized by using descriptive statistics, i.e. number of lesions/ patients/ patients' sides, mean, standard deviation (SD), minimum, first quartile, median, third quartile, and maximum. Categorical data in the FU were presented by using frequency (counts) and percentages. In addition, the life table method was used to analyze recurrence rates.

Lesions with missing FU assessments were set to "recurrent" for sensitivity FU analyses (conservative approach). Missing patient's satisfaction, skin quality assessments and overall cosmetic outcome on FU visits were not imputed.

Follow-up safety variables

All safety variables were analyzed descriptively and in an exploratory way with the safety analysis set (SAFFUP).

Recruitment/ Conduct of the study

Three patients discontinued during FU. Two patients discontinued the follow-up due to their own decision, one patient due to SAEs that were assessed as not related to one of the IMPs. This means 49 patients completed FU.

52 patients formed the SAF-FUP. 47 patients were in the FAS-FUP, 46 in the PPS-FUP.

Baseline data

In the PPS-FUP (N=46), the mean ± SD age was 72.8 ± 7.3 years, with 5 (10.9%) patients <65 years old, and 41 (89.1%) patients ≥65 years old. 95.7% of the patients were male. The Fitzpatrick skin type was I-III for 42 (91.3%) patients and IV-V for 4 (8.7%) patients. Demographics and baseline characteristics were similar for the SAF-FUP and the FAS-FUP.

There were a mean ± SD of 6.4 ± 2.2 target AK lesions at baseline for both, the BF-200 ALA/daylight PDTand Metvix®/daylight PDT-treated sides (PPS-FUP). The mean total area of target lesions was 528.7 ± 270.9 and 503.0 ± 239.1 mm^2 for the BF-200 ALA- and the Metvix®-treated sides of face and scalp, respectively (PPS-FUP). The SAF-FUP and FAS-FUP showed similar target lesion attributes.

Numbers analysed

All patients initially randomised into the study 52 entered the FU (follow-up) period; 52 safety analysis set (SAF-FUP), 47 full analysis set (FAS-FUP), 46 per protocol set (PPS-FUP).

Outcomes and estimation

Efficacy results from the 1-year Follow-up period:

The lesion recurrence rate per patient's side (percentage of completely cleared individual lesions 12 weeks after the PDT per patient's side showing recurrence during FU) is summarized in table 12.

Table 12: Lesion recurrence rate per patient's side during follow-up

	PPS-FUP				FAS-FUP			
	BF-200 ALA		Metvix®		BF-200 ALA		Metvix®	
	N	Mean ± SD (%)	N	Mean ± SD (%)	N	Mean ± SD (%)	N	Mean ± SD (%)
FU1	46	8.6 ± 15.5	45	13.2 ± 22.3	47	8.5 ± 15.4	46	12.9 ± 22.1
FU2	45	13.1 ± 21.0	44	22.9 ± 31.2	46	12.8 ± 20.8	45	22.7 ± 30.9
FU1, FU2	45	19.9 ± 24.1	44	31.6 ± 31.4	46	19.5 ± 24.0	45	31.2 ± 31.1

FAS-FUP: full analysis set follow-up;

FU1: follow-up 1 visit, 6 months after PDT; FU2: follow-up 2 visit, 12 months after PDT;

FU1, FU2: accumulated FU data; N: number of patients;

PPS-FUP: per protocol set follow-up; SD: standard deviation.

Ancillary analyses

- **Subgroup analyses by sex, age group, and by country** are summarized in Table 13 for the PPS-FUP. Results were similar for the FAS-FUP (data not shown).

Table 13: Lesion recurrence rate per patient's side by demographic characteristics, PPS-FUP

			BF-200 ALA		Metvix®	
			n	Mean ± SD (%)	n	Mean ± SD (%)
By sex [a]	Male	FU1	44	8.5 ± 15.7	43	12.2 ± 21.1
		FU2	43	12.1 ± 19.7	42	21.7 ± 29.4
		FU1, FU2	43	19.1 ± 22.9	42	30.8 ± 29.9
By age group, years	<65	FU1	5	16.0 ± 26.1	5	25.0 ± 30.6
		FU2	5	20.0 ± 21.7	5	60.0 ± 43.5
		FU1, FU2	5	34.0 ± 26.5	5	61.7 ± 43.9
	≥65	FU1	41	7.8 ± 14.0	40	11.7 ± 21.1
		FU2	40	12.2 ± 21.0	39	18.2 ± 26.5
		FU1, FU2	40	18.2 ± 23.5	39	27.8 ± 27.9
By country	Germany	FU1	41	9.7 ± 16.2	40	13.5 ± 22.5
		FU2	40	12.6 ± 20.9	39	21.4 ± 31.8
		FU1, FU2	40	20.4 ± 24.4	39	29.9 ± 32.6
	Spain	FU1	5	0.0 ± 0.0	5	10.0 ± 22.4
		FU2	5	16.7 ± 23.6	5	35.0 ± 25.3
		FU1, FU2	5	16.7 ± 23.6	5	45.0 ± 16.2

FU1: follow-up 1 visit, 6 months after PDT; FU2: follow-up 2 visit, 12 months after PDT; FU1, FU2: accumulated FU data; n: number of patients' sides per subgroup; PPS-FUP: per protocol set follow-up; SD: standard deviation.

[a] No basic statistics provided for female since n < 5.

Lesion recurrence rate is defined as the percentage of completely cleared individual lesions (grade 0 according to Olsen criteria) 12 weeks after the PDT per patient's side showing recurrence during follow-up.

Lesion recurrence rate is only calculated for patients' sides with at least one cleared lesion in the preceding visit.

- **Subgroup analyses by treatment area, total area of AK lesions at baseline, maximum severity grade of AK lesions at baseline, and maximum number of target AK lesions per side at baseline** are summarized in Table 14 for the PPS-FUP. Results were similar for the FAS-FUP (data not show).

For the entire FU period (FU1, FU2), similar lesion recurrence rates per patient's side were observed for the treatment area 'face' and for patients with only mild lesions. Lower lesion recurrence rates for BF-200 ALA-treated sides compared with Metvix-treated sides were seen regarding the treatment area 'scalp', for patients with at least one moderate lesion, for patients with a total treatment area of ≤ 1000 mm² or > 1000 mm², and for patients with ≤ 5 lesions.

Table 14: Lesion recurrence rate per patient's side by baseline characteristics, PPS-FUP

			BF-200 ALA		Metvix®	
			n	Mean ± SD (%)	n	Mean ± SD (%)
By treatment area	Face	FU1	19	7.5 ± 14.2	19	7.9 ± 18.8
		FU2	19	13.5 ± 21.6	19	20.6 ± 29.7
		FU1, FU2	19	20.1 ± 22.9	19	25.0 ± 29.0
	Scalp	FU1	23	11.1 ± 17.5	22	20.1 ± 25.1
		FU2	22	15.0 ± 22.0	21	29.4 ± 33.9
		FU1, FU2	22	23.4 ± 26.0	21	43.7 ± 31.0
	Face/ Scalp	FU1	4	0.0 ± 0.0	4	0.0 ± 0.0
		FU2	4	0.0 ± 0.0	4	0.0 ± 0.0
		FU1, FU2	4	0.0 ± 0.0	4	0.0 ± 0.0
By total area of AK lesions at baseline, mm²	≤1000	FU1	24	7.1 ± 13.9	23	14.1 ± 23.6
		FU2	24	16.0 ± 21.4	23	24.0 ± 27.7
		FU1, FU2	24	21.0 ± 23.9	23	36.4 ± 27.7
	>1000	FU1	22	10.4 ± 17.3	22	12.2 ± 21.4
		FU2	21	9.7 ± 20.5	21	21.8 ± 35.3
		FU1, FU2	21	18.8 ± 24.9	21	26.4 ± 34.9
By maximum severity grade of AK lesions at baseline	Mild	FU1	7	7.1 ± 13.1	7	3.2 ± 8.4
		FU2	7	9.5 ± 16.3	7	14.3 ± 20.2
		FU1, FU2	7	16.7 ± 16.7	7	17.5 ± 19.4
	Moderate	FU1	39	8.9 ± 16.1	38	15.0 ± 23.6
		FU2	38	13.7 ± 21.8	37	24.6 ± 32.8
		FU1, FU2	38	20.5 ± 25.3	37	34.3 ± 32.7
By maximum number of target AK lesions per side at baseline	≤5	FU1	17	3.9 ± 11.1	16	16.4 ±27.3
		FU2	17	12.4 ± 18.1	16	20.3 ± 22.1
		FU1, FU2	17	16.3 ± 18.6	16	36.7 ± 23.0
	>5	FU1	29	11.4 ± 17.2	29	11.4 ± 19.3
		FU2	28	13.5 ± 22.9	28	24.4 ± 35.7
		FU1, FU2	28	22.2 ± 26.9	28	28.8 ± 35.4

FU1: follow-up 1 visit, 6 months after PDT; FU2: follow-up 2 visit, 12 months after PDT; FU1, FU2: accumulated FU data; n: number of patients' sides per subgroup; PPS-FUP: per protocol set follow-up; SD: standard deviation.

Lesion recurrence rate is defined as the percentage of completely cleared individual lesions (grade 0 according to Olsen criteria) 12 weeks after the PDT per patient's side showing recurrence during follow-up.

Lesion recurrence rate is only calculated for patients' sides with at least one cleared lesion in the preceding visit.

- **Subgroup analyses of lesion recurrence rates per patient's side by minimum temperature during PDT and by worst weather condition during PDT** are summarized in Table 15 for the PPS-FUP. Results were similar for the FAS-FUP (data not shown).

Altogether, BF-200 ALA-treated sides showed lower lesion recurrence rates regarding weather conditions during PDT than Metvix®-treated sides, especially for outdoor temperatures > 20°C and sunny weather during PDT.

Table 15: Lesion recurrence rate per patient's side by weather condition during PDT, PPS-FUP

			BF-200 ALA		Metvix®	
			n	Mean ± SD (%)	n	Mean ± SD (%)
By minimum temperature during PDT	≤ 20°C	FU1	22	10.8 ± 17.6	22	13.5 ± 24.0
		FU2	21	13.6 ± 22.2	21	20.0 ± 32.3
		FU1, FU2	21	21.5 ± 26.5	21	26.8 ± 32.7
	> 20°C	FU1	24	6.7 ± 13.5	23	12.8 ± 21.0
		FU2	24	12.6 ± 20.3	23	25.6 ± 30.7
		FU1, FU2	24	18.6 ± 22.2	23	36.1 ± 31.1
By worst weather condition during PDT	Cloudy	FU1	12	8.1 ± 11.1	11	7.7 ± 10.8
		FU2	11	8.9 ± 15.7	10	13.3 ± 21.9
		FU1, FU2	11	15.9 ± 17.7	10	20.8 ± 21.8
	Mixed	FU1	13	13.9 ± 19.8	13	12.5 ± 24.7
		FU2	13	15.4 ± 25.9	13	19.5 ± 32.5
		FU1, FU2	13	25.4 ± 29.6	13	26.6 ± 33.8
	Sunny	FU1	21	5.7 ± 14.6	21	16.4 ± 25.3
		FU2	21	13.8 ± 20.7	21	29.6 ± 33.8
		FU1, FU2	21	18.7 ± 23.8	21	39.9 ± 32.7

FU1: follow-up 1 visit, 6 months after PDT; FU2: follow-up 2 visit, 12 months after PDT; FU1, FU2: accumulated FU data; n: number of patients' sides per subgroup; PPS-FUP: per protocol set follow-up; SD: standard deviation.

Lesion recurrence rate is defined as the percentage of completely cleared individual lesions (grade 0 according to Olsen criteria) 12 weeks after the PDT per patient's side showing recurrence during follow-up.

Lesion recurrence rate is only calculated for patients' sides with at least one cleared lesion in the preceding visit.

- **Changes in skin quality assessments**

Skin quality parameters (including skin surface, hyperpigmentation, hypopigmentation, mottled or irregular pigmentation, scarring, and atrophy) were assessed by the investigator at FU1 (six months after PDT) and FU2 visits (12 months after PDT) using a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe).

Table 16: Skin quality improvement from baseline - Patients with baseline skin quality of at least mild impairment, PPS-FUP

		BF-200 ALA		Metvix®	
		n/N	%	n/N	%
Skin surface	FU1	7/18	38.9	7/18	38.9
	FU2	10/17	58.8	9/17	52.9
Hyperpigmentation	FU1	7/19	36.8	5/19	26.3
	FU2	9/18	50.0	6/18	33.3
Hypopigmentation	FU1	6/18	33.3	5/20	25.0
	FU2	6/17	35.3	5/19	26.3
Mottled or irregular pigmentation	FU1	7/22	31.8	6/22	27.3
	FU2	8/21	38.1	8/21	38.1
Scarring	FU1	2/6	33.3	2/7	28.6
	FU2	3/5	60.0	3/6	50.0
Atrophy	FU1	5/9	55.6	5/9	55.6
	FU2	5/9	55.6	5/9	55.6

FU1: follow-up 1 visit, 6 months after PDT; FU2: follow-up 2 visit, 12 months after PDT; n: number of patients' sides with improvement; N: number of patients' sides with baseline skin quality of at least mild impairment per skin category; PPS-FUP: per protocol set follow-up.

The last non-missing value until treatment / PDT visit is used as baseline value.

Only patients with baseline assessment of at least mild in respective category are considered irrespective of their lesion status during FU.

- **Changes in cosmetic outcome**

Table 17: Overall cosmetic outcome during FU - Patients with sum of all baseline skin quality assessments > 0, PPS-FUP

		BF-200 ALA		Metvix®	
		FU1 N=29	FU2 N=28	FU1 N=29	FU2 N=28
Very good	n (%)	8 (27.6)	11 (39.3)	7 (24.1)	10 (35.7)
Good		3 (10.3)	3 (10.7)	5 (17.2)	3 (10.7)
Satisfactory		13 (44.8)	8 (28.6)	12 (41.4)	10 (35.7)
Unsatisfactory		4 (13.8)	3 (10.7)	4 (13.8)	3 (10.7)
Impaired		1 (3.4)	3 (10.7)	1 (3.4)	2 (7.1)

FU1: follow-up 1 visit, 6 months after PDT; FU2: follow-up 2 visit, 12 months after PDT; n: number of patients sides per category; N: number of patients' sides per treatment arm and FU visit with sum of all baseline skin quality assessments > 0 for both sides; PPS-FUP: per protocol set follow-up.

Only patients with sum of all baseline skin quality assessments > 0 for both sides are considered irrespective of their lesion status during FU.

The cosmetic outcome is calculated for each patient's side on the basis of the skin quality assessment and is calculated as follows:

Very good: The sum of all ratings for each skin quality sign has improved by at least 2 points as compared to baseline. If at least one sign has worsened by 1 point, the sum score must have improved by at least 3 points; Good: Sum score has improved by at least 1 point; Satisfactory: Sum score is identical to the one at baseline; Unsatisfactory: Sum score has worsened by 1 point; Impaired: Sum score has worsened by at least 2 points.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study 010

In the scope of the current application for variation the MAH intends to extend the indication to the treatment on the trunk/neck and extremities, based on the phase III study 010. This study compares ALA (Ameluz)/ BF-RhodoLED lamp to placebo/ BF-RhodoLED lamp in the treatment of mild to severe actinic keratosis on extremities, trunk/ neck. It is a randomised, double-blind, intra-individual comparison (test product vs. placebo), multi-center study.

There were 50 patients in the SAF (safety analysis set; 26 female, 24 male), N=49 patients in the FAS, and N=43 patients in the PPS. Two patients in the FAS withdrew their consent during the study, but after their first study treatment. Drop-out in this study was low.

In the FAS, the mean age was 70.9 ± 8.4 years (mean ± SD), with 10 (20.4%) patients <65 years old, and 39 (79.6%) patients ≥65 years old, including 16 (32.7%) patients ≥75 years old).

The Fitzpatrick skin type was I-III for 47 (95.9%) patients and IV-VI for 2 (4.1%) patients. Demographics were very similar for the PPS.

Thirty-nine (79.6%) patients were treated on the extremities and 10 (20.4%) patients on the trunk/neck (FAS).

There was a mean of 5.3 ± 1.1 and 5.5 ± 1.2 target AK lesions at baseline for the Ameluz- and placebo-treated sides, respectively. The mean total area of target lesions was 254.3 ± 125.5 mm² and 262.0 ± 124.0 mm² for the Ameluz- and placebo-treated sides, respectively. Together, 258 lesions and 268 lesions were treated with Ameluz and placebo, respectively.

93 (36.0%) Ameluz-treated lesions had a mild, 158 (61.2%) a moderate, and 7 (2.7%) a severe grade at baseline (according to Olsen), which was similar to the placebo-treated lesions with 109 (40.7%) mild, 152 (56.7%) moderate, and 7 (2.6%) severe lesions at baseline. The mean size of the target lesions was 48 ± 28.8 mm² for the Ameluz-treated lesions and 47.9 ± 26.7 mm² for the placebo-treated lesions (all in the FAS). The PPS showed very similar target lesion attributes.

The duration of the clinical observation period was approx. 14 weeks for patients receiving one PDT and approx. 26 weeks for patients receiving two PDTs. The duration of the follow-up phase was resp. is 1 year and has not been reported yet, as the study is ongoing.

The primary efficacy parameter (total lesion clearance rate in percent per patient's side) was evaluated 12 weeks after last PDT.

Study 009

Moreover, in the scope of this application for variation the MAH submitted the results of the 1-year follow-up (without treatment) of study 009. This study compares ALA (Ameluz)/ daylight to Metvix/ daylight in the treatment of mild to moderate actinic keratosis of face and/or scalp. It is a randomised, observer-blind, intra-individual comparison (test product vs. active comparator), multi-center study. 50 patients were randomized.

The timing of PDTs (one resp. two PDTs) was the same as in study 010.

All 52 patients, which were initially randomized into study 009 entered the FU (follow-up) period.

52 patients formed the safety analysis set (SAF-FUP* [*= Follow-up population]). Drop-out was low, 47 full analysis set (FAS-FUP) and 46 per protocol set (PPS-FUP).

In the PPS-FUP (N=46), the mean ± SD age was 72.8 ± 7.3 years, with 5 (10.9%) patients <65 years old, and 41 (89.1%) patients ≥65 years old. 95.7% of the patients were male. The Fitzpatrick skin type was I-III for 42 (91.3%) patients and IV-V for 4 (8.7%) patients. Demographics and baseline characteristics were similar for the SAF-FUP and the FAS-FUP.

There were a mean ± SD of 6.4 ± 2.2 target AK lesions at baseline for both, the Ameluz/daylight PDT and Metvix/daylight PDT-treated sides (PPS-FUP). The mean total area of target lesions was 528.7 ± 270.9 and 503.0 ± 239.1 mm² for the Ameluz- and the Metvix-treated sides of face and scalp, respectively (PPS-FUP). The SAF-FUP and FAS-FUP showed similar target lesion attributes.

During follow-up, the lesion recurrence rate of patients BF-200 ALA-treated sides was compared to Metvix-treated sides. The follow-up phase was without treatment.

Efficacy data and additional analyses

Study 010

The objective of the study was to compare the efficacy of Ameluz with placebo for the treatment of mild to severe AK located on extremities and trunk/neck with PDT when using the BF-RhodoLED lamp.

The patients received one or two PDTs, depending on the lesion clearance. Retreatment was done in case the patient's lesion were not cleared completely on one side 12 weeks after the first PDT. 56% of the patients received two PDTs.

The study was designed as an intra-individual comparison, thus demographics for both treatment groups were the same. Moreover, baseline disease characteristics (e.g. number of lesions, lesion severity, total treatment area) for both patients' sides were comparable and allowed the assessment of the efficacy of Ameluz compared with placebo.

The primary efficacy variable, the total lesion clearance rate in percent per patient's side 12 weeks after the last PDT, defined as the percentage of individual lesions with complete remission on the respective side of the patient, was significantly higher for Ameluz treated sides than for placebo-treated sides (86.0% ± 23.2% versus 32.9% ± 37.1%; FAS, LOCF), clearly demonstrating superiority of Ameluz over placebo ($p<0.0001$; Wilcoxon signed rank test). The robustness of this result was confirmed by the PPS analysis (90.0% ± 19.5% versus 28.5% ± 36.7%; $p<0.0001$; Wilcoxon signed rank test). Total lesion clearance rates for the treatment area trunk/neck were generally higher than for the treatment area extremities. Exploratory subgroup analyses by sex, age group, Fitzpatrick skin type category, and baseline AK severity showed results consistent with the primary analysis. Most of the results showed a statistically significant difference between both treatments. Few subgroups (e.g. baseline AK severity 'severe') included a limited number of patients such that the differences were not statistically significant, but numerically in favor of BF-200 ALA.

All confirmatory hypothesis testing of the secondary efficacy variables (including patient complete clearance, total lesion clearance rate of moderate lesions, total lesion clearance rate by treatment area, histopathologically confirmed lesion response rate, total lesion clearance rate 12 weeks after PDT-1, patient complete clearance 12 weeks after PDT-1, and cosmetic outcome) in the given hierarchical order showed statistically significant superiority of Ameluz® over placebo and supported the results of the primary efficacy analysis; in all instances, the PPS showed similar results.

Analysis of the patient complete clearance per patient's side 12 weeks after the last PDT showed higher responder rates with Ameluz than with placebo: 33 (67.3%) BF-200 ALA-treated sides and 6

(12.2%) placebo-treated sides showed complete clearance of all treated AK lesions (p<0.0001; McNemar test).

The HCR rate (histologically confirmed response) 12 weeks after the last PDT was higher for Ameluz- than for placebo-treated biopsied lesions (85.1% versus 63.8%; p=0.0032; McNemar test). One (2.1%) of the Ameluz-treated lesions, but 36.2% of the placebo-treated lesions were neither clinically nor histopathologically cleared.

Analyses of the cosmetic outcome 12 weeks after last PDT showed a significantly better effect of the Ameluz treatment compared to placebo (p<0.0001; Wilcoxon signed rank test). 'Very good' or 'good' cosmetic outcomes were calculated for 28 (57.1%) patients on the Ameluz-treated sides and for 10 (20.4%) patients on the placebo-treated sides. 'Unsatisfactory' or 'impaired' cosmetic outcomes were calculated for more patients on the placebo-treated sides (19 [38.8%] patients) than on the Ameluz treated sides (12 [24.5%] patients).

Assessment of skin quality 12 weeks after the last PDT showed numerically higher proportions of improvement in most of the skin quality parameters for Ameluz treated sides compared with placebo-treated sides. Improvement of skin surface was in favor of Ameluz, as demonstrated by non-overlapping 95% CIs. Other skin quality parameters showed overlapping 95% CIs.

This study demonstrated the efficacy of Ameluz PDT in the treatment of AK lesions on extremities and trunk/neck: the primary efficacy variable and all secondary efficacy variables showed statistically significant superiority of Ameluz over placebo. Additional exploratory subgroup analyses showed consistent results. For small subgroups (e.g. baseline AK severity 'severe') the differences were not statistically significant, but numerically in favour of Ameluz.

Study 009

No confirmatory tests were performed for the FU analysis. All FU efficacy variables were analyzed descriptively.

For the entire FU period (FU1, FU2), subgroup analyses revealed lower mean lesion recurrence rates for BF-200 ALA compared with Metvix® for patients with at least one moderate AK lesion at baseline, for AKs on the scalp, when treated at >20°C, and during sunny weather; for patients with a total treatment area of ≤ 1000 mm² or > 1000 mm², and for patients with ≤ 5 lesions. The other subgroups showed similar results between both study treatments.

The accumulated lesion recurrence rates per IMP for the entire FU period were 19.7% for BF-200 ALA-treated lesions and 27.1% for Metvix®-treated lesions for the PPS-FUP. Subgroup analyses for lesion recurrence rate per IMP revealed similar recurrence rates for the treatment area 'face', for mild lesions, for lesions treated at outdoor temperatures ≤ 20°C, and at cloudy or mixed weather during PDT.

Lower recurrence rates for BF-200 ALA-treated lesions compared with Metvix®-treated lesions were seen regarding the treatment area 'scalp', moderate lesions, lesions treated at outdoor temperatures > 20°C, and at sunny weather during PDT.

The lower recurrence rates achieved with BF-200 ALA/daylight PDT are reflected in the 1-year estimated lesion-based clearance rates (pi*RLC) that are in favor for BF-200 ALA. The probability that BF-200 ALA-treated lesions are cleared 1 year after daylight PDT was 62.9% compared with 56.6% for Metvix®-treated lesions. pi*RLC values for the more difficult-to-treat lesions were 56.8% vs. 47.0% for the scalp, and 53.1% vs. 43.4% for all moderate lesions for BF-200 ALA and Metvix®, respectively (PPS-FUP).

Both treatment groups showed similar results during FU for patient recurrence rates, improvement in skin quality, cosmetic outcome, and patient's satisfaction.

The efficacy variables analyzed in the FU (follow-up) period were: lesion recurrence, patient recurrence,

changes from baseline in skin quality and cosmetic outcome during the FU as well as patient's satisfaction on FU visits regarding PDT treatment and cosmetic outcome. All FU efficacy variables were analyzed descriptively.

Lesion recurrence rate assessments were based on the number of completely cleared AK lesions (per patient's side or per IMP) 12 weeks after daylight PDT. Overall, 1-year lesion recurrence rates for patient sides treated with Ameluz® gel were lower than for sides treated with Metvix® cream (19.9% vs. 31.6%; PPS-FUP). Subgroups analyses revealed lower mean recurrence rates for BF-200 ALA compared with Metvix® for patients with at least one moderate AK lesion at baseline (20.5% vs. 34.3%), for AKs on the scalp (23.4% vs. 43.7%), when treated at >20°C (18.6% vs. 36.1%), and during sunny weather (18.7% vs. 39.9%); for patients with a total treatment area of ≤ 1000 mm² (21.0% vs. 36.4%) or > 1000 mm² (18.8% vs. 26.4%), and for patients with ≤ 5 lesions (16.3% vs. 36.7%). The other subgroups showed similar results between both study treatments. Of all mild AKs treated with Ameluz® gel that were cleared 12 weeks after daylight PDT, 17.7% were recurrent after 1 year, compared with 19.3% of the lesions treated with Metvix®. Of all cleared moderate lesions, 22.1% of the Ameluz® treated lesions recurred during FU compared with 36.4% of the Metvix®-treated lesions (PPS-FUP).

Patient recurrence rate assessments were based on the number of patients with all lesions on a specific side completely cleared (Olsen score of 0) 12 weeks after daylight PDT. Overall, patient recurrence rates were slightly lower for Ameluz® than for Metvix®. Furthermore, lower recurrence rates were observed for the first 6-month period (fromV4 to FU1) than for the second 6-month period (from FU1 to FU2). The accumulated patient recurrence rates for the entire FU period were 52.4% for Ameluz® treated sides and 58.8% for Metvix®-treated sides for the PPS-FUP. Similar results were observed for the FAS-FUP.

The analysis of changes in skin quality during the FU (including assessments of skin surface, hyper-pigmentation, hypopigmentation, mottled or irregular pigmentation, degree of scarring, and atrophy) showed a trend towards improvement in most skin parameters from FU1 to FU2 in both treatment groups. Values for the Ameluz® treated sides ranged from 31.8% to 55.6% (FU1) and from 35.3% to 60.0% (FU2); values for the Metvix®-treated sides ranged from 25.0% to 55.6% (FU1) and from 26.3% to 55.6% (FU2) (only patients with at least mild impairment at baseline are included; PPS-FUP).

The overall cosmetic outcome for patients with sum of all baseline skin quality assessments > 0 was comparable between the treatment groups and the FU visits in the Per Protocol Set. It was assessed as "very good or good" for 11 (37.97%) and 12 (41.3%) patients for Ameluz® and Metvix®, respectively, at FU1 (6 months after PDT) and for 14 (50.0%) and 13 (46.4%) patients for Ameluz® and Metvix®, respectively, at FU2 (1 year after PDT).

Patient's satisfaction regarding overall cosmetic outcome was "very good, good or satisfactory" for 44 (95.7%) patients for both treatments at FU1 and for 41 (91.1%) and 42 (93.3%) patients for Ameluz/daylight PDT and Metvix®/daylight PDT, respectively, at FU2 (PPS-FUP). Overall, 45 (97.8%) patients at FU1 and 42 (93.3%) patients at FU2 stated that they would choose daylight PDT again (PPS-FUP). Similar results were observed for the FAS-FUP and for the PDT treatment in respect of the applied IMP.

Pooled Analysis of the phase III studies of actinic keratosis of face and/or scalp

The efficacy from **study 010** in the body region "extremities and/or trunk/neck" was lower compared to the results presented for the body region "face and/or scalp". In study 010 the percentage of patients for whom all treated AK lesions were completely cleared 12 weeks after the last PDT was evaluated as secondary efficacy parameter. Analysis of the patient complete clearance per patient's side 12 weeks after the last PDT showed higher responder rates with Ameluz® (BF-200 ALA) than with placebo: 67.3% BF-200 ALA-treated sides and 12.2% placebo-treated sides showed complete clearance of all treated AK lesions ($p<0.0001$; McNemar test). The difference between both treatment arms was 55.1%. In study 007, which evaluated PDT also with the narrow spectrum BF-RhodoLED, but in field-directed treatment of face/scalp, the efficacy of Ameluz compared to placebo was more pronounced. Ameluz was superior to placebo with respect to the primary efficacy parameter patient complete clearance rates (90.9% vs. 21.9%) for Ameluz and placebo, respectively; $p < 0.0001$). The difference between both treatment arms was 69%.

2.4.3. Conclusions on the clinical efficacy

Topical application of Ameluz® with PDT using BF-RhodoLED® was superior to placebo PDT for the treatment of mild to severe AK on extremities and trunk/neck. Results of the confirmatory analyses of all secondary efficacy variables also supported the superiority of Ameluz® over placebo.

The follow-up data from study 009 demonstrate daylight PDT with Ameluz® to be highly efficacious. One year after a single treatment, Ameluz® treated lesions showed lower recurrence rates than lesions treated with the marketed product Metvix®, especially for lesions of moderate severity and lesions on the scalp.

2.5. Clinical safety

Introduction

In clinical trials with Ameluz, local skin reactions at the application site were observed in most of the subjects treated for actinic keratosis and basal cell carcinoma. This is to be expected as the therapeutic principle of photodynamic therapy is based on phototoxic effects of protoporphyrin IX which is synthesized from the active ingredient 5-aminolaevulinic acid.

The most common currently listed signs and symptoms are application site irritation, erythema, pain (incl. burning pain), and oedema. But also pruritus, scab, exfoliation, induration, paraesthesia are very frequent. All of these ADRs are listed with the frequency "very common" in the SmPC.

The intensity of these effects is dependent on the type of illumination used for photodynamic therapy. The increased effects correlate with the higher clearance rate of narrow spectrum lamps (see SmPC section 5.1). Intensity of adverse reactions, particularly pain, was lower when Ameluz was used in combination with daylight PDT.

Most adverse reactions occur during illumination or shortly afterwards. The symptoms are usually of mild or moderate intensity (investigator's assessment on a 4-point scale), and last for 1 to 4 days in most cases; in some cases, however, they may persist for 1 to 2 weeks or even longer. In rare cases, the adverse reactions required interruption or discontinuation of the illumination.

Patient exposure

Study 010

The 1-year follow-up of this study is ongoing. Thus, safety data from this study refer to the clinical observation period only (including 12 weeks after last PDT).

All 50 patients in the SAF (safety analysis set) were exposed to PDT in the first session (Visit 2). 22 (44%) of them were completely cleared on one side 12 weeks after their first PDT and 28 (56%) patients were retreated during this visit. This means 56% of the patients received two PDTs.

During PDT-2, one of the patients accidently received BF-200 ALA on the placebo-assigned side and placebo on the BF-200 ALA-assigned side. This crossover was documented, and the patient was allocated to BF-200 ALA for both sides for safety analyses. In the FAS, the assignment of patients' sides to the treatment groups is as randomized.

On the day of PDT the skin was exposed for a mean of 185 minutes (range 177 to 200 min) to Ameluz resp. placebo gel. The 10 min-illumination time with the BF-RhodoLED lamp could have been interrupted for pain management but was performed without interruptions for all patients.

Study 009 - FU

Daylight-Study 009 of the face/scalp is completed. The safety data presented in the scope of the current application for variation refer to the 1-year follow-up period of this study only. The 1-year FU was without application of study drug. In the preceding clinical study period BF-200 ALA/ daylight PDT was compared in an intra-individual comparison to Metvix/ daylight PDT in 52 patients. One session of PDT was applied. Daylight PDT was performed for 2 continuous hours in full daylight.

52 patients formed the SAF-FUP (safety analysis set of follow-up period).

Adverse events

Study 010

All 50 patients had at least one TEAE on the Ameluz® (BF-200 ALA)-treated side and 28 (56%) had at least one TEAE on the placebo-treated side. Furthermore, there were 20 (40%) patients with TEAEs that were not allocated to one treatment side ('relation to side not applicable'), which means that the TEAE was a general TEAE, e.g. a cold; 5 (10%) patients had a TEAE with an unknown location.

Related TEAEs were reported for 50 (100%) BF-200 ALA-treated sides, 22 (44%) placebo-treated

sides, and 1 (2%) patient had a related TEAE without allocation to a specific treatment side. There was no TEAE that was leading to discontinuation or to death during the study.

Table 18: Overview of adverse events, SAF

N = 50	Treated side of extremities or trunk/neck			
n (%)	BF-200 ALA	Placebo	Not allocated to a specific patient's side	Side unknown
Any AEs	50 (100)	28 (56.0)	22 (44.0)	5 (10.0)
Any serious AEs	2 (4.0)	0	3 (6.0)	0
Any TEAEs	50 (100)	28 (56.0)	20 (40.0)	5 (10.0)
Any serious TEAEs	2 (4.0)	0	2 (4.0)	0
Any TEAEs leading to death	0	0	0	0
Any related TEAEs	50 (100)	22 (44.0)	1 (2.0)	0
Any TEAEs resulting in discontinuation of study	0	0	0	0

AE: adverse event; N: number of patients; n: number of patients/patients' sides with event; SAF: Safety analysis set; TEAE: treatment emergent adverse event

Treatment emergent adverse events (TEAEs) are defined as all AEs with time of onset or worsening on or after the time of first drug application. If unclear due to incomplete start time/date of AE or PDT, AEs will be assumed as TEAEs.

Related TEAEs with relationship to investigational drug possibly, probably or definitely related, or with missing relationship.

TEAE (Treatment emergent adverse events)

The overall incidence of TEAEs was higher on the BF-200 ALA-treated sides (100%) than on the placebo-treated sides (56%). In both groups, the most commonly reported TEAEs were those of the application site. The incidences of these TEAEs were also higher on the BF-200 ALA-treated sides than on the placebo-treated sides. Application site pain was the most common individual TEAE on both sides, reported for 50 (100%) patients on the BF-200 ALA-treated side and for 20 (40%) patients on the placebo-treated side.

Table 19: Frequently reported TEAEs, SAF

N = 50	Treated side of extremities or trunk/neck			
MedDRA SOC Preferred term n (%)	BF-200 ALA	Placebo	Not allocated to a specific patient's side	Side unknown
Total	50 (100)	28 (56.0)	20 (40.0)	5 (10.0)
Eye disorders	0	1 (2.0)	0	2 (4.0)
Eczema eyelids	0	0	0	2 (4.0)
General disorders and administration site conditions	50 (100)	22 (44.0)	3 (6.0)	1 (2.0)
Application site erosion	2 (4.0)	2 (4.0)	0	0
Application site erythema	45 (90.0)	7 (14.0)	0	0
Application site exfoliation	12 (24.0)	2 (4.0)	0	0
Application site induration	3 (6.0)	2 (4.0)	0	0
Application site oedema	16 (32.0)	0	0	0
Application site pain	50 (100)	20 (40.0)	0	0
Application site paraesthesia	1 (2.0)	2 (4.0)	0	0
Application site pruritus	24 (48.0)	9 (18.0)	0	0
Application site scab	15 (30.0)	2 (4.0)	0	0
Application site vesicles	9 (18.0)	3 (6.0)	0	0
Pain	0	0	2 (4.0)	0

Infections and infestations	2 (4.0)	1 (2.0)	11 (22.0)	0
Nasopharyngitis	0	0	7 (14.0)	0
Urinary tract infection	0	0	2 (4.0)	0
Respiratory, thoracic and mediastinal disorders	0	0	3 (6.0)	0
Dyspnoea	0	0	2 (4.0)	0

N: number of patients; n: number of patients/patients' sides with event; SAF: Safety analysis set; SOC: system organ class; TEAE: treatment emergent adverse event

Related TEAEs (at least possibly related)

Most of the application site TEAEs on the BF-200 ALA- and placebo-treated sides were considered to be at least possibly related to the study treatment by the investigator. The most frequent related TEAE was application site pain, which was reported for 50 (100%) of the BF-200 ALA-treated sides and 20 (40%) of the placebo-treated sides; application site erythema reported for 45 (90%) and 7 (14%) treated sides, respectively; application site pruritus for 24 (48%) and 9 (18%) treated sides, respectively; application site oedema for 16 (32%) and 0 treated sides, respectively; application site scab for 15 (30%) and 2 (4%) treated sides, respectively; application site exfoliation for 12 (24%) and 1 (2%) treated sides, respectively; and application site vesicles for 9 (18%) and 3 (6%) treated sides, respectively.

Table 20: Related TEAEs, SAF

N = 50	Treated side of extremities or trunk/neck		
MedDRA SOC Preferred term n (%)	BF-200 ALA	Placebo	Not allocated to a specific patient's side
Total	50 (100)	22 (44.0)	1 (2.0)
General disorders and administration site conditions	50 (100)	22 (44.0)	1 (2.0)
Application site discharge	1 (2.0)	0	0
Application site discomfort	1 (2.0)	0	0
Application site eczema	1 (2.0)	0	0
Application site erosion	2 (4.0)	1 (2.0)	0
Application site erythema	45 (90.0)	7 (14.0)	0
Application site exfoliation	12 (24.0)	1 (2.0)	0
Application site hyperaesthesia	1 (2.0)	0	0
Application site induration	2 (4.0)	1 (2.0)	0
Application site oedema	16 (32.0)	0	0
Application site pain	50 (100)	20 (40.0)	0
Application site paraesthesia	1 (2.0)	1 (2.0)	0
Application site pruritus	24 (48.0)	9 (18.0)	0
Application site scab	15 (30.0)	2 (4.0)	0
Application site vesicles	9 (18.0)	3 (6.0)	0
Chills	0	0	1 (2.0)
Swelling	1 (2.0)	0	0
Skin and subcutaneous tissue disorders	2 (4.0)	0 (0.0)	0
Dry skin	1 (2.0)	0	0
Skin tightness	1 (2.0)	0	0

N: number of patients; n: number of patients/patients' sides with event; SAF: Safety analysis set; SOC: system organ class; TEAE: treatment emergent adverse event

Treatment emergent adverse events (TEAEs) are defined as all AEs with time of onset or worsening on or after the time of first drug application. If unclear due to incomplete start time/date of AE or PDT, AEs will be assumed as TEAEs.

Related TEAEs with relationship to investigational drug possibly, probably or definitely related, or with missing relationship.

TEAES of severe intensity

On the verum treated side 40% of the patients had application site pain of severe intensity, whereas on the placebo-treated side only 12% of the patients. For further TEAEs with severe intensity please see the table below.

Table 21: Related TEAEs, SAF

N = 50	Treated side of extremities or trunk/neck		
MedDRA SOC Preferred term n (%)	BF-200 ALA	Placebo	Not allocated to a specific patient's side
Total	20 (40.0)	6 (12.0)	2 (4.0)
Cardiac disorders	0	0	1 (2.0)
Acute myocardial infarction	0	0	1 (2.0)
Myocardial infarction	0	0	1 (2.0)
General disorders and administration site conditions	20 (40.0)	6 (12.0)	0
Application site erythema	5 (10.0)	1 (2.0)	0
Application site induration	1 (2.0)	1 (2.0)	0
Application site pain	20 (40.0)	6 (12.0)	0
Application site pruritus	5 (10.0)	2 (4.0)	0
Application site scab	1 (2.0)	1 (2.0)	0
Application site vesicles	1 (2.0)	0	0
Injury, poisoning and procedural complications	0	0	1 (2.0)
Lumbar vertebral fracture	0	0	1 (2.0)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0	1 (2.0)	0
Keratoacanthoma	0	1 (2.0)	0

N: number of patients; n: number of patients/patients' sides with event; SAF: Safety analysis set; SOC: system organ class; TEAE: treatment emergent adverse event

Treatment emergent adverse events (TEAEs) are defined as all AEs with time of onset or worsening on or after the time of first drug application. If unclear due to incomplete start time/date of AE or PDT, AEs will be assumed as TEAEs.

Local Skin Reactions (LSR)

LSRs were documented as 'application site skin reactions' that started during illumination or after illumination on PDT day.

LSRs were reported for 42 (84%) patients on the BF-200 ALA-treated sides and for 9 (18%) patients on the placebo-treated sides, respectively. The most frequently reported LSR was erythema, reported for 42 (84%) patients on the BF-200 ALA-treated side and 7 (14%) patients on the placebo-treated side, followed by oedema which was reported for 35.9% resp. 0% of the patients on the verum resp. placebo treated side.

As expected, due to the nature of the procedure, the incidence and intensity of LSRs occurring during and after PDT was higher on the BF-200 ALA-treated sides compared with the placebo-treated sides (see table below).

Table 22: TEAEs of severe intensity, SAF

	Extremities		Trunk/Neck	
	BF-200 ALA	Placebo	BF-200 ALA	Placebo
n (%)	N=39	N=39	N=11	N=11
Local skin reactions	34 (87.2)	7 (17.9)	8 (72.7)	2 (18.2)
Erosion	0	1 (2.6)	0	0
Erythema	34 (87.2)	5 (12.8)	8 (72.7)	2 (18.2)
Exfoliation	2 (5.1)	0	0	0
Induration	1 (2.6)	1 (2.6)	0	0
Oedema	14 (35.9)	0	1 (9.1)	0
Pruritus (itching)	1 (2.6)	1 (2.6)	0	0
Scab (scabbing/crusting)	3 (7.7)	1 (2.6)	0	0
Vesicles	1 (2.6)	1 (2.6)	1 (9.1)	0

N: number of patients; n: number of patients/patients' sides with event; PDT: photodynamic therapy; SAF: safety analysis set

Local Discomfort (Burning, Itching, Other)

Local discomfort during PDT-1 was reported by 49 (98%) patients for the BF-200 ALA treated sides and by 16 (32%) patients for the placebo-treated sides. The most frequently reported local discomfort during PDT-1 was burning, reported for 48 (96%) patients on the BF-200 ALA-treated side and 16 (32%) patients on the placebo-treated side. Local discomfort rates during PDT-2 were similar, but incidences shifted to less severe and more moderate TEAEs rated as discomfort during and after PDT-2 compared with PDT-1 for the BF-200 ALA-treated sides.

Table 23: Local discomfort during PDT, SAF

	Extremities		Trunk/Neck	
n (%)	BF-200 ALA	Placebo	BF-200 ALA	Placebo
PDT-1	38 (97.4)	9 (23.1)	11 (100)	7 (63.6)
Burning	37 (94.9)	9 (23.1)	11 (100)	7 (63.6)
Itching	8 (20.5)	3 (7.7)	4 (36.4)	3 (27.3)
Other	3 (7.7)	0	2 (18.2)	0
PDT-2	23 (100)	4 (17.4)	5 (100)	4 (80.0)
Burning	22 (95.7)	4 (17.4)	5 (100)	4 (80.0)
Itching	10 (43.5)	3 (13.0)	2 (40.0)	2 (40.0)
Other	2 (8.7)	0	1 (20.0)	1 (20.0)

N: number of patients; n: number of patients/patients' sides with event; PDT: photodynamic therapy; SAF: safety analysis set

Pain Intensity during PDT

Mean pain intensity reported (on an 11-point numeric rating scale ranging from 0 to 10) during PDT is presented in the table below.

Table 24: Pain during PDT as reported by the patient, SAF

	Extremities		Trunk/Neck	
n (%)	BF-200 ALA	Placebo	BF-200 ALA	Placebo
PDT-1	N =40	N = 38	N = 11	N = 11
Mean ± SD	4.6 ± 3.3	0.8 ± 2.3	4.5 ± 2.7	2.5 ± 3.0
Median	5.0	0.0	4.0	1.0
Range	0 to 10	0 to 10	0 to 9	0 to 8
PDT-2	N = 24	N = 22	N = 5	N = 5
Mean ± SD	4.0 ± 3.6	0.8 ± 2.2	3.8 ± 2.5	2.8 ± 1.8
Median	5.0	0.0	4.0	4.0
Range	0 to 10	0 to 8	0 to 6	0 to 4

N: number of patients; PDT: photodynamic therapy; SAF: safety analysis set; SD: standard deviation
Patient's pain intensity during PDT is assessed at the end of each illumination period using a numeric rating pain scale ranging from no pain at all (0) to worst possible pain (10).

Patients reported higher mean pain intensities for BF-200 ALA-treated sides compared with placebo-treated sides for both, PDT-1 and PDT-2, but mean pain intensity for BF-200 ALA treated sides was lower during PDT-2 than during PDT-1. Actions taken against pain during/after PDT included cooling with the airstream integrated in the BF-RhodoLED® lamp and the use of cooling pads after the PDT. In no case, PDT had to be interrupted

The phase III study 010 included 50 patients with actinic keratosis. 12 weeks after last PDT the most common related TEAEs at the application site that had not resolved yet were erythema (16x), followed by application site pruritus (3x), application site scab (3x), exfoliation (2x), oedema (1x). Most of the application site TEAEs that had not recovered at week 12 were mild or moderate. Only single TEAEs that had not recovered at week 12 after PDT were of severe intensity: erythema (1x), pruritus (1x) and induration (1x), at the application site each.

New Lesions

Three (6%) patients presented with new lesions on the side assigned to BF-200 ALA, all lesions were located outside the treatment field. One patient each had a new BCC, a new SCC, and a new AK lesion; the latter was located outside the treatment subarea but within the treatment area, all the others were located outside the treatment area.

Three (6%) patients presented with new lesions on the side assigned to placebo. One patient each had a new keratoacanthoma, a new BCC, and a new AK lesion; the latter was located inside the treatment field.

Study 009, follow-up data

In total, 37 (71.2%) patients experienced at least one AE that started or worsened in the FU.

None of these was assessed by the investigator as possibly, probably, or definitely related to one of the IMPs. Three (5.8%) patients experienced at least one serious adverse event (SAE); one discontinued due to SAEs, but none of the AEs was leading to death. Results were comparable between BF-200 ALA- and Metvix®-treated patient's sides (see table 25 below).

Table 25: Overview of adverse events during FU with respect to the treated patient's side, SAF-FUP

		Treated patient's side			
		BF-200 ALA	Metvix®	Not applicable	Unknown
		N=52	N=52	N=52	N=52
Any AEs [a]	n (%)	25 (48.1)	23 (44.2)	4 (7.7)	9 (17.3)
Any serious AEs		1 (1.9)	0	2 (3.8)	0
Any AEs leading to death		0	0	0	0
Any related AEs [b]		0	0	0	0
Any AEs resulting in discontinuation of study		0	0	1 (1.9)	0

AE: adverse event; FU: follow-up; n: number of patients' sides per category; N: number of patients' sides per treatment arm; SAF-FUP: safety analysis set follow-up.

[a] Any documented AEs that started or worsened after the date of Visit 4: 12 weeks (± 2 weeks) post-PDT.

[b] Related AEs with relationship to investigational drug possibly, probably or definitely related, or with missing relationship.

Only relevant AEs had to be reported during follow-up:

- Any relevant local adverse events (AEs) or conditions that may impair a proper assessment of the recurrence rate of the treated AK lesions as well as any SAE that have occurred since the end of the clinical study period
- New lesions (AK, non-melanoma skin cancer (NMSC), melanoma) on follow-up visits per patient's side,

Therefore, the most frequently reported PT during FU was the underlying disease – actinic keratosis – from the SOC "skin and subcutaneous tissue disorders". AK was reported for 23 (44.2%) patients' sides treated with BF-200 ALA or Metvix®, respectively, and for 9 (17.3%) patients, where the respective side was unknown.

Most of the AEs were of mild intensity. Only two patients (3.8%) experienced a total of three severe AEs (facial bones fracture, wrist fracture, actinic keratosis). None of the severe AEs was considered to be related to the IMPs. Most AEs resolved by the end of the FU.

Apart from actinic keratosis only few AEs were reported during FU:

1x hyperglycemia (resolved), 1x hypertonus (not resolved), dehydration (resolved), 1x impetigo lower arm (resolved), 1x application site dermatitis on scalp (resolved), 1x tinea versicolor (ongoing), 1x eczema asteatotic (resolved), 1x nasopharyngitis (resolved).

Further details on the occurrence of new lesions are provided below:

Occurrence of new lesions

New lesions occurred in 33 (63.5%) patients. 32 (61.5%) patients presented new AK lesions and 4 (7.7%) patients had other NMSC lesions. 15 (28.8%) patients had new lesions that where not located in the treatment area (face, scalp); 21 (40.4%) patients that were treated on the scalp presented new lesion on the scalp and 9 (17.3%) patients that were treated on the face had new lesions on the face. Most of the new lesions that occurred inside the treatment area were ≥ 10 mm away from the nearest target lesion (data not shown); thus, the respective area with the new lesion was not treated during the study.

For new lesions inside the treated areas face and scalp during the FU period please see Table 26 below. None of the new lesions was considered to be related to one of the IMPs.

Table 26: Occurrence of new lesions inside the treated areas during FU, SAF-FUP

MedDRA SOC Preferred term		Treated side of face / scalp BF-200 ALA N=52	 Metvix® N=52	 Unknown N=52
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	n (%)	2 (3.8)	1 (1.9)	1 (1.9)
Basal cell carcinoma		2 (3.8)	0	1 (1.9)
Bowen's disease		0	1 (1.9)	0
Skin and subcutaneous tissue disorders		19 (36.5)	19 (36.5)	9 (17.3)
Actinic keratosis		19 (36.5)	19 (36.5)	9 (17.3)

FU: follow-up; n: number of patients' sides per category; N: number of patients' sides per treatment arm; SAF-FUP: safety analysis set follow-up.

Serious adverse event/deaths/other significant events

Study 010

There were no deaths. According to the investigator all 7 SAEs during the clinical observation period of the study were clearly unrelated to the study treatment:

Acute myocardial infarction, myocardial infarction, humerus fracture, intervertebral disc protrusion, actinic keratosis, mechanical ileus, cervicobrachial syndrome) were reported for 5 (10%) patients during the clinical observation period of the study.

Study 009 - FU

There were no deaths. All SAE – apart from vestibular neuronitis - during the follow-up were clearly unrelated to the study treatment.

Overall, 8 SAEs (anal abscess, pelvic abscess, urinary tract infection, vestibular neuronitis [8 months after treatment with Ameluz/PDT], facial bone fracture, wrist fracture, dehydration, cerebrovascular accident) were reported for 3 (8.5%) patients in the FU. All SAEs were assessed by the investigators as unrelated to study medication.

One patient (1.9%) discontinued the FU period due to SAEs (fracture of the cheekbone and the wrist as a consequence of a fall and hospitalization). It is agreed to the MAH and investigator that this SAE and the other SAE are not related to Ameluz/PDT.

SAEs associated to patients' side treated with Ameluz: 1 patient with vestibular neuronitis.

SAEs associated to patients' side treated with Metvix: 0

SAEs with relation to side not applicable: Seven SAEs: anal abscess, pelvic abscess, urinary tract infection, facial bones fracture, wrist fracture, dehydration, cerebrovascular accident.

All SAEs and severe AEs resolved by the end of the FU except for one event, that remained resolving at the end of the study.

Laboratory findings

Study 010

Hematology, blood chemistry, and urinalysis data were examined for changes that occurred during the clinical observation period. Clinical laboratory safety tests were performed at screening (Visit 1) and 12 weeks after PDT-1 (Visit 4) or 12 weeks after PDT-2 if patients were retreated (Visit 6).

There were no clinically meaningful findings at screening, whereas 12 weeks after the last PDT one patient had an abnormal glucose value.

Urinanalysis: There was one clinically meaningful finding at screening (specific gravity), which was due to a medical condition at that time, whereas 12 weeks after the last PDT no abnormal value was observed.

Vital signs: Blood pressure and pulse rate were measured at each clinical visit, after 5 minutes of rest in a sitting position. Mean values for blood pressure and heart rate were similar at all visits, and mean changes from baseline to week 12 were minimal.

Study 009 - FU

No blood samples were taken during the follow-up.

Safety related to drug-drug interactions and other interactions

No interaction studies have been performed (see SmPC).

Discontinuation due to adverse events

Study 010

There was no AE leading to discontinuation of the study.

Study 009 - FU

One patient (1.9%) discontinued in the FU period due to SAEs (fracture of the cheekbone and the wrist and hospitalization as a consequence of a fall).

Post marketing experience

World-wide marketing safety experience

Ameluz (BF-200 ALA gel) was authorized for marketing in the EU on December 14, 2011. Ameluz is currently on the market in Germany, Sweden, Norway, Denmark, Austria, Spain, and the UK.

Marketing authorization for the USA was granted on May 10, 2016; Ameluz was launched in October 2016.

Furthermore, Ameluz was approved in November 2015 in Switzerland (launch April 2016) and in April 2016 in Israel (launch June 2017).

The cumulative post-authorization exposure since the international birth date (IBD) has been estimated at 364,721 2g-units/patient (based on the available sales figures since IBD until July 3st, 2019). The AEs reported during post-marketing are in agreement with the main AEs observed during clinical studies.

2.5.1. Discussion on clinical safety

Study 010

Safety data from the placebo-controlled phase III study 010 have been presented. This is the first study with Ameluz/BF-RhdoLED PTD in actinic keratosis in the region "extremities/trunk/neck". Up to now, the list of ADRs in the SmPC, section 4.8, refers to red-light PDT and daylight-PDT of actinic keratosis in the face/scalp and red-light PDT of basal cell carcinoma (face/scalp and/or all other body parts). Most of the treatment-related application site reactions reported for study 010 are listed in the SmPC, section 4.8, and most of them with the same frequency category.

The ADRs which were observed in study 010 but are not listed ADRs were:

In one patient (2.0%) "eczema" was reported in the Ameluz/BF-RhdoLED PTD treatment site (application site reaction). For one patient each (2.0%) "dry skin", "swelling", resp. "skin tightness" was observed on the Ameluz/BF-RhdoLED PTD treated site (but obviously these were no direct application site reaction). Consequently, "eczema infected", "swelling" and "skin tightness" were added to SmPC section 4.8.

All 50 patients in the safety analysis set had PDT-1. 56% of the patients received a second PDT (=PDT-2). At least one TEAE was reported for all 50 (100%) patients' sides treated with Ameluz and 28 (56%) patients' sides treated with placebo. Application site pain was the most common individual TEAE in both groups, reported for 100% sides treated with Ameluz resp. for 40% sides treated with placebo; it was followed by application site erythema, reported for 90% resp. 14% patients' sides; application site pruritus (48% resp. 18%); application site oedema (32% resp. 0%); application site scab (30% resp. 4%); application site exfoliation (24% resp. 2%); and application site vesicles (18% resp. 6%) patients' sides. Analysis of severity revealed, that the most commonly reported severe TEAE was application site pain, reported by 40% patients for BF-200 ALA-treated sides and by 12% patients for placebo-treated sides. No patient discontinued treatment due to a TEAE. The most commonly reported TEAEs for both treatments were also the most commonly reported related TEAEs.

Six (12%) patients reported SAEs, all of which were assessed by the investigator as not related to the study medication (acute myocardial infarction, myocardial infarction, humerus fracture, intervertebral disc protrusion, actinic keratosis, mechanical ileus, cervicobrachial syndrome). No deaths occurred.

No pregnancies were reported during the study. Laboratory parameters, vital signs variables, and results of physical examination showed no clinically relevant changes related to the study treatment.

On the sides treated with Ameluz, new lesions occurred only outside the treatment fields, whereas on the sides treated with placebo, one new AK lesion occurred within a treatment field.

The profile of TEAE findings is generally consistent with the elderly AK patient population represented in this study, the nature of the underlying disease, and the known safety profile of Ameluz. Local application site AEs associated with the treatment lasted for less than two weeks after PDT in most cases.

No new safety concern requiring an update of the RMP was identified.

Study 009 - FU

All 52 patients initially randomized entered the 1-year follow-up and only one patient discontinued from the FU due to an SAE. The safety data presented within the current scope of the application for variation refer to the FU period only. In the SAF-FUP (safety analysis set of follow up) the mean age was 72.2 years (range 48 to 85 years). 96.2% of the patients were male. 92.3% of the patients had skin type Fitzpatrick I-III.

During the follow-up no IMPs were applied. During FU one or more AEs were reported for 48.1% of patients regarding the Ameluz/daylight PDT-treated sides and for 44.2% patients regarding the Metvix)/daylight PDT-treated sides. Most of the AEs were of mild intensity. Skin and subcutaneous tissue disorders was the system organ class (SOC) in which AEs in FU were most commonly reported in both treatment groups. Due to the reporting of new lesions, AK was the most common preferred term in both groups (reported for 44.2% of Metvix and 42.3% of Ameluz-treated sides). Most of these new lesions were ≥ 10 mm away from the nearest target lesion, which means that the respective area was not treated during the study. Basal cell carcinoma occurred in 2 patients inside the Ameluz treated area and Bowen's disease occurred in one patient inside the Metvix treated area. None of the AEs/ new lesions was considered related to one of the IMPs.

Overall, 8 SAEs (anal abscess, pelvic abscess, urinary tract infection, vestibular neuronitis [8 months after treatment with Ameluz/PDT], facial bone fracture, wrist fracture, dehydration, cerebrovascular accident) were reported for 3 (8.5%) patients in the FU. All SAEs were assessed by the investigators as unrelated to study medication. One patient (1.9%) discontinued the FU period due to SAEs (fracture of the cheekbone and the wrist as a consequence of a fall and hospitalization). It is agreed that this SAE is not related to Ameluz/PDT.

No deaths or other significant AEs were reported in the FU phase of the study. No pregnancies occurred. All SAEs and most of the other AEs resolved by the end of the FU.

2.5.2. Conclusions on clinical safety

The safety profile from study 010 was predominantly in line with the currently listed ADRs of Ameluz. Most of the treatment-related application site reactions reported for study 010 are listed in the SmPC, section 4.8. and most of them with the same frequency category.

The profile of relevant AE findings in the follow-up of study 009 was generally consistent with the AK population represented in the study, the nature of the underlying disease, and the known safety profile of Ameluz and Metvix. All documented AEs during FU were considered unrelated to the IMPs. As new lesion had to be documented as AE, the occurrence of actinic keratosis was the most reported AE during follow-up (reported for 44.2% of Metvix and 42.3% of Ameluz-treated sides). The safety during follow-up was comparable between Ameluz/daylight PDT-treated sides and for Metvix/daylight PDT-treated sides.

The SAEs were generally not related to the study drugs and no new (significant) safety concern was identified from the data presented within this application.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Please refer to Attachment 1 which contains all agreed changes to the Product Information.

2.6.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Ameluz 78 mg/g gel. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Treatment of actinic keratosis of mild to moderate severity on the trunk, neck and/or extremities.

3.1.2. Available therapies and unmet medical need

The appropriate treatment for AK is generally chosen based on the number and location of the lesions present. Treatment options belong to 2 broad categories: surgical destruction of the lesions (e.g. using cryotherapy or curettage with or without electrosurgery, laser) and medical therapy. Surgical destruction is restricted to limited areas and frequently associated with a flawed cosmetic result. Topical pharmaceutical therapy allows the treatment of extended areas with many AK lesions, and generally affords a treatment duration of several weeks. The following medications for the treatment of AK are approved:

• Topical 1% and 5% 5-fluorouracil cream (e.g. Efudix; twice daily for several weeks).

• Topical 5% imiquimod cream (e.g. Aldara; trice weekly for 4 to 8 weeks).

• Topical 3% diclofenac gel (eg Solaraze; twice daily for 60 to 90 days)

• Topical 70 µg/1 g gel ingenol mebutate (e.g. Picato; once daily for 3 consecutive days)

• Photodynamic therapy (PDT) with topical 5-aminolevulinic acid (ALA; Ameluz) or methyl-aminolevulinic acid (MAL; Metvix)

3.1.3. Main clinical studies

ALA-AK-CT010 is a randomized, double-blind, intra-individual, multi-center Phase III study to evaluate the safety and efficacy of BF-200 ALA (Ameluz) versus placebo in the treatment of mild to severe actinic keratosis on extremities, trunk/ neck with photodynamic therapy (PDT) when using the BF-RhodoLED lamp.

3.2. Favourable effects

The primary efficacy variable, the total lesion clearance rate in percent per patient's side 12 weeks after the last PDT, defined as the percentage of individual lesions with complete remission on the respective side of the patient, was significantly higher for Ameluz treated sides than for placebo-treated sides (86.0% ± 23.2% versus 32.9% ± 37.1%), clearly demonstrating superiority of Ameluz over placebo ($p<0.0001$; Wilcoxon signed rank test). The robustness of this result was confirmed by the PPS analysis (90.0% ± 19.5% versus 28.5% ± 36.7%; $p<0.0001$; Wilcoxon signed rank test).

Exploratory subgroup analyses by sex, age group, Fitzpatrick skin type category, and baseline AK severity showed results consistent with the primary analysis. Most of the results showed a statistically significant difference between both treatments. The differences were not statistically significant, but numerically in favour of Ameluz in a few subgroups (e.g. baseline AK severity 'severe') with limited number of patients .

All confirmatory hypothesis testing of the secondary efficacy variables (e.g. analysis of the patient complete clearance, HCR [histopathologically confirmed lesion response] and cosmetic outcome) in the given hierarchical order showed statistically significant superiority of Ameluz over placebo and supported the results of the primary efficacy analysis.; in all instances, the PPS showed similar results.

3.3. Uncertainties and limitations about favourable effects

The rate of lesions assessed as fully cleared by the investigator and simultaneously cleared according to histopathology of a small biopsy were lower in both groups: only 70.2% in the Ameluz and 19.1 % in the placebo group. Moreover, a high rate (44.7%) of lesions was not cleared according to the investigator's assessment but cleared according to histopathology in the placebo group.

Due to the following, extrapolation from narrow-spectrum red light to other types of PDT (PDT with broad spectrum red light lamp and PDT with daylight) without data is not possible:

- uncertainty in difference in skin thickness between treatment regions and consequences on skin penetration with different PDTs. E.g. efficacy on AKs on the scalp is consistently lower than that on the face, with thinner skin.
- the complete clearance rate (67.3% [secondary efficacy parameter]) in the study 010 in trunk/neck/extremities is lower than in face/scalp in the previous study 007, (90.9% [primary efficacy parameter]) (see p. 39 of AR). In both studies narrow-spectrum red light was used.
- concerning daylight PDT: possibly insufficient exposure to daylight and suboptimal angle of light in treating trunk/neck/extremities.

Therefore, narrow-spectrum red light for the treatment of AK on the trunk/neck/extremities has been specified in SmPC section 4.2.

3.4. Unfavourable effects

The safety profile from study 010 was predominantly in line with the currently listed ADRs of Ameluz. ADRs occurred in 100% of Ameluz-treated and 44% of placebo-treated sides. Most of the treatment-related application site reactions reported for study 010 are listed in the SmPC, section 4.8. and most of them with the same frequency category. The most frequent ADRs on the Ameluz compared to placebo treated sides were reactions at the application site: pain (100% vs. 40), erythema (90% vs. 14%), pruritus (48% vs. 18%), oedema (32%), scab (30%) and exfoliation (24%). There were only few ADRs, currently not listed in the SmPC, which were observed in study 010: In one patient (2.0%) "eczema" was reported in the Ameluz/BF-RhdoLED PTD treatment site (application site reaction). For one patient each (2.0%) "dry skin", "swelling", resp. "skin tightness" was observed on the Ameluz/BF-RhdoLED PTD treated site (but these were not direct application site reaction).

The phase III study 010 included 50 patients with actinic keratosis. 12 weeks after last PDT the most common related TEAEs at the application site that had not resolved yet were erythema (16x), followed by application site pruritus (3x), application site scab (3x), exfoliation (2x), oedema (1x). Most of the application site TEAEs that had not recovered at week 12 were mild or moderate. Only single TEAEs

that had not recovered at week 12 after PDT were of severe intensity: erythema (1x), pruritus (1x) and induration (1x), at the application site each.

No deaths occurred and SAEs were considered unrelated by the investigator.

3.5. Uncertainties and limitations about unfavourable effects

None

3.6. Effects Table

Table 27: Effects Table for Ameluz® compared to placebo with BF-RhodoLED PDT in mild to severe AKs on extremities, trunk, neck (data cut-off: 13 March 2019), Phase III Study ALA-AK-CT010

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
		%	Ameluz®	Placebo		Study 010
TLC	**Primary efficacy parameter** Total Lesion Clearance Rate 12 weeks after last PDT	%	86.0	32.9	P<0,0001	" "
	median of differences	%	60 (Ameluz® - Placebo)		33 (one –sided non parametric CI, lower 97.5% limit)	" "
PCC	**Second. efficacy Parameter** Patient complete clearance per patient's side 12 weeks after last PDT	%	67.3	12.2	P<0,0001	" "
Unfavourable Effects						
	Application site pain	%	100	40		" "
	Application site erythema	%	90	14		" "
	Application site pruritus	%	48	18		" "

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The results of the study demonstrated that the treatment of AK lesions on the extremities and trunk/neck with Ameluz is efficacious, with good cosmetic outcome and high patient satisfaction. The primary efficacy variable was significantly higher for Ameluz treated sides than for placebo-treated sides, clearly demonstrating superiority of Ameluz over placebo. Results in the Full Analysis Set are robust as only 2 patients did withdraw from the study and robustness of this result was confirmed by the PPS analysis. Exploratory subgroup analyses by demographic and baseline disease characteristics showed results consistent with the primary analysis. Most of the results demonstrated a statistically significant difference between both treatments. The number of patients in some subgroups, like the subgroup 'baseline AK severity severe', was too small to show statistically significant improvements, but results were numerically favorable for Ameluz. The confirmatory analyses of the secondary efficacy variables for the FAS supported the superiority of Ameluz over placebo shown in the primary analysis. The results demonstrated significant treatment effects of Ameluz compared with placebo in all secondary efficacy variables tested in the predefined hierarchical order.

The safety profile from study 010 was predominantly in line with the listed ADRs in the SmPC.

3.7.2. Balance of benefits and risks

The previously authorised indication of Ameluz was restricted to AK on the face and scalp. The results of study 010 demonstrated that the treatment of AK lesions on extremities/trunk/neck with Ameluz is efficacious, with no new safety concerns. Considering the known safety profile of Ameluz, it can be concluded that the benefits of photodynamic therapy with Ameluz when using the BF-RhodoLED for the treatment of actinic keratosis on extremities/trunk/neck outweigh its risks.

3.7.3. Additional considerations on the benefit-risk balance

Based on the results of the phase III study 010 and the previous clinical trial program of Ameluz, sufficient efficacy of Ameluz in the scope of broad spectrum red-light or daylight PDT in the region extremities/trunk/neck cannot be anticipated, although this has been established for the face/scalp region. Apart from the absence of data to support the use of daylight PDT and broad spectrum red-light PDT in the region trunk/neck/extremities, moreover, especially daylight PDT might not be appropriate for the treatment of extremities/trunk/neck. The angle of irradiation is of importance. With daylight PDT there are practical concerns as it will be difficult to achieve effective UV-light irradiation for trunk and extremities, taking into consideration the probable unfavourable angle of radiation. With red-light PTD a focussed irradiation is guaranteed. Please see also the publication "Photodynamic and photobiological effects of light-emitting diode (LED) therapy in dermatological disease: an update; Sorbellini E et al.; September 2018, Volume 33, Issue 7, pp 1431–1439". The authors explain, that the "penetration into the skin is dependent on the wavelength". They conclude that wavelength, irradiation, power density, and treatment time period can influence clinical outcomes.

Better efficacy of Ameluz/narrow-spectrum red-light PDT compared to Ameluz/broad-spectrum red-light PDT in actinic keratosis of the face/scalp is seen from the pooled efficacy results of the studies 002, 003 and 007. In the studies, different sources of red-light (narrow resp. broad spectrum lamps) were applied. Separate analysis of the different light sources revealed, that narrow spectrum lamps (e.g. BF-RhodoLED) were more efficacious compared to broad-spectrum lamps. It is clearly stated in

the SmPC of Ameluz that narrow spectrum lamps were more efficacious in the treatment of AK of the face/scalp.

Therefore, SmPC Section 4.2 has been updated to clarify that a treatment of actinic keratosis in the region "extremities/trunk/neck" is indicated in the scope of PDT with the narrow spectrum BF-RhodoLED lamp only, but does not refer to PDT with broad spectrum red-light or daylight.

In the scope of the current variation, the 1-year follow-up data of the phase III study 009 daylight PDT on face/scalp have been presented. One year after a single PDT, Ameluz treated lesions showed numerically lower recurrence rates than lesions treated with the marketed product Metvix (19.5% as compared to 31.2%). Nevertheless, during the study treatment-free follow-up period, the most frequently documented concomitant medications applied to treat new or remaining lesions were "antineoplastic and immunomodulating agents" and "dermatologicals". 15 (28.8%) patients received topical antineoplastic and immunomodulating agents, and 12 (23.1%) patients received dermatologicals (Ameluz, Luxerm, Actikerall, Picato, Zyklara, and Solaraze were applied). Concomitant medications were applied during or after follow-up in Ameluz treatment fields, Metvix treatment fields and outside the treatment fields. On the Ameluz treatment area 3 new lesions and on the Metvix treatment area 4 new lesions occurred during follow-up in close vicinity (<15 mm) to a treated lesion. All were treated concurrently and with the same medication as non-responding or recurrent lesions. For the calculation of recurrence, lesions displaying total clearance 12 weeks after PDT (at Visit 4) and assigned at least to the FAS FU analysis set were considered. Once a lesion was assessed as recurrent at the FU1 or FU2 visit, the lesion kept the status "recurrent" until the end of the study, irrespective of whether the lesion was treated and cured afterwards or not. New and non-responding lesions were not included for recurrence evaluation. During FU, only single lesions were treated; no field treatment was applied. On the Ameluz side, a total of 13 of the 47 patients in the FAS received concomitant medications due to treatment of non-responding or recurrent AKs. Because of the higher number of non-responding or recurrent lesions on the Metvix side, 17 of the 47 patients received treatments on that side. The MAH calculated the average recurrence rate per lesion with or without concomitant treatment during FU, and observed 6/37 (16.2%) recurrent lesions in Ameluz patients after treatment with, and 30/207 (14.5%) recurrent lesions on Ameluz patients without concomitant treatment prior to FU2, respectively. For Metvix, 8/45 (17.8%) lesions on average were recurrent on patients after treatment with and 43/189 (22.8%) lesions on patients without concomitant treatments, respectively.

3.8. Conclusions

The overall B/R of Ameluz is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIA

C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the treatment of mild to severe actinic keratosis on extremities, trunk and neck for Ameluz; as a consequence, sections 4.1, 4.8 and 5.1 of the SmPC and the Package Leaflet are updated accordingly. In addition, section 5.1 of the SmPC is updated based on follow-up data from study ALA-AK-CT009, a randomised, observer-blind, intra-individual phase III study to evaluate the safety and efficacy of Ameluz (5-aminolevulinic acid) in combination with daylight PDT (photodynamic therapy) in comparison with methyl-5-aminolevulinate for the treatment of mild to moderate actinic keratosis. Additionally, the PI was adapted to the new QRD template version 10.1.

The group of variations leads to amendments to the Summary of Product Characteristics and Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the group of variations, amendments to Annex(es) I, II, IIIA and IIIB are recommended.