CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208081Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208081
Priority or Standard	S
Submit Date(s)	7/10/15
Received Date(s)	7/10/15
PDUFA Goal Date	5/10/16
Division / Office	DDDP/ODE III
Reviewer Name(s)	Denise Cook, M.D.
Review Completion Date	March 21, 2016
Established Name	5-aminolevulinic acid HCl
(Proposed) Trade Name	Ameluz
Therapeutic Class	Porphyrin precursor used in combination with photodynamic therapy with the BF-RhodoLED lamp (photodynamic therapy photosensitizer)
Applicant	Biofrontera Bioscience GmbH
Formulation(s)	gel
Dosing Regimen	Apply 1mm thick of the gel to the lesion or field and to

	include approximately 5 mm of surrounding skin. Occlude treated area and illuminate after 3 hours. Treated lesions or fields that have not completely resolved after 3 months should be retreated.
Indication(s)	Ameluz in combination with photodynamic therapy with the BF-RhodoLED lamp is indicated for the treatment of actinic keratoses of mild to moderate severity of the face and scalp
Intended Population(s)	Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

It is recommended, from a clinical perspective, that Ameluz Gel, 10%, [redacted] (b) (4) in combination with photodynamic therapy using the BF-RhodoLED® lamp, be approved for the treatment of actinic keratoses of mild to moderate severity of the face and scalp (b) (4) [redacted]

1.2 Risk Benefit Assessment

Ameluz Gel, 10% in combination with a narrow band red light source, has been shown in three randomized, double-blind, vehicle-controlled clinical trials to be statistically significantly superior to vehicle ($p<0.0001$) in the treatment of mild to moderate actinic keratoses. The most common adverse reactions were related to the integument and were not unexpected for photodynamic therapy. Most reactions were mild to moderate and most subjects did not discontinue because of these application site reactions.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

A Risk Evaluation and Mitigation Strategy (REMS) is not required for this drug product.

1.4 Recommendations for Postmarket Requirements and Commitments

There are no post marketing requirements or commitments for this drug product.

2 Introduction and Regulatory Background

2.1 Product Information

BF-200 ALA (5-aminolevulinc HCl acid) is a nanoemulsion-based gel formulation that contains 5-aminolevulinic acid hydrochloride as active substance and belongs to the class of medications called "photodynamic therapy photosensitizers". Ameluz, the proposed trade name was developed for (b) (4) treatment of mild to moderate actinic keratoses (AKs) on the face and scalp in combination with photodynamic therapy (PDT). Ameluz contains 10% of the active substance as a salt, 5-aminolevulinic acid hydrochloride (ALA), which equals 7.8% of 5-aminolevulinic acid as free acid.
Ameluz Gel (BF-200 ALA 10%)) contains 5- aminolevulinate hydrochloride (ALA) acid as the active ingredient. The metabolism of aminolevulinic acid (ALA) is the first step in the biochemical pathway resulting in heme synthesis. Aminolevulinic acid is not a photosensitizer, but rather a metabolic precursor of protoporphyrin IX (PpIX), which is a photosensitizer. Ameluz Gel, plus illumination with the BF-RhodoLED lamp, a red light with a wavelength at 635nm, is the basis for Ameluz photodynamic therapy (PDT).
BF-200 ALA is an innovative, nanoemulsion-based formulation of 10% ALA hydrochloride in a gel matrix which provides for excellent solubility of the hydrophilic ALA, enhances the chemical stability of the active ingredient ALA, presumably by allowing it to adhere to the outside of the vesicles, and thus improving skin and cell penetration of ALA.
This drug-device combination when used in combination constitutes Photodynamic Therapy (PDT) and is intended for treatment of actinic keratosis. Treatment is administered in a two-step process involving drug application followed 3 hours later by illumination. The entire process can be repeated in 3 months for any lesions that did not completely resolve.

ALA is not an NME. A similar product, Metvixia (methyl aminolevulinate hydrochloride) was approved on July 27, 2004 under NDA 21415 to be used with the Aktilite CL128 lamp, a narrowband red light illumination source, for the treatment of thin and moderately thick, non-hyperkeratotic, non-pigmented actinic keratosis of the face and scalp in immunocompetent patients used in conjunction with lesion preparation in the physician's office when other therapies are considered medically less appropriate.
The sponsor requested withdrawal of this NDA on December 12, 2012, as the sponsor had stopped marketing the drug product due to a lack of commercial opportunities and not for safety reasons. Notice of withdrawal of this NDA was published in the Federal Register on 10/13/15.

In this application, the sponsor is seeking an indication in combination with photodynamic therapy using the BF-RhodoLED lamp, for the treatment of actinic keratoses of mild to moderate severity of the face and scalp (b) (4)

2.2 Tables of Currently Available Treatments for Proposed Indications

Actinic keratoses (AKs) are premalignant skin lesions that occur mainly in sun-exposed areas such as the face, scalp, or dorsum of the hands. The lesions are skin-colored or reddish-brown macules or papules, usually 3 to 10 mm in diameter, with dry, rough, adherent scale. Current therapy for AK include cryosurgery, electrodessication and curettage, topical application of 5-fluorouracil (5-FU), 5% imiquimod cream 3% diclofenac gel, or photodynamic therapy with Levulan® Kerastick™ (aminolevulinate hydrochloride), which was approved on December 3, 1999. As mentioned earlier, Metvixia (methyl aminolevulinic HCl) was recently withdrawn from the market. Table 1 shows the currently available drug products for actinic keratoses.

Table 1
Currently Available Drug Products for Actinic Keratoses

Drug Product	Approval Date	Indication	Dosage and Administration
Efudex (5-FU), (b) (4) 2%, & 5% solution	July 29, 1970	Multiple actinic keratoses (AKs)-face/scalp	Apply bid for 2-4 weeks until inflammatory response reaches the erosion stage; healing may take 1-2 months
Efudex (5-FU), 5% cream	July 29, 1970	Multiple actinic keratoses-face/scalp	Apply bid for 2-4 weeks until inflammatory response reaches the erosion stage; healing may take 1-2 months
Aldara® (imiquimod) cream, 5%	February 27, 1997	Nonhyperkeratotic, nonhypertropic AKs on the face or scalp in immunocompetent adults	Apply twice a week prior to normal sleeping hours, leave on skin for approximately 8 hours. The maximum recommended dose is one package applied to the contiguous treatment area at each application, but not both face and scalp concurrently. Treat for a full 16 weeks.
Solaraze® (diclofenac), 3% gel	October 16, 2000	Treatment of AK	Apply to lesion bid. Normally 0.5 g of gel is used on each 5 cm x 5cm lesion site for 60-90 days. May take up to 30 days following cessation of therapy for therapeutic effect.
PDT with Levulan Kerastick (20% 5-	December 3, 1999	Treatment of AK of the face or scalp	Apply directly to AK once followed by blue light

aminolevulinic acid HCl in alcoholic solution		but not both simultaneously	illumination after 14-18 hours. Treated lesions that have not resolved after 8 weeks may be treated again.
Source: Drugs at FDA			

2.3 Availability of Proposed Active Ingredient in the United States

Levulan Kerastick (aminolevulinic acid HCl) for topical solution, 20% was approved in 1999 and is available for photodynamic therapy with blue light illumination for the treatment of minimally to moderately thick actinic keratoses of the face or scalp. According to the last updated labeling in March 2010, adverse reactions from the photodynamic therapy are restricted to cutaneous adverse events and less than 3% of subjects in the clinical trials discontinued because of an adverse event. There have been no post-marketing updates for this drug product.

2.4 Important Safety Issues With Consideration to Related Drugs

There are no major safety issues with consideration to the already approved product, Levulan Kerastick and Metvixia was not withdrawn from the market due to safety considerations.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

PreIND Meeting – held 7/11/12
As the sponsor had already completed the two confirmatory trials ALA-AK-CT002 and CT003, no agreements could be made with the Division. However, they were advised that the design of the trials appeared reasonable. The sponsor did use an approved light source in these trials, Aktilite CL 128 (630 nm) which is a narrow spectrum red light source, along with Omnilux PDT (633 nm), another narrow spectrum light source. Since the conduct of those trials, the sponsor wants to use BF Rhodo LED (635 nm), another narrow spectrum red light source to be approved with their drug product, BF-200 ALA for PDT. The sponsor planned to do one trial (CT007) using the new light source and wanted to use the other trials with the Aktilite CL 128 and Omnilux PDT (633 nm) as their other pivotal data for approval. The sponsor was advised of the data needed for evaluation by CDRH regarding the ability to bridge from the trial lamps that were used in CT002 and CT003 to that of the proposed lamp (BF Rhodo LED) for this NDA.

PreNDA Meeting – held 10/8/14
The sponsor stated at that meeting that the NDA would follow a 505(b)(2) pathway, as they will rely in part on literature to support the non-clinical portion of the NDA. However, with the submission of the NDA, the application is taking a 505(b)(1) pathway.

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

According to the sponsor, all clinical studies were conducted according to Good Clinical Practices. OSI inspected a clinical site from the largest trial, ALA-AK-CT002 from December 14-17, 2015, and they concluded from their review of the establishment inspection report and the documents submitted with that report that the investigator at that site adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. In particular, they audited the data for the 47 subjects in the trial at that site and found the following:

> "Signed informed consent was obtained from all enrolled subjects prior to study entry. Source data was compared to line listings. The records of all 46 subjects were reviewed. Records reviewed included, but were not limited to, financial disclosure, delegation of duties, inclusion/exclusion criteria, drug randomization, sponsor, IRB and CRO communications, laboratory results, adverse events, concomitant medications, and test article storage and accountability."[1]

3.2 Compliance with Good Clinical Practices

The sponsor provides the following rationale for the applicability of foreign clinical data to the US population for this proposed indication according to ICH E5:

No data were used from non-European countries. Biofrontera conducted its clinical studies in Switzerland and within the EU with active sites in Germany and Austria. These clinical data can be used for US populations as:
The main risk factors for developing AK are fair skin type which burns easily, blue eyes and red hair, factors which are represented exclusively in the Caucasian population (Fitzpatrick skin type I, II, III). No prevalences are documented for Hispanics where the disease thus is estimated as low. No indication for AK was found for people with black skin and AK was described as uncommon for Native Americans. Therefore, the population at risk in Europe is also representative of the respective population in the USA.

Reviewer's Comment: *I agree with the applicant that for this indication which primarily, if not totally, occurs in Caucasian people, a European Caucasian population is not different from an*

[1]NDA 208081: Roy Blay, OSI Communication: DARRTS 2/29/16.

American Caucasian population. Thus, the trials from Europe would be representative of the affected U.S. population.

3.3 Financial Disclosures

The applicant submitted form FDA 3454 providing certification regarding the financial interests and arrangement of the clinical investigators who conducted trial ALA-AK-CT200, trial ALA-AK-CT003, or ALA-AK-CT007. None of the investigators were employees of the applicant, Biofrontera. Biofrontera was able to obtain financial disclosure from all investigators with the exception of one sub-investigator in trial ALA-AK-CT007. None of the investigators had financial interests to disclose. For the one sub-investigator for whom there is no financial disclosure form (FDF), due to (b) (6) drug law financial disclosure forms (FDF) have only to be submitted to Ethic Committees for the Principal Investigator and his deputy but not for sub-investigators. Their forms should be filed on site. By mistake it was forgotten to obtain the FDF of (b) (6) in time. (b) (6) left the site in (b) (6). Several approaches failed to contact him in order to file this declaration subsequently. According to Biofrontera's financial department (b) (6) did not receive any payments. However, a FDF concerning Biofrontera AG is already available.

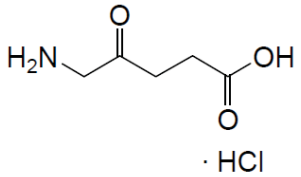
Reviewer's Comment: *For trial CT007, there were 7 principal investigators and many more sub-investigators.* (b) (6) *was one of* (b) (6) *sub-investigators at one clinical site in the trial,* (b) (6) *This site had a treatment effect of only* (b) (6) *% compared to 100% for* (b) (6) *Thus, in this reviewer's opinion, the site where* (b) (6) *was a sub-investigator did not drive the efficacy results of trial CT007, and thus the lack of a financial disclosure form from this sub-investigator is not relevant.*

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Drug Substance/Drug Product

BF-200 ALA (aminolevulinic acid hydrochloride) Gel, 10% for topical use is a non-sterile white-to-yellowish gel. Aminolevulinic acid, a porphyrin precursor, is a white to off-white crystalline solid. It is readily soluble in water, methanol, and dimethylformamide. Its chemical name is 5-amino-4-oxo-pentanoic acid hydrochloride, its molecular weight is 167.59 and, and its molecular formula is $C_5H_9NO_3 \cdot HCl$. The structural formula of aminolevulinic acid hydrochloride is represented below:



Each gram of BF-200 ALA contains 100 mg of aminolevulinic acid hydrochloride as the active ingredient and the following inactive ingredients: xanthan gum, soybean phosphatidylcholine, polysorbate 80, medium-chain triglycerides, isopropyl alcohol, dibasic sodium phosphate, monobasic sodium phosphate, propylene glycol, sodium benzoate and purified water.

Reviewer's Comment: *The product quality reviewer, Dr. Roger Farr in his review, has deemed that the drug substance is quite stable and deemed adequate. At the close of this review, the chemistry review is ongoing to determine the adequacy of the drug product.*

From the Center for Devices and Radiological Health (CDRH) and the Office of Compliance, Division of Manufacturing & Quality (DMQ), their recommendation is the following:

(1) Deficiencies were identified during the documentation review. Additional information from the firm is needed to complete the documentation review.
(2) A pre-Approval inspection covering compliance with applicable 21 CFR 820, Quality System Requirements, is recommended for the following firm:
    a. Biofrontera Pharma GmbH
    Hemmelrather Weg 201
    D-51377 Leverkusen
    FEI# 3011764519

Reviewer's Comment: *At the completion of this review, this issue is still outstanding.*

4.2 Clinical Microbiology

N/A

4.3 Preclinical Pharmacology/Toxicology

The following is from the pharmacology/toxicology review by Dr. Barbara Hill regarding 5-aminolevulinic acid (ALA).

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 the drug substance in the to-be-marketed Ameluz (ALA HCl) gel, 10% formulation. ALA is used in this topical drug product as a photodynamic therapy photosensitizer. ALA functions as a pro-drug and is metabolized to the photoactive substance protoporphyrin IX (PpIX) in mitochondria. PpIX is a natural

metabolite of ALA within the heme pathway. PpIX can be activated by the absorption of energy at several different wave lengths, ranging from blue to red light.
The sponsor has demonstrated that there is a negligible systemic increase in plasma levels of ALA above background endogenous levels and no increase in PpIX plasma levels (which is a biomarker of systemically absorbed ALA pharmacology) under maximal clinical use conditions for Ameluz gel. The need for reproductive toxicity studies and a systemic carcinogenicity study were waived based on the level of systemic exposure demonstrated under maximal clinical use conditions for Ameluz gel. The need for a dermal carcinogenicity study for Ameluz gel was waived due to the clinical conditions of use (single application followed by another single application after 3 months, if needed).
The target organ of toxicity identified in a 14 day repeat dose intravenous dog toxicity study was the liver.

A repeat dose dermal minipig study was conducted with once monthly topical administration of ALA gel, 10% or vehicle gel for 3 months with and without red light exposure. The results from this study were the expected effects based on the pharmacologic mechanism of photodynamic therapy. Mild to moderate erythema and eschar formation were noted at ALA gel, 10% treated sites. The symptoms were more pronounced at ALA gel, 10% treated sites exposed to red light. No increase in local toxicity was noted after repeat dose administration and the recovery process appeared to be quicker from the second application through the fourth application of ALA gel, 10% plus red light treated sites. Histopathological evaluation of treated skin sites 28 days after the last ALA gel, 10% treated site exposed to red light demonstrated complete recovery.

An ICH battery of genotoxicity studies were conducted with ALA HCl. ALA HCl revealed no evidence of mutagenic or clastogenic potential based on the results of three in vitro genotoxicity tests (Ames assay, HPRT test in V79 cells and Human lymphocyte chromosomal aberration assay) and one in vivo genotoxicity test (mouse micronucleus assay). The in vitro genotoxicity studies were conducted without red light exposure. There is literature data that indicates a low genotoxicity potential of ALA when combined with UVA light exposure. The observed DNA damage is probably caused by the oxidative free radicals formed when ALA derived PpIX is exposed to light of the correct wavelength. This is the desired pharmacologic effect that is utilized for the treatment of actinic keratosis lesions.

ALA gel, 10% without red light exposure was not a dermal irritant or ocular irritant in rabbits. ALA gel, 10% without red light exposure was not a sensitizer in the murine LLNA assay. The toxicity profile of ALA gel, 10% has been adequately characterized by the nonclinical studies conducted by the sponsor. The toxicity profile elicited by ALA gel, 10% in the presence of red light exposure was what is anticipated for PDT.
Dr. Hill has recommended approval from a pharmacology /toxicology perspective provided the recommended labeling changes are incorporated into the label.[2]

[2] Pharmacology/Toxicology Review: pages 3-4, in DARRTS 3/9/16.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

BF-ALA 200 is a prodrug. It is metabolized into protoporphyrin IX (PpIX), a photoactive compound which accumulates in the skin. When exposed to red light of a suitable wavelength and energy, PpIX is activated resulting in an excited state of porphyrin molecules, which in presence of oxygen, reactive oxygen species are formed which destroys the cells producing drug effect.

4.4.2 Pharmacodynamics

N/A

4.4.3 Pharmacokinetics

A maximum use pk trial, Trial ALA-AK-CT006, was conducted in 12 subjects who had at least 10 AKs on the face or forehead with a total application treatment area of approximately 20 cm^2. One 2 gram tube was used to treat the entire area of involvement. The area of involvement was covered with BF-200 ALA 10% gel or placebo for 3 hours with occlusion. After excess gel was removed, the area was illuminated with the BF-RhodoLED lamp light source. Each subject received a vehicle gel treatment with PDT first and after a wash-out period of 7 days, received the BF-200 ALA 10% treatment. Baseline 5-ALA (5-aminoleulenic acid) and protoporphyrin IX (PpIX) were obtained prior to treatment.
Dr. Chinmay Shukla found in his analysis of the maximum use pk trial that although plasma concentration of BF-200 ALA was higher compared to baseline after application of the drug product and treatment, the systemic exposure increase relative to the endogenous concentration was small and limited to about 6 hours duration. The concentration of PpIX was generally low in all subjects and in none of the subjects, was there an increase in PpIX plasma concentration after application of BF-200 ALA compared to baseline.[3] The reader is referred to Dr. Shukla's full review in DARRTs dated 3/9/16.

[3]Clinical Pharmacology Review, pages 10-11, in DARRTs 3/9/16 under NDA 208081.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2
Pivotal Phase 3 Trials

Study Number, Location	Study Objective - Main inclusion criteria	Study design	IMPs (PDT lamp)	Duration of Treatment and follow-up	N Enrolled/ planned
ALA-AK-CT002 Germany, Austria, Switzerland - 26 centers 17Apr2008-11May2010 Completed	To compare the efficacy of PDT with BF-200 ALA vs. the marketed product MAL cream (Metvix®) and placebo in the treatment of AK. Patients with 4 to 8 AK target lesions 0.5 to 1.5 cm diameter of mild to moderate intensity on the face or bald scalp.	Phase III, randomized, multinational,, reference therapy con-trolled and placebo controlled, observer blind to reference therapy and double blind to placebo, parallel group study (ratio 3:3:1).	- BF-200 ALA 10% - Vehicle - MAL cream (Aktilite® CL 128, 630 nm), Omnilux® PDT, 633 nm) Waldmann® PDT 1200L, 600-750 nm) (Hydrosun®/ PhotoDyn®, 580-1400 nm).	Up to two PDTs; 12 weeks after the first PDT, non-responders or partial responders were to be retreated. Follow-up was 6 months and 12 months after the last PDT.	571 / 616
ALA-AK-CT003 Germany -8 centers 04Dec2007-03Nov 2009 Completed	Evaluation of the efficacy of PDT with BF-200 ALA for AK and demonstration of superiority of BF-200 ALA over placebo. Patients with 4 to 8 AK target lesions 0.5 to 1.5 cm diameter of mild to moderate intensity on the face or bald scalp.	Phase III, randomized, doubleblind, placebo controlled, interindividual, 2-armed (2:1 ration), multi-center study.	- BF-200 ALA 10% - Placebo/ vehicle (Aktilite® CL 128, 630 nm) (Hydrosun®/ PhotoDyn® 750, 580 – 1400 nm)	Up to two PDTs. Twelve weeks after the first PDT, non-responders or partial responders were to be retreated. Follow-up was 6 and 12 months after last PDT.	122 / 120
ALA-AK-CT007	The primary objective was to	Phase III, multicenter,	- BF-200 ALA 10%	Up to two PDTs. Twelve weeks	87 / 84

Germany -7 centers 27Aug2013-24Apr2015 Completed (data analyses of follow-up ongoing)	compare the efficacy of BF-200 ALA with placebo, for the field-directed treatment of AK with PDT. Patients with 4 to 8 AK target lesions 0.5 to 1.5 cm diameter of mild to moderate intensity [a] on the face or bald scalp located within 1-2 fields of an overall size of ca. 20 cm^2.	randomized, doubleblind, placebo controlled, parallel-group (2:1 ratio) study.	- Placebo/ vehicle (BFRhodoLED®, 635 nm).	after the first PDT, nonresponders or partial responders were to be retreated. Follow-up was 6 and 12 months after last PDT.	
Source: NDA 208081, Module 2: Clinical Overview- adapted from Table 1, pages 10-11					

Table 3
Other Studies

Study Number, Location	Study Objective - Main inclusion criteria	Study design	IMPs (PDT lamp)	Duration of Treatment and follow-up	N Enrolled/ planned
ALA-AK-CT001 Germany -13 centers 10/25/06 – 3/12/07 Completed	The primary objective was to define the effective therapeutic dose of the ALA in the treatment of AK with topical PDT and to assess the efficacy of topical PDT with a new nanoemulsion formulation of ALA in the treatment of AK. Patients with 3 to 10 AK target lesions 0.5 to 1.5 cm diameter of mild to moderate intensity on the face or bald	Phase IIb, randomized, doubleblind, placebocontrolled multicenter study with adaptive design c.	- ALA 1% - ALA 3% - ALA 10% - Vehicle (Waldmann® 600 - 750 nm, (PhotoDyn® 505, 580 –1400 nm)	Each subject received a single dose of one of four treatments for all selected plaques. Follow-up was 6 months and 12 months after PDT.	105 / 104

	scalp.				
ALA-AK-CT006 Germany -1 center 7/11/13-12/16/13	To obtain base-line adjusted plasma concentration-time curves for ALA and PpIX after a single treatment with Ameluz® (BF 200 ALA 10%) in subjects with ≥ 10 AK lesions on face or fore-head with a maximum of 2 illumination areas with each lesion being not more than 2 mm thick with a side margin of at least 5 mm (maximal use).	Phase I, single center, non-randomized, open-label, placebo controlled, fixed sequence, 2-treatment, intraindividual comparison study.	- BF-200 ALA 10% - Vehicle (BFRhodoLED ®, 635 nm)	Each patient will receive a PDT after application of placebo (Period 1) and after application of ALA (Period 2) with a washout period of at least 1 week between treatments. Approximately 20 cm² were treated applying sequentially one tube (2 g) vehicle and BF200 ALA 10% gel, respectively. Follow-up was within 7±1 days after last PDT	12 /12
ALA-AK-CT005 Germany -2centers 7/13/13-12/16/13	To investigate the skin sensitization potential of Ameluz® (BF 200 ALA 10%) and its vehicle after repeated topical applica-tion in male and female subjects aged 18 to 85 years with healthy skin.	Phase I, two-center, randomized, doubleblind trial, intra-individual comparison of treatments.	- BF-200 ALA 10% - Vehicle	Treatment (200 µl in Finn Chambers) over 48 hours (72 h weekends) 3 times weekly for 3 weeks during induction and single application, for 48 h challenge and re-challenge phases as applicable.	220 /200
Source: NDA 208081, Module 2: Clinical Overview- adapted from Table 1, pages 10-11					

5.2 Review Strategy

The pivotal trials, ALA-AK-CT002, ALA-AK-CT003, and ALA-AK-CT007, were reviewed in detail, as these 3 trials are the basis for efficacy and safety of Ameluz PDT therapy for mild to moderate actinic keratoses (AKs). The photosensitization trial, ALA-AK-CT005, was also reviewed. The maximum use PK trial, ALA-AK-CT006 was reviewed in detail by the clinical pharmacologist, Dr. Chimany Shukla. Efficacy was verified by the biostatistician, Dr. Carin Kim. Dr. Richard Feldman from CDRH reviewed the NDA to determine if an adequate bridge

has been established by the sponsor between the lamp that the sponsor wants to market with Ameluz for PDT, the BF-RhodoLED lamp, a narrow spectrum lamp (NSL) and the other NSLs that were used in the trials (Omnilux and Aktilite).

Consults were submitted to the following:

- DMEPA – carton and immediate container labels, PI, PPI, proprietary name
- OPDP – all labeling
- DMPP – PPI

5.3 Discussion of Individual Studies/Clinical Trials

Efficacy was established with 3 controlled trials, ALA-AK-CT002, ALA-AK-CT003 and ALA-AK-CT007, none of which were exactly the same and were all performed in foreign countries.

Trial ALA-AK-002
This was a randomized, observer blind, multinational phase 3 trial to evaluate the safety and efficacy BF-200 ALA in comparison with Metvix and vehicle for the treatment of actinic keratosis with photodynamic therapy. The trial had 26 centers, 23 in Germany, 2 in Austria, and I in Switzerland.

The key inclusion criteria were as follows:

●Written informed consent.
●Men and women between 18 and 85 years of age
●4-8 AK lesions of 0.5 to 1.5 cm diameter of mild to moderate intensity (Olsen grade 1 and 2) in the face and/or on the bald scalp; Lesions on the eyes, nostrils, ears and mouth were not considered for treatment during the planned study.
● Target AK lesions were to be discrete and quantifiable; adjacent AK lesions were to show a minimum distance of 1.0 cm from one another.
● Confirmation of AK by biopsy taken at screening
●Free of significant physical abnormalities (e.g., tattoos, dermatoses) in the potential treatment region that could have caused difficulty with examination or final evaluation
●Willingness to stop the use of moisturizers and any other topical treatments within the treatment region
●Good general health condition
●Healthy subjects and subjects with clinically stable medical conditions including, but not limited to the following diseases (controlled hypertension, diabetes mellitus type II, hypercholesterolemia, osteoarthritis) were permitted to be included in the study if the medication taken for the treatment of the disease did not match an exclusion criterion or was not specified as prohibited concomitant medication.

●No extensive sunbathing or solarium use during the trial
●Negative pregnancy test at screening
● Effective contraception in women of childbearing potential

The key exclusion criteria were as follows:
● Known hypersensitivity to BF-200 ALA, MAL (methyl-aminolevulinic acid) and/or any of the ingredients of the formulations
●Clinically significant medical conditions (tumor disease etc.) making implementation of the protocol or interpretation of the study results difficult
●Presence of photodermatoses
●Presence of other tumors in the treatment areas within the last 4 weeks
●Start of treatment with phototoxic or photoallergic drugs within 8 weeks prior to screening
●Current treatment with immunosuppression therapy
●Hypersensitivity to porphyrins
●Presence of porphyria
●Presence of inherited or acquired coagulation defect
●Any topical treatment within the treatment area within 12 weeks before PDT1
●Topical treatment with ALA or MAL outside the treatment area during participation in the study
●None of the specified systemic treatments within the designated period before PDT1

Study Plan
Subjects (616 were to be randomized) in the trial in a 3:3:1 ratio receive BF-200 ALA, Metvix (methyl-aminolevulinic acid), or placebo. After thorough preparation of the lesions, including removal of all scabs, crusts and hyperkeratotic parts by curettage, the skin sites were to be cleaned with alcohol (ethanol or isopropanol). For each subject, one of these formulations was applied to the target AK lesions and covered with occlusive tape material for 3 hours. Thereafter, the remnants of these applied formulations were removed carefully and the PDT was administered.
Subjects with non-responding AK lesions were re-treated with the same medication after 12 weeks with a second application of the red light source.

Reviewer's Comment: *In this trial the light source used were both broad band [WaldmannPDT 1200 L (600-750 nm)/Hydrosun/PhotoDyn 505 (580-1400 nm) or narrow band Aktilite CL 128 (630 nm) or Omnilux PDT 1200 L (633 nm)]. The applicant is seeking an indication with a narrow band light source-BF RhodoLED lamp (635nm).*

The primary efficacy variable was the overall subject complete response assessed 12 weeks after the last PDT. An overall complete responder was defined as a subject in whom all treated lesions were cleared after either the first PDT or re-treatment.

The secondary efficacy analysis variables included (as stated in the statistical analysis plan [SAP]):
●Subject complete response (complete clearance of all treated lesions) at each assessment.

●Subject partial response (complete clearance of at least 75% of the treated lesions) at each assessment
●Lesion complete response (completely cleared individual lesions) at each assessment
Reduction of total lesion area (summation of sizes of all treated lesions) per subject at each assessment
●The change in skin quality assessments compared to baseline assessed 12 weeks after PDT1 and 12 weeks after the last PDT
●The overall cosmetic outcome 12 weeks after the last PDT

For the follow-up period, the following variables were analyzed:
●Subject recurrence rate defined as the number of subjects with completely cleared lesions 12 weeks after the last PDT with at least one recurrent lesion during follow-up.
●Lesion recurrence rate defined as the number of lesions of complete responders 12 weeks after the last PDT showing recurrence during follow-up 1. For follow-up 2 it was defined as the number of complete responders after follow-up 1 showing recurrence during follow-up 2. If a patient received further AK therapy after the last PDT, but before the time point of derivation of the recurrent lesions rate, all of the patient's lesions were defined as recurrent.

Safety analysis variables were as follows:

●Frequency and extent of treatment-emergent adverse events (TEAEs), including serious AEs (SAEs). TEAEs were defined as all AEs with onset or worsening after first treatment with randomized IP. At the follow-up visits any local AEs or conditions considered relevant for proper assessment of the recurrence rate of the treated AK lesions was documented, and SAEs that occurred after the End-of-study visit were also documented.
●Local skin reactions at the treatment area assessed by the investigators
●Local discomfort and pain reported during illumination by the subjects.
●Vital signs data.
●Safety laboratory data
● Data from the physical examinations

Trial ALA-AK-CT003
This was a double-blind multicenter trial in 8 centers in Germany to evaluate the safety and efficacy of BF-200 ALA against vehicle in which 120 subjects were enrolled in a 2:1 ration to BF-200 ALA and placebo.

The key inclusion criteria were:

● Men and women aged between 18 and 85 years of age, inclusive
● Have at least 4 but not more than 8 clinically confirmed AK target lesions of mild to moderate intensity within the face or bald scalp
● A pre-study biopsy must be taken from a second representative AK lesion and thin sections should be histopathologically evaluated by a dermatolpathological expert

● AK lesions must be discrete and quantifiable; the distance from one lesion to its neighbor lesion is greater than 1.0 cm
● The diameter of each AK lesion is to be not less than 0.5 cm and not greater than 1.5 cm

The key exclusion criteria were:
● have known hypersensitivity to ALA
● are patients under immunosuppressive therapy
● suffer from porphyria
●show hypersensitivity to porphyrins
●suffer from phtodermatoses
●have inheritied or acquired coagulation defects.
●Have received medication with hypericin or systemically acting drugs with phototoxic or photoallergic potential such as psoralenes, tetracyclines, nalidixic acid, furosemide, amiodarone, phenothiacines, chinolons, fibrates, or phytotherapy with St. John's wort, arnica, or valerian or topically applied phototoxic substances like tar, pitch, psoralenes or some dyes like thiazide, methylene blue, toluidine blue, eosine, Bengal rose, acridine within 8 weeks prior to treatment with study drug and PDT.

Study Plan
Scabs, crusts, or hyperkeratosis were thoroughly removed from the AK lesions. In addition, all lesion surfaces were abraded using a curette or scalpel blade avoiding bleeding and were cleaned with an ethanol-soaked cotton pad prior to drug application and incubation. One tube containing 2 g of test drug was dispensed for one PDT session, enough to cover up to 8 distinct AK lesions with a maximum diameter of 1.5 cm.
After application, the gel was allowed to dry for approx. 10 minutes. Thereafter, an occlusive, light-tight dressing was placed over the lesions. After the incubation time of 3 hours ± 10 minutes, the occlusion was removed and the remnant gel wiped off with a 0.9% saline solution immediately before illumination of the target area with a suitable red light source for 11-15 minutes.

Reviewer's Comment: *The light sources used for this trial were both red light sources; the broad band light source Hydrosun/PhotoDyn 750 (580-140 nm) and the narrow band light source Aktilite CL 128 (630 nm).*

The primary endpoint was the AK clearance rate, defined as the number of subjects with complete remission of all AK lesions in the target area(s) assessed 12 weeks after the last PDT.

The secondary endpoints were:
• proportion of AK lesions showing complete remission at week 12 after the last PDT, i.e. the lesion was completely cleared and no adherent scaling plaques of AK were visible any longer;
• reduction of total lesion area within the target treatment area per subject (face or bald scalp) at week 12 after the last PDT when compared to baseline;

• proportion of subjects with complete clearance after the first treatment, proportion of subjects with clearance of at least 75% of lesions after the first treatment and at 12 weeks after the last PDT treatment;
• change in skin quality assessment compared to baseline of all target lesions located within the target treatment area;
• local skin reactions at the target treatment area assessed by the investigator;
• overall cosmetic outcome at 12 weeks post-treatment;
• number of days with discomfort within 7 days after PDT – based on phone contact;
• frequency and extent of AEs during illumination and throughout the study;
• frequency of abnormal vital signs at each clinical visit, and hematology and clinical chemistry parameters at baseline and at the end of the clinical trial

Safety parameters
Safety parameters were the same as for trial ALA-AK-002 and were assessed at week 3 and 12 after each PDT treatment.

Trial ALA-AK-007
This was a randomized, double-blind, phase 3 multicenter trial to evaluate the safety and efficacy of BF-200 ALA (Ameluz) versus placebo in a field-directed treatment of mild to moderate AKs with photodynamic therapy (PDT) when using the BF-RhodoLED lamp. This trial took place in 7 centers in Germany.
Subjects were randomized 2:1 to receive BF-200 ALA or vehicle. The inclusion criteria and exclusion criteria were essentially the same as for the previous two trials discussed above. The main difference in this trial was that the drug product was applied with a film of about 1 mm thickness using glove-protected fingertips or a spatula to a treatment field of approximately 20 cm^2 that contained 4-8 AKs that were 0.5 cm to 1.5 cm in diameter. The area was occluded with 3M Tegaderm and a light-tight cover was affixed over the dressing (eg aluminum foil). After 3 hours the dressing was removed and any remaining drug product was wiped off with a 0.9% saline solution.
Subjects also had biopsy proven AK at baseline and another biopsy 12 weeks after the last PDT treatment for histopathologic confirmation of clearance of lesion.
Planned duration of the trial was 1 day to 12 weeks: BF-200 ALA or placebo was administered for the first PDT session (PDT-1) after all screening procedures had been performed. A second PDT session (PDT-2) with BF-200 ALA or vehicle was performed 12 weeks later if there were lesions that were not completely cleared.

Table 4 shows the recommended conditions for exposure to the BF-RhodoLED lamp.

Table 4
Recommended Conditions for Exposure to the BF-RhodoLED Lamp

Light dose (energy)	37 J/cm2
Intensity	Approximately 77 mW/cm2
Illumination time	10 minutes automatically calculated by the lamp; however the illumination time can be manually paused (in this case the remaining time is held by the lamp software to fulfill the requirements for light dose)
Distance skin-lamp	6 cm (5-8 cm)
Source: NDA 208081; Module 5; Clinical study report ALA-AK-CT007, Study report; Table 1., page 44	

Safety assessments included recording of any adverse events and specifically assessment of local skin reactions as follows:

- AEs, including local skin reactions in the treatment area(s) assessed by the investigators
- Local discomfort and pain during PDT reported by the patients
- New lesions in the treatment area (AK, non-melanoma skin cancer [NMSC], melanoma)
- Laboratory safety (hematology, biochemistry) and urinalysis
- Vital signs (blood pressure, heart rate)
- Physical examinations

The primary efficacy variable was the overall patient complete response rate assessed 12 weeks after the last PDT. A patient was classified as an overall complete responder if all treated lesions were cleared (Olsen score 0) after PDT-1 or PDT-2, if re-treated.

Secondary efficacy variables included:

- Patient histopathological confirmed response (HCR) rate.
- Patient complete response (complete clearance of all treated lesions) assessed 12 weeks after PDT-1.
- Lesion complete response (completely cleared individual lesions) assessed 12 weeks after last PDT.
- Patient partial response (complete clearance of at least 75% of the treated lesions) assessed 12 weeks after last PDT.
- Reduction of total lesion area (the size of all treated lesions added up) per patient 12 weeks after last PDT.
- Overall cosmetic outcome 12 weeks after last PDT

6 Review of Efficacy

Efficacy Summary

The efficacy of BF-200 ALA in combination with PDT using a narrow spectrum (red light lamp) source were evaluated in three randomized, multicenter trials (ALA-AK-CT002, ALA-AK-CT003, and ALA-AK-CT007). Trials -CT003 and -CT007 were vehicle-controlled and double-blind. Trial -CT002 was double-blind with respect to vehicle and observer-blind regarding the active comparator arm. All clinical trials included a follow-up assessment after 6 and 12 months. In these trials, 212 subjects with 4 to 8 mild to moderate AK lesions on the face/forehead and/or bald scalp were treated with BF-200 ALA and a narrow band spectrum lamp. Subjects ranged from 49 to 87 years of age (mean 71 years), and 92% had Fitzpatrick skin type I, II, or III. No subjects had Fitzpatrick skin type V or VI. Approximately 86% of subjects were male, and all subjects were Caucasian.

All sessions were comprised of lesion preparation to roughen the surface and remove crusts, application of BF-200 ALA with occlusion for 3 hours, and removal of the residual gel. Subsequently, the entire treatment area was illuminated with a narrow spectrum red light source, a lamp of either 630 nm or 633 nm and a light dose of approximately 37 J/cm^2. In Trial –CT007, illumination was performed with BF-RhodoLED®, a red light source with a narrow spectrum around 635 nm and a light dose of approximately 37 J/cm^2.

In all trials, the lesions that were not completely cleared 12 weeks after the initial treatment were treated a second time with an identical regimen. In the clinical trials, 42% (88/212) subjects on BF-200 ALA needed a second PDT.

The primary endpoint for all trials was complete clearance 12 weeks after the last PDT. In each of the trials, PDT with BF-200 ALA was statistically significantly superior to PDT with vehicle ($p<0.0001$).

In trials ALA-AK-CT002, ALA-AK-CT003, and ALA-AK-CT007, the subjects, who received BF-200 ALA with the narrowband PDT and achieved complete clearance 12 weeks after the last PDT, had recurrence rates of 14%, 11%, 25%, respectively (at 6 months) and 40%, 22%, and 37%, respectively (at 12 months). Recurrence was defined as the percentage of subjects with at least one recurrent lesion during the 6-month or 12-month follow up period in subjects with completely cleared lesions 12 weeks after the last PDT.

As the list and order of secondary endpoints across the three phase 3 trials are different, and given the lack of multiplicity adjustment plan to control the Type I error rate in ALA-AK-CT002 and ALA-AK-CT003, without replication of trial findings, most of the secondary endpoints will not be analyzed.

6.1 Indication

AMELUZ® Gel, a porphyrin precursor, in combination with photodynamic therapy using the BF-RhodoLED® lamp, is indicated for the treatment of actinic keratoses of mild to moderate severity of the face and scalp (b) (4)

Reviewer's Comment: *This is the applicant's proposed indication. The indication will be modified to "…is indicated for the treatment of actinic keratoses of mild to moderate severity of the face and scalp* (b) (4) (b) (4)

6.1.1 Methods

The three pivotal phase 3 trials, ALA-AK-CT002, ALA-AK-CT003, and ALA-AK-CT003 were reviewed along with the clinical summary of efficacy to support the proposed indication of the applicant. These trials were double-blind, placebo controlled, multicenter trials except for ALA-AK-CT003, which had an active comparator arm to satisfy EU requirements (See section 5.1 &5.3.3). For purposes of the indication in the United States, the active comparator arm will not be considered in determining the efficacy of Ameluz in the treatment of AKs with photodynamic therapy (PDT).

6.1.2 Demographics

For trial ALA-AK-002, there were 570 subjects enrolled. The majority (83.5%) of subjects were age 65 and older, which is to be expected for this indication of treatment of actinic keratoses. All of the subjects were Caucasian and the age range was from 39 years old to 87 years old. Table 5 shows the demographics for this trial.

Table 5
Demographic Baseline Characteristics
Trial ALA-AK-002

Demographic Baseline Characterisitcs		BF200ALA N=248		Metvix N=246		Vehicle N=76		Overall N=570	
Age (years)	Mean	70.2		71.0		71.5		70.7	
	Min	39		44		51		39	
	Median	70		71.5		70.5		71	
	Max	87		85		84		87	
		Count	%	Count	%	Count	%	Count	%
Age Group	39-65 years	47	19.0	38	15.4	9	11.8	94	16.5
	65 and over	201	81.0	208	84.6	67	88.2	476	83.5
Sex	F	34	13.7	41	16.7	16	21.1	91	16
	M	214	86.3	205	83.3	60	78.9	479	84
Race	White	248	100.0	246	100.0	76	100.0	570	100.0

Source: NDA 208081: Reviewer analysis of data via JReview tool

Reviewer's Comment: *Although this trial had an active comparator arm, as required for consideration for approval in the EU, for purposes of approval in the U.S., the active drug product BF-200 ALA will only be analyzed in relation to its performance against vehicle.*

For trial ALA-AK-003, there were 122 subjects enrolled. The majority (87.7%) of subjects were age 65 and older, which is to be expected for this indication of treatment of actinic keratoses. All of the subjects were Caucasian and the age range was from 57 years old to 85 years old. Table 6 shows the demographics for this trial.

Table 6
Baseline Demographic Characteristics
Trial ALA-AK-003

Demographic Baseline Characterisitcs		BF200ALA N=81		Placebo N=41		Overall N=122	
Age (years)	Mean	70.4		70.6		70.5	
	Min	58		57		57	
	Median	70		69		70	
	Max	82		85		85	
		Count	%	Count	%	Count	%
Age Group	58-65 years	10	12.3	5	12.2	15	12.3
	65 and over	71	87.7	36	87.8	107	87.7
Sex	F	8	9.9	9	22.0	17	13.9
	M	73	90.1	32	78.0	105	86.1
Race	White	81	100.0	41	100.0	122	100.0
Source: NDA 208081: Reviewer analysis of data via JReview tool							

For trial ALA-AK-007, there were 87 subjects enrolled. The majority (85.1%) of subjects were age 65 and older, which is to be expected for this indication of treatment of actinic keratoses. All of the subjects were Caucasian and the age range was from 51 years old to 84 years old. Table 7 shows the demographics for this trial.

Table 7
Baseline Demographic Characteristics
Trial ALA-AK-007

Demographic Baseline Characteristics		BF200ALA N=55		Placebo N=32		Overall N=87	
Age (years)	Mean	71.9		71.0		71.6	
	Min	56		51		51	
	Median	73		72		72	
	Max	84		84		84	
		Count	%	Count	%	Count	%
Age Group	58-65 years	9	16.4	5	12.2	13	14.9
	65 and over	46	83.6	36	87.8	74	85.1
Sex	F	5	9.1	3	9.4	17	9.2
	M	50	90.9	29	90.6	105	90.8
Race	White	81	100.0	32	100.0	87	100.0
Source: NDA 208081: Reviewer analysis of data via JReview tool							

6.1.3 Subject Disposition

Table 8 shows the subject disposition for all subjects in the pivotal trials regardless of lamp used.

Table 8
Subject Disposition – ITT Population

	Vehicle		**BF-200 ALA**	
ITT Population	**N=149**		**N=384**	
	No. patients	**%**	**No. patients**	**%**
Completed	131	87.9	372	96.9
Discontinued	18	12.1	12	3.1
Adverse event	0	0	2*	16.7
Lack of efficacy	2	11.1	0	0
Lost to follow-up	2	11.1	2	16.7
Other	5	27.8	3	25.0
Protocol deviation	0	0	1	8.3
Withdrawal by subject	9	50.0	4	33.3
*Reviewer's analysis reveals 4 subjects who discontinued because of an adverse event (see section 7.1.3) Source: NDA 208081; Table 5, page 24; module 2 – ISS; and review of line listing C.3.2.3- trial CT002				

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for all trials was complete clearance of AK lesions 12 weeks after the last PDT treatment. The results of Trials 1, 2, and 3 for subjects treated with narrow band lamps is delineated in table .9

Table 9
Complete Clearance 12 Weeks After PDT Treatment
ITT Population -Narrow Band Lamp

	Narrow Spectrum PDT	
	Ameluz	**Vehicle**
ALA-AK-CT002*	106/125 (85%)	5/39 (13%)
ALA-AK-CT003*	27/32 (84%)	2/16 (13%)
ALA-AK-CT007*	50/55 (91%)	7/32 (22%)

*In labeling, these trials are referred to as trial 1, trial 2, and trail 3, respectively.
Source: Adapted from statistical review, table 8, page 13 and table 10, page 14

6.1.5 Analysis of Secondary Endpoints(s)

Trial ALA-AK-CT007 had a secondary endpoint which was "histologically confirmed response rate 12 weeks after last PDT." As stated before, all the subjects in this trial were treated with a narrow band lamp. All subjects, 5 in the BF-200 ALA arm and 32 in the vehicle arm, had a biopsy at baseline to histologically confirm the presence of an actinic keratosis. Of those subjects, 54 in the BF-200 ALA arm and 27 in the vehicle arm were available for biopsy 12 weeks after the last PDT. Overall, 77.8% of patients in the BF-200 ALA group compared with 22.2% of patients in the vehicle group experienced a complete histologically confirmed response.

Another important secondary endpoint in this trial was "Lesion complete response rate 12 weeks after last PDT". For this endpoint, the reduction from baseline to 12 weeks after the last PDT in the total lesion area was 98.2% in the BF-200 ALA group compared to 45.5% in the vehicle group and lesion complete response rate 12 weeks after the last PDT was 94.3% (281/298) in the BF-200 ALA group compared to 32.9% (57/173) in the vehicle group (see table 10).

Table 10
Key Secondary Efficacy Endpoints
Trial ALA-AK-CT007

		BF-200 ALA	Vehicle	Difference in % points [95% CI)	P value (Fisher's exact test)
Histologically confirmed response rate 12 weeks after last PDT	n [a]	54	27	55.6 [36.3, 74.8]	<0.0001
	n (%)	42 (77.8)	6 (22.2)		
	95% CI	64.4, 88.0	8.6, 42.3		
Lesion complete response rate 12 weeks after last PDT	n [b]	298	173	61.3 [53.9, 68.8]	<0.0001
	n (%)	281 (94.3)	57 (32.9)		
	95% CI	91.0, 96.6	26.0, 40.5		

a: number of patients; b: number of lesions
Source: NDA 208081: Clinical Efficacy Summary: adapted from table 6, page 17

Reviewer's Comment: *It should be noted, however, that each trial listed several secondary endpoints, however, the analysis of the secondary endpoints, the list and the order of these endpoints were different across the three phase 3 trials. According to our statistical reviewer, Dr. Kim, there was a lack of plan for multiplicity adjustment to control the Type I error rate in trials ALA-AK-003 and -007, thus there was no replication of study findings for secondary endpoints*.

6.1.6 Other Endpoints

N/A

6.1.7 Subpopulations

Efficacy by Gender and Age

Tables 11 and 12 show the efficacy by gender and age. As most of the subjects, 86% were male and most of the subjects (84%) were over 65 years of age, no meaningful differences for gender and age can be detected.

Table 11
Complete clearance at 12 weeks after the last PDT
Gender and Age (Trial ALA-AK-002)

Trial 02				
Light Source		Ameluz N=248	Vehicle N=76	Metvix N=246[1]
Narrow		106/125 (85%)	5/39 (13%)	85/126 (67%)
Broad		88/123 (72%)	8/37 (22%)	73/119 (61%)
Light Source	Subgroup	Ameluz	Vehicle	Metvix
Narrow	Gender			
	Male	87/106 (82%)	5/29 (17%)	67/105 (64%)
	Female	19/19 (100%)	0/10 (0%)	18/21 (86%)
	Age Groups			
	≤65	26/29 (90%)	0/3 (0%)	21/27 (78%)
	>65	80/96 (83%)	5/36 (14%)	64/99 (65%)
Broad	Gender			
	Male	77/108 (71%)	8/31 (26%)	62/99 (63%)
	Female	11/15 (73%)	0/6 (0%)	11/20 (55%)
	Age Groups			
	≤65	22/26 (85%)	2/8 (25%)	16/21 (76%)
	>65	66/97 (68%)	6/29 (21%)	57/98 (58%)

Source: Statistical Review, table 13, page 17, in DARRTS 3/9/16 under NDA 208081

Table 12
Complete Clearance at 12 weeks after the last PDT
Gender and Age (Trials ALA-AK-003 and -007)

		Trial 03		Trial 07	
		Ameluz N=81	Vehicle N=41	Ameluz N=55	Vehicle N=32
Complete Clearance at Week 12 after the last PDT		53 (65%)	5 (12%)	50/55 (91%)	7/32 (22%)
	Narrow	27/32 (84%)	2/16 (13%)	50/55 (91%)	7/32 (22%)
	Broad	26/49 (53%)	3/25 (12%)	N/A	N/A
Narrow	Gender				
	Male	24/29 (83%)	1/13 (8%)	45/50 (90%)	7/29 (24%)
	Female	3/3 (100%)	1/3 (33%)	5/5 (100%)	0/3 (0%)
	Age				
	≤65	5/5 (100%)	0/4 (0%)	8/9 (89%)	6/26 (23%)
	>65	22/27 (81%)	2/12 (16%)	42/46 (91%)	1/6 (17%)
Broad	Gender			N/A	
	Male	23/44 (52%)	3/19 (16%)		
	Female	3/5 (60%)	0/6 (0%)		
	Age				
	≤65	4/7 (57%)	1/4 (25%)		
	>65	22/42 (52%)	2/21 (10%)		

Source: Statistical Review, table 14, page 18, in DARRTS 3/9/16 under NDA 208081

Reviewer's Comment: *As all the subjects were Caucasian there was no subgroup analysis for race. A subgroup analysis was not performed for ethnicity, either. On analysis by treatment area, face/forehead vs scalp, the majority of subjects had treatment on the face/forehead, and although this area had a higher response rate than on the scalp, the number of subjects treated on the scalp was small; therefore drawing any comparative conclusions would be difficult (see statistical review pages 18-20).*

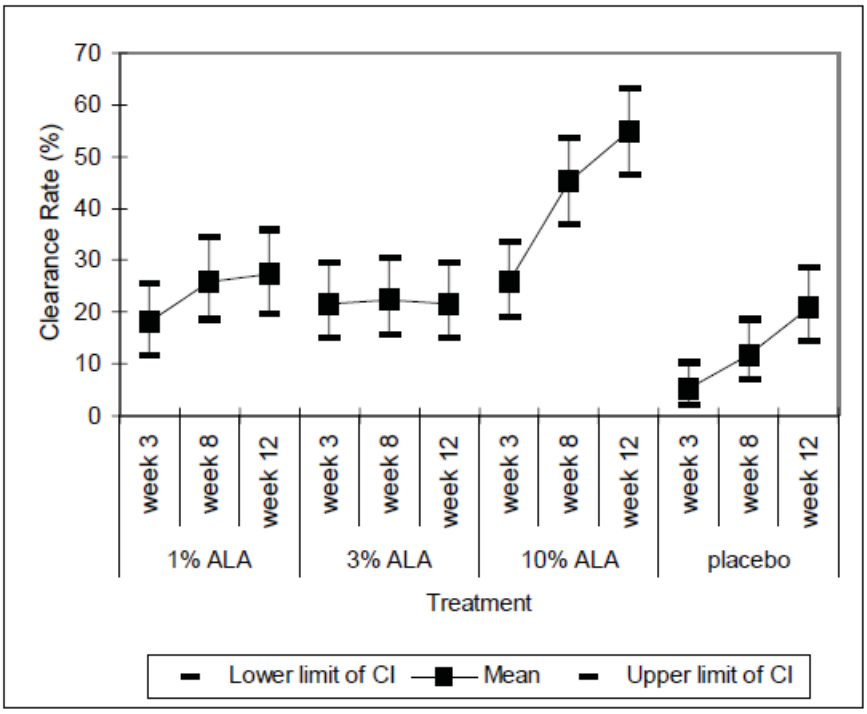
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The sponsor conducted a phase 2 dose ranging trial, Trial ALA-AK-CT001 randomized, double-blind, placebo controlled multicenter study to evaluate 3 concentrations of BF-200 ALA, ALA 1%, ALA 3%, and ALA 10% against vehicle. The primary objective was to define the effective therapeutic dose of the ALA in the treatment of AK with topical PDT and to assess the efficacy of topical PDT with a new nanoemulsion formulation of ALA in the treatment of AK. The trial was conducted at 11 centers in Germany. The trial enrolled 105 subjects of which 104 completed. One subject withdrew due to a preplanned cox-arthrosis surgery, prior to the 8 week assessment.

Subjects with 3 to 10 AK target lesions 0.5 to 1.5 cm diameter of mild to moderate intensity on the face or bald scalp were enrolled in the trial. All were Caucasian with ages that ranged between 69.9 years to 72.6 years with a mean age of 71.1 years.
Each subject received a single dose of one of four treatments for all selected plaques followed by light treatment with either the Waldmann® 600 - 750 nm lamp or the PhotoDyn® 505, 580-1400 nm lamp. Only 10.5% of the subjects were irradiated with the Waldmann lamp. Follow-up was 6 months and 12 months after PDT. Efficacy was assessed at week 12.

Efficacy Results
At week 12 after treatment 54.9% of the lesions showed complete remission for 10% ALA. Lower clearance rates were observed for placebo (20.7%), 1% ALA (27.3%) and 3% ALA (21.6%). The difference between the 10% ALA group and placebo was statistically significant ($p < 0.0001$). For the other concentrations, no relevant drug-related difference was observed (see figure 1).

Figure 1
Clearance Rate and 95% CI for the Clearance Rate by Week and Treatment



Source: NDA 208081 – Final Clinical Study Report- ALA-AK-CT001, page 6.

Safety
Nearly all subjects reported adverse events: the incidence increased from 77.8% of the subjects in the placebo group to 84.0% and 92.0% in the 1% and 3% ALA groups and 100% in the 10% ALA group. Most adverse events were of mild to moderate intensity, severe adverse events were

reported in one subject each in the placebo and 1% ALA groups, by seven subjects (28%) in the 3% ALA group and by three subjects (10.7%) in the 10% ALA group.
The most frequently reported adverse events were application site disorders, reported by 77.8% of the subjects in the placebo group, and by 80.0%, 92.0% and 100% of the subjects in the 1%, 3% and 10% ALA groups, respectively. All other adverse events were only reported by single subjects, except for nasopharyngitis, which was reported by three subjects in the 10% ALA group.
Most adverse events on the application site were considered as drug related by the investigator. Application site erythema, the most frequently reported AE, was observed in all treatment groups without showing a drug-related pattern (incidence 77.8%, 68.0%, 92.0% and 78.6% in the placebo, 1%, 3% and 10% ALA groups, respectively).
All other signs of application site disorder were more often reported after active treatment than after placebo. Besides erythema, more frequent application site disorders were application site irritation, application site pain, application site reaction and application site pruritus (see table 13). Most application site reactions started on the day of PDT and resolved within one week.
No subject discontinued due to an adverse event.

Table 13
Summary of Application Site Disorders
Trial ALA-AK-CT001

	Treatment Groups			
	Placebo	**1% ALA**	**3% ALA**	**10% ALA**
	x (y,z%)	**x (y,z%)**	**x (y,z%)**	**x (y,z%)**
Total	48 (21, 77.8)	77 (20, 80.0)	80 (23, 92.0)	101 (28, 100.0)
Application site erosion	-	-	1 (1, 4.0)	-
Application site erythema	28 (21, 77.8)	23 (17, 68.0)	33 (23, 92.0)	28 (22, 78.6)
Application site exfoliation	-	2 (1, 4.0)	-	-
Application site induration	-	3 (2, 8.0)	1 (1, 4.0)	1 (1, 3.6)
Application site irritation	7 (6, 22.2)	18 (14, 56.0)	16 (13, 52.0)	21 (14, 50.0)
Application site oedema	-	2 (1 4.0)	7 (5, 20.0)	5 (4, 14.3)
Application site pain	2 (2, 7.4)	11 (8, 32.0)	10 (6, 24.0)	15 (12, 42.9)
Application site pruritus	6 (4, 14.8)	9 (7, 28.0)	4 (4, 16.0)	12 (9, 32.1)
Application site reaction	2 (1, 3.7)	4 (3, 12.0)	5 (4, 16.0)	12 (10, 35.7)
Application site scab	1 (1, 3.7)	2 (2, 8.0)	1 (1, 4.0)	2 (2, 7.1)
Application site vesicles	-	-	-	2 (1, 3.6)
Application site warmth	2 (2, 7.4)	3 (3, 12.0)	1 (1, 4.0)	3 (3, 10.7)

x (y, z%): x = number of adverse events
y = number of subjects with particular adverse event
z = percentage of subjects with particular adverse event who received respective treatment
Source: NDA 208081: Final Clinical Study Report; table 14, page 79.

One subject of the placebo group with a history of cardiovascular anomalies had a serious adverse event: he experienced syncope 54 days after drug application and received a pacemaker. This SAE was not considered to be related to the test product.

Reviewer's Comment: *On review of the data, the sponsor did an adequate dose ranging trial, albeit that it was not performed with the to-be-marketed formulation and subjects were exposed to broad band lamps, but it is somewhat relevant in that the concentration of the active substance is what was chosen for the final to-be-marketed drug product. In subsequent trials, narrowband light exposure demonstrated better efficacy than broadband and safety was only marginally worse, as will be discussed in the review. Thus, the results demonstrated in this phase 2 trial that 10% ALA was the optimal concentration to choose, as efficacy was only shown for this concentration when compared to placebo and the safety profile was acceptable.*

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

In Trials ALA-AK-002, -003, and -007, the subjects who received AMELUZ® with the narrowband PDT and achieved complete clearance 12 weeks after the last PDT, had recurrence rates of 14%,11%, and 25% (at 6 months) and 40%, 22%, and 37% (at 12 months), respectively. Recurrence was defined as the percentage of subjects with at least one recurrent lesion during the 6-month or 12-month follow up period in subjects with completely cleared lesions 12 weeks after the last PDT (see table 14).

Table 14
Recurrence Rates at Months 6 and 12 After Last PDT
All Trials

Narrowband PDT	Length of Follow-up	Ameluz	Vehicle
Trial 002	6 months	14/101 (14%)	1/5 (20%)
	12 months	39/98[(1)] (40%)	2/5 (40%)
Trial 003	6 months	3/27 (11%)	-
	12 months	6/27 (22%)	-
Trial 007	6 months	12/49 (25%)	1/7 (14%)
	12 months	18/49 (37%)	1/7 (14%)

Source: Adapted from statistical review, table A.5, page 26, in DARRTS 3/9/16 under NDA 208081

6.1.10 Additional Efficacy Issues/Analyses

A collaborative review was done by Dr. Richard Feldman in CDRH to determine if the sponsor has established an adequate bridge between the BF-RhodoLED lamp, the narrow band lamp that the sponsor wants approved with the drug product, and the other narrow band lamps, Omnilux EL1258S and Aktilite CL-128, which were used in the clinical trials. This is important to

establish because only a small number of subjects (55) were exposed to the BF-RhodoLED lamp and it was only in one trial (ALA-AK-CT007). Two adequate and well-controlled trials are recommended for non-life threatening conditions. In the other two trials, the subjects (157) were exposed to either the Omnilux EL1258S or the Aktilite CL-128 narrow band lamps.

Dr. Feldman concluded the following:

"In terms of spectral output the peak output for the BF-RhodoLED is 635 nm; for the Aktilite CL-128 it is 628 nm; and for the Omnilux it is 630 nm. Because of the narrowness of these peak outputs these three light systems can be considered as "Narrowband Lamp Systems". As part of this testing the company also examined the output power stability across the 10 minute treatment time and this testing does show stable output for the total treatment time. All of these wavelengths are within the spectral absorption band for protoporphyrin IX which is the targeted photosensitizer within the actinic keratotic lesion. Thus clinical data obtained using any of these three lamps can be equivalent since the light interaction and activation processes from each lamp on protoporphyrin IX would be considered identical." [4]

Reviewer's Comment: *Dr. Feldman went on to state that based on the test data provided by the sponsor, the clinical data generated in clinical trials provided in which the identified narrowband lamps were used are equivalent and could be considered together to support this application.*

7 Review of Safety

Safety Summary

The clinical program for BF-200 ALA included three double-blind and placebo-controlled trials (ALA-AK-CT002, ALA-AK-CT003, and ALA-AK-CT007), enrolling a total of 299 subjects that were treated with narrow band light. Trial subjects were adults greater than or equal to 49 years of age, and the majority had Fitzpatrick skin type I, II, or III. No subjects had Fitzpatrick skin type V or VI. Approximately 86% of subjects were male, and all subjects were Caucasian. For all trials, the enrolled subjects had mild to moderate AKs (Olsen grade 1 and 2) with 4 to 8 lesions on the face and scalp. Overall, 87 placebo-treated subjects (n=16, n=32, n=39) and 212 BF-200 ALA treated subjects (n=32, n=55, and n=125) were illuminated with BF-RhodoLED® or similar narrow spectrum lamps.
Local skin reactions at the application site were observed in about 99.5% of subjects treated with BF-200 ALA and narrow spectrum lamps. The most frequent adverse reactions during and after PDT were application site erythema, pain, burning,irritation, edema, pruritus, exfoliation, scab, induration and vesicles.
Most adverse reactions occurred during illumination or shortly afterwards, were generally of mild or moderate intensity, and lasted for 1 to 4 days in most cases; in some cases, however, they persisted for 1 to 2 weeks or even longer. Severe burning and pain occurred in up to 30% and

[4]CDRH Review: page 1.

24% of subjects, respectively. In rare cases, the adverse reactions required interruption or discontinuation of the illumination.
Common (≥1%, < 10%) adverse reactions not limited to the application site were chills, headache and skin exfoliation.
Uncommon (≥ 0.1%) adverse reactions at the application site for BF-200 ALA were hemorrhage and swelling. The adverse reactions not limited to the application site were eye edema, eyelid edema, feeling hot, pain, pyrexia, ulcer, hyperalgesia, nasopharyngitis, rash pustular, nervousness, blister, dermatitis allergic, petechiae, pruritus, scap, and skin erosion.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The integrated summary of safety includes the phase 3 trials, ALA-AK-CT002, ALA-AK-CT003, and ALA-AK-CT007. These were double-blind, vehicle controlled with one active controlled trials to evaluate the safety of BF-200 ALA (5-aminolevulinic HCl) gel, 10% in combination with a red light source, in the treatment of actinic keratoses where the subject received photodynamic treatment 1 (PDT1) and if not clear received a second treatment (PDT2) at week 12 and the last visit was at week 24.
One dermal safety trial was conducted to evaluate photosensitization (ALA-AK-CT005).

7.1.2 Categorization of Adverse Events

Adverse events in the trials were described by symptom and or diagnosis as appropriate. As the vast majority of the reactions were under the category of general disorders and administration site conditions, it was appropriate to list the AE by symptom (e.g. application site erythema, application site exfoliation). AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Treatment emergent AEs (TEAEs) are summarized by MedDRA preferred term (PT) and system organ class (SOC).
For the integrated analysis of safety only treatment emergent AEs (TEAEs) have been evaluated. They are defined as AEs that occurred from the start of the first PDT (Visit 2) to Week 12 (Visit 4) for PDT1, and for those subjects who received retreatment, for AEs that occurred from the start of PDT2 (week 12, Visit 4) to Week 24 (Visit 6).

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data from the three vehicle-controlled trials in subjects with AKs were combined for the integrated analysis of safety. The integrated Intent-To-Treat (ITT) analysis set consists of all randomized subjects in these 3 trials who received either drug product (BF-200 ALA) or placebo whether or not an illumination was performed. Overall, 87.9% of subjects on vehicle and 96.9% of subjects on BF-200 ALA completed the phase 3 trials. Of the 12 subjects that discontinued in

the drug product arm, only 2 (16.7%) discontinued due to an adverse event (see table 15). Adverse events in the treatment arm will be compared to the vehicle arm.

Table 15
Disposition – Safety Analysis
ITT Population

	Vehicle		BF-200 ALA	
Safety Analysis	**N=149**		**N=384**	
	No. patients	**%**	**No. patients**	**%**
Completed	131	87.9	372	96.9
Discontinued	18	12.1	12	3.1
Adverse event	0	0	2*	16.7
Lack of efficacy	2	11.1	0	0
Lost to follow-up	2	11.1	2	16.7
Other	5	27.8	3	25.0
Protocol deviation	0	0	1	8.3
Withdrawal by subject	9	50.0	4	33.3

*Reviewer's analysis reveals 4 subjects who discontinued because of an adverse event
Source: NDA 208081; Table 5, page 24; module 2 – ISS; and review of line listing C.3.2.3- trial CT002

Table 16 shows the subject disposition for those only using the narrowband lamps.

Table 16
Disposition – Safety Analysis
Subjects Using Narrow Band Lamp

	Vehicle		BF-200 ALA	
Safety Analysis	**N=87**		**N=212**	
	No. patients	**%**	**No. patients**	**%**
Completed	73	84	202	95
Discontinued	14	16	10	5
Adverse event	0	0	1	<1
Lack of efficacy	2	2	0	0
Lost to follow-up	0	0	1	<1
Other	4	5	3	1
Protocol deviation	0	0	0	0
Withdrawal by subject	7	8	4	2

Source: Compiled from statistical review: tables 5, page 11, and tables A.1 and A.2, page 24

Reviewer's Comment: *On this reviewer's analysis of the disposition, there were actually 4 subjects that discontinued on the BF-200 ALA arm because of an adverse event. However, only 1 discontinuation was because of treatment related adverse events. One subject had 2 treatment related adverse events, subject 113/39 in trial CT002, a 73 year old male, experienced application site pain and application site burning. Illumination for this subject stopped one minute after start because of the severity of the pain and burning. Thus the sponsor may have been only analyzing these types of events in the table above, in which case it should be 1 and the*

other category (3) would account for the other 3 discontinuations (see section 7.3.3 – Dropouts and Discontinuations).
This analysis includes subjects that used narrow spectrum lamps and broad spectrum lamps. The total number of subjects that used narrow spectrum lamps for BF-200 ALA was 212 and the number of subjects on vehicle for narrow spectrum lamps was 87. For purposes of examining adverse event profiles, all subjects will be evaluated together for adverse events but subjects using the narrow spectrum lamps alone will also be evaluated to look for any major difference in safety, as the sponsor is seeking approval of BF-200 ALA to be used with a narrow spectrum lamp, BF-RhodoLED, for PDT.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The ITT safety population for this IND is composed of the subjects that participated in the 3 pivotal trials, CT002, CT0003 and CT007. Overall, 533 subjects were randomized in the trials to receive either vehicle or BF-200 ALA, of which 384 subjects were exposed to BF-200 ALA.

Reviewer's Comment: *For purposes of this safety review, the active comparator arm of trial CT002 was not evaluated.*

The majority of subjects exposed to BF-200 ALA were ≥ 65 (82.8%), had moderate AKs (81.8) and slightly more than half had ≥ 6 target AK lesions. All of the subjects were Caucasian, with 88% having Fitzpatrick skin type I-III. The majority of the subjects exposed to BF-200 ALA were male (87.8%). Table 17 denotes the overall demographics of the ITT population for safety and table 18 shows the demographics for the subjects exposed only to narrow band light.

Table 17
Demographics
ITT Population

		Vehicle N=149		BF-200 ALA N=384		Total N=533	
		n	%	n	%	n	%
Gender – n (%)	Male	121	81.2	33.7	87.8	458	85.9
	Female	28	18.8	47	12.2	75	14.1
Race – n (%)	Caucasian	149	100	384	100	533	100
Age, years – (%)	18 to <65 years	18	12.1	66	17.2	84	15.8
	65 to < 75 years	91	61.1	211	54.9	301	56.7
	≥ 75 years	40	26.8	107	27.9	147	27.6
Age, years	Mean ± SD	71.1	6.6	70.5	6.7	70	39-87
	Medina (min-max)	70.0	51-85	71.0	39-87		
Source: NDA 208081 – Table 8, page 5 – module 2, ISS							

Table 18
Demographics
ITT Population – Narrow Band Only Light

		Vehicle N=87		BF-200 ALA N=212		Total N=299	
		n	%	n	%	n	%
Gender – n (%)	Male	71	82	185	87		
	Female	16	18	27	13		
Race – n (%)	Caucasian	87	100	212	100	299	100
Fitzpatrick Skin Type							
	I	2	2	5	2	7	2
	II	39	49	90	42	129	43
	III	44	51	95	45	139	46
	IV	3	3	21	10	24	8
	V	0	0	1	<1	1	<1
Age, years	Mean ± SD	71.1	6.7	70.6	6.5	-	-
	(min-max)	51	85	49	87		

Source: Statistical review, adapted from tables A.3 and A.4, page 25, under NDA 208081 in DARRTS 3/9/16.

In terms of exposure, the large majority of subjects (75.2% in the vehicle group and 75.0% in the BF-200 ALA group) had a single illumination during PDT1 and during PDT2 (78.6% and 80.9%, respectively). One PDT session was required by 201 (52.3%) subjects and 183 subjects (47.7%) required 2 PDT sessions. No PDT session was interrupted for patients treated with vehicle, whereas 3.9% of patients in the BF-200 ALA group experienced an interruption of PDT. The majority of subjects (55% in the vehicle group and 60.2% in the BF-200 ALA group) had target lesions on the face, 30.9% and 28.9%, respectively, had lesion on the bald scalp, and 14.1% and 10.9%, respectively, had target lesions in both areas. PDT was administered with a narrow spectrum lamp for 87 (58.4%) subjects in the vehicle group and 212 (55.2%) subjects in the BF-200 ALA group, and 62 (41.6%) and 172 (44.8%) subjects, respectively, received PDT with a broad spectrum lamp (see table 19 for further details on study drug exposure).

Table 19
Study Drug Exposure
ITT Population

		Vehicle		BF-200 ALA	
		N=149		N=384	
		n	%	n	%
Number of PDT sessions, n (%)	One PDT session	23	15.4	201	52.3
	Two PDT sessions	126	84.6	183	47.7
Number of illuminations – PDT1, n (%)	1	112	75.2	288	75.0
	2	37	24.8	95	24.7
	3	0	0	1	0.3
Number of illuminations – PDT2, n (%)	1	99	78.6	148	80.9
	2	27	21.4	34	18.6
	3	0	0	1	0.5
Interruption in any PDT session	Yes	0	0	15	3.9
Any pain-relief measure during PDT 1 or PDT2, n(%)	Yes	15	10.1	107	27.9
Region of skin illuminated	Face (including forehead)	82	55.0	231	60.2
	Bald Scalp	46	30.9	111	28.9
	Face and Bald Scalp	21	14.1	42	10.9
Lamp used for PDT, n (%)	Narrow spectrum lamps, pooled (ca. 630 nm)	87	58.4	212	55.2
	Aktilite® CL 128 (630 nm)	44	50.6	124	58.5
	Omnilux® PDT (633 nm)	11	12.6	35	16.5
	BF-RhodoLED® lamp (635 nm)	32	36.8	53	25.0
	Broad spectrum lamps, pooled	62	41.6	172	44.8
	Waldmann® PDT 1200L (600 to 750 nm)	3	4.8	15	8.7
	Hydrosun®/PhotoDyn® 750 (580 to 1400 nm)	59	95.2	157	91.3

Source: NDA 208081: Integrated Summary of Safety: Module 2: table 6, page 25

7.2.2 Explorations for Dose Response

There were no explorations for dose response as it relates to safety, as the amount of drug product for topical application in the pivotal trials was limited to 1 tube (2g) of medication.

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

Subjects in the pivotal trials had routine laboratory testing which included general chemistry and hematology. Shift tables showed no evidence of clinically relevant change in alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin or alkaline phosphatase plasma concentrations; creatinine or blood urea nitrogen, or in hemoglobin, platelets or white blood cell count.

Reviewer's Comment: *It was not expected that any significant changes would occur in laboratory values, as the absorption of BF-200 ALA has very limited absorption, and although there was a slight increase in Cmax for the 3 hour period of occlusion, the AUC did not change.*

7.2.5 Metabolic, Clearance, and Interaction Workup

N/A

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

N/A

7.3 Major Safety Results

7.3.1 Deaths

Subject 116/39 was a 65 year old male who was in trial CT002 in the BF-200 ALA arm and who had a history of hypertension and vertigo suffered a cerebellar infarct 321 days after receiving the last study treatment. Subject 104/46 was a 79 year old female who was in trial CT002 in the Metvix arm who had a myriad of chronic medical diseases including type 2 diabetes, lymphedema, chronic pancreatitis, and hypertension, who was reported to have died from weakness 322 days after receiving the last study treatment. Subject 302/02 was a 78 year old man in trial CT002 who also had a myriad of medical diseases including history of malignant melanoma, diabetes, atrial fibrillation, cardiomyopathy, hypertension, and chronic renal failure who died 1 year after receiving the last study treatment from an unknown cause, although the

investigator presumed the cause of death to be cardiac failure after colonoscopy. Subject 102/06 was an 81 year old female who died of a cardiac arrest nearly 1 year after receiving the last study treatment. She was in the Metvix arm of trial CT002.

Reviewer's Comment: *After reviewing these cases, I would agree with the investigators that treatment with aminolevulinic acid, whether Metvix or BF-200 ALA, and illumination with red light, is not in any way related to the deaths of these individuals. The events were far removed from the treatment event, and the absorption of ALA is short term and minimal, as are the cutaneous effects of light illumination.*

7.3.2 Nonfatal Serious Adverse Events

In the vehicle group, a total of 4 (2.7%) patients had 1 or more SAEs; 1 (0.7%) patient each had SAEs of arrhythmia, gastritis, myocardial infarction, myositis and respiratory tract infection.
In the BF-200 ALA group, 9 (2.3%) patients had 1 or more SAEs; 1 (0.3%) patient each had the SAEs of acute myocardial infarction, angina pectoris, arrhythmia, arterial stenosis limb, bursitis, contusion, epilepsy, glaucoma, hemorrhagic stroke, malignant melanoma and sarcoma (see table 20).

Table 20
Treatment Emergent SAEs
ITT Population

	Treatment Group					
	Placebo (N=149)			BF-200ALA (N=384)		
	Number of AEs (N#)	No. of subjects with AE (N)	Subjects with AE (%)	Number of AEs (N#)	No. of subjects with AE (N)	Subjects with AE (%)
Cardiac Disorders						
Myocardial Infarction	1	1	0.7	1	1	0.3
Arrhythmia	1	1	0.7	1	1	0.3
Eye Disorders						
Glaucoma	0	0	0	1	1	0.3
Gastrointestinal Disorders						
Gastritis	1	1	0.7	0	0	0
Infections and infestations						
Respiratory Tract Infection	1	1	0.7	0	0	0
Injury, poisoning and procedural complications						
Contusion	0	0	0	1	1	0.3
Musculoskeletal and Connective Tissue Disorders						
Bursitis	0	0	0	1	1	0.3
Myositis	1	1	0.7	0	0	0
Nervous System Disorders						
Epilepsy	0	0	0	1	1	0.3

Hemorrhagic stroke	0	0	0	1	1	0.3
Vascular Disorders Arterial stenosis limb	0	0	0	1	1	0.3
Source: NDA 208081 – adapted from table 3.7 - ALA-AK-CTpooled-ISS-1, page 673; Program: \Final\Prog\Table\T3_7_AE_SAE.sas						

Reviewer's Comment: *The incidence of SAEs is very low (<1%) and there is essentially no difference between the placebo and BF-200 ALA group. The SAEs in this trial are not unusual for the age of subjects being treated for AKs (>80% older ≥ 65 years old). There is no signal that exposure to ALA with illumination increases a subject's risk for any of these SAEs.*

7.3.3 Dropouts and/or Discontinuations

As shown in table 5 in section 7.1.3, there were 18 (12.1%) of subjects who discontinued on vehicle and 12 (3.1%) who discontinued on BF-200 ALA. No subject on vehicle discontinued because of an adverse event. Four subjects (33%) discontinued on BF-200 because of an adverse event but only 1 subject (0.08%) discontinued because of treatment related AEs. This subject, subject 113/39 in trial CT002, a 73 year old male, experienced application site pain and application site burning. Illumination for this subject stopped one minute after start because of the severity of the pain and burning. The other 3 discontinuations were for herpes zoster in the face (70 year old female), nasopharyngitis (a 72 year old female), and pneumonia (74 year old male). Table 21 delineates the discontinuations in the pivotal trials.

Table 21
Discontinuations in the Pivotal Trials – Adverse Events
ITT Population

System Organ Class **Preferred term**	**Vehicle** **N=149**	**BF-200 ALA** **N=384**
Subjects with any adverse event resulting in discontinuation, n(%)	0 (0)	4 (1)
General Disorders and Administration Site Conditions Application site pain/burning	0	1 (0.2)
Infections/Infestations Nasopharyngitis Pneumonia	0 0	1 (0.2) 1 (0.2)
Nervous System Disorders Herpes Zoster	1	1 (0.2)
Source: NDA 208081; Module 5; trial ALA-AK-CT002; Listing C.3.2.3		

7.3.4 Significant Adverse Events

Most of the treatment related adverse events for this drug therapy (PDT with BF-200 ALA) were cutaneous in nature and the significant AEs are those from the general disorders and administration site conditions that were severe. Overall, for the entire ITT population, those treated with either narrow band or broad band lamps, 36.7% of subjects in the BF-200 ALA group had a severe cutaneous reaction compared to only 1.3% in the vehicle group. The leading

causes of severe reaction were application site pain (25.3%), irritation (21.4%) and erythema (15.1%). However, it is important to note that only one subject discontinued from the trial due to a severe application site adverse event. Table 22 denotes the incidence of frequently reported severe treatment emergent adverse events (TEAEs).

Table 22
Severe TEAEs – Pivotal Trials
ITT Population

MedDRA System Organ Class Preferred Term	Vehicle		BF-200 ALA	
	N=149		N=384	
	n	%	n	%
General disorders and administration site conditions	2	1.3	141	36.7
Application site erythema	1	0.7	58	15.1
Application site exfoliation	0	0	6	1.6
Application site irritation	0	0	82	21.4
Application site edema	0	0	4	1.0
Application site pain	1	0.7	97	25.3
Application site paresthesia	0	0	9	2.3
Application site pruritus	0	0	5	1.3
Application site scab	0	0	7	1.8

Source: NDA 208081, Module 2, Clinical Summary, Table 15, page 36: ISS table 3.3

However, for subjects on drug product who received PDT with the narrow spectrum lights, application site burning and pain deserve special mention. During the first PDT treatment where all subjects were treated (87 in vehicle and 212 in ALA arms, respectively), up to 30% of subjects in the ALA arm (63/212) experienced severe burning compared to none in the vehicle arm. In reference to pain, up to 24% of subjects (51/212) in the ALA arm experienced severe pain compared to none in the vehicle arm (see table 23). For subjects who received a second PDT treatment, less subjects experienced severe burning and pain, suggesting a development of tolerance.

Table 23
Severe Burning and Pain
Narrow Spectrum Light Population

		Vehicle, N=87							BF-200 ALA, N=212						
			Mild		Moderate		Severe			Mild		Moderate		Severe	
			n	%	n	%	n	%		n	%	n	%	n	%
Narrow spectrum lamps															
PDT1															
Burning	Scalp		10	11.0	1	1.1	0	0		10	4.7	27	12.7	41	19.3
	Face		12	14.0	0	0	0	0		27	12.7	55	25.9	63	29.7
Pain	Scalp		9	1.0	0	0	0	0		8	3.8	35	16.5	39	18.4
	Face		2	12.6	0	0	1	1.1		29	13.6	61	28.8	51	24.0

Source: NDA 208081 – ISS pooled analysis, adapted from table 4.2.1, page 724 and table 4.3.1, page--- and ISE, tables 23& 24, pages 54-56

Reviewer's Comment: *Since the sponsor is seeking approval with a narrow spectrum lamp, it will be important to mention in labeling that up to 30% of subjects who experienced burning and up to 24% of subjects who experienced pain, the burning and pain were severe in nature. Again, only 1 subject discontinued due to an application site reaction of intolerance.*

7.3.5 Submission Specific Primary Safety Concerns

The primary safety concern for this drug product with narrow band red light illumination was patient tolerance of the PDT treatment at the application site. Results revealed that although the majority of subjects did have application site reactions, it did not result in discontinuation from the pivotal trials, except in one subject who could not tolerate the light treatment, which was stopped prematurely (see section 7.5.2).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 24 shows the common adverse reactions for the ITT population whether the subject was illuminated with a broad spectrum red light or narrow spectrum light. Table 25 includes the

common adverse reactions in the subpopulation of subjects who only used narrow band red light illumination.

Table 24
Incidence of Common Adverse Reactions
ITT Population

MedDRA System Organ Class Preferred Term	Vehicle		BF-200 ALA	
	N=149		N=384	
	n	%	n	%
Any related TEAE	88	59.1	368	95.8
General disorders and administration site conditions	87	58.4	367	95.6
Application site discharge	0	0	5	1.3
Application site discomfort	1	0.7	7	1.8
Application site erosion	1	0.7	8	2.1
Application site erythema	57	38.3	321	83.6
Application site exfoliation	6	4.0	61	15.9
Application site hypersensitivity/ hyperalgesia [a]	0	0	10	2.6
Application site induration	0	0	36	9.4
Application site irritation	35	23.5	289	75.3
Application site edema	3	2.0	106	27.6
Application site pain	39	26.2	272	70.8
Application site paresthesia	2	1.3	19	4.9
Application site pruritus	15	10.1	107	27.9
Application site reaction	2	1.3	11	2.9
Application site scab	3	2.0	48	12.5
Application site vesicles	1	0.7	29	7.6
Nervous system disorders	1	0.7	8	2.1
Headache	1	0.7	7	1.8
Skin and subcutaneous tissue disorders	3	2.0	27	7.0
Erythema	1	0.7	7	1.8
Pruritus	0	0	6	1.6
Skin exfoliation	1	0.7	17	4.4

[a] Faulty classification used at a single center in study ALA-AK-CT002 (b) (4) Correct term should have been "application site hyperalgeisa" as clarified by the investigator after database lock.
Source: NDA 208081: Module 2, Clinical Summary, table 14, page 35; ISS Table 3.3

Table 25 denotes the incidence of common adverse events by lamp type. Again, the column of most importance is that of subjects that used the narrow spectrum lamp.

Table 25
Incidence of Common Adverse Events by Lamp Type – ITT Population

MedDRA System Organ Class Preferred Term	Narrow spectrum lamp [a]				Broad spectrum lamp [b]			
	Vehicle		BF-200 ALA		Vehicle		BF-200 ALA	
	N=87		N=212		N=62		N=172	
	n	%	n	%	n	%	n	%
General disorders and administration site conditions	57	65.5	211	99.5	30	48.4	156	90.7
Application site bleeding	0	0	3	1.4	0	0	0	0
Application site burning*	12	14.0	145	68.0	10	16.0	81	47.0
Application site discharge	0	0	4	1.9	0	0	1	0.6
Application site discomfort	0	0	7	3.3	1	1.6	0	0
Application site erosion	0	0	6	2.8	1	1.6	2	1.2
Application site erythema	34	39.1	195	92.0	23	37.1	126	73.3
Application site exfoliation	4	4.6	41	19.3	2	3.2	20	11.6
Application site hypersensitivity/ hyperalgesia [c]	0	0	10	4.7	0	0	0	0
Application site induration	0	0	26	12.3	0	0	10	5.8
Application site irritation	17	19.5	153	72.2	18	29.0	136	79.1
Application site edema	3	3.4	75	35.4	0		31	18.0
Application site pain	26	29.9	195	92.0	13	21.0	77	44.8
Application site paresthesia	2	2.3	18	8.5	0	0	1	0.6
Application site pruritus	14	16.1	72	34.0	1	1.6	35	20.3
Application site reaction	2	2.3	8	3.8	0	0	3	1.7
Application site scab	2	2.3	41	19.3	1	1.6	7	4.1
Application site vesicles	1	1.1	25	11.8	0	0	4	2.3
Application site warmth	1	1.1	3	1.4	0	0	0	0
Chills	0	0	3	1.4	0	0	0	0
Infections and infestations	0	0	5	2.4	0	0	2	1.2
Application site pustules	0	0	3	1.4	0	0	0	0
Nervous System Disorders	1	1.1	5	2.4	0	0	3	1.7
Headache	1	1.1	5	2.4	0	0	2	1.2
Skin & subcutaneous tissue disorders	1	1.1	9	4.2	2	3.2	18	10.5
Erythema	0	0	0	0	1	1.6	7	4.1
Pruritus	0	0	0	0	0	0	4	2.3
Skin exfoliation	0	0	4	1.9	1	1.6	13	7.6

*Adapted from Table 4.2.1, pooled ISS – AE of the face and forehead & Table 4.2.2, pages 724 and 725 (this was not included by the sponsor).
Source: NDA 208081; Module 2, clinical summary-adapted from table 19, page 43 and ISS Table 3.3.1 and table 3.3.2

Reviewer's Comment: *Subjects who were treated with the narrow spectrum lamps, of which BF-RhodoLED is one, had a slight increase in the incidence of TEAEs. All but one subject, 211/212 (99.5%), had a general disorder and administration site condition versus 156/172 (90.7%) of subjects who were treated with broad band lamps.*
When looking at individual adverse reactions at the application site, the difference is more marked: application site erythema occurred with 92% of subjects using the narrow band lamps versus 73.3% with broad band, application site pain 92% vs. 44.8% and burning 68% vs.47%.. These three TEAEs had the starkest differential. In addition, there was essentially no difference between the type of narrow band light that was used (Aktilite, 93.4%; BFRhodoLED 92.5%; Omnilux 82.9% for erythema and Aktilite 90.2%; BFRhodoLED 96.2% Omnilux 91.4% for pain).[5] *However, for application site irritation, it was much closer, 72.2% vs. 79.1%. This increase in burning, pain and erythema in subjects using narrow band lights did not translate into markedly more subjects experiencing vesicles or scabs at the treatment site as compared to broad band treatment, 19.3% and 11.8% vs. 4.1% and 2.3%.*
In this reviewer's opinion, for labeling, the safety results of those subjects treated with narrow band illumination in combination with BF-200 ALA should be reported in the labeling, for to report the combined results, although the total TEAEs is close, the individual events are different enough, and the sponsor is seeking approval of a narrow band lamp.

7.4.2 Laboratory Findings

Subjects in the pivotal trials had routine laboratory testing which included general chemistry and hematology. Shift tables showed no evidence of clinically relevant change in alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin or alkaline phosphatase plasma concentrations; creatinine or blood urea nitrogen, or in hemoglobin, platelets or white blood cell count.

Reviewer's Comment: *It was not expected that any significant changes would occur in laboratory values, as the absorption of BF-200 ALA has very limited absorption, and although there was a slight increase in Cmax for the 3 hour period of occlusion, the AUC did not change*

7.4.3 Vital Signs

In the pivotal trials, descriptive statistics for systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate between baseline and end of trials showed small and inconsistent changes, which are not considered clinically significant. Overall, differences between treatment groups were generally small.

[5] NDA 208081: Module 2 – Summary of Clinical Safety, Table 20, page 45.

The rates of maximum change from baseline in SBP and DBP are shown below by baseline hypertension status, and show only small changes, and similar results for the BF-200 ALA and vehicle group (see table 26).

Table 26
Rates of Maximum Change from Baseline in Blood Pressure, Overall, and by Baseline Hypertension Status
ITT Population

	Vehicle						BF-200 ALA					
	Hypertensive status [a]						Hypertensive status [a]					
	controlled hypertensive		hypertensive		normotensive		controlled hypertensive		hypertensive		normotensive	
	n	%	n	%	n	%	n	%	n	%	n	%
DBP increase from baseline [mmHg]												
<=20	39	100.0	75	100.0	33	97.1	91	96.8	179	97.8	102	99.0
>20 to 30	0	0	0	0	1	2.9	3	3.2	3	1.6	0	0
>30 to 40	0	0	0	0	0	0	0	0	0	0	1	1.0
missing	0	0	0	0	0	0	0	0	1	0.5	0	0
SBP Increase from baseline [mmHg]												
<=20	38	97.4	72	96.0	31	91.2	83	88.3	178	97.3	95	92.2
>20 to 30	1	2.6	3	4.0	2	5.9	7	7.4	3	1.6	5	4.9
>30 to 40	0	0	0	0	1	2.9	1	1.1	2	1.1	1	1.0
>40	0	0	0	0	0	0	3	3.2	0	0	2	1.9

Source: NDA 208081: Module 2, Clinical Summary, table 21, page 52.

Reviewer's Comment: *In the clinical trials, changes in blood pressure did not result in any changes in end organ status.*

7.4.4 Electrocardiograms (ECGs)

No ECGs were conducted for any of the trials. As ALA is an endogenous substance and absorption was very minimal (see section 4.4, Clinical Pharmacology) and there was essentially no change in the levels of PpIX, the active metabolite, compared to baseline endogenous levels, changes to subjects' ECG are not expected.

7.4.5 Special Safety Studies/Clinical Trials

As this is a topical drug product, the sponsor performed a dermal safety trial, namely trial ALA-AK-CT005, "A randomized, vehicle-controlled, double-blind phase 1 trial to investigate the sensitization potential of a topical formulation containing 5-aminolevulinic acid (ALA) in volunteers with healthy skin."

The primary objective of the trial was to investigate the skin sensitization potential of Ameluz® (BF-200 ALA) and its vehicle after repeated topical application to healthy skin. The secondary objective was to evaluate the skin irritation potential of Ameluz® and its vehicle after repeated topical application to healthy skin. The trial consisted of 4 trial periods, screening, induction phase, rest phase, and challenge phase.
The indication phase is a 21-day phase in which 200 µl of Ameluz and approximately 200 µl of the vehicle were occlusively applied to the test fields on the left side of the back using 180mm Finn Chambers, 3 times weekly for 3 weeks. The subjects then rested for approximately 2 weeks (10-17 days). Then they entered the challenge phase where the same amount of drug product and vehicle was placed on naïve sites and occluded for one 48 hour period. Clinical assessments using an 8-point scale in combination with a 6-point scale (see Scale 1 and Scale 2 below) were performed 30 ± 5 minutes, 24 ± 2 hours, 48 ± 4 hours and 72 ± 4 hours after removal of occlusion. Observations at the naïve sites during challenge phase and the patterns of reactivity during induction phase provided a basis for assessment of sensitization. Re-challenge was performed 6-8 weeks after the challenge phase of the results of the challenge phase were equivocal.

Scale 1 – Dermal response

0 = no evidence of irritation
1 = minimal erythema, barely perceptible
2 = definite erythema, readily visible; minimal edema or papular response
3 = erythema and papules
4 = definite edema
5 = erythema, edema, and papules
6 = vesicular eruption
7 = strong reaction spreading beyond the application site

Scale 2 – Other effects

A (0) = slightly glazed appearance
B (1) = marked glazed appearance
C (2) = glazing with peeling and cracking
F (3) = glazing with fissures
G (3) = film of dried serous exudates covering all or part of the patch site
H (3) = small petechial erosions and/or scabs

The opinion of the investigator was recorded according to the following score:

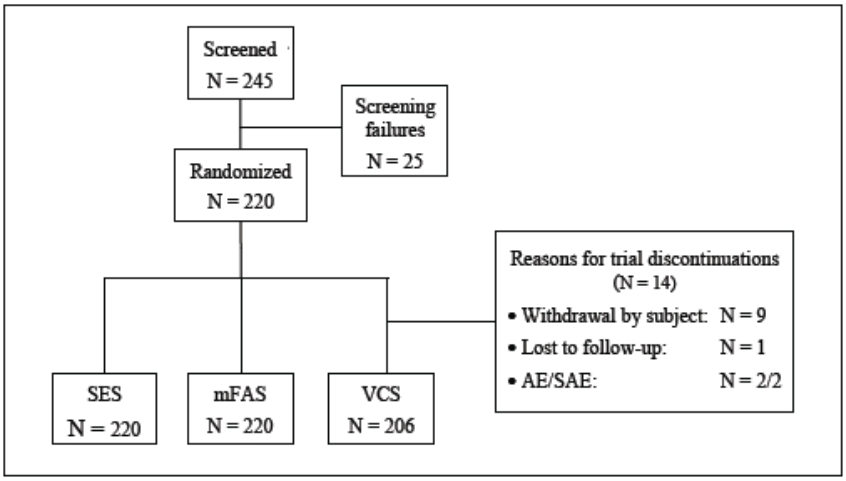
Final clinical assessment of incidence of sensitization

0 = negative (no allergy)
1 = equivocal
2 = positive (allergic contact dermatitis)

Results

Figure 2 shows the disposition of the subjects in this dermal safety trial.

Figure 2
Disposition of Subjects[6]



VCS = the number of subjects who completed all phases of the trial.

Subjects were all Caucasian, between the ages of 10 and 83 years old, with the median age being 49 years old and were almost evenly divided between male (47%) and female (53%). All were of Fitzpatrick skin types I (2%), II (31%), or III (68%).

Table 27 shows the results of the skin sensitization dermal safety trial. Of the 206 subjects who completed all phases, 12 (6%) showed definite allergic contact dermatitis. The subject who had the equivocal decision withdrew before the re-challenge phase and thus was listed as equivocal.

Table 27
Final Clinical Assessment of Incidence of Sensitization

	Ameluz	Vehicle
Completer test fields	206	206
Dermal Sensitization		
N	206	206
No allergy	193 (94%)	206 (100%)
Equivocal decision	1 (0%)	0 (0%)
Assured allergic contact dermatitis	12 (6%)	0 (0%)
95%-Confidence intervals		
Assured allergic contact dermatitis or at least equivocal decision	13 (6%) (3.7%, 10.5%)	0 (0%) (0.0%, 1.8%)
Assured allergic contact dermatitis	12 (6%) (3.7%, 10.5%)	0 (0%) (0.0%, 1.8%)
Source: NDA 208081: Module 5, Final study report, ALA-AK-CT005, adapted from table 5, page 59.		

[6] NDA 208081: Module 5, Final Study Report ALA-AK-CT005, Figure 2, page 52.

All 216 subjects in the Ameluz arm showed irritation after Day 22, mainly erythema and papules. In the vehicle arm, only a few subjects showed minimal erythema.

Reviewer's Comment: *The dermal safety study, as far as contact irritation is borne out in the clinical trials, as irritation was a common adverse reaction, even in the vehicle arm, with 19% having irritation in the vehicle arm and 72% showing irritation in the ALA arm. The same can be said for erythema which occurred in 39% of subjects in the vehicle arm, and 92% in the ALA arm. However, there were not any cases of allergic contact sensitization, which only could have occurred in subjects who returned and needed a 2nd PDT treatment.*

7.4.6 Immunogenicity

No trials were conducted to evaluate immunogenicity, as aminolevulinic hydrochloride is an endogenous substance.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

N/A

7.5.2 Time Dependency for Adverse Events

The mean duration of the most common AEs (incidence of 10% or more of patients in the BF-200 ALA group) was 124.59 and 25.59 hours in the vehicle and BF-200 ALA groups, respectively for application site erythema; 141.60 and 96.39 hours, respectively for application site irritation; 170.25 and 159.14 hours, respectively for application site pain; 63.81 and 84.58 hours, respectively for application site pruritus; 4.0 and 22.80 hours, respectively for application site edema, 50.11 and 33.92 hours, respectively for application site exfoliation; and 7.25 and 22.81 hours, respectively for application site scab. See table 28.

Table 28
Frequently (>10%) TEAEs by Duration
ITT Population

MedDRA System Organ Class Preferred Term	Vehicle N=149		BF-200 ALA N=384	
	n*	Median hours	n*	Median hours
General Disorders and administration site conditions				
Application site erythema	82	124.59	496	25.59
Application site irritation	43	141.60	426	96.39
Application site pain	57	170.25	480	159.14
Application site pruritus	21	63.81	133	84.58
Application site edema	3	4.00	127	22.80
Application site exfoliation	9	50.11	83	33.92
Application site scab	4	7.75	59	22.81

*n=number of events (is larger than the number of subjects, as some subjects received a 2nd PDT treatment 12 weeks after the 1st PDT treatment)
Source: NDA 208081: Module 2, Clinical Summary - adapted from table 16, page 37 and ISS, table 3.6 – pages 1-11.

7.5.3 Drug-Demographic Interactions

There was no difference in terms of age grouping for the most common adverse reactions, which were mostly in the application site conditions, a representative of which is delineated in table 29.

Table 29
Frequently Reported TEAEs by Age Group
ITT Population – Narrow Spectrum Lamps

	Vehicle						BF-200 ALA					
Age of patients (years):	<65		65-<75		≥75		<65		65-<75		≥75	
Narrow spectrum lamp stratum[a]:	n=9		n=54		n=24		n=37		n=120		n=55	
	n	%	n	%	n	%	n	%	n	%	n	%
General disorders and administration site conditions	4	44.4	35	64.8	18	75.0	37	100.0	120	100.0	54	98.2
Application site erythema	2	22.2	21	38.9	11	45.8	34	91.9	111	92.5	50	90.9
Application site pain	2	22.2	18	33.3	6	25.0	36	97.3	107	89.2	52	94.5
Application site irritation	3	33.3	12	22.2	2	8.3	26	70.3	93	70.5	34	61.8

Source: NDA 208081: Module 2 – adapted from table 28, Clinical Summary of Safety page 64 and ISS Table 3.2.1.2

There was no difference in terms of sex for the most common adverse reactions, which were mostly in the application site conditions, a representative of which is delineated in table 30.

Table 30
Frequently Reported TEAEs by Sex
ITT Population

	Vehicle				BF-200 ALA			
Sex:	**Female**		**Male**		**Female**		**Male**	
MedDRA system organ class	**n=28**		**n=121**		**n=47**		**n=337**	
Preferred term	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
General disorders and administration site conditions	18	64.3	69	57.0	44	93.6	323	95.8
Application site erythema	13	46.4	44	36.4	39	83.0	282	83.7
Application site irritation	7	25.0	28	23.1	36	76.6	253	75.1
Application site pain	6	21.4	33	27.3	30	63.8	242	71.8

Source: NDA 208081: Module 2 – adapted from table 30, Clinical Summary of Safety page 68and ISS Table 3.2.4.

Drug demographic interactions were not analyzed for race or ethnicity, as all subjects in the trial were Caucasian. However, an analysis was done for frequency of adverse reactions by Fitzpatrick skin types. Again, there was essentially no difference in the frequency of adverse reactions between the skin types. See table 31 for a representation of the most common adverse reactions (in the category of general disorders and administration site conditions).

Table 31
Frequently Reported TEAEs by Fitzpatrick Skin Type
ITT Population

MedDRA System Organ Class	Vehicle				BF-200 ALA			
Preferred Term	**N=149**				**N=384**			
Fitzpatrick skin type:	**I-III**		**IV**		**I-III**		**IV**	
	n=144		**n=5**		**n=338**		**n=46**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
General disorders and administration site conditions	84	58.3	3	60.0	322	95.3	45	97.8
Application site erythema	56	38.9	1	20.0	282	83.4	39	84.8
Application site irritation	35	24.3	0	0.0	255	75.4	34	73.9
Application site pain	39	27.1	0	0.0	239	70.7	33	71.7

Source: NDA 208081: Module 2 – adapted from table 40, Clinical Summary of Safety page 88and ISS Table 3.2.7.

7.5.4 Drug-Disease Interactions

The incidence of adverse reactions were similar based on the number of target lesions, with a slightly increased incidence for some adverse reactions with higher number of lesions, e.g. for irritation. However, there were no major differences that would require specific labeling (see table 32 for a representation of ARs based on number of lesions).

Table 32
Frequently Reported TEAEs by Number of Target Lesions
ITT Population – Narrow Spectrum Lamps

Number of lesions: Narrow spectrum lamp stratum [a]:	Vehicle				BF-200 ALA			
	Up to 5		6 or more		Up to 5		6 or more	
	n=31		n= 56		n= 80		n=132	
	n	%	n	%	n	%	n	%
General disorders and administration site conditions	25	80.6	32	57.1	80	100.0	131	99.2
Application site pain	14	45.2	12	21.4	75	93.8	120	90.9
Application site erythema	15	48.4	19	33.9	73	91.3	122	92.4
Application site irritation	4	12.9	13	23.2	46	57.5	107	81.1
Application site edema	2	6.5	1	1.8	29	36.3	46	34.8

Source: NDA 208081: Module 2 – adapted from table 32, Clinical Summary of Safety page 72and ISS Table 3.2.1.9.

The incidence of adverse reactions were similar based on the size of the target lesions, with again, a slightly increased incidence for some adverse reactions with increasing size, e.g. for irritation. However, there were no major differences that would require specific labeling (see table 33 for a representation of ARs based on lesion size).

Table 33
Frequently Reported TEAEs by Lesion Size
ITT Population – Narrow Spectrum Lamps

Size of lesions:	Vehicle				BF-200 ALA			
	≤4 cm^2		>4 cm^2		≤4 cm^2		>4 cm^2	
MedDRA System Organ Class	n=87		n=62		n=178		n=206	
Preferred Term	n	%	n	%	n	%	n	%
General disorders and administration site conditions	57	65.5	30	48.4	170	95.5	197	95.6
Application site erythema	40	46.0	17	27.4	155	87.1	166	80.6
Application site pain	25	28.7	14	22.6	128	71.9	144	69.9
Application site irritation	24	27.6	11	17.7	112	62.9	177	85.9
Application site edema	2	2.3	1	1.6	44	24.7	62	30.1

Source: NDA 208081: Module 2 – adapted from table 34, Clinical Summary of Safety page 76and ISS Table 3.2.1.8.

The incidence of adverse reactions were similar based on the region of treatment (face vs. bald scalp), with again, a slightly increased incidence for some adverse reactions in the face vs. the scalp, e.g. for irritation. However, there were no major differences that would require specific labeling (see table 34 for a representation of ARs based on region treated).

Table 34
Frequently Reported TEAEs by Region Treated
ITT Population – Narrow Spectrum Lamps

Region of application:	Vehicle						BF-200 ALA					
Narrow spectrum stratum [a]:	Face		Scalp		Both		Face		Scalp		Both	
	N=51		N=28		N=8		N=128		N=58		N=26	
	n	%	n	%	n	%	n	%	n	%	n	%
General disorders and administration site conditions	33	64.7	18	64.3	6	75.0	127	99.2	58	100	26	100
Application site erythema	22	43.1	10	35.7	2	25.0	115	89.8	54	93.1	26	100
Application site pain	14	27.5	11	39.3	1	12.5	115	89.8	55	94.8	25	96.2
Application site irritation	11	21.6	5	17.9	1	12.5	95	74.2	34	58.6	24	92.3

Source: NDA 208081: Module 2 – adapted from table 38, Clinical Summary of Safety page 84and ISS Table 3.2.1.3.

The incidence of adverse reactions was similar based on maximum baseline severity of AKs, with again, a slightly increased incidence in adverse reactions for the moderate category. However, there were no major differences that would require specific labeling (see table 35).

Table 35
Frequently Reported TEAEs by Maximum Baseline Severity of AKs
ITT Population – Narrow Spectrum Lamps

MedDRA System Organ Class Preferred Term	Vehicle				BF-200 ALA			
	N=87				N=212			
Maximum baseline AK severity	Mild		Moderate		Mild		Moderate	
Narrow spectrum lamp stratum	n=18		n=69		n=34		n=178	
	n	%	n	%	n	%	n	%
General disorders and administration site conditions	9	50.0	48	69.6	33	97.1	178	100
Application site erythema	6	33.3	28	40.6	29	85.3	166	93.3
Application site pain	5	27.8	21	30.4	28	82.4	167	93.8
Application site irritation	4	22.2	13	18.8	21	61.8	132	74.2
Application site edema	0		3	4.3	14	41.2	61	34.3

Source: NDA 208081: Module 2 – adapted from table 44, Clinical Summary of Safety page 96 and ISS Table 3.2.1.6.

7.5.5 Drug-Drug Interactions

Neither in-vitro studies of drug-drug interactions using human biomaterials nor clinical pharmacology studies on PK or PD interactions of BF-200 ALA 10% with other drugs have been conducted. No clinically relevant changes in ALA plasma concentrations and urine excretion after topical application of BF-200 ALA 10% were observed in studies ALA-AKCT001 and ALA-AK-CT006. Also, no AEs suggestive of clinically relevant interactions have been observed in the clinical studies with BF-200 ALA 10% gel.

Theoretically, however, it is possible that concomitant use of other known photosensitizing agents such as St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulphonamides, quinolones and tetracyclines may enhance the phototoxic reaction to PDT (see clinical pharmacology review in DARRTS dated 3/9/16).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There have been no reported cases of human carcinogenicity associated with the use of 5-aminolevulinic acid 10% gel, either in clinical trial data or post-marketing data from the EU where the drug product was approved on December 14, 2011.

7.6.2 Human Reproduction and Pregnancy Data

There are no available data on AMELUZ use in pregnant women to inform a drug associated risk. Animal reproduction studies were not conducted with aminolevulinic acid. Systemic absorption of aminolevulinic acid in humans is negligible following topical administration of AMELUZ under maximal clinical use conditions (see clinical pharmacology review). It is not expected that maternal use of AMELUZ will result in fetal exposure to the drug.

7.6.3 Pediatrics and Assessment of Effects on Growth

The sponsor submitted an iPSP on 11/11/14 requesting a full waiver, as actinic keratosis generally does not occur in the pediatric population. The Division met with PeRC on 1/7/15. PeRC was in agreement with the Division and the sponsor. The sponsor submitted an agreed upon iPSP on 2/24/15 which was presented to PeRC on 3/18/15 and an agreed PSP letter was issued to the sponsor on 3/26/15.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Accidental or intentional overdose in the study program has not been reported. If the subject for any reason cannot have the illumination during the prescribed period after application (the 3-h time span), the cream should be rinsed off with saline and water, and the subject should protect the exposed area from sunlight, prolonged or intense light for 2 days. There is no information on overdose of red light from the BF-RhodoLED® following BF-200 ALA application.
BF-200 ALA is not expected to have any potential for drug abuse. Therefore Section 9 in the PI is not considered necessary.

Reviewer's Comment: *The sponsor has been asked to provide references for subjects who have had Ameluz gel, 10% applied and occluded but did not receive illumination to be protected from light for 2 days, as Ameluz is a prodrug and without the proper wavelength, there should not be a risk for phototoxic reactions.*

Assessment of withdrawal is not relevant for BF-200 ALA, which is applied topically with single applications separated by several weeks or only one single treatment.

7.7 Additional Submissions / Safety Issues

The sponsor submitted the 120 day safety update on 11/10/15. This covers the period from 4/30/15, which was the day after the cut-off day for the NDA, through 9/15/15.

There were no significant new adverse events that could be attributed to Ameluz gel, 10% with PDT in the follow-up period of the clinical trials or in an ongoing trial in Europe for the

treatment of basal cell carcinoma with Ameluz and BF-RhodoLED. However, in a literature search one entry[7] was found of a potentially concerning safety issue, that of temporary global transient amnesia (TGA).
According to the authors, the reported memory impairment was similar to symptoms of transient global amnesia (TGA), a neurological condition with an acute and severe disturbance of anterograde memory accompanied by lesser degrees of retrograde amnesia. Three patients were reported to have suffered this adverse event after receiving PDT with aminolevulinic acid. The history of these 3 patients is as follows:

"The age of the three patients ranged from 66 to 74 years. None of three patients had a medical history of stroke, thrombosis, embolism, or transient ischemic attacks and all patients were treated for actinic keratosis on the forehead. After the PDT the patients experienced the above mentioned events, including blood pressure increased for patient 1 and 3.
CTA (computed tomography angiography) imaging performed in patient 3 did not lead to any significant pathological findings. MRI (magnetic resonance imaging) revealed punctual dysfunctional diffusions in the hippocampus, but no evidence for infarction, stenosis or bleeding. No neurological imaging for patients 2 and 3 had been performed. All events had been resolved within 24 hours."

According to Borroni et al., 2013 acute postoperative hypertension occurs in 22% of patients treated with methyl aminolevulinate-PDT. The mental confusion and disturbed orientation occurred in context with the transient global amnesia, which is often associated with stressful events, in this case possibly with the intense pain. Furthermore the patient's increased blood pressure might have promoted the events. The premedication with codeine (only patients 1 and 3) might have also contributed to the mental confusion. The events have been assessed as possibly related to PDT with aminolevulinic acid.

Reviewer's Comment: *While the investigators suggest that the transient TGA suffered by these patients could possibly be related to PDT with aminolevulinic acid, it is also possible that subjects in this age group can spontaneously have TIAs for a multitude of reasons. Given the small number of events, this issue should be monitored post marketing.*
In the instance of the subjects being treated with methyl aminolevulinate-PDT referred to in the Borroni article, it cannot be assumed that increases in blood pressure would lead to the same adverse events with 5-aminolevulinic acid. In the clinical trials for this NDA, there were no such events in the small percentage of subjects who had an elevation in blood pressure.

8 Postmarket Experience

Ameluz® (BF-200 ALA gel) was authorized for marketing in the EU on December 14, 2011 with a red light source. A narrow spectrum light source is recommended in their labeling but a broader and continuous spectrum can be used if narrow-spectrum light sources are not tolerated.[8]

[7]Reinholz M, Heppt MV, Hoffmann F, Lummel N,Ruzicka T, Lehmann P, et al. Transient memory impairment and transient global amnesia induced by photodynamic therapy. Br J Dermatol.2015 June 30. Doi: 10.1111/bjd.13985.

Ameluz® has been launched in Germany, Sweden, Norway, Denmark, The Netherlands, Austria, Slovenia, Spain, and the UK. At the time of the last PSUR to the EU (June 2014), a total of (b) (4) 2 g tubes had been sold. Thus, the cumulative post-authorization exposure since the international birth date (IBD) has been estimated at (b) (4) units/patients (based on the available sales figures since IBD).
Since the IBD, there have been 320 adverse events in 128 patients that have been spontaneously reported in the adverse event reporting system outside of the United States. Of these, the Company assessed that 185 of these events a causal relationship to Ameluz could be suspected. The largest number of adverse events was in the General disorders and administration site conditions with 163 reported and 131 suspected to be due to Ameluz. This was followed by eye disorders, where 10 eye disorders, all suspected to be due to Ameluz. Table 36 denotes the most common spontaneously reported post-marketing adverse events.

[8]NDA 208081, module 1, section 1.14.5: Foreign Labeling: EU labeling pg 3, http://www.ema.europa.eu.

Table 36
Most Common Adverse Events
Post-Marketing Data Sources

Adverse reaction (MedDRA PT)	Cumulative spontaneous events, including competent authorities (worldwide) and literature	Number of events considered plausibly related to Ameluz® by the Company
Eye disorders	10	10
Diplopia	1	1
Eye irritation	2	2
Eyelid edema	4	4
Ocular hyperemia	1	1
Photophobia	1	1
Vision blurred	1	1
General disorders and administration site conditions	163	131
Application site hemorrhage	5	5
Application site inflammation	4	4
Application site edema	7	7
Application site erosion	10	10
Application site erythema	28	27
Application site exfoliation	12	12
Application site pain	21	20
Application site reaction	4	4
Application site scab	8	8
Application site swelling	5	4
Application site vesicles	3	3
Immune system disorders	4	0
Hypersensitivity	4	0
Infections and infestations	12	11
Application site pustules	8	8
Skin and subcutaneous tissue disorders	28	24
Blister	3	3
Eczema	1	1
Erythema	10	9
Photoonycholysis	1	1
Pigmentation disorder	1	1
Scab	2	2
Skin atrophy	1	1
Skin discoloration	2	2
Skin exfoliation	1	1
Skin irritation	2	2
Swelling Face	1	1

Source: NDA 208081: Module 2: Clinical Summary of Safety, adapted from table 47, page 103.

Reviewer's Comment: *The relevant post-marketing adverse events that can be classified as adverse reactions will be added to the post-market experience section of labeling.*

9 Appendices

9.1 Literature Review/References

Reinholz M, Heppt MV, Hoffmann F, Lummel N,Ruzicka T, Lehmann P, et al. Transient memory impairment and transient global amnesia induced by photodynamic therapy. Br J Dermatol.2015 June 30. Doi: 10.1111/bjd.13985.

Borroni, Riccardo G, Carugno, A, Rivetti, Nicolo, Arbustini, Eloisa, Brazzelli. Risk of acute postoperative hyperteinsion after topical photodynamic therapy for non-melanoma skin cancer. Journal of Photodermatology, Photoimmunology & Photomedicine 2013; 29: 73-77.

9.2 Labeling Recommendations

The following contains the language recommended to the applicant for the major clinical sections of the labeling. The reader is referred to the entire labeling for all changes. At the close of the review, the Division is in labeling negotiations with the applicant.

1.INDICATIONS AND USAGE

AMELUZ® Gel, in combination with photodynamic therapy (PDT) using BF-RhodoLED lamp, a narrowband, red light illumination source, is indicated for (b) (4) treatment of actinic keratoses (AKs) of mild to-moderate severity on the face and scalp (b) (4)

2.DOSAGE AND ADMINSTRATION

Important Administration Information

AMELUZ® is only to be administered by a health care provider.

AMELUZ (b) (4) is for topical use only. Not for ophthalmic, oral, or intravaginal use.

Treat single lesions or an entire field affected by multiple lesions with AMELUZ, in combination with red light photodynamic therapy (PDT). PDT requires administration of both AMELUZ Gel and the BF-RhodoLED light. Retreat lesions that have not completely resolved after 3 months after the initial treatment.

5.WARNINGS AND PRECAUTIONS

Photosensitivity

AMELUZ (b) (4) increases photosensitivity. Avoid sunlight, prolonged or intense light on lesions and surrounding skin treated with AMELUZ for approximately 48 hours following treatment (whether exposed to illumination or not) Concomitant use of AMELUZ with other known photosensitizing agents may increase the risk of phototoxic reaction to PDT *[see Drug Interactions (7)]*.

Coagulation (b) (4).

AMELUZ® (b) (4) has not been tested on patients with inherited or acquired coagulation (b) (4)

Irritation

(b) (4) Rinse with water in case of accidental contact.

(b) (4)

6.ADVERSE REACTIONS

The following serious adverse reactions are discussed in (b) (4) detail in other sections of the labeling:

(b) (4)

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical program for AMELUZ® included three double-blind and placebo-controlled trials (Trials 1, 2, and 3), enrolling a total of 299 subjects that were treated with narrow band light. Trial subjects were adults greater than or equal to 49 years of age, and the majority had

Fitzpatrick skin type I, II, or III. No subjects had Fitzpatrick skin type V or VI. Approximately 86% of subjects were male, and all subjects were Caucasian.

For all trials, the enrolled subjects had mild to moderate AKs (Olsen grade 1 and 2) with 4 to 8 lesions on the face and scalp. Overall, 87 placebo-treated subjects (n=16, n=32, n=39) and 212 AMELUZ®-treated subjects (n=32, n=55, and n=125) were illuminated with BF-RhodoLED® or similar narrow spectrum lamps.

Local skin reactions at the application site were observed in about 99.5% of subjects treated with AMELUZ® and narrow spectrum lamps. The most frequent adverse reactions during and after PDT were application site erythema, pain, burning,irritation, edema, pruritus, exfoliation, scab, induration and vesicles.

Most adverse reactions occurred during illumination or shortly afterwards, were generally of mild or moderate intensity, and lasted for 1 to 4 days in most cases; in some cases, however, they persisted for 1 to 2 weeks or even longer. Severe (b) (4) occurred in up to 30% (b) (4) of subjects, (b) (4). In (b) (4) case (b) (4) the adverse reactions required interruption or discontinuation of the illumination.

The incidence of common (≥1%, <10%) and very common (≥10%) adverse reactions in randomized, multicenter trials trials are presented in Table 1.

In a clinical trial designed to investigate the sensitization potential of aminolevulinic acid with 216 healthy subjects, 13 subjects (6%) developed allergic contact dermatitis after continuous exposure for 21 days with doses of aminolevulinic acid that were higher than doses normally used in the treatment of AK.

Reviewer's Comment: *The reader is referred to the labeling for Table 1. Other than using whole integers, one category of adverse reaction was added, that of burning which occurred in 14% (12/87) subjects in placebo and 68% (145/212) subjects in the Ameluz arm.* (b) (4)

14.Clinical Studies

The efficacy and safety of AMELUZ® in combination with PDT using a narrow spectrum (red light lamp) source were evaluated in three randomized, multicenter trials (Trials 1, 2, and 3). Trials 2 and 3 were vehicle-controlled and double-blind. Trial 1 was double-blind with respect to vehicle and observer-blind regarding the active comparator arm. All clinical trials included a follow-up assessment after 6 and 12 months.

In these trials, 212 subjects with 4 to 8 mild to moderate AK lesions on the face/forehead and/or bald scalp were treated with AMELUZ and a narrow band spectrum lamp. Subjects ranged from 49 to 87 years of age (mean 71 years), and 92% had Fitzpatrick skin type I, II, or III. No subjects

had Fitzpatrick skin type V or VI. Approximately 86% of subjects were male, and all subjects were Caucasian.

All sessions were comprised of lesion preparation to roughen the surface and remove crusts, application of AMELUZ® Gel with occlusion for 3 hours, and removal of the residual gel. Subsequently, the entire treatment area was illuminated with a narrow spectrum red light source, a lamp of either 630 nm or 633 nm and a light dose of approximately 37 J/cm^2. In Trial 3, illumination was performed with BF-RhodoLED®, a red light source with a narrow spectrum around 635 nm and a light dose of approximately 37 J/cm^2.

In all trials, the lesions that were not completely cleared 12 weeks after the initial treatment were treated a second time with an identical regimen. In the clinical trials, 42% (88/212) subjects (b) (4) needed a second (b) (4)

The primary endpoint for all trials was complete clearance 12 weeks after the last PDT. The results of Trials 1, 2 and 3 are presented in Table 2.

Reviewer's Comment: *The reader is referred to the labeling for Table 2 or to section 6.1.4, table 9, page* (b) (4) *of this review.*

(b) (4) subjects, who received AMELUZ® with the narrowband PDT and achieved complete clearance 12 weeks after the last PDT, had recurrence rates of 14%, 11%, 25%, respectively (at 6 months) and 40%, 22%, and 37%, respectively (at 12 months). Recurrence was defined as the percentage of subjects with at least one recurrent lesion during the 6-month or 12-month follow up period in subjects with completely cleared lesions 12 weeks after the last PDT.

Reviewer's Comment: *All references to secondary endpoints that the applicant included in labeling were deleted.*

17 Patient Counseling Information

Photosensitivity

Advise patients that for approximately 48 hours following treatment to avoid exposure to sunlight, prolonged or intense light on the treated lesion sites and surrounding skin.

Advise patients to avoid certain medications that may enhance the phototoxic reaction to PDT *[see Warnings and Precautions (5.1) and Drug Interactions (7)]*.

Common Adverse Reactions

Inform patients that treatment with AMELUZ® in combination with PDT may result in adverse reactions which include local skin reactions at the application site such as erythema, pain, irritation, (b) (4) edema, pruritus, exfoliation, induration, scab and vesicles.

9.3 Advisory Committee Meeting

No advisory committee meeting was held for this NDA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DENISE COOK
03/21/2016

GORDANA DIGLISIC
03/22/2016