CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208081Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 30, 2016
From	Gordana Diglisic, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	208081
Applicant	Biofrontera Bioscience GmbH
Date of Submission	Letter date: July 10, 2015 Received date: July 10, 2015
PDUFA Goal Date	May 10, 2016
Proprietary Name / Established (USAN) names	AMELUZ (5-aminolevulinic acid hydrochloride)
Dosage forms / Strength	Gel /10 %
Proposed Indication(s)	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
Recommended:	***Tentative** Approval*

1. Introduction

AMELUZ (5-aminolevulinic acid hydrochloride) Gel, 10% is a topical drug product for which the applicant seeks approval under Section 505(b)(1) of the Federal Food Drug and Cosmetic Act for the treatment of mild to moderate actinic keratoses (AK) on the face and scalp in combination with photodynamic therapy (PDT) using BF-RhodoLED lamp (narrowband, red light illumination source).

The active ingredient, 5-aminolevulinic acid hydrochloride (ALA), is a porphirin precursor. Aminolevulinic acid is a delta-amino acid and occurs as an endogenous molecule of the heme biosynthesis pathway. 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 can be activated by the absorption of energy at several different wave lengths, ranging from blue to red light resulting in an excited state of porphyrin molecules. In the presence of oxygen, reactive oxygen species are formed which causes damage to cellular components, and eventually destroys the target cells.

Aminolevulinic acid hydrochloride is currently marketed in the United States (US) as topical solution, 20 % (Levulan® Kerastick®; NDA 20965). Levulan® Kerastick® (aminolevulinic acid hydrochloride), 20% for Topical Solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy (PDT) Illuminator is indicated for the treatment of minimally to moderately thick actinic keratoses of the face or scalp. It was approved in 1999.

A similar product, METVIXIA® (methyl aminolevulinate) Cream, 16.8% was approved in 2004 (NDA 21415) in combination 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. METVIXIA® Cream was recently withdrawn from the market (not for safety reasons; published in the Federal Register on 10/13/15).

AMELUZ Gel, 10%, to be used with a red light source, was authorized for marketing in the EU on December 14, 2011.

This memo will summarize the findings of the multi-disciplinary review team and provide the rationale for my recommended action.

2. Background

AMELUZ (5-aminolevulinic acid hydrochloride) Gel, 10% (BF-ALA 200) was developed under IND 115412. During the development program, the applicant interacted with the Agency at two milestone meetings [PreIND Meeting (July11, 2012) and Pre-NDA Meeting (October 8, 2014)].

At the PreIND Meeting, the following key points were discussed:

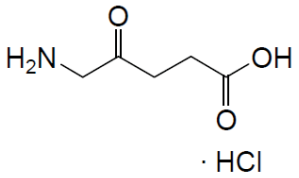
- As the applicant had already completed the two confirmatory trials ALA-AK-CT002 and CT003, no agreements could be made with the Division. However, the applicant was advised that the design of the trials appeared reasonable.
- Light based systems used for activating photosensitive drugs for photodynamic therapy are considered medical device Class III which is the equivalent class of the NDA. As a Class III medical device the review process is via the Premarket Approval Application (PMA). This is a combination product with a CDER lead, therefore an NDA (i.e. one marketing application) containing all information is sufficient. A separate PMA is not required by the Agency.
- The decision to allow the approval of the light source to be based on technological comparisons between the new light source and a previously approved light source will be a review issue. The Agency requested a full side by side list of features for all lamp products used in their clinical trials and a side by side comparison with the new lamp proposed for market.
- The applicant indicated that they were planning to conduct a maximal use PK study in subjects with at least 10AK lesions. The Agency recommended that the sponsor obtain an adequate number of samples to fully characterize the baseline profile of endogenous levels of 5 ALA and its active metabolite, PpIX.

At the Pre-NDA, the proposed format for data in the planned marketing application was discussed.

During the development program, the applicant submitted an Initial Pediatric Study Plan (iPSP) on November 11, 2014 requesting a full waiver of the requirement to perform pediatric studies. The applicant stated that the reason for waiving pediatric studies is that studies are impossible or highly impractical since the disease practically does not occur in the pediatric population. The Division issued an Advice Letter confirming agreement with the initial agreed PSP on March 27, 2015.

3. CMC/Device

AMELUZ (aminolevulinic acid hydrochloride) Gel, 10% for topical use is a non-sterile white-to-yellowish gel. The active pharmaceutical ingredient in the drug product is aminolevulinic acid hydrochloride. 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 AMELUZ Gel 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 (Table 1).

Table 1: Composition of AMELUZ Gel

Ingredient	Function	Content per mL
5-Aminolevulinic acid hydrochloride	Active ingredient	100.0
Xanthan gum, Ph.Eur / USP-NF		(b) (4)
Soybean phosphatidylcholine		
Polysorbate 80		
Medium chain Triglycerids, d Ph.Eur / USP-NF		

Isopropyl alcohol, Ph.Eur / USP-NF	(b) (4)
(b) (4)	
Propylene glycol, Ph.Eur / USP-NF	
Sodium benzoate, Ph.Eur / USP-NF	
Purified water, Ph.Eur / USP-NF	

The specification of AMELUZ Gel, 10% includes tests for appearance, drug substance identification and assay, sodium benzoate assay, viscosity, pH, impurities, particle size distribution, minimal fill and microbial contamination.
The identity, strength, purity and quality of the drug product are assured by adequate raw material controls, validated manufacturing process and drug product specification.

Container Closure System:

The drug product is supplied in an aluminum tube with a white, high density polyethylene (HDPE) screw cap. Each tube contains 2 g of gel.

On the basis of the drug product stability data, proposed 24-month expiration dating period when it is stored at 2ºC-(b) (4)ºC in the proposed container closure system is deemed justified.

The CMC review team concluded that the applicant has submitted sufficient information to assure the identity, strength, purity, and quality of the drug substance and drug product. However, the Office of Process and Facilities has not made a final overall manufacturing inspection "Approval" recommendation for the facilities involved in this application. Therefore, from the OPQ perspective, this NDA is not ready for approval at this time in its present form per 21 CFR 314.125 (b)(6) and 21 CFR 314.125 (b)(13), until the above issue and label/labeling revisions are satisfactorily resolved. At the completion of this review, these issues are still outstanding.

The reader is referred to the comprehensive reviews by Hitesh Shroff, Ph.D., ONDP Branch V/DNDP II; Roger Far, Ph.D.; ONDP Branch II/DLA; Kejun Cheng, Ph.D., OPF Branch VIII/DIII; Eric Adeeku, Ph.D., OPF Branch I/DIV; Vipulchandra Dholakia, Ph.D., OPF/DIAV/ Branch III; Vidula Kolhatkar, Ph.D., ONDP Branch II/DB, dated March 30, 2016.

BF-RhodoLED light system

The BF-RhodoLED light system incorporates 128 LED's with a peak output of 635 nm. The output fluence for treatment is fixed at 37 J/cm^2 using a fixed treatment time of 10 minutes. The output fluence for successful treatment has been tested with the lamp placed 5-8 cm from the targeted treatment site with the optimal distance being stated as 6 cm. The light output area is 8 x 18 cm with the effective treatment area being 6 x 16 cm.

Per Dr. Felten: "review of the revised User Manual provided for the BF-RhodoLED lamp system has identified no issues with the device labeling and instructions for use. Use of this manual is acceptable. From a device perspective there are no outstanding issues related to the BF-RhodoLED lamp system. Based on my review of the device information submitted in this NDA I would recommend Approval from the device perspective."

The reader is referred to the comprehensive review by Dr. Richard P. Felten, Center for Devices and Radiological Health (CDRH), ONE, DSD, GSDB 1 dated March 17, 2016

4. Nonclinical Pharmacology/Toxicology

The toxicity profile of AMELUZ Gel, 10% has been adequately characterized by the nonclinical studies conducted by the applicant. There are no novel excipients.

Per Dr. Hill, "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. Maternal use of AMELUZ is not expected to result in fetal exposure to the drug and breastfeeding is not expected to result in exposure of the child to the drug due to the negligible systemic absorption of ALA following topical administration of AMELUZ clinical maximal use conditions. The need for a dermal carcinogenicity study for AMELUZ was waived due to the clinical conditions of use (single application followed by another single application after 3 months, if needed)."

Based on the results of three in vitro genotoxicity tests (Ames assay, HPRT test in V79 cells and Human lymphocyte chromosomal aberration assay) that were conducted without red light exposure and one in vivo genotoxicity test (mouse micronucleus assay), ALA HCL did not show evidence of mutagenic or clastogenic potential. However, per Dr. Hill "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."

The applicant conducted two safety pharmacology studies:

- Study Number ALA-AK-PT0036 : 5-Aminolevulinic acid, hydrochloride: Effect on hERG tail currents recorded from stably transfected HEK 293 cells
- Study Number ALA-AK-PT (b) (4) 10115-1-96: Examination of the influence of MC 506 (5-aminolevlinic acid hydrochloride) on several cardiovascular parameters and the respiration in anesthetized beagle dogs following intravenous administration

No effects were noted in the in vitro hERG assay at a high concentration of 6 mM ALA HCl; and no significant treatment related effects were noted in the in vivo study in anesthetized Beagle dogs at a single intravenous dose up to 45 mg/kg ALA HCl.

The applicant also conducted two repeat-dose toxicity studies:

- Study number ALA-AK-PT (b) (4) 11664-98: 14-Day subchronic toxicity study of MC 506/1 (5-aminolevlinic acid hydrochloride) by intravenous administration to beagle dogs
- Study number 24945: 3-Month local tolerance and toxicity study of BF-200 ALA in minipigs following repeated dermal administration (once monthly)

Key study findings: Topical treatment with ALA gel, 10% in minipigs, with and without red light illumination, resulted in pronounced erythema 3 hours after illumination which reached levels comparable to severe sunburn. No edema was noted at any of the treatment sites and a mild to moderate superficial purulent dermatitis with inflammatory reactions in the dermis was noted at ALA gel, 10% treated sites on test day 88 (3 days after last application). An almost complete reversibility of the skin changes was noted after 28 days. The morphological structure of the skin treated with ALA gel, 10% with illumination was comparable to vehicle gel treated skin 28 days after the last application.

Labeling recommendation (the underlined wording to be inserted into and the strikeout wording to be deleted from the labeling):

There will be no Section 8.3 of the labeling because there is no concern about possible treatment related effects on fertility due to the negligible systemic absorption of ALA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

(b) (4)

There are no available data on AMELUZ use in pregnant women to inform a drug associated risk. Animal reproduction studies were not conducted with ALA. Systemic absorption of ALA in humans is negligible following topical administration of AMELUZ under maximal clinical use conditions *[See Clinical Pharmacology (12.3)]*. It is not expected that maternal use of AMELUZ will result in fetal exposure to the drug.

8.2 Lactation

Risk Summary

(b) (4)

~~The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for AMELUZ® and any potential adverse effects on the breastfeeding child from AMELUZ® or from the underlying maternal condition.~~

No data are available regarding the presence of ALA in human milk, the effects of ALA on the breast fed infant or on milk production. However, breastfeeding is not expected to result in exposure of the child to the drug due to the negligible systemic absorption of ALA in humans following topical administration of AMELUZ under maximal clinical use conditions *[See Clinical Pharmacology (12.3)]*.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies to evaluate the carcinogenic potential of AMELUZ or ALA have not been performed.

(b) (4)

(b) (4)

(b) (4) ALA 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). These genotoxicity studies were conducted without exposure to light. (b) (4) There is a literature report that indicates that (b) (4) may cause genotoxic effects in the presence as well as in the absence of activating light. These genotoxic effects are likely (b) (4) caused by the formation of reactive oxygen species (b) (4)

(b) (4)

(b) (4)

Animal fertility studies have not been conducted with ALA because of the negligible systemic absorption of ALA in humans following topical administration of AMELUZ under maximal clinical use conditions.

The reader is referred to the comprehensive review by Barbara A Hill, Ph.D., recommended *Approval* of this application (review dated March 9, 2016).

There are no outstanding pharmacology-toxicology issues.

The pharmacology-toxicology reviewer, Barbara A Hill, Ph.D., recommended *Approval* of this application (review dated March 9, 2016).

5. Clinical Pharmacology/Biopharmaceutics

The applicant conducted the maximal use pharmacokinetics (PK) trial (Trial ALA-AK-CT-006) to evaluate PK of ALA and PpIX in subjects with AK following topical application of AMELUZ Gel, 10% (BF-200 ALA Gel) under maximal use conditions when using PDT.

The Trial ALA-AK-CT-006 was a single center, non-randomized, open-label, fixed-sequence, vehicle-controlled trial which enrolled 12 adult subjects (18-85 years of age) with at least 10 mild or moderate AK lesions on the face and forehead. After preparation of all lesions by removal of scales and crusts and gentle roughening and degreasing of the skin surface with an 70% isopropanol soaked cotton pad, the clinical staff applied 2 g of Vehicle Gel or AMELUZ Gel, 10% at a thickness of about 1 mm to the lesions and the surrounding areas covering approximately 20 cm² area. The application area was covered with an occlusive dressing for about 3 hours after which the excess gel from the treatment area was wiped off and the treatment area was illuminated with an LED narrow spectrum device (BF-RhodoLED®, emission at around 635 nm, light dose approximately 37 J/cm²). Each subject received first a Vehicle Gel treatment with PDT and after a wash-out period of 7 days, the subject received a second PDT treatment with AMELUZ Gel, 10%. The same AK lesions/areas were treated in both periods.

Plasma samples for PK assessment was obtained at -0.5 and - 0 h prior to application of the gel and at 0.5, 1, 1.5, 2, 2.5 and 3h after Vehicle Gel or AMELUZ Gel, 10% application but before starting illumination and at 3.5, 4, 5, 6, 8, 10, 12 and 24 h after start (t = 0 h) of Vehicle Gel or AMELUZ Gel, 10%, 10% application. Plasma concentrations of ALA and PpIX were used for obtaining baseline corrected plasma concentrations-time curves and calculation of the PK parameters.

Systemic concentrations of ALA were quantifiable in all subjects. The mean ± SD baseline concentrations of ALA and PpIX were 20.16 ± 16.53 ng/mL and 3.27 ± 2.40 ng/mL, respectively. After application of the Vehicle Gel, the mean plasma concentrations of ALA were similar compared to baseline. After application of AMELUZ Gel, 10%, the mean plasma concentrations of ALA increased compared to baseline and the baseline corrected mean ± SD C_{max} (maximum concentration), AUC0-t (area under the concentration time curve) and median t_{max} (time at which C_{max} occurred) were 27.19 ± 20.02 ng/mL, 142.83 ± 75.50 ng*h/mL, and 3.00 h, respectively. Baseline corrected systemic concentrations of PpIX was estimated only in one subject due to the values being negative in other subjects. The baseline corrected C_{max} and AUC0-t in the single subject was 0.29 ng/mL and 0.07 ng*h/mL, respectively.

Clinical Pharmacology Team Labeling Recommendations:

The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion.

2. DOSAGE AND ADMINISTRATION

(b) (4)

Application area should not exceed 20 cm^2 and no more than 2 grams of AMELUZ® gel (one tube) should be used at one time. The gel can be applied to healthy skin around the lesions. Avoid application near mucous membranes such as the eyes, nostrils, mouth, and ears (keep a distance of 1 cm from these areas). (b) (4)

7. DRUG INTERACTIONS

There have been no formal studies of the interaction of AMELUZ® with other drugs (b) (4) **It** is possible that concomitant use of (b) (4) (b) (4) **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.

12. CLINICAL PHARMACOLOGY

(b) (4)

(b) (4)

12.3 Pharmacokinetics

(b) (4)

Pharmacokinetics (PK) of ALA and PpIX was evaluated in a trial of 11 adult subjects with mild to moderate AK with at least 10 AK lesions on the face or forehead. A single dose of one entire tube of AMELUZ® gel (2 grams) was applied under occlusion for 3 hours followed by PDT to a total area of 20 cm^2. The mean ± SD baseline plasma ALA and PpIX concentrations were 20.16 ± 16.53 ng/mL and 3.27 ± 2.40 ng/mL, respectively. In most subjects an up to 2.5-fold increase of ALA plasma concentrations was observed during the first 3 hours after AMELUZ® application. The mean ± SD area under the concentration time curve (AUC0-t) and maximum concentration (Cmax) for baseline corrected ALA (n=12) were 142.83 ± 75.50 ng.h/mL and 27.19 ± 20.02 ng/mL, respectively. The median tmax (time at which C_{max} occurred) was 3 h.
The majority (about 55%) of the PpIX concentrations were below the limit of quantification (LOQ = 1 ng/mL) and baseline corrected values were negative in all subjects except for one. The baseline corrected AUC0-t and Cmax in the single subject was 0.07 ng.h/mL and 0.29 ng/mL. PK of ALA and PpIX following treatment on the scalp was not evaluated.

(b) (4)

(b) (4)

The reader is referred to the comprehensive review by Chinmay Shukla, PhD. for a full discussion of the clinical pharmacology data (dated March 8, 2016).

The clinical pharmacology reviewer, Chinmay Shukla, PhD., Office of Clinical Pharmacology/ Division of Clinical Pharmacology 3, recommended *Approval* of this application pending agreement on recommended labeling changes.

6. Clinical Microbiology

The applicant did not conduct microbiologic studies.

7. Clinical/Statistical- Efficacy

The applicant submitted data from three pivotal Phase 3 trials, ALA-AK-CT002 (Trial 02), ALA-AK-CT003 (Trial 03), and ALA-AK-CT007 (Trial 07), to establish the effectiveness of their product, AMELUZ (5-aminolevulinic acid hydrochloride) Gel, 10%, for the topical treatment of mild to moderate actinic keratoses on the face and scalp in combination with photodynamic therapy using BF-RhodoLED lamp. Al trials were conducted outside the United States.

Trial 02 was randomized, observer-blind, multinational trial to evaluate the safety and efficacy of AMELUZ Gel, 10%, in comparison with Metvix® (methyl aminolevulinate) Cream, and Vehicle, for the treatment of AK with PDT. Five hundred seventy one (571) subjects were randomized in a 3:3:1 ration to the following arms: AMELUZ Gel, 10%, Metvix® Cream, and Vehicle arm. 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)].

Trial 03 and 07 were randomized, double-blind, vehicle-controlled, inter- individual, 2-armed, multicenter trials. One hundred twenty two (122) subjects and 87 subjects in Trials 03 and 07, respectively, were randomized in a 2:1 ratio to the following arms: AMELUZ Gel, 10% and Vehicle. The light sources used for Trial 03 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 light source used for Trial 07 was BF-RhodoLED lamp (narrowband, red light illumination source).

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. The clearance of AK lesions was assessed 12 weeks after the first PDT. All lesions that were not completely cleared were treated with a second PDT. For all subjects, two follow-up visits (6 months and 12 months after the last PDT) were scheduled. An overview of the trials is presented in Table 2.

Table 2: Overview of pivotal Clinical Trials

	ALA-AK-CT002 (Trial 02)	**ALA-AK-CT003 (Trial 03)**	**ALA-AK-CT007 (Trial 07)**
Study design	Randomized, **observer-blind**, multinational Phase 3 trial to evaluate the safety and efficacy of a nanoemulsion gel formulation AMELUZ, in comparison with Metvix* and placebo**, for the treatment of AK with PDT	Randomized, double-blind, Phase 3, placebo-controlled, inter-individual, 2-armed, multicenter study using AMELUZ and placebo	Randomized, double-blind, placebo-controlled, inter-individual, 2-armed, multicenter study using AMELUZ and placebo
Treatment	4-8 single AK lesion (up to 20 cm^2)	4-8 single AK lesion (up to 20 cm^2)	Field treatment of 4-8 AK lesions (20 cm^2)
Number of Centers	23 centers in Germany 2 centers in Austria 1 in Switzerland	8 centers in Germany	7 centers in Germany
Number of subjects	571 randomized in 3:3:1 • 248 AMELUZ • 247 Metvix • 76 Placebo	122 randomized in 2:1 • 81 AMELUZ • 41 Placebo	87 randomized in 2:1 • 55 in AMELUZ • 32 in Placebo
Lamps	Narrow • Aktilite CL 128 • Omnilux PDT Broad • Waldman PDT 1200L • HydroSun Photodyn 505 or 750	Narrow • Aktilite CL 128 Broad • Hydrosun Photodyn 750	Narrow • BF-RhodoLED

Source: An excerpt from the applicant's submission
*Metvix (methyl aminolevulinate); ** placebo (gel vehicle without the active ingredient ALA)

The population enrolled was subjects 49 years of age and older with 4-8 clinically confirmed AK target lesions of mild to moderate intensity within the face or bald scalp excluding eyes, nostrils, ears and mouth, (i.e., AK grade I or II according to Olsen *et al*., 1991) at baseline.

The demographics and baseline disease characteristics were generally balanced across the treatment arms for all trials. The majority of the subjects were male (approximately 86%) and all subjects were Caucasian. The mean age of subjects was approximately 70 years (range 49 years to 87 years). Most subjects had moderate AK severity based on the Olsen scale (82%), Fitzpatrick skin type I, II or III (90%).The majority of subjects (72%) had the AK on the face and/or forehead.

For Trial 02, a total of 7 subjects (3%) in AMELUZ group, 8 subjects (11%) in Vehicle group, and 7 subjects (3%) in Metvix group discontinued the trial. For Trial 03, a total of 4 subjects (5%) in AMELUZ group, and 4 subjects (10%) in Vehicle group discontinued the trial. For Trial 07, 6 subjects (19%) in the Vehicle group discontinued the trial. The most common reason (for all three trial) was "subject's decision". One subject in the AMELUZ group (Trial 02) discontinued from the trial due to AR (application site pain and application site burning). Regarding the Trial 03 and 07, none of subjects in the AMELUZ group discontinued from the trial due to AE.

The primary analysis population for Trial 02 was the intent-to-treat (ITT) population, defined as "all randomized subjects and treated at least once with investigation product after randomization. Treatment with investigational product consists of "application of study drug followed by illumination". For Trial 03, the protocol specified that the Full Analysis Set (FAS) was the primary analysis set, and that the FAS was as close to the Intent-to-Treat principle as possible, defined as all subjects who received treatment and had at least one post-dose assessment of the clearance of the AK lesions in the target area of the primary variable. For Trial 07, a similarly defined analysis set as that in Trial 02, denoted as FAS, was the primary analysis set.

For the analysis of the primary endpoint, the protocol for Trial 02 specified using the Chi-square test with a two-sided significance level of 0.05. As randomization was not stratified by center, the applicant's approach was reasonable per the statistical review by Dr. Carin Kim. For Trials 03, the protocol specified using the CMH test stratified by site as the primary analysis method, and the protocol for Trial 07 specified using the Fisher's Exact test as the primary analysis method.

The primary efficacy endpoint for all three trials was the overall subject complete response assessed 12 weeks after the last PDT, and an overall complete responder was defined as a subject, in whom all treated lesions were cleared, including subjects receiving the second treatment, if necessary.

Efficacy results for the primary endpoint were statistically significant for all three trials (p-value<0.0001), as presented in tables 3, 4 and 5 below:

Table 3: Trial 02 - Complete clearance at 12 weeks after the last PDT by light source, lamp type, and PDT

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	Lamp Type	BF200ALA	Vehicle	Metvix
Narrow	Omnilux	32/35 (91%)	3/11 (27%)	23/31 (74%)
	1st PDT	17/36 (47%)	0/11 (0%)	9/31 (29%)
	2nd PDT	15/18 (83%)	3/11 (27%)	14/22 (63%)
	Aktilite	74/90 (82%)	2/28 (7%)	62/96 (65%)
	1st PDT	50/89 (56%)	0/28 (0%)	39/96 (41%)
	2nd PDT	23/39 (59%)	2/28 (7%)	23/57 (40%)
Broad	Waldmann	13/15 (87%)	0/3 (0%)	12/13 (92%)
	1st PDT	10/15 (67%)	0/3 (0%)	8/13 (62%)
	2nd PDT	3/5 (60%)	0/3 (0%)	4/5 (80%)
	Hydrosun Photodyn	75/108 (69%)	8/34 (24%)	61/106 (58%)
	1st PDT	43/108 (40%)	3/34 (9%)	35/106 (33%)
	2nd PDT	32/65 (49%)	5/31 (16%)	26/71 (37%)

Source: Statistical review : (1) Subject # 109/20 that received BF200ALA switched from Omnilux to Aktilite; Subject #109/10 that received Metvix switched from Omnilux to Waldmann; as the subject switched from narrow to broad, this subject was neither classified as "narrow" nor "broad". (p 13, Table 8)

For Trial 02, following the comparison of AMELUZ vs. Vehicle, if statistically significant, the applicant's testing hierarchy called for comparing the AMELUZ to Metvix using non-inferiority (NI) testing with the NI margin of 15%. However, it should be noted that Metvix was not used as per approved labeling (requires two PDTs, 1 week apart; with Aktilite CL128 lamp). In Trial 02, the PDT for Metvix included broadband (Waldmann, Hydrosun Photodyn lamps) as well as narrowband (Omnilux, Aktilite lamps) light sources, and those randomized to Metvix did not receive a 2nd PDT one week after the 1st PDT. Therefore, comparison of AMELUZ against Metvix would not be appropriate and has no regulatory utility.

As with Trial 02, in Trials 03 and 07, the treatment effects of the narrowband PDTs were higher than that of the broadband (Photodyn) PDT. The complete clearance rates at 12 weeks after the 1st PDT were similar to those after the 2nd PDT. Table 4 presents primary efficacy results for Trials 03 and 07.

Table 4: Trial 03 and Trial 07: Complete clearance at 12 weeks after the last PDT by light source, lamp type, and PDT

Trial 03				Trial 07		
		Ameluz N=81	Vehicle N=41		Ameluz N=55	Vehicle N=32
Complete Clearance		53 (65%)	5 (12%)	Complete Clearance	50/55 (91%)	7/32 (22%)
Light	Lamp			Light source		
Narrow	Aktilite	27/32 (84%)	2/16 (13%)	BF-RhodoLED	50/55 (91%)	7/32 (22%)
	1st PDT	22/32 (69%)	2/16 (13%)	*1st PDT*	34/55 (62%)	3/32 (9%)
	2nd PDT	5/10 (50%)	0/14 (0%)	*2nd PDT*	16/21 (76%)	4/29 (14%)
Broad	Photodyn	26/49 (53%)	3/25 (12%)			
	1st PDT	16/49 (33%)	2/25 (8%)			
	2nd PDT	10/33 (30%)	1/22 (5%)			

Source: Statistical review (p 15, Table 10)

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 Gel, 10% and a narrow band spectrum lamp. The efficacy results of Trial 02, 03 and 07 were represented in Table 5 below:

Table 5: Complete Clearance 12 Weeks After the Last Narrow Spectrum PDT in Subjects with Actinic Keratoses

	Narrow Spectrum PDT	
	AMELUZ	**Vehicle**
Trial 1	106/125 (85%)	5/39 (13%)
Trial 2	27/32 (84%)	2/16 (13%)
Trial 3	50/55 (91%)	7/32 (22%)

Subjects who achieved complete clearance 12 weeks after the last PDT entered a 6 to 12-month follow-up period. Eighty eight subjects (88/212; 42%) who were treated with AMELUZ Gel needed a second treatment. In Trials 02, 03, and 07, the subjects that received AMELUZ Gel with the narrowband PDTs and achieved complete clearance 12 weeks after the last PDT, had recurrence rates of 14%, 11%, 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 follow up period in subjects with completely cleared lesions 12 weeks after the last PDT.

Each Phase 3 trial listed several secondary endpoints including the proportion of subjects or AK lesions with complete clearance after each assessment, partial response assessed 12 weeks after the last PDT, overall cosmetic outcome after the last PDT, among other endpoints. However, for the analysis of the secondary endpoints, the list and the order of the secondary endpoints across the three Phase 3 trials were different, and given the lack of

multiplicity adjustment plan to control the Type I error rate in Trials 02 and 03, there was no replication of study findings for secondary endpoints across the three Phase 3 trials.

Subpopulation; Efficacy by Gender, Age and Race:
The majority of the subjects enrolled was male (86%), and of >65 of age (approximately 84%). Therefore, any differences in efficacy for the female subjects and ≤65 years of age subgroups would be difficult to detect. As all the subjects were Caucasian there was no subgroup analysis for race. Table 6 and Table 7 presents the complete clearance rate at 12 weeks after the last PDT by gender, and age subgroups by the respective light source (narrow vs. broad) for the PDT in Trial 02 and Trials 03 and 07 retrospectively.

Table 6: Trial 02: Complete Clearance at 12 weeks after the last PDT by gender, age groups

Trial 02				
Light Source		Ameluz N=248	Vehicle N=76	Metvix N=246(1)
Complete Clearance at Week 12 after the last PDT		194 (78%)	13 (17%)	158 (64%)
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: (1) Subject # 109/20 that received BF200ALA switched from Omnilux to Aktilite; Subject #109/10 that received Metvix switched from the Omnilux to the Waldmann lamp; ; as the subject switched from narrow to broad, this subject was neither classified as "narrow" nor "broad".

Table 7: Trial 03 and Trial 07: Complete Clearance at 12 weeks after the last PDT by gender, age groups

		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 (p 18, Table 14)

Additional Efficacy Issues/Analysis:
A collaborative review was done by Dr. Richard Feldman in CDRH to determine if the applicant has established an adequate bridge between the BF-RhodoLED lamp (Trial 07) and the other narrow band lamps, Omnilux EL1258S and Aktilite CL-128, which were used in the clinical trials 02 and 03. 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."

In summary, the applicant has established the efficacy of their product AMELUZ (5-aminolevulinic acid hydrochloride) Gel, 10% in the (b) (4) treatment of mild to moderate

actinic keratoses on the face and scalp in combination with photodynamic therapy using BF-RhodoLED lamp (narrowband, red light illumination source).

The reader is referred to the comprehensive statistical review and evaluation by Carin Kim, Ph.D. (Division of Biostatistics III) for a more complete discussion of the efficacy results (dated March 9, 2016).

8. Safety

The applicant submitted data from three pivotal trials, ALA-AK-CT002 (Trial 02), ALA-AK-CT003 (Trial 03), and ALA-AK-CT007 (Trial 07) to establish the safety of their product in the treatment of mild to moderate actinic keratoses on the face and scalp in combination with photodynamic therapy. Additional safety data are available from Trial ALA-AK-CT-006 (maximal PK trial), and dermal safety study (Trial ALA-AK-CT005). All of the trials were conducted with the final-to-be-marketed formulation.

Trials 02, 03 and 07 (integrated summary of safety) were multicenter, randomized, vehicle/active -controlled and parallel group trials in adult subjects with mild to moderate actinic keratoses (Olsen grade 1 and 2; with 4 to 8 lesions) on the face and scalp. Overall, 87 subjects who received Vehicle [Trial 02 (n=16, Trial 03 n=32, Trial 07 n=39) and 212 subjects who received treatment with AMELUZ Gel, 10% (Trial 02 n=32, Trial 03 n=55, and Trial 07 n=125] were illuminated with BF-RhodoLED® or similar narrow spectrum lamps.

There were no deaths reported, and no serious adverse events (SAE) attributable to AMELUZ/PDT. One subject in the AMELUZ Gel group discontinued because of treatment related AE (application site pain and application site burning).

Local skin reactions at the application site were observed in about 99.5% of subjects treated with AMELUZ Gel, 10% and narrow spectrum lamps. The most frequent adverse reactions during and after PDT were application site erythema (92% AMELUZ arm; 39% Vehicle arm), pain (92% AMELUZ arm; 30% Vehicle arm), burning (68% AMELUZ arm; 14% Vehicle arm), irritation (72% AMELUZ arm; 20% Vehicle arm), edema (35% AMELUZ arm; 3% Vehicle arm), pruritus (34% AMELUZ arm; 16% Vehicle arm), exfoliation (19% AMELUZ arm; 5% Vehicle arm), scab (19% AMELUZ arm; 2% Vehicle arm), induration (12% AMELUZ arm; 0% Vehicle arm) and vesicles (12% AMELUZ arm; 1% Vehicle arm).

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 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 in AMELUZ Gel, 10 group 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.

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.

Dermal safety study:

In a clinical trial (Trial ALA-AK-CT005) 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.

Post marketing Data

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 applicant assessed that 185 of these events a causal relationship to AMELUZ could be suspected. The majority of the cases were localized to the treatment area: erythema and pain have been the most common reported related adverse events. Less frequent events were exfoliation, erosion, scab, pustules, edema, hemorrhage, inflammation, application site reactions, application site swelling, vesicles and skin discoloration. At non-application sites there have been reports of blister, eyelid edema, erythema, pain, pyrexia, and swelling. There have been very occasional reports of eye disorders including eye irritation, diplopia, ocular hyperemia, photophobia, and blurred vision. The relevant post-marketing adverse events that can be classified as adverse reactions will be added to the post-market experience section of labeling.

The reader is referred to the clinical review by Dr. Denise Cook, MD for a comprehensive discussion of the safety database (March 22, 2016)

No postmarketing commitments or requirements to address safety concerns are warranted.

9. Advisory Committee Meeting

No Advisory Committee Meeting was held as the application did not raise controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

Actinic keratoses are caused by chronic ultraviolet radiation exposure and occur almost exclusively in adults. The applicant requested a waiver for all pediatric age groups on the grounds that pediatric studies would be impossible or highly impracticable because there are too few children with the disease/condition to study. The application was presented to the Pediatric Review Committee (PeRC) on December 2, 2015. The committee concurred with the Division's recommendation to grant a complete pediatric waiver for ages 0 to 16 years 11 months because rosacea is rare in pediatric population.

11. Other Relevant Regulatory Issues

The Division of Medication Error Prevention and Analysis, Office of Medication Error Prevention and Risk, reviewed the proposed proprietary name, AMELUZ, and concluded that it is conditionally acceptable. This was communicated to the applicant in a letter dated November 15, 2015.

A total of three investigator sites were inspected in support of this NDA. No deficiencies were found that would preclude reliance upon the data that was submitted. The reader is referred to the Clinical Inspection Summary by Roy Blay, Ph.D.; Good Clinical Practice Assessment Branch; Division of Clinical Compliance Evaluation; Office of Scientific Investigations; dated March 4, 2016.

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

- Deficiencies were identified during the documentation review. Additional information from the firm is needed to complete the documentation review.
- 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

At the completion of this review, this issue is still outstanding. The reader is referred to the review by Crystal Lewis, CDRH; DMQ dated March 11, 2016.

12. Labeling

The applicant submitted proposed labeling in the format that complies with the Physicians' Labeling Rule. Professional and patient labeling were reviewed, and negotiations regarding their content are ongoing at the time of close of this review.

Significant changes incorporated into revised draft labeling, following labeling review, include:

- Revision to the applicant's proposed Section **8 USE IN SPECIFIC POPULATIONS** (Nonclinical Pharmacology/Toxicology recommendation regarding labeling: see section 4 of this review)
- Revision to the applicant's proposed Section **12. CLINICAL PHARMACOLOGY** (Clinical pharmacology recommendation regarding labeling: see section 5 of this review)
- Revision to the applicant's proposed Section **13 NONCLINICAL TOXICOLOGY** (Nonclinical Pharmacology/Toxicology recommendation regarding labeling: see section 4 of this review)
- Revision to the applicant's proposed Section **14 CLINICAL STUDIES**

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

- Tentative Approval
  - In principle, I concur with the recommendations of the multi-disciplinary review team for approval of NDA 208081, AMELUZ (5-aminolevulinic acid hydrochloride) Gel, 10% in combination with photodynamic therapy (PDT) using BF-RhodoLED lamp in in conjunction with lesion preparation in the physician's office for the treatment of mild to moderate actinic keratoses on the face and scalp pending agreement of the applicant with the recommended labeling revisions , *"Approval"* recommendation from the Office of Process and Facilities regarding facilities inspections for the drug product and *"Approval"* recommendation CDRH, Office of Compliance, Division of Manufacturing & Quality (DMQ).

Risk Benefit Assessment

- The risk-benefit assessment supports approval of this product for the treatment of actinic keratoses

Recommendation for Postmarketing Risk Evaluation and Management Strategies

- Postmarketing risk management beyond professional labeling, prescription status and routine pharmacovigilance is not needed.

Recommendation for other Postmarketing Requirements and Commitments:

- None

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/s/

GORDANA DIGLISIC
03/30/2016