CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208081Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA #:	208081
Submission Date:	July 10, 2015
Brand Name:	Ameluz®
Generic Name:	5-aminolevulinic acid hydrochloride 10% Gel with BF-RhodoLED® lamp
Dosage Form:	Gel
Dosage Strength:	10% Gel
Reviewer:	Chinmay Shukla, Ph.D.
Team Leader:	Doanh Tran, Ph.D.
OCP Division:	DCP-3
OND Division:	Division of Dermatology and Dental Products
Sponsor:	Biofrontera Bioscience GmbH
Relevant IND(s):	115412
Submission Type:	New-submission
Indication:	Treatment of actinic keratosis of mild to moderate severity on the face and scalp (b) (4)

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1. Executive Summary

The applicant has submitted this NDA for BF-200 ALA 10% (Ameluz®), which is a non-sterile topical formulation of 10% 5-aminolevulinic acid (5-ALA) hydrochloride (equaling 7.8% of free acid) in a gel-matrix with nanoemulsion. The BF-200 ALA 10% gel will be used in combination with red-light photodynamic therapy (PDT) performed with BF-RhodoLED® lamp for the (b) (4) treatment of actinic keratosis (AKs) of mild to moderate severity on the face and scalp. 5-ALA is an endogenous substance and is a pro-drug. 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 destroys the cells producing drug effect. This product is intended as a single

dose treatment to occur in the clinician's office. Treatment could be repeated after 3 months if treated lesions have not resolved completely.

This product is considered as a drug-device combination by the Agency. The applicant has proposed to use a 505(b)(1) regulatory pathway.

Reviewer comments: *The terms 5-aminolevulinic acid (5-ALA) and aminolevulinic acid (ALA) have been used interchangeably by the applicant and also in this review. Both terms mean the same thing.*

In order to support this NDA the applicant has conducted the following clinical trials:

- ALA-AK-CT-005: Skin sensitization potential of BF-200 ALA 10%
- ALA-AK-CT-006: Maximal use pharmacokinetics (PK) trial
- ALA-AK-CT-007: Phase III efficacy and safety trial
- ALA-AK-CT-003: Phase III efficacy and safety trial
- ALA-AK-CT-002: Phase III efficacy and safety trial including an active control arm (Metvixia®)
- ALA-AK-CT-001: Phase IIb dose finding study

1.1 Recommendation

From a Clinical Pharmacology standpoint, this application is acceptable provided the labeling comments are adequately addressed by the applicant.

1.2 Post-Marketing Requirements/Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

Pharmacokinetics:

The applicant assessed PK of 5-ALA and PpIX via serial sampling in the maximal use PK trial (ALA-AK-CT-006) and in Phase IIb dose finding study (ALA-AK-CT-001). The Phase IIb trial was not conducted with the to-be-marketed formulation and light source and was not reviewed in detail.

The maximal use PK trial enrolled 12 adult subjects with at least 10 mild or moderate AK lesions on the face and forehead. The clinical staff applied 2 g of vehicle gel or BF-200 ALA 10% gel (1 tube) at a thickness of about 1 mm to the lesions and the surrounding areas covering approximately 20 cm^2 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/cm^2). 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 BF-200 ALA 10% gel. The same AK lesions/areas were treated in both periods.

Systemic concentrations of 5-ALA were quantifiable in all subjects. The mean ± SD baseline concentrations of 5-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 5-ALA were similar compared to baseline. After application of BF-200 ALA 10% gel, the mean plasma concentrations of 5-ALA increased compared to baseline and the baseline corrected mean ± SD C_{max} (maximum concentration), AUC_{0-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 AUC_{0-t} in the single subject was 0.29 ng/mL and 0.07 ng*h/mL, respectively.

Drug formulation and light source: The applicant made changes to the formulation during development and the Phase IIb dose finding study was conducted using old formulation. The maximal use PK trial and the 3 Phase III safety and efficacy trials were conducted with the to-be-marketed formulation of BF-200 ALA 10%, gel. The maximal use PK trial was also conducted with the to-be-marketed light source. Only one Phase III trial (ALA-AK-CT-007) was conducted with the to-be-marketed light source. Information about the changes in the formulation is provided in Section 2.6.2 in this review. See Clinical review for information on comparability of different light sources used in the different clinical trials.

Drug interaction assessment: The applicant has not conducted any drug-drug interaction (DDI) assessment and in this case. DDI assessment is not needed because this is a single dose treatment only to be repeated after 3 months if treated lesions have not resolved completely; hence drug interaction potential is expected to be limited. In addition, the drug substance ALA is an endogenous substance and exogenous application of BF-200 ALA 10% gel resulted relatively small increase (~2.5 fold) in mean systemic 5-ALA concentration for a duration of up to approximately 6 hours. Therefore, drug interaction assessment is not warranted.

Pediatric assessment: The applicant has requested a full waiver for pediatric assessment in subjects 0 to 16 years and 11 months of age due to low prevalence of AK in this age group. This application was reviewed by the Pediatric Review Committee (PeRC) on December 02, 2015 and the PeRC agreed to the waiver request (see meeting minutes in DARRTS dated December 15, 2015).

Clinical Pharmacology Briefing: An Optional Intra-Division Level Clinical Pharmacology briefing was held on March 02, 2016 with the following in attendance: CAPT. E. Dennis Bashaw, Doanh Tran, Yanhui Lu and Chinmay Shukla.

2. Question Based Review

2.1 General Attributes

2.1.1 What regulatory pathway has the Applicant followed?

This product is considered as a drug-device combination by the Agency. The applicant has proposed to use a 505(b)(1) regulatory pathway.

Reviewer Comments: *In the United States, the following 2 photodynamic therapies are approved for the treatment of AK:*

NDA No.	*Approval Date*	*Brand Name*	*Active Ingredient*	*Light to be used*
(b) (4)	12/03/1999	Levulan® 20% Solution	Aminolevulinic acid HCl	Blue light (BLU-U)
021415	07/27/2004	Metvixia® 16.8% Cream	Methyl aminolevulinate	Red light (Aktilite CL 128)

Both aminolevulinic acid HCl and methyl aminolevulinate are prodrugs and are converted into their active form called Protoporphyrin IX (PpIX) in the body. Aminolevulinic acid is an endogenous substance produced as the 1st compound in the porphyrin synthesis pathway which produces heme (the pigment in red blood cells).

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation?

Drug substance and Formulation: BF-200 ALA 10% gel is a non-sterile (b) (4) (b) (4) nanoemulsion gel formulation containing 10% of 5-aminolevulinic acid hydrochloride (ALA.HCl) (equal to 7.8% of the 5-aminolevulinic acid as free acid). The gel is packaged in a (b) (4) aluminum tube and the nominal content of each tube is 2 g. The qualitative and quantitative composition of the formulation is given in the Table 1 below and the structural formula of ALA.HCl (molecular weight = 167.59) is shown in Figure 1 below.

Figure 1: Structural formula of 5-aminolevulinic acid hydrochloride

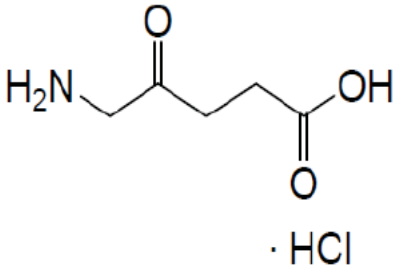


Table 1: Composition of BF-200 ALA 10% gel

Components	Amount per 1 gram [mg]	Amount per percentage [%]	Function	Quality standards
5-Aminolevulinic acid hydrochloride	100.000	10.000	Drug substance	In-house
Xanthan gum	[redacted] (b) (4)			Ph.Eur / USP-NF
Soybean phosphatidylcholine				In-house / DMF [redacted] (b) (4)**
Polysorbate 80				Ph.Eur / USP-NF
Triglycerides, medium-chain				Ph.Eur / USP-NF
Isopropyl alcohol				Ph.Eur / USP-NF
[redacted] (b) (4)				Ph.Eur / USP-NF
				Ph.Eur / USP-NF
Propylene glycol				Ph.Eur / USP-NF
Sodium benzoate				Ph.Eur / USP-NF
Purified water				Ph.Eur / USP-NF
Total	1g	100%		

* current edition of the respective pharmacopoeial monograph
** related to [redacted] (b) (4)

Reviewer comments: *The applicant changed the formulation after the Phase IIb dose finding trial. Details about the formulation changes are provided in section 2.6.2 in this review.*

Light source: To be marketed light source (BF-RhodoLED®- a red light source with a narrow spectrum around 635 nm) was used in the maximal use PK trial (ALA-AK-CT-006) and one of the Phase III trials (ALA-AK-CT-007). For further information on the different light sources used in the development program, see Section 2.3.1 and see Clinical review for further information on comparability between different light sources.

2.1.3 What are the proposed mechanism of action and the therapeutic indications?

Mechanism of action: Photoactivation following topical application of 5-aminolevulinic acid (prodrug) occurs as the substance is metabolized to 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. In the presence of oxygen, reactive oxygen species are formed which causes damage to cellular components, and eventually destroys the cells.

Therapeutic indication: AMELUZ® in combination with red light photodynamic therapy (PDT) using the BFRhodoLED® lamp, is indicated for [redacted] (b) (4) treatment of actinic keratosis (AKs) of mild to moderate severity on the face and scalp [redacted] (b) (4)

2.1.4 What is the proposed route of administration and dosage?

Proposed route of administration: Topical

Proposed dosage: Apply AMELUZ®gel approximately 1 mm thick to cover the single lesions or the entire cancerized field and approximately 5 mm of the surrounding skin. 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.

2.2 General Clinical Pharmacology

2.2.1 What are the clinical trials conducted to support this application?

Summary of clinical trials conducted to support this application are shown in Table 2.

Table 2: Summary of clinical 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-CT005 - Germany - 2 centers 13Jun2013-19Oct2013	To investigate the skin sensitization potential of Ameluz® (BF 200 ALA 10%) and its vehicle after repeated topical application in male and female subjects aged 18 to 85 years with healthy skin.	Phase I, two-center, randomized, double-blind 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
ALA-AK-CT006 - Germany - 1 center 11Jul2013-16Dec2013	To obtain baseline-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 forehead 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, intra-individual comparison study.	- BF-200 ALA 10% - Vehicle (BF-RhodoLED®, 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 cm^2 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-CT007 Germany -7 centers 27Aug2013-24Apr2015	The primary objective was to compare the efficacy of BF-200 ALA with placebo, for the field-directed treatment of AK with PDT. Patients with 4 to 8 AK	Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-	- BF-200 ALA 10% - Placebo/ vehicle (BF-RhodoLED®	Up to two PDTs. Twelve weeks after the first PDT, non-responders or partial responders were to be retreated.	87 / 84

Study Number, Location	Study Objective - Main inclusion criteria	Study design	IMPs (PDT lamp)	Duration of Treatment and follow-up	N Enrolled/ planned
Completed (data analyses of follow-up ongoing)	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.	group (2:1 ratio) study.	,635 nm).	Follow-up was 6 and 12 months after last PDT.	
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 [a] on the face or bald scalp.	Phase III, randomized, double-blind, placebo-controlled, inter-individual, 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-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 a on the face or bald scalp.	Phase III, randomized, multinational, reference therapy controlled 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-CT001 Germany - 13 centers 27Oct2006- 12Mar2007 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	Phase IIb, randomized, double-blind, placebo-controlled multicenter study with adaptive design c.	- ALA 1% - ALA 3% - ALA 10% - Vehicle (Waldmann® 600 - 750 nm, (PhotoDyn® 505, 580 –	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

Study Number, Location	Study Objective - Main inclusion criteria	Study design	IMPs (PDT lamp)	Duration of Treatment and follow-up	N Enrolled/ planned
	the treatment of AK. Patients with 3 to 10 AK target lesions 0.5 to 1.5 cm diameter of mild to moderate intensity a on the face or bald scalp.		1400 nm)		

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

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

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

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

2.2.2 What are the design features of the clinical pharmacology studies and what were the pharmacokinetic (PK) results?

The systemic exposure of ALA and PpIX was assessed in 2 studies as shown below.

- Phase I maximal use PK trial (ALA-AK-CT006)
- Phase IIb dose finding study (ALA-AK-CT001)

Phase I maximal use PK trial (ALA-AK-CT006): This was a single center, non-randomized, open-label, placebo-controlled, fixed-sequence Phase I study to evaluate the pharmacokinetics (PK) of ALA and PpIX in subjects with AK following topical application of a gel formulation containing 78 mg/g ALA (BF-200 ALA, brand name Ameluz®) under maximal use conditions when using photo dynamic therapy (PDT).

Study design and number of subjects: 12 adult subjects with at least 10 mild or moderate AK lesions on the face and forehead were studied. After preparation of lesional skin by removal of scales and crusts and gentle roughening and degreasing of the skin surface with an isopropanol soaked cotton pad, 2 g of vehicle gel or BF-200 ALA 10% gel (1 tube) was applied at a thickness of about 1 mm to the lesions and the surrounding areas covering approximately 20 cm², and covered with an occlusive dressing for about 3 hours. After 3 hours, the remaining gel was removed and the treatment area was subsequently 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 first, and after a wash-out period of 7 days, the subject received a second PDT treatment with BF-200 ALA 10% gel. The same lesions/areas were treated in both periods.

The study was performed in 2 phases: a pilot phase with 3 subjects and additional 9 subjects were treated in the main phase. 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 or Ameluz® gel application but before starting illumination and at 3.5, 4, 5, 6, 8, 10, 12 and 24 h after start (t = 0 h) of placebo or Ameluz® application. Plasma concentrations of ALA and PpIX were used for obtaining baseline corrected plasma concentrations-time curves and calculation of the PK parameters.

Reviewer comments: *The trial enrolled only subjects having at least 10 AK lesions on face or forehead with a total topical treatment area of approximately 20 cm^2 (including at least 5 mm side margin of each lesion). As per the applicant, the size of the treatment area roughly corresponded to the maximal area that can be treated with a single package (2 g tube) of Ameluz® gel.*

The Phase 3 trials (ALA-AK-CT007, ALA-AK-CT003 and ALA-AK-CT002) applied one 2 g tube of gel to an area of 20 cm^2 in subjects with mild to moderate AKs with at least 4 to 8 lesions. Hence the design of the maximal use trial compliments the Phase 3 trials in terms of number of AK lesions treated and the total amount of gel used.

PK results: All subjects showed 5-ALA concentrations above LLOQ at all sampling time points. The mean ± SD baseline concentration of ALA was 20.16 ± 16.53 ng/mL. After application of the vehicle gel, the mean plasma concentrations of ALA were similar compared to baseline. However, after application of BF-200 ALA gel, the mean plasma concentrations of 5-ALA increased compared to baseline. The summary of PK parameters is shown in Table 3 below.

Table 3: Summary of baseline corrected PK parameters of 5-ALAfollowing application of Ameluz® Gel (Total number of subjects = 12)

Statistical parameter	AUC_{0-t} (h*ng/mL)	C_{max} (ng/mL)	t_{max} (ng/mL)
No. of subjects	11	11	11
Mean	142.83	27.19	2.96
SD	75.50	20.02	0.41
Median	171.58	22.89	3.00
Minimum	33.20	4.76	2.50
Maximum	269.44	77.53	3.50

Reviewer comments: *In one subject (19004) the baseline concentrations of ALA was 3 fold higher in the second period (Ameluz® gel treatment) compared to first period (Placebo gel treatment). The reason for this increase in baseline values could not be explained. The baseline corrected concentrations of 5-ALA for subject 19004 resulted in negative values and hence mean PK parameters could be estimated only in 11 subjects.*

Figures 2 and 3 show the baseline uncorrected and baseline corrected concentration versus time profiles of 5-ALA after application of Ameluz and placebo gel

Figure 2: Baseline uncorrected mean plasma concentration-time profile of 5-ALA after application of Ameluz® gel and placebo gel (LLOQ = 1 ng/mL)

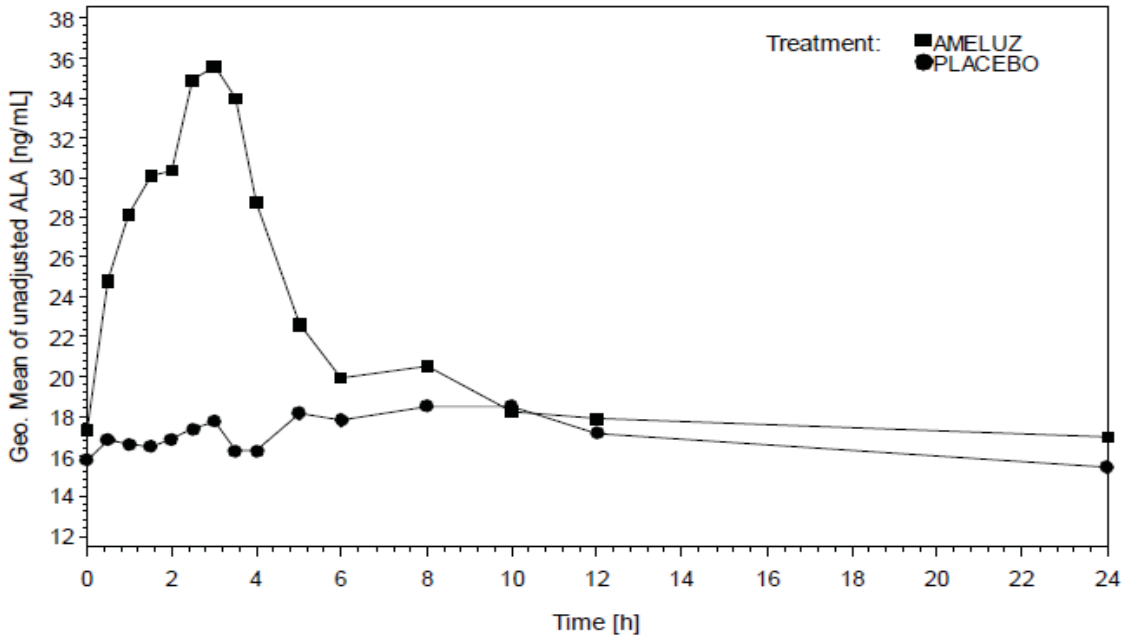
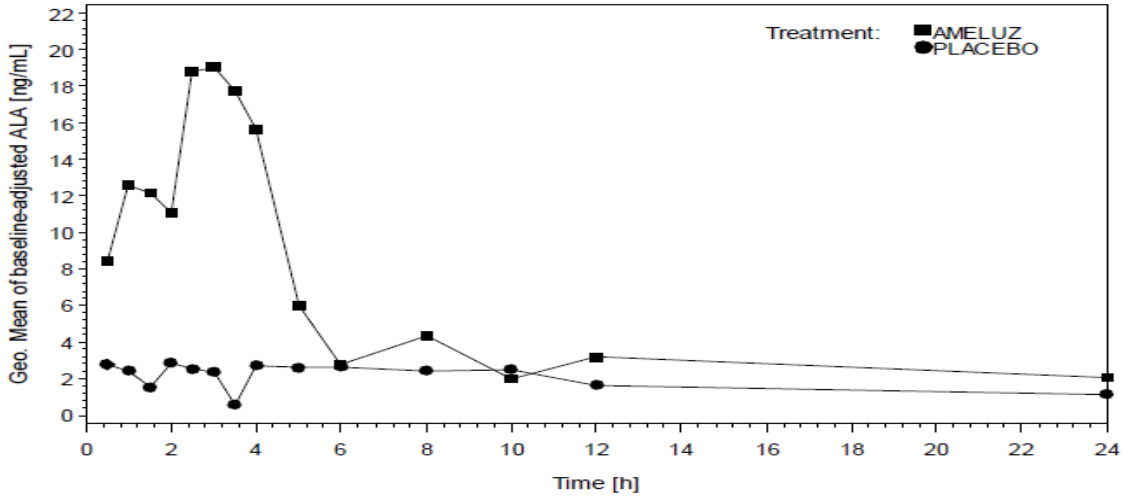
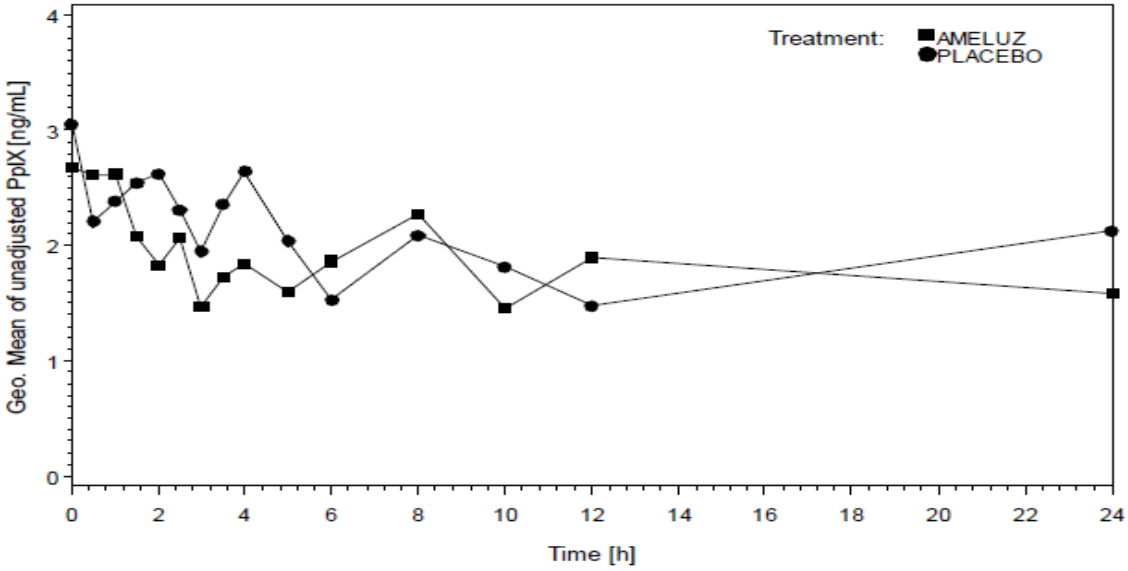


Figure 3: Baseline corrected mean plasma concentration-time profile of 5-ALA after application of Ameluz® gel and placebo gel (LLOQ = 1 ng/mL)



The concentrations of PpIX were generally low in all subjects. In none of the subjects, an increase of PpIX plasma concentrations was observed after application of BF-200 ALA compared to baseline. The mean ± SD baseline PpIX concentration was 3.27 ± 2.40 ng/mL. Baseline corrected PK parameters could not be reliably estimated in most of the subjects due to negative PpIX concentration values. The baseline corrected C_{max} and AUC_{0-t} could be estimated only in one subject and the values were 0.29 ng/mL and 0.07 ng*h/mL, respectively. Figure 4 shows baseline uncorrected concentration versus time profile for PpIX. Baseline corrected concentration versus time profile could not be produced due to negative values of baseline corrected concentrations.

Figure 4: Baseline uncorrected mean plasma concentration-time profile of PpIX after application of Ameluz® gel and placebo gel (LLOQ = 1 ng/mL)



Reviewer comments: *Looking at the concentration versus time profiles of placebo, there appears to be no circadian rhythm in the baseline profiles of 5-ALA and PpIX.*

PK assessment following application to the scalp: The applicant has not assessed PK following application to the scalp. Application to the scalp might result in an increase in systemic exposure. However, because of several reasons, namely (1) The systemic exposure increase relative to endogenous concentration observed with application to the face was small and limited to about 6 hours duration, (2) Lack of systemic safety signals following drug application to the scalp and face in the Phase III trials, and (3) Lack of any systemic safety concerns based on animal toxicity data (see Pharmacology-Toxicology review for further details), requiring the conduct of a maximal use PK assessment following application to the scalp as a Post Marketing Requirement (PMR) is not warranted.

Phase IIb dose finding study (ALA-AK-CT001): This was a Phase II dose-ranging study in subjects with AK.

Study design: In this randomized, placebo-controlled, double-blind study, BF-200 ALA gel (old formulation) was administered at concentrations of 1, 3, or 10% and compared to vehicle. Incubation time was 3 h. A total of 105 adult subjects with AK were enrolled and PK evaluation was performed in a subset of 26 subjects (n= 5-7 subjects per gel concentration). Plasma PK samples were obtained at baseline and 3 h and 24 h after the start of the incubation. In addition, urine was collected for a period of 24 h before start of treatment and for 24 h following drug application. Concentrations of 5-ALA and its metabolite PpIX, were determined in plasma; urinary excretion was determined for 5-ALA only.

PK results: 5-ALA and PpIX in human plasma were analyzed by a validated HPLC method. Due to low systemic concentrations, plasma samples had to be reassessed after spiking with 5-ALA and PpIX, respectively, to obtain quantifiable values (standard addition method).

Reviewer comments: *The bioanalytical method used to analyze PK samples from this trial was different as compared to maximal use PK trial. HPLC with fluorescence detection was used to quantify 5-ALA concentrations (LLOQ = 10 ng/mL) and HPLC with mass spectrometry was used to quantify PpIX plasma concentrations (LLOQ = 5 ng/mL); while LC MS/MS was used to quantify 5-ALA (LLOQ = 1 ng/mL) and PpIX (LLOQ = 1 ng/mL) concentrations in the maximal use PK trial. Furthermore, the formulation used in this trial was not the to-be-marketed formulation (see Section 2.6.2 for further details on formulation modifications). In addition to the above, because of spiking of samples with 5-ALA and PpIX, the PK results from this trial are not considered reliable and hence not discussed in this review. Due to the aforementioned reasons, the results of this trial will have little impact on regulatory decision and hence this trial is not reviewed in detail in this submission.*

2.2.3 Did the applicant assess drug metabolism?

The applicant has not conducted any new drug metabolism studies because the metabolic fate of endogenous ALA is well known. The applicant has provided the following information about the metabolic fate of ALA based on published literature. Enzyme aminolevulinic acid dehydratase (ALAD) condenses 2 molecules of ALA to form the monopyrrole porphobilinogen (PBG). Enzyme PBG deaminase catalyzes the polymerization of four molecules of PBG to hydroxymethylbilane. Hydroxymethylbilane is further metabolized to uroporphyrinogen I and III (by enzyme uroporphyrinogen cosynthase). Uroporphyrinogen decarboxylase sequentially removes a carboxylic group from the acetic side chains of each of the pyrrole rings to yield coproporphyrinogen. Coproporphyrinogen oxidase removes a carboxyl group from the propionic groups on 2 of the pyrrole rings to yield protoporphyrinogen IX. Enzyme protoporphyrinogen oxidase forms PpIX by removing 6 hydrogen atoms from protoporphyrinogen IX.

Reviewer comments: *The applicant has assessed PK of metabolite PpIX in the maximal use PK trial.*

2.2.4 What is the summary of efficacy?

The summary of efficacy from the 3 Phase III trials is shown in Table 4. The primary endpoint was complete clearance by PDT. See Clinical review for further details.

Table 4: Complete patient clearance by PDT in the 3 Phase III trials

	Number (%) of subjects	
Treatment Group	**Narrow Spectrum PDT**	**Broad Spectrum PDT**
ALA-AK-CT002		
AMELUZ®	106/125 (84.8)	88/123 (71.5)
Metvixia®	85/126 (67.5)	73/119 (61.3)
Vehicle	5/39 (12.8)	8/37 (21.6)
ALA-AK-CT003		
AMELUZ®	27/31(87.1)	26/49 (53.1)
Vehicle	2/15 (13.3)	3/25 (12.0)
ALA-AK-CT007		
AMELUZ®	50/55 (90.9)	Not applicable
Vehicle	7/32 (21.9)	Not applicable

2.2.5 What is the summary of safety?

The clinical program for Ameluz® included 3 Phase III studies enrolled a total of 780 subjects with mild to moderate AKs (with 4 to 8 lesions) on the face and scalp. Overall, 87 placebo-treated subjects and 212 Ameluz® treated subjects were illuminated with BF-RhodoLED® or similar narrow spectrum lamps in the 3 Phase III trials studies (ALA-AKCT003, ALA-AK-CT007 and ALA-AK-CT002). The rest of the subjects were

illuminated with lamps having a broader light spectrum. The summary of safety provided below is for the 212 subjects treated with Ameluz® in the 3 Phase III trials who 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, irritation, edema, pruritus, exfoliation, scab, induration and vesicles. Most adverse reactions occurred during illumination or shortly afterwards, and as per the applicant they were generally of mild or moderate intensity, and lasted for 1 to 4 days in most cases. In some cases, the local skin reactions persisted for 1 to 2 weeks or even longer. In rare cases, the adverse reactions required interruption or discontinuation of the illumination. There were no major systemic adverse events reported except for headache and chills. For further information, see Clinical review.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

2.3.1.1 Effect of age and gender on PK

The applicant has not evaluated the effect of age and gender on the PK of ALA and PpIX.

2.3.2 Pediatric subjects

The applicant has requested a full waiver for pediatric assessment in subjects 0 to 16 years and 11 months of age due to low prevalence of AK in this age group. This application was reviewed by the Pediatric Review Committee (PeRC) on December 02, 2015 and the PeRC agreed to the waiver request (see meeting minutes in DARRTS dated December 15, 2015).

2.3.3 Renal and hepatic impairment

The effect of renal and hepatic impairment on PK of ALA and PpIX was not evaluated by the applicant

2.3.4 What pregnancy and lactation use information is there in the application?

The applicant has not conducted any trials in pregnant and lactating women.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or response and what is the impact of any differences in exposure or response?

The influence of extrinsic factors on dose-exposure and/or response was not evaluated by the applicant.

2.4.2 Drug-drug interactions

The applicant has not conducted any new drug interaction studies with this NDA. This product is intended to be used as a single dose application, to be repeated after 3 months only if needed; hence drug interaction potential is expected to be limited. In addition, the drug substance ALA is an endogenous substance and exogenous application of BF-200 ALA 10% gel resulted relatively small increase (~2.5 fold) in mean systemic ALA concentration for a duration of up to approximately 6 hours. Therefore, drug interaction assessment is not warranted.

2.5 General Biopharmaceutics

2.5.1 Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

The concept of BCS classification does not apply to topically applied products.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

To-be-marketed formulation was used in the maximal use PK trial (ALA-AK-CT006) and the 3 Phase III trials. Hence relative bioavailability assessment is not needed. Details about the formulations used in the clinical trials are provided below.

Formulation: During development the BF-200 ALA 10% formulation used in the Phase IIb trial (ALA-AK-CT001) was modified prior to the start of Phase III trials. Specifically the modification involved a change in (b) (4)

(b) (4)

Table 6: Summary of the formulations used during development

Formulation	Nonclinical studies		Clinical trials
BF-200 ALA 10% gel (Formulation A)	• ALA-AK-PT001 • ALA-AK-PT002[a] • ALA-AK-PT005 • ALA-AK-PT007[a] • ALA-AK-PT009[a]	Dermal tolerance study Human skin penetration study Human skin penetration study Sensitization study LLNA Mouse skin penetration study	• ALA-AK-CT001 [a] (phase IIb study)
BF-200 ALA 10% gel (Formulation B)	• ALA-AK-PT009 • ALA-AK-PT012 • ALA-AK-PT013 • ALA-AK-PT014 • ALA-AK-PT017 • ALA-AK-PT018[b] • ALA-AK-PT019[b] • • ALA-AK-PT027 • ALA-AK-PT029[b] • • ALA-AK-PT030[b] • ALA-AK-PT037	Mouse skin penetration study Dermal tolerance study Skin sensitization study (LLNA) Pig skin penetration study Repeat-dose toxicology and tolerability study in minipigs Dermal tolerance study Skin sensitization study (LLNA) Ocular tolerance study Skin sensitization study (LLNA) Dermal tolerance study Human skin penetration study	• EudraCT no 2007-006854-24 (ALA-AK-CT002; phase III study, completed) • EudraCT no 2007-003371-39 (ALA-AK-CT003, phase III study, completed) • udraCT no 2013-000230-35 (ALA-AK-CT005, phase I study) • EudraCT no 2013-000339-28 (ALA-AK-CT006 phase I study) • EudraCT no: 2013-002510-12 (ALA-AK-CT007, phase III study, completed) • EudraCT no 2013-003241-42 (ALA-BCC-CT008, ongoing)

[a]: In these studies 1% and 3% ALA gel formulations were tested in addition to the BF-200 ALA 10% gel.
[b]. Qualification of impurities using stressed gel (Module 2.6.6)
LLNA: local lymph node assay

2.5.3 What data support or do not support a waiver of in vivo BE data?

The to-be-marketed formulation was used in the maximal use PK trial (ALA-AK-CT006) and the 3 Phase III trials (ALA-AK-CT002, ALA-AK-CT003 and ALA-AK-CT007).

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Effect of food on the BA is not evaluated for topical formulations.

2.6Analytical Section

2.6.1 How are the active moieties identified, and measured in the clinical trials?

ALA and PpIX concentrations in the plasma samples of the maximal use PK trial (ALA-AK-CT006) were analyzed using high performance liquid chromatography and tandem mass spectrometry (LC-MS/MS).

2.6.2 Which metabolites have been selected for analysis and why?

PpIX was the metabolite selected for analysis because ALA is a pro-drug which is metabolized into PpIX. During photodynamic therapy PpIX is activated resulting in an excited state of porphyrin molecules which are responsible for drug activity.

2.6.3 For all moieties measured, is free, bound, or total measured?

Total concentration was measured.

2.6.4 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The range of standard curve was:

- For 5-ALA: 1 ng/mL to 100 ng/mL
- For PpIX: 1 ng/mL to 100 ng/mL

ALA plasma concentrations in the maximal use PK trial were within the range of the assay. Plasma PpIX concentration were measurable in approximately 45% of the plasma samples and in approximately 55% of the samples the PpIX concentrations were below the LLOQ of the assay.

2.6.5 What are the accuracy and precision at LLOQ?

Analyte	**Inter-Day**		**Intra-Day**	
	Accuracy	***Precision***	***Accuracy***	***Precision***
5-ALA	-8.4%	9.9%	-15.5%	9.9%
PpIX	4.1%	15.0%	5.6%	18.8%

Reviewer comments: *The quality control (QC) concentrations for 5-ALA were 3, 10, 32.5 and 77.5 ng/mL and for PpIX were 2, 23 and 80 ng/mL. The inter-day and intra-day precision and accuracy for the QC samples were all within ±15% acceptable limit.*

2.6.6 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler, etc.)?

Parameter	***5-ALA***	***PpIX***
Freeze/Thaw cycle stability	10 cycles at - 20ºC	3 cycles at - 20ºC
Room temperature stability	24 hours	6 hours
Auto-sampler stability	64 hours at 4 ºC	55 hours at 4 ºC
Long term stability	15 months at - 20 ºC	3.5 months at - 20 ºC

Reviewer comments: *The duration of long term PK sample stability was adequate to cover the duration of PK sample storage for the maximal use PK trial.*

2.6.7 What are the results of incurred sample reanalysis (ISR)?

36 plasma samples of 5-ALA (10% of the total samples) were selected for incurred sample reanalysis. The results showed that 88.9% samples met the ISR requirements. ISR for PpIX was not performed.

3. Detailed Labeling Recommendations

The following changes are recommended in the Sponsor's proposed labeling. The **bold and underlined** text indicates insertion recommended by the reviewer and the ~~strikethrough~~ text indicates recommended deletion.

1. INDICATIONS AND USAGE

AMELUZ®, in combination with (b) (4) photodynamic therapy (PDT) using (b) (4) BFRhodoLED® lamp, is indicated for (b) (4) treatment of actinic keratosis (AKs) of mild to moderate severity on the face and scalp (b) (4)

2. DOSAGE AND ADMINISTRATION

(b) (4)

2.1 Preparation of Lesions

Before applying AMELUZ®, (b) (4) with an ethanol or isopropanol-soaked cotton pad to ensure degreasing of the skin.

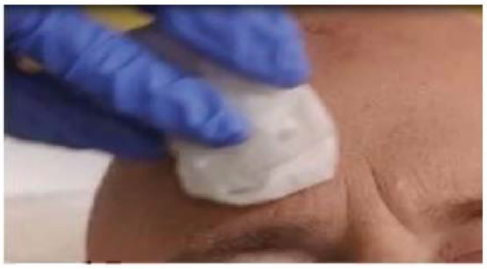


Figure 1A: Degreasing (b) (4) the skin

Thereafter, remove any scaling and crusts and gently roughen all lesion surfaces, taking care to avoid bleeding.

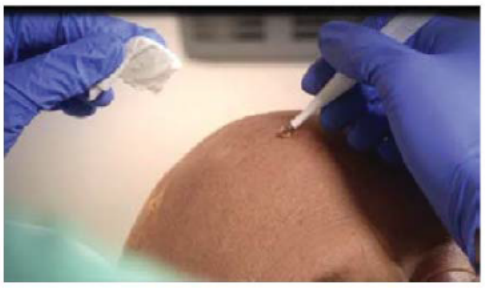


Figure 1B: Removal of scales and crust

2.2 Application of AMELUZ®

[redacted] glove protected fingertips or a spatula. Apply gel approximately 1 mm thick and include approximately 5 mm of the surrounding skin. [redacted] to cover the single lesions or [redacted] **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). In case of accidental contact with these areas, [redacted] to dry for approximately 10 minutes before applying occlusive dressing.

Figure 2: Drug application

2.3 Occlusion for 3 Hours

Cover the area where the gel has been applied with a light blocking, occlusive dressing. Following 3 hours of occlusion, remove the dressing and wipe off any remaining gel.

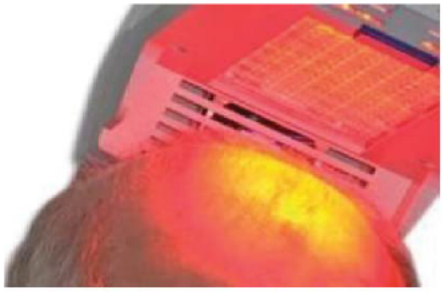
Figure 3: Occlusion

2.4 Illumination with Red Light

[redacted] During illumination patient and medical personnel [redacted] wear suitable protective eyewear.

Immediately after removing occlusion and any remaining gel, illuminate the treatment area with BF-RhodoLED®, a red light source with a narrow spectrum around 635 nm that delivers a light dose of approximately 37 J/cm^2 within 10 minutes. Calibration by the operator is not needed, and the illumination time is calculated automatically. Position the lamp head 5-8 cm from the skin's surface. [redacted]

(b) (4) Larger areas can be illuminated in several steps. (b) (4)



Illumination

3. DOSAGE FORMS AND STRENGTHS

(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) **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.

Reviewer comments: *The listed photosensitizing agents, except St. John's wort, appear in Levulan Kerastick topical solution label* (b) (4) *On 02/09/2016 the applicant was sent an information request (IR) to provide evidence to support inclusion of St. John's wort in Section 7 of the labeling (see communication in DARRTS). The applicant responded to the IR on 02/10/2016 and provided a review article by Joanne Barnes et al., 2001, Journal of Pharmacy and Pharmacology [Title: St John's wort (Hypericum perforatum L.): a review of its chemistry, pharmacology and clinical properties] to support inclusion of St John's wort. Based on information in this review, this reviewer concurs with the inclusion of St. John's wort in section 7.*

8. USE IN SPECIFIC POPULATIONS

8.3 Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 have not been established. AK is not a condition generally seen in the pediatric population.

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Photoactivation following topical application of [redacted] is metabolized to protoporphyrin IX (PpIX), a photoactive compound which accumulates in the [redacted] **skin**. When exposed to red light of a suitable wavelength and energy, PpIX is activated 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 [redacted] cells.

[redacted]

[redacted]

12.3 Pharmacokinetics

[redacted]

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)

4. INDIVIDUAL STUDY REVIEW

Trial: ALA-AK-CT006 – Maximal use PK trial

Title: A single center, non-randomized, open-label, placebo-controlled, fixed sequence Phase I study to evaluate the PK of 5-aminolevulinic acid (ALA) in patients with actinic keratosis following topical application of a gel formulation containing 78 mg/g ALA (Ameluz®) under maximal use conditions when using photodynamic therapy.

Primary Objective: The primary objective of the study was to obtain baseline-adjusted plasma concentrations-time curves for ALA and its metabolic product protoporphyrin IX (PpIX) after a single treatment with Ameluz® in patients with actinic keratosis under maximal use conditions.

Secondary Objectives:

- Evaluation of PK parameters of ALA and PpIX derived from baseline-adjusted plasma concentrations
- Assessment of safety and tolerability of Ameluz® under maximal use conditions

Study design: This was a single-center, non-randomized, open-label, placebo-controlled, fixed sequence, 2-treatment, intra-individual comparison Phase I study to evaluate the PK profiles of 5-ALA and its metabolite PpIX after a single treatment with Ameluz® in patients with AK under maximal use conditions using Photo Dynamic Therapy (PDT).

The study was performed in 2 phases:
Pilot phase with frequent PK sampling (15 samples per patient per treatment) and a ***Main phase*** in which the frequency of PK sampling might be reduced provided the results of the analysis of the pilot phase fulfilled predefined criteria. The predefined criteria were not fulfilled and the PK sampling schedule for the Main Phase was not changed.

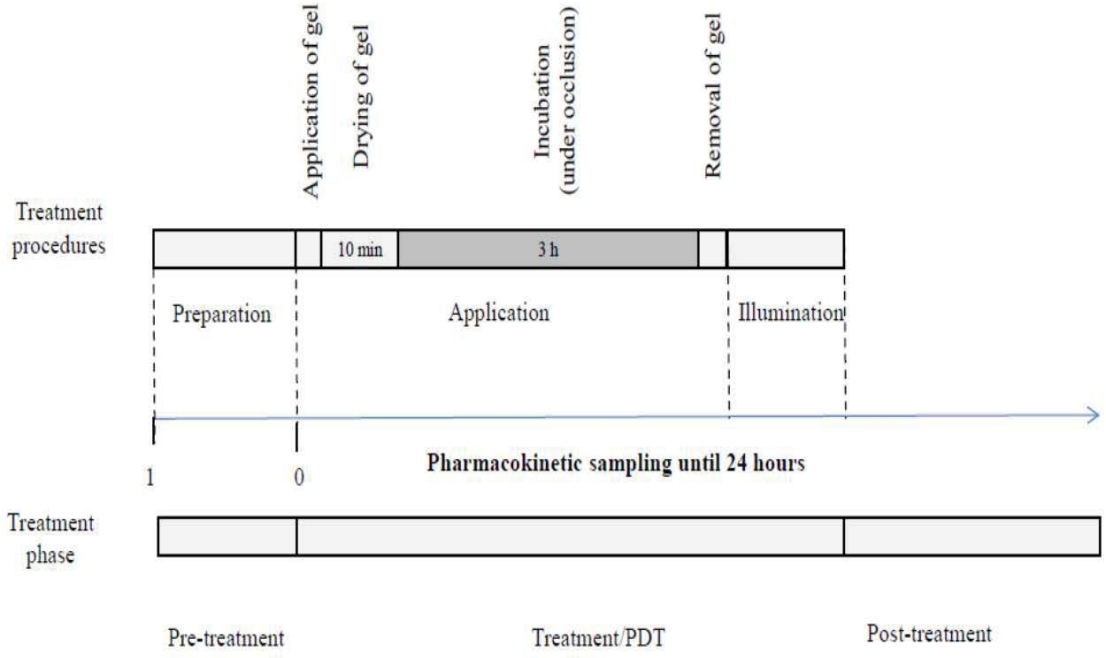
Each phase of the study consisted of:

- A Screening period (within 21 days before the first treatment), in which eligibility of subjects for study participation was assessed.
- A 2-day in-patient period in which patients were treated with PDT after receiving topical application of placebo on Day 1 and discharged from the study site after completion of the last assessment on Day 2.
- A washout period of 7 days between treatments.
- A 2-day in-patient period in which patients were treated with PDT after receiving topical application of Ameluz® on Day 1 and discharged from the study site after completion of the last assessment on Day 2.
- A follow-up visit (7±1 days after the last treatment) at which safety and tolerability assessments were performed.

In each treatment period, patients arrived at the study center in the morning of Day 1 and remained at the study center until discharge on Day 2. No formal interim analysis was

performed. However, after 3 patients with evaluable PK profiles had completed the pilot phase, their data was displayed. An overview of the treatment procedure is shown in Figure 5.

Figure 5: An overview of treatment procedure



Study population: 12 adult subjects (18 to 85 years old) with mild to moderate AK as defined by Olsen Scale shown in Table 7 below were included as follows.
Pilot Phase: 3 subjects
Main Phase: 9 subjects

Table 7: Olsen scale for actinic keratosis lesion intensity

Olsen Grade		**Clinical description of intensity grading**
Grade 0	none	no actinic keratosis lesions, neither visible or palpable
Grade 1	mild	flat, pink maculae without signs of hyperkeratosis and erythema, slight palpability, with actinic keratosis felt better than seen
Grade 2	moderate	pink to reddish papules and erythematous plaques with hyperkeratotic surface, moderately thick actinic keratoses that are easily seen and felt
Grade 3	severe	very thick and / or obvious actinic keratoses

Subjects included had to have at least 10 AK lesions on the face or forehead in a total topical treatment area of approximately 20 cm^2 with a maximum of 2 illumination areas with each lesion being not more than 2 mm thick and having a side margin of at least 5 mm. All 12 subjects completed the trial and all subjects included in this trial had mild AK, except for one as shown in Table 8.

Table 8: Intensity of AK lesions

Screening No.	Intensity of Actinic Keratosis Lesions	Visit	Date of Assesment [YYYY-MM-DD]
19001	GRADE 1, MILD	SCREENING	2013-07-15
19002	GRADE 1, MILD	SCREENING	2013-08-19
19004	GRADE 1, MILD	SCREENING	2013-09-02
19005	GRADE 1, MILD	SCREENING	2013-10-10
19006	GRADE 1, MILD	SCREENING	2013-10-14
19007	GRADE 1, MILD	SCREENING	2013-10-14
19008	GRADE 1, MILD	SCREENING	2013-10-11
19009	GRADE 2, MODERATE	SCREENING	2013-11-19
19010	GRADE 1, MILD	SCREENING	2013-11-26
19011	GRADE 1, MILD	SCREENING	2013-11-22
19012	GRADE 1, MILD	SCREENING	2013-11-25
19013	GRADE 1, MILD	SCREENING	2013-11-25

Reviewer comments: *The applicant did not consider the severity of the lesions to be critical with respect to drug penetration because hyperkeratoses were removed by gentle curettage prior to drug application. Subject 19009 with moderate AK was not the one with highest exposure of 5-ALA) and PpIX systemic concentrations were not quantifiable in this subject. Subject 19003 was considered as a screen failure and was not included in the PK analysis.*

Demographic data: The demographic data are shown in Table 9.

Table 9: Individual subject demographic data

Screening No.	Date of Screening [YYYY-MM-DD]	Age at Screening [years]	Sex	Childbearing Potential	Ethnicity	Race	Height at Screening [cm]	Weight at Screening [kg]	BMI at Screening [kg/m²]
19001	2013-07-11	69	MALE		NOT HISPANIC OR LATINO	WHITE	162	77.4	29.5
19002	2013-08-06	70	MALE		NOT HISPANIC OR LATINO	WHITE	184	96.5	28.5
19003	2013-08-21	67	MALE		NOT HISPANIC OR LATINO	WHITE	177	87.0	27.8
19004	2013-08-28	64	MALE		NOT HISPANIC OR LATINO	WHITE	176	87.8	28.3
19005	2013-10-04	71	MALE		NOT HISPANIC OR LATINO	WHITE	177	75.8	24.2
19006	2013-10-08	58	MALE		NOT HISPANIC OR LATINO	WHITE	181	97.0	29.6
19007	2013-10-10	75	MALE		NOT HISPANIC OR LATINO	WHITE	173	78.7	26.3
19008	2013-10-11	77	MALE		NOT HISPANIC OR LATINO	WHITE	179	102.2	31.9
19009	2013-11-19	63	MALE		NOT HISPANIC OR LATINO	WHITE	181	83.1	25.4
19010	2013-11-22	72	MALE		NOT HISPANIC OR LATINO	WHITE	182	87.4	26.4
19011	2013-11-22	71	FEMALE	NON-CHILDBEARING POTENTIAL	NOT HISPANIC OR LATINO	WHITE	164	60.4	22.5
19012	2013-11-22	73	FEMALE	NON-CHILDBEARING POTENTIAL	NOT HISPANIC OR LATINO	WHITE	156	57.5	23.6
19013	2013-11-22	75	MALE		NOT HISPANIC OR LATINO	WHITE	182	73.6	22.2

At screening, the external dermatologist localized most of the treatment areas on the forehead (illumination area A: face: 1 patient, forehead: 11 patients, illumination area B: face: 2 patients, forehead: 6 patients). The mean total size of the treatment area in both illumination areas (A and B) determined by the investigator on Day 1 of both periods was 20.9 cm^2. Summary of the demographic data is shown in Table 10 below.

Table 10: Summary of demographic data

Parameter		Total
Age [years]	N Arithmetic mean (SD) Median Minimum - Maximum	12 69.83 (5.59) 71.0 58.0 - 77.0
BMI [kg/m^2]	N Arithmetic mean (SD) Median Minimum - Maximum	12 26.53 (3.08) 26.4 22.2 - 31.9
Total size of treatment area in both illumination areas (A and B) on Day 1 of Period 1 [cm^2]	N Arithmetic mean (SD) Median Minimum - Maximum	12 20.9 (1.00) 21.3 19.5 - 22.0
Total size of treatment area in both illumination areas (A and B) on Day 1 of Period 2 [cm^2]	N Arithmetic mean (SD) Median Minimum - Maximum	12 20.9 (0.96) 21.0 19.5 - 22.0

Method of treatment administration:

Treatments administered: During the study, patients underwent 2 photodynamic therapy (PDT) sessions with 2 topical applications in a fixed sequence:

- Period 1: Vehicle gel application
- Period 2: Ameluz® gel application

Drug application was done by qualified study personnel who have been trained in PDT and there was no self-application in this study and following steps will be followed:

- **Preparation of the application area:** The application area was prepared within 1 h before application of placebo or Ameluz® gel. Lesions were localized and documented. Scales and crusts were accurately removed, and all lesion surfaces were gently roughened. Care was taken to avoid bleeding. Immediately before application of placebo or Ameluz® gel, all lesions were carefully wiped off with a 70% isopropanol-soaked cotton pad to ascertain degreasing of the skin. Start and stop time of the preparation procedure as well as any bleedings were documented.
- **Application of the investigational medicinal product:** On Day 1 of each treatment period, a complete tube of placebo or Ameluz® (2 g) was applied onto the lesions and the surrounding area, covering the skin with a film of approximately 1 mm thickness. The weight of the tube before and after drug application was recorded. This resulted in a total treatment area of approximately 20 cm^2. The same lesions/areas were treated in both periods. Application near the eyes, nostrils, mouth, ears, or mucosa was avoided. The gel was allowed to dry for approximately 10 min before an occlusive light tight dressing was placed over

the treatment site. Following incubation of 3 h, the dressing was removed and the remnant gel wiped off.

- **Illumination of the treatment area:** Immediately after cleaning the lesions (i.e., removal of remaining gel), the entire treatment area was irradiated with BF-RhodoLED®, a red light source (approximately 635 nm), until a total light dose of 37 J/cm^2.
- **Treatments after illumination:** Special treatment after illumination was generally not planned. Cooling of the treatment area with a refrigerant lotion had to be provided on demand. Patients experiencing disagreeable pain were given non-steroidal anti-inflammatory drugs as monotherapy.

Identity of investigational products:

Test product

Name:	Ameluz® 78 mg/g gel
Active ingredient (INN):	5-aminolevulinic acid (hydrochloride)
Formulation:	Gel, BF-200
Strength or concentration:	78 mg/g
Mode of administration:	Topical
Dose:	1 tube containing 2 g gel corresponding to 156 mg 5-aminolevulinic acid (as hydrochloride) as film of approximately 1 mm thickness over the treatment area of approximately 20 cm^2
Marketing authorization holder:	Biofrontera Bioscience GmbH Hemmelrather Weg 201 51377 Leverkusen, Germany (see Note to File No. 3)
Manufacturer:	Biofrontera Pharma GmbH Hemmelrather Weg 201 51377 Leverkusen, Germany
Storage conditions:	Refrigerator at 2–8°C
Batch number:	201306V
Expiry date:	November 2014

Reference product (placebo)

Formulation:	Gel, BF-200
Mode of administration:	Topical
Dose:	1 tube containing 2 g gel as film of approximately 1 mm thickness over the skin area of approximately 20 cm^2
Manufacturer:	Biofrontera Pharma GmbH Hemmelrather Weg 201 51377 Leverkusen, Germany
Storage conditions:	Refrigerator at 2–8°C
Batch number:	201306P
Expiry date:	November 2014

Medical device (photodynamic therapy lamp)

Name:	BF-RhodoLED®
Type:	Narrow spectrum (approximately 635 nm) PDT lamp
Manufacturer:	Biofrontera Pharma GmbH Hemmelrather Weg 201 51377 Leverkusen, Germany

PK sampling: Blood sampling for PK of ALA and PpIX were obtained before (-0.5-0 h, after treatment area was prepared) and 0.5, 1, 1.5, 2, 2.5, 3 (before starting illumination), 3.5, 4, 5, 6, 8, 10, 12, and 24 h after start (t = 0 h) of placebo or Ameluz® application.

Reviewer comments: *The applicant was considering a reduced sample scheme for the main phase based on some predefined criteria. Those pre-defined criteria were not met and hence the PK sampling schedule for the Main phase was identical to Pilot phase. The criteria will not be discussed in this review.*

PK analyses:

Baseline plasma concentrations and baseline correction: Baseline plasma concentrations of ALA and PpIX were determined as the mean plasma concentration value before application of placebo or Ameluz® (-0.5 – 0 h, after treatment area was prepared). The mean ± SD baseline plasma concentrations of 5-ALA and PpIX were 20.16 ± 16.53 ng/mL and 3.27 ± 2.40 ng/mL. Baseline-adjusted plasma concentrations of ALA and PpIX were obtained by subtraction of the mean baseline plasma concentration from a post-dose concentrations. If any of the baseline-adjusted concentrations were negative, they were set to zero. Table 11 provides information on subjects excluded from PK analysis.

Table 11: Subjects excluded from PK analysis

Screening No.	Assigned to the PK Set for Evaluation of ALA	Reason for PK Exclusion ALA	Assigned to the PK Set for Evaluation of PpIX	Reason for PK Exclusion PpIX
19003	N	Screen Failure	N	Screen Failure
19007	Y		N	No PpIX concentrations >=LLOQ
19009	Y		N	No PpIX concentrations >=LLOQ
19010	Y		N	No PpIX concentrations >=LLOQ
19013	Y		N	Only predose PpIX concentrations >=LLOQ

PK evaluation of ALA: All 12 patients included into the treatment phase had evaluable pre-dose and post-dose PK samples for ALA in each period and were thus included into the PK evaluation of ALA. The mean concentration versus time profile and the summary of PK parameters is shown under Section 2.2.2 of this review. Individual subject baseline uncorrected concentration of ALA is shown in Figure 6 below.

Individual subject baseline unadjusted PK profile of 5-ALA following Amulez® gel application is shown in Figure 6 and baseline adjusted concentration is shown in Figure 7, respectively.

Figure 6: Baseline unadjusted individual plasma concentration-time profiles of ALA after application of Ameluz® gel (LLOQ = 1 ng/mL)

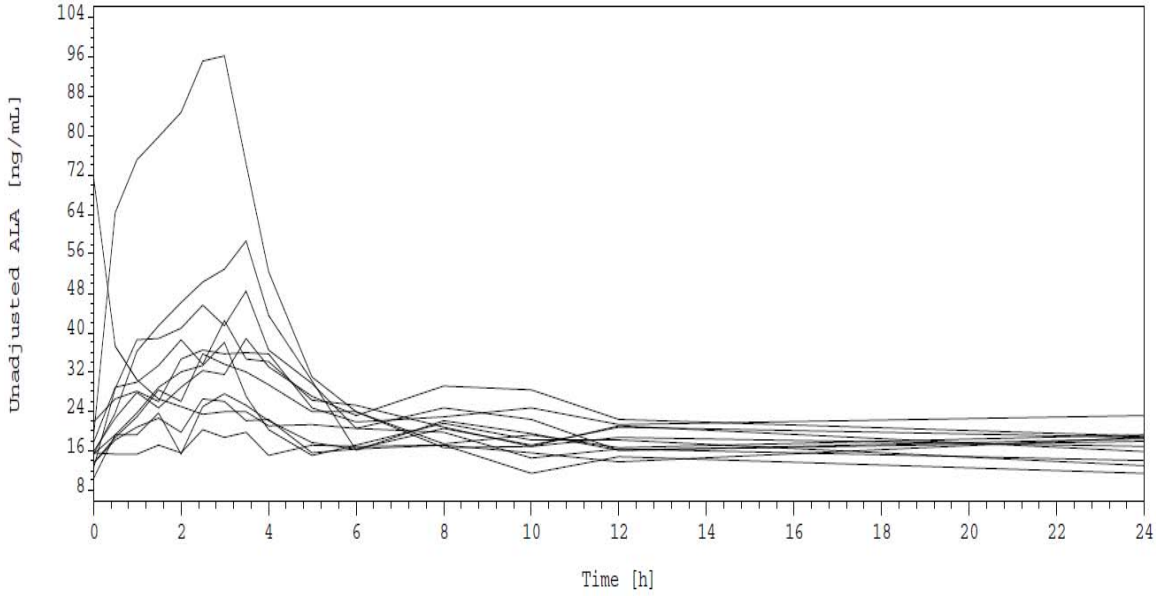
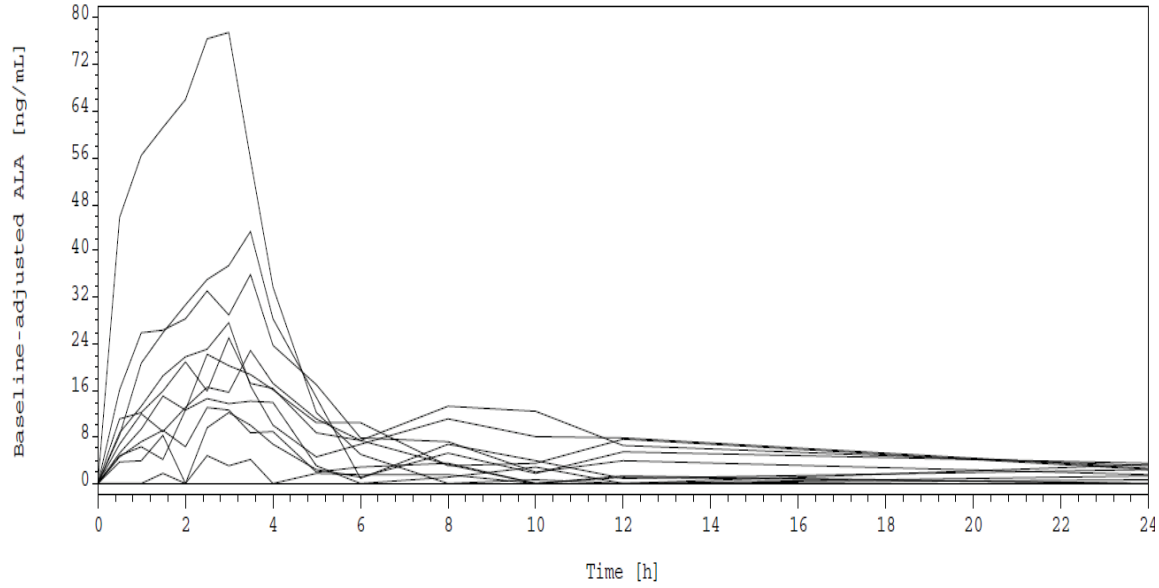


Figure 7: Baseline adjusted individual plasma concentration-time profiles of ALA after application of Ameluz® gel (LLOQ = 1 ng/mL)



Reviewer comments: *Subject 19002 (70 year old male with mild AK) had the highest drug exposure and the baseline corrected C_{max} and AUC_{0-t} were 77.53 ng/mL and 269.44 h*ng/mL, respectively.*

PK evaluation of PpIX: 8 of the 12 subjects included into the treatment phase had evaluable pre-dose and post-dose PK samples for PpIX and were thus included into the PK analysis. The following subjects were excluded from the PK set of PpIX:
• Subject No. 19007 as no PpIX concentrations were ≥ Lower limit of quantification (LLOQ)
• Subject No. 19009 as no PpIX concentrations were ≥LLOQ
• Subject No. 19010 as no PpIX concentrations were ≥LLOQ
• Subject No. 19013 as only pre-dose PpIX concentrations were ≥LLOQ

The mean ± SD baseline PpIX concentration was 3.27 ± 2.40 ng/mL. Baseline corrected PK parameters could not be reliably estimated in all but one of the subjects due to negative PpIX concentration values. The baseline corrected C_{max} and AUC_{0-t} in the single subject and the values were 0.29 ng/mL and 0.07 ng*h/mL, respectively. The mean concentration versus time profile of baseline uncorrected PpIX is shown in Section 2.2.2 of this review. The baseline unadjusted individual subject PpIX concentration is shown in Figure 8 and the baseline adjusted PK profile of PpIX in the single subject is shown in Figure 9.

Figure 8: Baseline unadjusted individual plasma concentration-time profiles of PpIX after application of Ameluz® gel (LLOQ = 1 ng/mL)

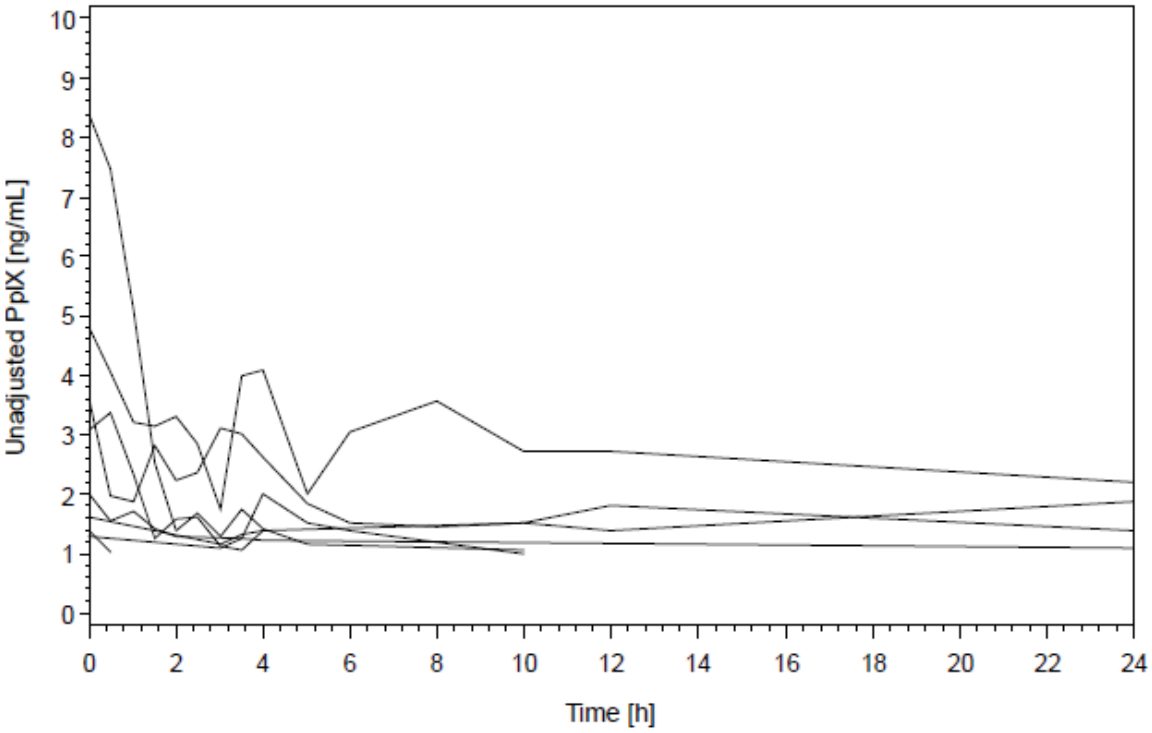
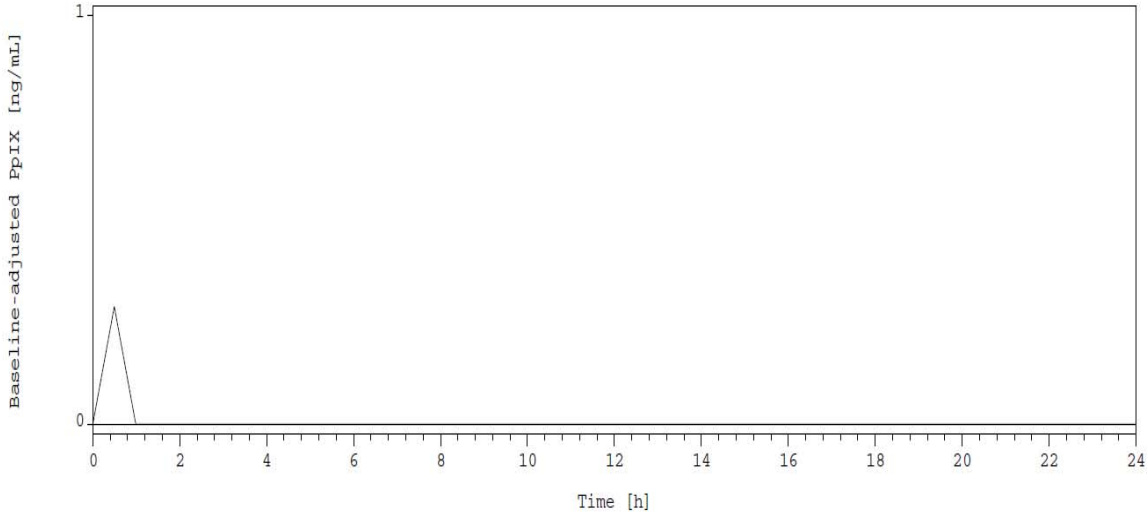


Figure 9: Baseline adjusted individual plasma concentration-time profiles of PpIX after application of Ameluz® gel (LLOQ = 1 ng/mL)



Summary of safety: See Section 2.2.5 of this review.

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/s/

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03/08/2016

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03/08/2016