COVER PAGE

CLINICAL STUDY PROTOCOL

Study ALA-AK-CT018

NCT05060237

A non-randomized, open-label, multicenter study to evaluate the safety and tolerability of BF-200 ALA (Ameluz®) in the expanded field-directed treatment of actinic keratosis on the face and scalp with photodynamic therapy (PDT)

TITLE PAGE

CLINICAL STUDY PROTOCOL

A non-randomized, open-label, multicenter study to evaluate the safety and tolerability of BF-200 ALA (Ameluz®) in the expanded field-directed treatment of actinic keratosis on the face and scalp with photodynamic therapy (PDT)

Amended Version 3.0

ALA-AK-CT018

Test Product:	BF-200 ALA (Ameluz®) [in combination with BF-RhodoLED® XL]
Indication:	Mild to severe actinic keratosis
Study Design:	Non-randomized, open-label, multicenter
Study Identifier:	ALA-AK-CT018
Study Phase:	I
Coordinating investigator:	Todd Schlesinger, MD Clinical Research Center of the Carolinas 1364 Ashley River Road Charleston, SC 29407, USA
Sponsor:	Biofrontera Bioscience GmbH Hemmelrather Weg 201 51377 Leverkusen, Germany
Sponsor's Signatory:	[redacted] Biofrontera Bioscience GmbH Hemmelrather Weg 201 51377 Leverkusen, Germany e-mail: [redacted] Tel.: [redacted] Fax: [redacted]
Date of issue	21-Apr-2022

The study is designed in accordance with the International Council for Harmonisation guideline for Good Clinical Practice (ICH-GCP E6).

DECLARATIONS OF SPONSOR AND INVESTIGATORS

DECLARATION OF SPONSOR AND COORDINATING INVESTIGATOR

This clinical study protocol was subject to critical review and has been approved by the sponsor. The information it contains is consistent with:

- the current risk-benefit evaluation of the investigational product in conjunction with an investigational device (combination product)
- the moral, ethical, and scientific principles governing clinical research as set out in the current version of the Declaration of Helsinki, the principles of ICH GCP E6, and the provisions of the applicable local law(s) and regulation(s).

The investigator will be supplied with details of any significant or new findings, e.g. unexpected serious suspected adverse reactions /unanticipated serious adverse device effects, related to treatment with the investigational products.

Sponsor

Date: _____ Signature: _____

Name (block letters):_____

Coordinating investigator

Date: _____ Signature: _____

Name (block letters):_____

DECLARATION OF INVESTIGATOR

I will work in accordance with the moral, ethical, and scientific principles governing clinical research as set out in the current version of the Declaration of Helsinki, and the International Council for Harmonisation guideline for Good Clinical Practice [ICH E6].

I will work according to the applicable local law(s) and regulation(s).

I confirm that I have read the protocol. I understand it, and I agree that it contains all the information required to conduct the study. I agree to conduct the study as set out in this protocol. I do not deviate from it without prior discussion with the sponsor except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change of telephone number(s)). If I become aware of any protocol deviation, I will communicate details to a representative of the sponsor.

Date: _____ Signature: _____

Name (block letters):_____

DECLARATION OF BIOSTATISTICIAN

The undersigned hereby declares his/her consent to the statistical part of the clinical trial protocol which is in compliance to current ICH guidelines.

Date: Signature: _____

Name (block letters):_____

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2 PROTOCOL OUTLINE

Title

A non-randomized, open-label, multicenter study to evaluate the safety and tolerability of BF-200 ALA (Ameluz®) in the expanded field-directed treatment of actinic keratosis on the face and scalp with photodynamic therapy (PDT)

Study no: ALA-AK-CT018	Clinical Phase: I

Study Design

This is a non-randomized, open-label, multicenter study to evaluate the safety and tolerability of BF-200 ALA in the treatment of actinic keratosis (AK) located on the face and scalp with photodynamic therapy (PDT) when using the BF-RhodoLED® XL lamp. Each subject will receive the content of 3 tubes (6 g) of BF-200 ALA for an expanded field-directed treatment.

Investigators / study sites

Approximately 10 sites in the United States of America (US) will participate in this study. Each site should dose between 5 and 15 subjects. No site should dose more than 20 subjects unless prior approval of the sponsor is obtained. The maximum number should in no case exceed 25 subjects.

Number of subjects

It is planned to dose approximately 100 subjects.

Subjects and lesions

Subjects with mild to severe AK (according to Olsen et al.,1991) of all sexes and of age 18 years and older will be enrolled.

Presence of at least 8 mild to moderate (Olsen et al., 1991)) clinically confirmed AK lesions with a diameter ≥ 4 mm within a treatment field on the face and/or scalp. In addition, severe AK lesions may be present in the treatment field. In case of severe AK lesions, a biopsy must be taken for confirmation of diagnosis. The treatment field may be continuous or in several patches, totaling about 60 cm² in each subject and must be located within one effective illumination area.

Definitions

- "illumination area" is the area effectively illuminated by one BF-RhodoLED® XL lamp in one illumination session
- "treatment field" is the part of the skin to which IMP is applied
- "treatment area" describes a region of the body in which the treatment field is located, distinguishing between face (including forehead, excluding eyes, nostrils, and mouth) and scalp (bald scalp, excluding ears)
- "target lesions" are all AK lesions (mild to severe) located within the treatment field

Investigational products (IP)

Investigational medicinal product (IMP)

BF-200 ALA.

BF-200 ALA is a gel formulation of 10 % 5-aminolevulinic acid hydrochloride, corresponding to 7.8 % 5-aminolevulinic acid (ALA). It is approved as Ameluz® by the Food and Drug Administration (FDA) in combination with photodynamic therapy using BF-RhodoLED® lamp and indicated for the lesion-directed and field-directed treatment of actinic keratoses (AK) of mild to moderate severity on the face and scalp. The IMP will be packed in tubes, containing 2 g each. Three tubes will be applied per subject.

Investigational medical device (IMD)

The study treatment requires illumination of the treatment field with ~37 J/cm² of red-light at ~635 nm. Approved for PDT in combination with Ameluz® is the BF-RhodoLED® lamp. In this study, the BF-RhodoLED® XL will be used which allows the illumination of a larger area than the BF-RhodoLED®.

Study Duration and Dates

Each subject will be in the study for approx. 6 weeks.

Within 14 days after the screening visit (Visit 1) and following confirmation of eligibility, subjects will be treated with PDT (Visit 2). At Visit 3 (7 days post PDT) and Visit 4 (14 days post PDT) assessment of transient side effects will be performed. At Visit 5, 28 days post PDT, the final evaluation of safety and tolerability will be performed.

In-/exclusion criteria

Inclusion criteria

1. Willingness and ability of subjects to provide informed consent and sign the Health Insurance Portability and Accountability Act (HIPAA) form. A study-specific informed consent and HIPAA form must be obtained in writing prior to starting any study procedures.
2. Subjects with mild to severe clinically confirmed AK lesions (according to Olsen (Olsen et al., 1991)) on the face and/or scalp. In case of severe AK lesions, a biopsy must be taken for confirmation of diagnosis. At least 8 mild to moderate AK lesions with a diameter of ≥4 mm must be present in the treatment field. The treatment field (continuous or in several patches) totaling about 60 cm^2 must be located within one effective illumination area. The AK lesions should be clearly distinguishable, without restrictions on the distance between lesions. Lesions should have a minimal distance of 1 cm between the lesion margin and the border of the treatment field.
3. All sexes, ≥18 years of age.
4. Willingness and ability to comply with study procedures, particularly willingness to receive a PDT session and to undergo 2 mm punch biopsy/biopsies in case of severe AK lesion(s) at the screening visit.
5. Subjects with good general health or with clinically stable medical conditions will be permitted to be included in the study. Subjects with clinically stable medical conditions will be permitted for inclusion into the study if not using prohibited medication.
6. Willingness to stop the use of moisturizers and any other non-medical topical treatments within the treatment field at least 24 h prior to the visits.

7. Acceptance to abstain from extensive sunbathing and the use of a solarium or tanning beds during the study.
8. For female subjects with reproductive potential: Negative serum pregnancy test.
9. For female subjects with reproductive potential: Effective contraception at screening visit and throughout the study.

Exclusion criteria

1. Any known history of hypersensitivity to ALA, porphyrins or excipients of BF-200 ALA.
2. History of soy or peanut allergy.
3. Subjects with sunburn or other possible confounding skin conditions (e.g. wounds, irritations, bleeding or skin infections) inside or in close proximity (< 10 cm distance) to the treatment field.
4. Clinically significant (CS) medical conditions making implementation of the protocol or interpretation of the study results difficult or impairing subject's safety such as:
    a. Presence of photodermatoses or porphyria
    b. Metastatic tumor or tumor with high probability of metastasis
    c. Infiltrating skin neoplasia (suspected or known)
    d. Unstable cardiovascular disease (New York Heart Association class III, IV)
    e. Unstable hematologic (including myelodysplastic syndrome), hepatic, renal, neurologic, or endocrine condition
    f. Unstable collagen-vascular condition
    g. Unstable gastrointestinal condition
    h. Immunosuppressive condition
    i. Presence of clinically significant inherited or acquired coagulation defect
5. Clinical diagnosis of atopic dermatitis, Bowen's disease, basal cell carcinoma, eczema, psoriasis, rosacea, squamous cell carcinoma, other malignant or benign tumors inside or in close proximity (< 10 cm distance) to the treatment field.
6. Presence of strong artificial pigmentation (e.g. tattoos) or any other abnormality that may impact lesion assessment or light penetration in the treatment field.
7. Any physical therapy such as cryosurgery, laser therapy, electrodessication, microdermabrasion, surgical removal of lesions, curettage, or treatment with chemical peels such as trichloroacetic acid inside or in close proximity (< 10 cm distance) to the treatment field within 4 weeks prior to screening.
8. Any of the topical treatments defined below within the designated periods prior to screening:
    a. Topical treatment with ALA or ALA esters (e.g. methyl aminolevulinic acid (MAL)) or an investigational drug in- and outside the treatment field within 8 weeks.

b. Topical treatment with immunosuppressive, cytostatic or cytotoxic drugs inside or in close proximity (< 10 cm distance) to the treatment field within 8 weeks.

c. Start of topical administration of a medication with hypericin or other drugs with phototoxic or photoallergic potential inside or in close proximity (< 10 cm distance) to the treatment field within 4 weeks. Subjects may, however, be eligible if such medication was applied for more than 4 weeks prior to screening without evidence of an actual phototoxic/photoallergic reaction.

9. Any use of the systemic treatments within the designated periods prior to screening:
    a. Cytostatic or cytotoxic drugs within 6 months.
    b. Immunosuppressive therapies or use of ALA or ALA esters (e.g. MAL) within 12 weeks.
    c. Drugs known to have major organ toxicity within 8 weeks or an investigational drug.
    d. Interferon or glucocorticosteroids within 6 weeks.
    e. Start of intake of medication with hypericin or systemically acting drugs with phototoxic or photoallergic potential within 8 weeks prior to screening. Subjects may, however, be eligible if such medication was taken in for more than 8 weeks prior to the screening visit without evidence of an actual phototoxic/photoallergic reaction.
10. Breast feeding women.
11. Suspicion of drug or alcohol abuse.
12. Subjects unlikely to comply with protocol, e.g. inability to return for visits, unlikely to complete the study, or inappropriate in the opinion of the investigator.
13. A member of study site staff or sponsor staff directly involved in the conduct of the protocol or a close relative thereof.
14. Simultaneous participation in another clinical study.

Re-screening of subjects is allowed once in case exclusion criterion 3 is met and eligibility can be achieved within 14 days.

Dosing day exclusion criteria

At Visit 2 (baseline, PDT-1)

Subjects with sunburn or other possibly confounding skin conditions (e.g. wounds, irritations, bleeding or skin infections) inside or in close proximity (< 10 cm distance) to the treatment field. Re-assessment of subjects is allowed within 14 days once the sunburn or other confounding skin conditions is/are expected to resolve.

Treatment

Subjects will be treated with PDT applying BF-200 ALA (Ameluz®). The IMP is packed in tubes, each containing 2 g gel. A pack of 3 tubes will be assigned to each subject to allow treatment with 3 tubes for PDT. For the PDT, the content of all 3 tubes will be homogenously applied as an ~1 mm thick layer to the assigned treatment field (approximately 60 cm^2).

The treatment field should be prepared for IMP application by degreasing (using ethanol or isopropanol) and removal of scabs and crusts, and if appropriate roughening of the surface, (e.g. by mild debridement). Care should be taken to avoid bleeding. The IMP (3 tubes á 2 g of BF-200 ALA) will then be applied to the entire treatment field, including all AK target lesions. All AK target lesions should have a minimal distance of 1 cm to the border of the treatment field. The study medication will be allowed to dry and subsequently covered with a light-blocking, occlusive dressing for approx. 3 h. Thereafter, the occlusive dressing and any remnants of the applied study medication will be removed and a 10 min illumination with approx. 37 J/cm^2 will be administered using the red-light LED device BF-RhodoLED® XL.

Study objective

The objective of the study is to evaluate the safety and tolerability of BF-200 ALA PDT, utilizing BF-RhodoLED® XL illumination, in the treatment of mild to severe actinic keratosis on the face and scalp in an expanded field-directed treatment.

The endpoints of the study are:

- Frequency and severity of adverse events (AEs), serious AEs (SAEs), and treatment-emergent adverse events (TEAEs). TEAEs are defined as all AEs with onset or worsening after treatment with IMP up to Visit 5
- Duration of TEAEs including the breakdown of severity category (mild, moderate, severe)
- Assessment of new lesions (AK, non-melanoma skin cancer [NMSC] such as BCC, SCC or Bowens disease, and melanoma) if they occur inside the treatment field
- Assessment of new lesions (AK, NMSC, and melanoma) if they occur around the treatment field at a distance of < 10 cm
- Application site skin reactions during and post PDT, assessed by the investigator
- Application site discomfort during and post PDT, reported by the subjects
- Application site pain during illumination, as assessed by the subjects using an 11-point numeric rating scale
- Changes in vital signs
- Safety laboratory data
- Physical examination data
- Neurological assessments

Sample size calculation

Not applicable

Statistics

Endpoints will be analyzed using the safety analysis dataset (SAF) and analyzed descriptively and in an exploratory way.

Schedule - study overview

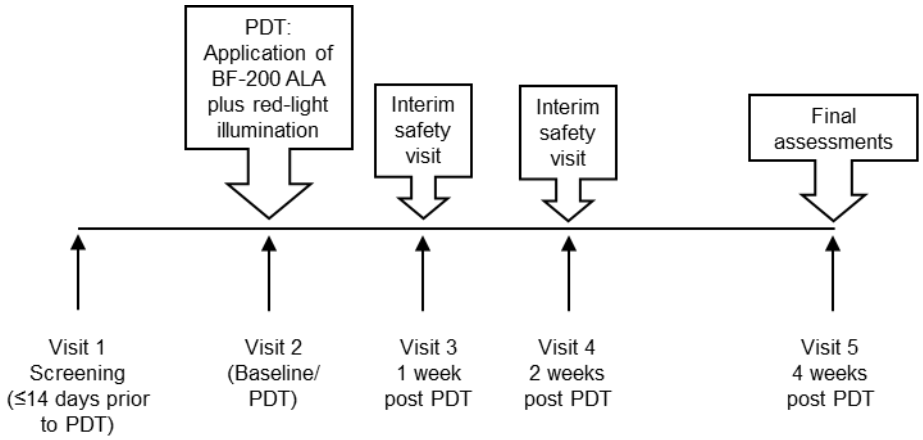


Table 1 Study schedule

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening	**PDT**	**Safety Interim Visit**	**Safety Interim Visit**	**Final Visit**
	≤ 14 days prior to PDT	**Baseline/ treatment**	**7 days (± 2 days) post PDT**	**14 days (± 2 days) post PDT**	**28 days (± 7 days) post PDT**
Clinical visit*	X	X	X	X	X
Obtain Informed consent	X				
Assignment of subject number	X				
Demographics	X				
Inclusion/exclusion criteria	X	X[a]			
Dosing day exclusion criterion		X[b]			
Relevant medical history (excluding medical skin history)/ concomitant medical conditions	X				
Medical skin history	X				
Skin type assessment	X[c]				
Body measures	X				
Vital signs	X	X[d]	X	X	X
Physical examination	X				X
Neurological assessments	X	X[e]			
Selection of the treatment field and assessment of AK target lesions (size, number, location, and severity)	X[f]				
Generation of templates (Grid foil, cartoon) for re-identification of AK lesions inside or in close proximity (< 10 cm distance) to the treatment field	X				
Skin assessment regarding new lesions (AK, NMSC and melanoma) inside or in close proximity (< 10 cm distance) to the treatment field [g]		X	X	X	X
Clinical laboratory tests[h] including serum pregnancy test, if applicable [i]	X				X
Urine pregnancy test [i]		X			

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Screening	**PDT**	**Safety Interim Visit**	**Safety Interim Visit**	**Final Visit**
	≤ 14 days prior to PDT	**Baseline/ treatment**	**7 days (± 2 days) post PDT**	**14 days (± 2 days) post PDT**	**28 days (± 7 days) post PDT**
Explanation of allowed/ forbidden medication before and after PDT to subjects	X	X			
Inform subjects about restrictions to sunlight, prolonged or intense light for 48 h after IMP application		X			
Explanation and handout of subject diary		X			
Collection of subject diary					X
Field-directed application of IMP and illumination (including preparation of the treatment field)		X			
Assessment of application site pain during illumination via NRS-11		X			
(S)AEs	X	X[j]	X	X	X
Concomitant medications/ treatments	X	X	X	X	X

(S)AE: (Serious) Adverse Event; AK: Actinic Keratosis; ALA: 5-aminolevulinic acid; BP: Blood Pressure; HR: Heart Rate; IMP: Investigational medicinal product; NMSC: Non-melanoma skin cancer; NRS: 11-point Numeric Rating Scale; PDT: Photodynamic Therapy
a Re-check of eligibility.
b Visit 2 can be rescheduled within 2 weeks after the scheduled date if the dosing day exclusion criterion is met
c Skin type will be evaluated according to Fitzpatrick criteria (Fitzpatrick 1988).
d Vital signs will be measured after the subject arrived at the site and will be additionally assessed within 10 min before start of illumination, within 10 min after end of illumination and 60 (±10) min after end of illumination
e Neurological assessments will be done prior to PDT and 60 (±10) min after end of illumination
f Lesions will be evaluated according to Olsen criteria (Olsen et al., 1991). Additionally, for severe AK lesions the diagnosis of AK must be confirmed by histopathological examination of biopsy.
g Any new AK, NMSC (such as BCC,SCC or Bowens's disease) and melanoma have to be reported as (S)AEs if they occur inside or in close proximity (< 10 cm distance) to the treatment field.
h Clinical laboratory tests will include routine hematology, blood chemistry, and urinalysis.
i All female participants of reproductive potential will undergo a pregnancy test.
j When the subject arrives at the site, within 10 min after end of illumination and 60 (±10) min after end of illumination

*Unscheduled visit: Unscheduled visits may be performed for safety reasons.

3 ABBREVIATIONS AND DEFINITIONS

β-hCG	Human chorionic gonadotropine
ADE	Adverse device event
AE	Adverse event
AK	Actinic keratosis
ALA	5-aminolevulinic acid
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
BCC	Basal cell carcinoma
BF	Biofrontera
BF-200 ALA	Nanoemulsion gel formulation containing 7.8 % ALA (development name for Ameluz®)
BP	Blood pressure
CI	Confidence interval
cm	centimeter
CRO	Contract Research Organization
CSP	Clinical study protocol
DSUR	Development safety update report
eCRF	Electronic case report form
EDTA	Ethylendiaminetetraacetic acid
EMA	European Medicines Agency
Enrolled	A subject is defined as enrolled when informed consent has been given
EoS	End-of-Study
EU	European Union
FDA	Food and Drug Administration
g	Gram(s)
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GmbH	Gesellschaft mit beschränkter Haftung, Ltd, limited liability company

GMP	Good manufacturing practice
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
Illumination area	Area which is effectively illuminated by one BF-RhodoLED® XL lamp in one illumination session
IMD	Investigational medical device
IMP	Investigational medicinal product
IND	Investigational New Drug
IRB	Institutional review board
ISF	Investigator Site File
LED	Light emitting diode
MedDRA	Medical Dictionary for Regulatory Activities
NMSC	Non-melanoma skin cancer
NRS-11	Numeric Rating Scale (11-point pain rating scale)
NSAID	Non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
PDT	Photodynamic therapy
PI	Prescribing Information
PpIX	Protoporphyrin IX
PTAEs	Pre-treatment adverse events
RSI	Reference safety information
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SCC	Squamous cell carcinoma
SD	Standard deviation

SOP	Standard Operating Procedure
TEAEs	Treatment-emergent adverse events
Treatment area	Body region in which the treatment field is located
Treatment field	Part of the skin to which IMP is applied
USADE	Unanticipated serious adverse device effect
UV	Ultraviolet

4 INTRODUCTION AND STUDY RATIONALE

4.1 Introduction

(Solar) actinic keratosis (AK), also known as squamous cell carcinoma (SCC) *in situ*, represents the most common neoplasia affecting fair-skinned subjects and develops in chronically sun-exposed skin areas. It is assumed that AK is the result of the accumulation of damage in keratinocytes caused by irradiation with ultraviolet (UV) light. Lesions of different sizes are found in affected subjects, characterized by rough, scaly and erythematous patches. Epidermal changes can include hyperkeratosis, parakeratosis, dyskeratosis, acanthosis, or keratinocyte atypia. In one prospective study by Czarnecki et al. (1), 72 % of 208 subjects with invasive SCC had AK contiguous to the SCC. It was concluded that the SCC arose in these AK lesions. In addition, epidemiological data have indicated that AK lesions, as an indicator for chronic sun damage, are a reliable marker for people who are predisposed to the development of an invasive SCC (2). Today, it is generally accepted that AK represents an early stage of a malignant condition (carcinoma in situ) that can progress to SCC (3,4). Between 0.025 % and 16 % of the AK lesions develop into SCC (5). Therefore, it was highly recommended to treat AK lesions before they progress to skin cancer. This was further manifested by several observations which conflicted with the initially assumed sequence of progression from mild AK lesions to lesions of moderate or severe phenotype and subsequent progression to SCC. First, the clinical classification of lesions using Olsen grading matches the histopathological classification according to Röwert-Huber or Cockerell only poorly (6). Second, if AKs progress to SCC they do this on average within about 24 months after coming into existence (7). Third, SCC arises more frequently from mild lesions than from more serious lesions according to Olsen grading (8).

This observation reinforces the need to also treat AK lesions of mild clinical phenotype and even cancerous fields, as both represent a high risk of progression to SCC.

Based on these observations, recent guidelines and expert recommendations advise early and field-directed treatment to address all AK severity grades, including subclinical manifestations (4,9–14). Photodynamic therapy (PDT) with Ameluz® (BF-200 ALA) in combination with the narrow-band BF-RhodoLED® lamp is FDA approved for the field-directed treatment of mild to moderate AK on the face and scalp.

BF-200 ALA gel contains 10 % ALA hydrochloride, equivalent to 7.8 % ALA in a nanoemulsion formulation and was shown to improve skin penetration and uptake of ALA in the target area due to the lipophilic component of the nanoemulsion (15,16). Thus, as a result of the better penetration capacities, the amount of ALA in the marketed formulation could be reduced to 7.8 %, half of comparable formulations on the market. Furthermore, this formulation significantly enhances the shelf-life as well as in-use stability of the active ingredient in an aqueous environment. This is considered a relevant advantage, given the instability of ALA in aqueous formulations.

Ameluz® in combination with the red-light BF-RhodoLED® lamp has been approved for the lesion- and field-directed PDT of actinic keratoses of mild to moderate severity on the face and scalp by the Food and Drug Administration (FDA) on May 10th, 2016 (NDA 208081).

In the European Union (EU), the European Medicines Agency (EMA) granted a centralized Marketing Authorization for Ameluz® for the treatment of mild to moderate AK on the face

and scalp in December 2011 (EU/1/11/740/001). In November 2012, the BF-RhodoLED® medical device was CE-marked and subsequently launched in the European market. In September 2016 the approval was extended to the indication of field cancerization, and in January 2017 to the treatment of superficial and nodular basal cell carcinoma (BCC). In March 2018, the EMA granted extension of the posology to the treatment of mild to moderate AK on the face and scalp and field cancerization with daylight PDT. On March 10, 2020, the European marketing authorization was extended to PDT treatment of mild to moderate AK on the extremities and neck/trunk using narrow spectrum red light, based on a European Phase III study (ALA-AK-CT010).

Ameluz® furthermore received marketing approval in Switzerland for the treatment of mild to moderate AK on the face and scalp with conventional PDT in November 2015 (Swissmedic number: 65693) and for the treatment with daylight PDT in September 2018. Subsequently, Swissmedic approved Ameluz® for the treatment of field cancerization and BCC in May 2018 (Swissmedic number: 65693).

Given that the size of fields with chronic actinic sun damage frequently exceeds the usually approved area size of 20-25 cm² (17), an open label safety study under maximal use conditions was conducted in the US additionally. This Phase I trial (ALA-AK-CT015) aimed at assessing pharmacokinetic data as well as subjects´ safety and tolerability after a single PDT with BF-200 ALA in conjunction with the BF-RhodoLED® applying the content of 3 tubes of BF-200 ALA in subjects with actinic keratosis to an expanded treatment field of 60 cm² located on the face/scalp or in the periphery (neck/trunk/extremities).

The Marketing Authorization Holder (Biofrontera Bioscience GmbH) now intends to perform a safety study in the US to confirm the safety profile of BF-200 ALA in the treatment of mild to severe actinic keratosis on the face and scalp with PDT when applying the content of 3 tubes of BF-200 ALA per PDT in conjunction with a new medical device, the BF-RhodoLED® XL lamp. This lamp allows the illumination of a larger area than the BF-RhodoLED®.

4.2 Study rationale

Current FDA-approved treatment options for field-directed treatment of AK on the face and scalp are formulations containing diclofenac/hyaluronic acid (3 %/2.5 %), imiquimod cream (3.75%) or 5-fluoruracil, which require repeated applications for up to several months or lead to side effects related to erosive and/or inflammatory reactions induced by the treatment that may last for the entire treatment period or even longer (18–20).

Compared to methods like surgery, abrasion, cryosurgery, and alternative topical treatments, the use of PDT is advantageous for the field-directed treatment especially due to the high selectivity of treatment, but also to the short treatment period that is entirely controlled by the physician, and the excellent cosmetic results (21).

In addition, a European network meta-analysis of the relative clinical efficacy of 10 different treatment modalities for mild to moderate AK on the face and scalp, including PDT products as well as formulations containing cryosurgery, 5-fluorouracil, imiquimod, ingenol mebutate or diclofenac/ hyaluronic acid, has shown that ALA PDT using BF-200 ALA was the most efficacious treatment option (22).

Besides Ameluz®, only one PDT product containing ALA is available in the US market. Levulan® Kerastick® providing ALA at a concentration of 20 % in a 2-component system that requires ALA to be compounded immediately before use. By label, the use of Levulan® Kerastick® is restricted to lesion-directed treatment of minimally to moderately thick AKs located on the face and scalp or the upper extremities. Ameluz® is the only PDT product available in the US market which has been approved for the field-directed treatment of AKs, but at the current time its label is restricted to the application of one tube of Ameluz®.

In contrast to the currently marketed BF-RhodoLED® lamp the BF-RhodoLED® XL enables the illumination of a larger skin area in one step. The BF-RhodoLED® XL has 5 LED panels which are positioned in a curved shape.

This safety study is designed to confirm the safety and tolerability of BF-200 ALA (Ameluz®) in combination with BF-RhodoLED® XL for the field-directed treatment of mild to severe AK located on the face and scalp in an expanded treatment field of 60 cm², applying the content of 3 tubes of BF-200 ALA for PDT. Using the curved shape configuration of BF-RhodoLED XL permits an even illumination of the entire face or scalp and facilitates the illumination of discontinuous treatment field in one step.

4.3 Risk/benefit analysis

This safety study will include diseased subjects presenting with at least 8 mild to moderate AK lesions (≥4 mm) within the treatment field of about 60 cm^2 in total. In addition, severe AK lesions may be present in the treatment field. Subjects will receive BF-200 ALA treatment - already marketed for the treatment of AK in the US, EU, and Switzerland under the brand name Ameluz® - with conventional red-light illumination.

Clinical efficacy and safety of BF-200 ALA in combination with conventional red-light illumination for the treatment of mild to moderate AK on the face and scalp were previously examined in one dose-finding study, and three confirmatory studies encompassing a total of 885 randomized subjects comprising 462 subjects (2674 lesions) exposed to BF-200 ALA (7.8% ALA) (23–25) treated on the face and scalp. All subjects received up to 1 tube (2 g) of BF-200 ALA. In these pivotal clinical trials, complete response of subjects 12 weeks after the last PDT with BF-200 ALA was shown to be up to 90.9 % and total lesion response was up to 94.3 % (23–26).

In previous clinical trials with BF-200 ALA, local application site reactions were observed in 84-100 % of the subjects. These reactions are expected, given the therapeutic principle of PDT, which is based on phototoxic effects. The most common signs and symptoms were application site erythema, pain/burning, irritation, and edema. Most adverse reactions occurred during illumination or shortly afterwards. Symptoms were usually of mild or moderate intensity (investigator's assessment on a 4-point scale). Subjects treated with a higher dose (6 g / 3 tubes BF-200 ALA) within an enlarged treatment field of 60 cm² experienced more severe application site reactions (mainly pain, erythema) when treated on the face and scalp which was not reported for subjects treated in the periphery. Given that PDT pain was already described to be related to the size of treatment field (27), a higher pain intensity during treatment of an expanded treatment field on the face and/or scalp was to be expected. Nonetheless, application site pain during PDT is transient and well manageable. In most cases the symptoms lasted for 1 to 4 days, however, in some cases, they persisted for 1

to 2 weeks or even longer. It is known that the intensity of AEs depends on the applied light spectrum used for PDT and correlates with the higher response rate achieved by the use of narrow spectrum lamps, emitting around 630 nm, e.g. BF-RhodoLED®. In rare cases, adverse reactions may require interruption or discontinuation of the illumination.

Common adverse reactions of PDT with BF-200 ALA include headache and reactions at the application site, such as erythema, pain/burning, irritation (burning), edema, pruritus, exfoliation, scab, induration, vesicles. More detailed information on known adverse reactions is provided in the prescribing information (PI) for Ameluz® (28). This drug is contraindicated in subjects with known hypersensitivity to ALA, to porphyrins or to any excipients of Ameluz®, and in subjects with porphyria or photodermatoses.

It is assumed that local adverse reactions in the present study will be similar to those known from treatment of AK lesions as well as cancerous fields described previously. If required, pain management will be performed according to established guidelines (29,30) but restrictions for co-medications/treatments described in this protocol must be taken into consideration.

In this study, inclusion and exclusion criteria have been chosen to minimize possible risks due to the administration of BF-200 ALA, and to ensure a uniform study population. BF-200 ALA and the PDT lamp BF-RhodoLED® XL will be handled by appropriately trained study personnel. The setting of BF-RhodoLED® XL is comparable to BF-RhodoLED® used in the previous studies such that the emitted wavelength is 635 nm and same light dose of 37 J/cm^2 will be applied.

5 STUDY OBJECTIVES

5.1 Study objective

The objective of the study is to evaluate the safety and tolerability of BF-200 ALA PDT, utilizing BF-RhodoLED® XL illumination, in the treatment of mild to severe AK on the face and scalp in an expanded field-directed treatment.

The endpoints of the study are:

- Frequency and severity of adverse events (AEs), serious AEs (SAEs), and treatment-emergent adverse events (TEAEs). TEAEs are defined as all AEs with onset or worsening after treatment with IMP up to Visit 5
- Duration of TEAEs including the breakdown of severity category (mild, moderate, severe)
- Assessment of new lesions (AK, NMSC such as BCC, SCC or Bowens disease, and melanoma) if they occur inside the treatment field
- Assessment of new lesions (AK, NMSC, and melanoma) if they occur around the treatment field at a distance of < 10 cm
- Application site skin reactions during and post PDT, assessed by the investigator
- Application site discomfort during and post PDT, reported by the subjects
- Application site pain during illumination, as assessed by the subjects using an 11-point numeric rating scale
- Changes in vital signs
- Safety laboratory data
- Physical examination data
- Neurological assessments

6 STUDY DESIGN, DURATION AND DATES

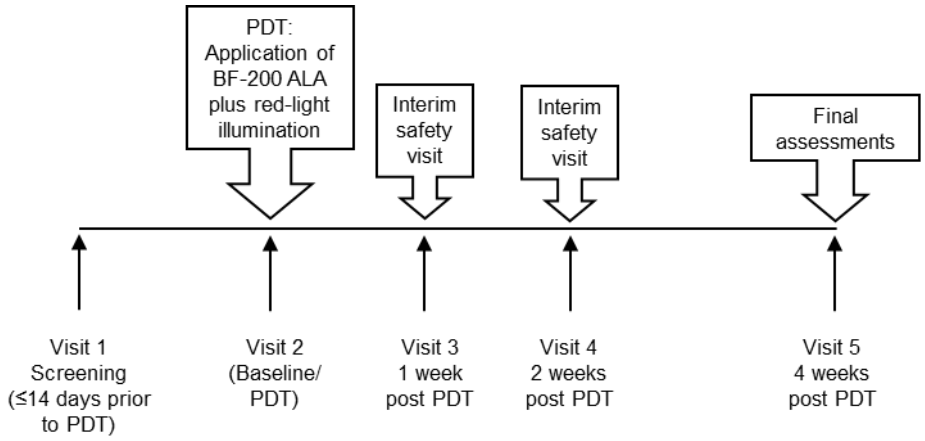
6.1 Study design

This protocol describes a multicenter, open label study that will be conducted in the United States of America (US). Approximately 10 sites in the US will participate in this study. Each site should dose between 5 and 15 subjects. No site should dose more than 20 subjects unless prior approval of the sponsor is obtained. The maximum number should in no case exceed 25 subjects.

The clinical study will consist of:

- a screening visit (within 14 days before treatment), at which eligibility of subjects for study participation will be assessed (Visit 1)
- a baseline/treatment visit, at which eligible subjects will receive PDT with application of the content of 3 tubes of BF-200 ALA (Visit 2)
- two interim visits for safety assessment 7 days (± 2 days) (Visit 3) and 14 days (± 2 days) (Visit 4) post PDT
- a final clinic visit, 28 (± 7) days post PDT, at which safety and tolerability assessments will be performed (Visit 5)

Figure 1 illustrates treatment details on study visits. An overview of scheduled assessments is provided in Table 1.



* Visit 2 can be rescheduled once within 14 days after the scheduled date if the dosing day exclusion criterion (sunburn or other possible confounding skin conditions inside or in close proximity (< 10 cm distance) to the treatment field) is met and if the sunburn or other confounding skin conditions is/are expected to resolve within 14 days.

Figure 1: Summary of study visits

The PDT procedure (preparation of treatment field, drug application, incubation, illumination) will be performed similar to the prescribing information of Ameluz® (28). Details will be described in Section 8.

6.2 Study duration, dates and end-of-study definition

For each subject the duration of the study is expected to be approx. 6 weeks. The overall study duration is estimated to be about 6.5 months (including an approx. 5-month recruitment phase). The duration of the overall study or the subject recruitment period may vary. The end of study will be defined as last subject last visit.

6.3 Definitions

Definition of treatment area:

For this study, the term treatment area defines the body region in which the treatment field is located. The following treatment areas will be investigated:

- **Face**: including forehead, excluding eyes, nostrils, and mouth
- **Scalp**: bald scalp, excluding ears

Definition of illumination area:

The "illumination area" is the area effectively illuminated by one BF-RhodoLED® XL lamp in one illumination session.

Definition of target lesions:

Target lesions are all AK lesions (mild to severe) located within the treatment field at Visit 1.

Definition of treatment field:

The "treatment field" is the part of the skin to which IMP is applied.

- The treatment field is defined as the skin surface area that is covered by IMP. In this study, the treatment field must comprise of a total skin area of approx. 60 cm² (~1 mm thick) and must contain at least 8 mild to moderate AK lesions with a diameter ≥4 mm. In addition, severe AK lesions might be present. AK target lesions included in the study should be entirely located within the treatment field, leaving a minimal distance of 1 cm of the lesion margin to the treatment field border. The treatment field has to be located on the face and/or the scalp (including forehead, excluding eyes, nostrils, ears, and mouth). The treatment field may be continuous or in several patches to form a total area of approximately 60 cm^2.
- In case of a discontinuous treatment field, all patches must be located within one effective illumination area.

Definition of new lesions

The term new lesion defines pre-neoplastic or neoplastic lesions including AK, NMSC such as BCC, SCC or Bowens disease, and melanoma that occur inside or in close proximity (< 10 cm distance) to the treatment field.

7 SELECTION OF SUBJECTS

7.1 Number of subjects

No sample size for the study was calculated. However, in agreement with FDA about 100 subjects are considered sufficient to evaluate the safety profile after application of the content of 3 tubes of BF-200 ALA. All subjects will receive BF-200 ALA.

7.2 Recruitment arrangements

Subjects will be screened at the study sites and if eligible, included into the study and subjected to PDT. Each site should dose between 5 and 15 subjects. A study site has to stop recruitment once 20 subjects have been treated unless prior sponsor approval is obtained. The maximum number should not exceed 25 subjects. Recruitment will be competitive within the limits described above.

7.3 Inclusion criteria

Eligible subjects must meet the following criteria:

1. Willingness and ability of subjects to provide informed consent and sign the Health Insurance Portability and Accountability Act (HIPAA) form. A study-specific informed consent and HIPAA form must be obtained in writing prior to starting any study procedures.
2. Subjects with mild to severe clinically confirmed AK lesions (according to Olsen (Olsen et al., 1991)) on the face and/or scalp. In case of severe AK lesions, a biopsy must be taken for confirmation of diagnosis. At least 8 mild to moderate AK lesions with a diameter of ≥4 mm must be present in the treatment field. The treatment field (continuous or in several patches) totaling about 60 cm^2 must be located within one effective illumination area. The AK lesions should be clearly distinguishable, without restrictions on the distance between lesions. Lesions should have a minimal distance of 1 cm between the lesion margin and the border of the treatment field.
3. All sexes, ≥18 years of age.
4. Willingness and ability to comply with study procedures, particularly willingness to receive a PDT session and to undergo 2 mm punch biopsy/biopsies in case of severe AK lesion(s) at the screening visit.
5. Subjects with good general health or with clinically stable medical conditions will be permitted to be included in the study. Subjects with clinically stable medical conditions will be permitted for inclusion into the study if not using prohibited medication.
6. Willingness to stop the use of moisturizers and any other non-medical topical treatments within the treatment field at least 24 h prior to the visits.
7. Acceptance to abstain from extensive sunbathing and the use of a solarium or tanning beds during the study.
8. For female subjects with reproductive potential: Negative serum pregnancy test.
9. For female subjects with reproductive potential: Effective contraception at screening visit and throughout the study.

7.4 Exclusion criteria

To reduce risks for the subjects and to ensure that the subjects are in a comparable status, subjects will be excluded if they meet at least one of the following exclusion criteria:

1. Any known history of hypersensitivity to ALA, porphyrins or excipients of BF-200 ALA.
2. History of soy or peanut allergy.
3. Subjects with sunburn or other possible confounding skin conditions (e.g. wounds, irritations, bleeding or skin infections) inside or in close proximity (< 10 cm distance) to the treatment field.
4. Clinically significant (CS) medical conditions making implementation of the protocol or interpretation of the study results difficult or impairing subject's safety such as:
    a. Presence of photodermatoses or porphyria
    b. Metastatic tumor or tumor with high probability of metastasis
    c. Infiltrating skin neoplasia (suspected or known)
    d. Unstable cardiovascular disease (New York Heart Association class III, IV)
    e. Unstable hematologic (including myelodysplastic syndrome), hepatic, renal, neurologic, or endocrine condition
    f. Unstable collagen-vascular condition
    g. Unstable gastrointestinal condition
    h. Immunosuppressive condition
    i. Presence of clinically significant inherited or acquired coagulation defect
5. Clinical diagnosis of atopic dermatitis, Bowen's disease, basal cell carcinoma, eczema, psoriasis, rosacea, squamous cell carcinoma, other malignant or benign tumors inside or in close proximity (< 10 cm distance) to the treatment field.
6. Presence of strong artificial pigmentation (e.g. tattoos) or any other abnormality that may impact lesion assessment or light penetration in the treatment field.
7. Any physical therapy such as cryosurgery, laser therapy, electrodessication, microdermabrasion, surgical removal of lesions, curettage, or treatment with chemical peels such as trichloroacetic acid inside or in close proximity (< 10 cm distance) to the treatment field within 4 weeks prior to screening.
8. Any of the topical treatments defined below within the designated periods prior to screening:
    a. Topical treatment with ALA or ALA esters (e.g. methyl aminolevulinic acid (MAL)) or an investigational drug in- and outside the treatment field within 8 weeks.
    b. Topical treatment with immunosuppressive, cytostatic or cytotoxic drugs inside or in close proximity (< 10 cm distance) to the treatment field within 8 weeks.
    c. Start of topical administration of a medication with hypericin or other drugs with phototoxic or photoallergic potential inside or in close proximity (< 10 cm distance) to the treatment field within 4 weeks. Subjects may, however, be

eligible if such medication was applied for more than 4 weeks prior to screening without evidence of an actual phototoxic/photoallergic reaction.

9. Any use of the systemic treatments within the designated periods prior to screening:
    a. Cytostatic or cytotoxic drugs within 6 months.
    b. Immunosuppressive therapies or use of ALA or ALA esters (e.g. MAL) within 12 weeks.
    c. Drugs known to have major organ toxicity within 8 weeks or an investigational drug.
    d. Interferon or glucocorticosteroids within 6 weeks.
    e. Start of intake of medication with hypericin or systemically acting drugs with phototoxic or photoallergic potential within 8 weeks prior to screening. Subjects may, however, be eligible if such medication was taken in for more than 8 weeks prior to the screening visit without evidence of an actual phototoxic/photoallergic reaction.
10. Breast feeding women.
11. Suspicion of drug or alcohol abuse.
12. Subjects unlikely to comply with protocol, e.g. inability to return for visits, unlikely to complete the study, or inappropriate in the opinion of the investigator.
13. A member of study site staff or sponsor staff directly involved in the conduct of the protocol or a close relative thereof.
14. Simultaneous participation in another clinical study.

Re-screening of subjects is allowed once in case exclusion criterion 3 is met and eligibility can be achieved within 14 days.

Dosing day exclusion criteria:

At Visit 2 (baseline, PDT-1)

Subjects with sunburn or other possibly confounding skin conditions (e.g. wounds, irritations, bleeding or skin infections) inside or in close proximity (< 10 cm distance) to the treatment field. Re-assessment of subjects is allowed within 14 days once the sunburn or other confounding skin conditions is/are expected to resolve.

7.5 Screening failures

All subjects whose eligibility cannot be confirmed at Visit 1 and /or Visit 2 will be considered as screening failures. Re-assessment of subjects is allowed as described in Section 7.4.

Subjects assessed as screening failures will not be treated. Only date of informed consent, demographics and date and reason for screen fail have to be reported in the eCRF.

7.6 Subjects of reproductive potential

Female subjects of reproductive potential (i.e. ovulating, pre-menopausal, or post-menopausal for less than one year, not surgically sterile) must use a medically accepted contraceptive regimen during the study as outlined below.

- Use of one highly effective method proven to have an acceptably low failure rate (Pearl Index below 1, failure rate less than 1 % per year) such as:
    - surgical sterilization (e.g., bilateral tubal ligation, hysterectomy),
    - hormonal contraception (implantable, patch, oral, injectable)
    - sexual intercourse with a vasectomized partner
    - true abstinence
- Combined use of two effective methods such as:
    - latex condoms with spermicidal gel
    - Diaphragms with spermicidal gel
    - Cervical caps with spermicidal gel
    - Vaginal sponge with spermicidal gel

Periodic abstinence (e.g. calendar, ovulation, symptothermal, post ovulation methods) and withdrawal are not acceptable methods of contraception.

If a subject becomes pregnant during the study, she must inform the investigator immediately.

If pregnancy occurs, the investigator must contact the sponsor immediately for further instructions and must be followed up until the outcome of the pregnancy is known. Both, the detection and the outcome of the pregnancy must be reported to the sponsor on special forms. Please also refer to Section 12.1.

8 STUDY TREATMENT

8.1 Details of investigational products

8.1.1 Investigational Medicinal Products

The drug component of the investigational medicinal product (IMP) will be BF-200 ALA, a gel formulation of 7.8 % ALA.

The compositions are as follows:

Table 2: Composition and manufacturer of study medication

Drug	**BF-200 ALA**
Brand name:	Ameluz®
Chemical name:	5-amino-4-oxopentanoat hydrochloride
International non-proprietary name:	ALA hydrochloride
Formulation:	BF-200 ALA containing 7.8 % ALA in a lecithin-based nanoemulsion gel with preservatives (sodium benzoate) and xanthan gum in purified water
Manufacturer:	Biofrontera Pharma GmbH Hemmelrather Weg 201 51377 Leverkusen, Germany

ALA: 5-aminolevulinic acid

No excipients of human or animal origin are contained in the IMP or are used during the manufacturing process. Furthermore, no novel excipients are contained in the IMP used in this study.

The BF-200 nanoemulsion gel is an oil-in-water dispersion of very small and homogenous vesicles, composed of a lipid core surrounded by a lecithin/co-surfactant monolayer. BF-200 nanoemulsion has a mean vesicle size of less than 30 nm with a very narrow size distribution. BF-200 ALA contains ingredients that are well established and approved worldwide in medicinal and cosmetic products. The formulation of BF-200 ALA, as applied in this study, is identical to the currently marketed formulation as well as the formulation that was used in the confirmatory clinical trials summarized in Section 4.

The IMP will be delivered in aluminum tubes containing 2 g gel (containing 156 mg ALA). Three tubes will be provided per subject for PDT, totaling in a total dose of 468 mg ALA per PDT an subject. The quantity of IMP provided for PDT is sufficient to cover the 60 cm^2 skin area of the treatment field with a ~1 mm thick layer.

8.1.2 Investigational Medical Device

The Class III device BF-RhodoLED® XL (in this document also referred to as investigational medical device, IMD) allows the illumination of a larger area than the BF-RhodoLED® and is yet unapproved in the US.

BF-RhodoLED® was granted US marketing approval as a combination product with Ameluz® for the lesion- or field-directed treatment of mild to moderate AK on the face and scalp in May 2016 (NDA 208081). BF-RhodoLED® emits red light at a typical peak wave length of approximately 635 nm and delivers a total light dose of 37 J/cm² within 10 min.

The BF-RhodoLED® XL used in this study will be manufactured by an ISO 13485:2016 certified manufacturer:

Biofrontera Pharma GmbH
Hemmelrather Weg 201
51377 Leverkusen
Germany

BF-RhodoLED® XL utilizes 225 LEDs (45 per panel arranged in a rectangle) to emit a uniform, visible red light with a typical peak wavelength at approximately 635 nm. The lamp is equipped with 5 LED panels which will be positioned in a curved shape. The maximal effective illumination area in this configuration is 23 cm x 29 cm (667 cm²).

The calibration of the lamp ensures that the skin area illuminated receives a total light dose of 37 J/cm^2 when maintaining a total illumination time of 10 min at a treatment distance between 11 – 14 cm. Each LED panel is equipped with a distance sensor to enable individual adjustment of each panel within this range. If a correct distance is achieved, it will be indicated a by a green light for each panel on the control unit and the panel lights up with a low light intensity. The low light intensity will allow for correct adjustment of LED panels regarding distance and treatment field. The lamp is programmed to automatically provide a total illumination time of 10 min. In case of necessary interruptions, e.g. due to pain or the need to reposition the subject, the lamp will continue until the required illumination time is achieved. More details will be given in the user manual BF-RhodoLED® XL.

For the purpose of this study, each study site will be equipped with one BF-RhodoLED® XL. All site personnel handling the lamp will be instructed properly on the handling and usage of the lamp, according to the user manual.

The recommended conditions for illumination with the LED lamp are shown in Table 3.

Table 3: Key light parameters of BF-RhodoLED® XL (curved shape)

	Recommendation
Peak wavelength (λ_{em})	approx. 635 nm
Light dose (energy)	approx. 37 J/cm²
Typical irradiance	61 (± 20 %) mW/cm^2
Typical illumination time	10 min
Typical distance skin-lamp	12.5 cm (± 1.5 cm) / 4.9 in (± 0.6 in) (range 11 - 14 cm / 4.3 - 5.5 in)

Detailed handling and operating instructions as well as a list of warnings and precautions when handling BF-RhodoLED® XL are provided in the user manual.

In case of lamp failure the BF-RhodoLED® can be used. The BF-RhodoLED® is substantially equivalent to the BF-RhodoLED® XL in terms of wavelength and light dose (energy). As in the BF-RhodoLED® XL the total light dose of 37 J/cm^2 is achieved in 10 min. Please note that in case the BF-RhodoLED has to be used, the distance to the treated skin must range between 5-8 cm. Please refer to the BF-RhodoLED® user manual for details.

8.2 Storage

At the study sites, study medication has to be stored at 2 °C to 8 °C (36 °F-46 °F) (rounded) in a temperature-controlled cabinet, located in an area inaccessible by unauthorized persons. Used study medication can be stored at room temperature. Temperature records (minimal-actual-maximal or continuously records) should be taken on a daily basis except for weekends and holidays if manually recorded. Deviations (e.g. temperature measures outside the range of 1.5 °C to 8.4 °C (35.5 °F-46.4 °F) or problems to store BF-200 ALA appropriately after delivery at study site) have to be immediately announced to the monitor and the sponsor, and study medication cannot be used unless sponsor's release for this specific event was given.

Transport of study medication to the study sites will be temperature-controlled. The control of correct transport and measures to be taken in case of deviations are in the responsibility of Biofrontera Pharma GmbH. Each delivered study medication cannot be used unless released by sponsor.

The BF-RhodoLED® XL study lamp must be stored inaccessible to unauthorized persons.

8.3 Application of BF-200 ALA

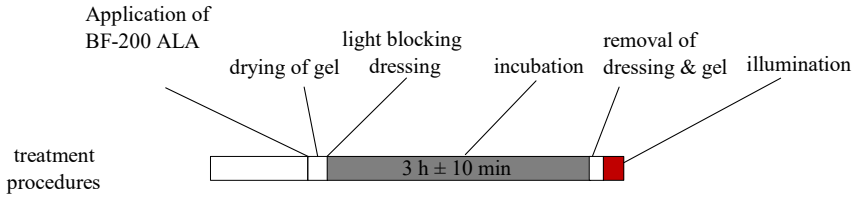
The treatment field will be localized and documented as described in Section 6.3. A treatment field does not necessarily have to be continuous, but the (discontinuous) treatment field should cover a total area of approximately 60 cm^2 and must allow illumination in one step (see Sections 6.3 and 8.4).

AK lesions located outside the specified treatment field will not be considered for treatment in this study. For treatment of these AK lesions, subjects will be treated according to standard of care at the discretion of the investigator considering requirements in Section 9. Most preferably, treatment of these lesions should be performed after final assessments at the end of the study (Visit 5).The treatment field should be prepared for IMP application by degreasing (using ethanol or isopropanol), removal of scabs and crusts, and if appropriate roughening of the surface, (e.g. by mild debridement). Care should be taken to avoid bleeding, especially when screened subjects report non-significant acquired or inherited coagulation defects and/or receive treatment with e.g. 81 mg acetylsalicylic acid per day or warfarin.

After this preparation, the content of three tubes of the IMP will be administered to the entire 60 cm² treatment field, covering the skin with a film of approximately 1 mm thickness. All AK target lesions should have a minimal distance of 1 cm to the border of the treatment field. The application will be performed using glove-protected fingertips or a spatula. Care should be taken to avoid that the study medication is applied to the upper and lower eyelids, the lip area (not past the vermilion border) and in the nostrils. In case of accidental contact of study medication with the eyes or mucous membranes, rinsing with water for at least 5 min will be performed.

The IMP will be allowed to dry for approximately 10 min, before a light-blocking, occlusive dressing (e.g. Tegaderm™ dressing plus aluminum foil) will be placed over the treatment field. After the incubation time of 3 h ± 10 min, the light-blocking, occlusive dressing will be removed and the remaining gel should be wiped off.

The incubation time starts when light-blocking, occlusive dressing is placed and ends with removal of the IMP. Figure 2 illustrates the treatment procedure.



Sequence of IMP application, placement of light-blocking, occlusive dressing, and illumination are specified. After drying of the applied study medication, incubation time starts with placement of the light-blocking dressing and ends with the removal of remaining gel followed by red light illumination.

Figure 2: Sequence of BF-200 ALA application, placement of light-blocking, occlusive dressing, and illumination at Visit 2.

The following information concerning this procedure will be documented in the eCRF:

- Preparation of the treatment field including lesions
- Occurrence of bleedings in the application area
- BF-200 ALA application start time
- Incubation time: start and stop time

8.4 Illumination with BF-RhodoLED® XL

After removal of remaining gel, the entire treatment field will be illuminated for 10 min with the BF-RhodoLED® XL until a total light dose of approximately 37 J/cm^2 is achieved. During illumination, the lamp will be positioned in 11 cm to 14 cm (optimum: 12.5 cm) distance from the skin surface as indicated in the user manual. Please also refer to Section 8.1.2.

In case of a discontinuous treatment field the treatment field must be covered by one illumination area.

During illumination, subjects and medical personnel must wear suitable protective eye goggles, even if PDT is performed in areas where little light reaches the subject's eyes.

Detailed handling and operating instructions as well as a list of warnings and precautions when handling BF-RhodoLED® XL can be derived from the user manual.

Discomfort and pain during illumination are caused by the intended phototoxic reaction. Although the emitted light is in the visible red spectrum and has no emission in the (heat-transmitting) infra-red light spectrum, submitted energy to the skin may create a warming sensation. In addition, some subjects may have the feeling of being burned. The latter is caused by a transient physiological reaction, which is in some subjects very unpleasant. The underlying biochemical reaction during illumination involves the activation of heat sensitive nerve endings in the skin, which may be enhanced by a strong psychological component (31).

As pain might be experienced during illumination investigators may consider to apply pain relieving measures prior to, during or post illumination considering requirements outlined in Section 9.2. However, pain will be evaluated by all subjects after the treatment.

The subject should be informed about restrictions defined in Table 4 and in Section 9.2. Although a nearly complete loss of PpIX by photobleaching is assumed to occur during illumination, subjects should avoid exposure to intensive sun light for about 48 h since new PpIX may accumulate from remaining ALA. Thus, additional light exposure may enhance the typical side effects of PDT. Subjects should not expose themselves to intensive ultraviolet (UV)-radiation (solarium, sun bathing, etc.) during the course of the study (see also Section 7.4) to avoid UV induced post inflammatory hyperpigmentation of the healing tissue.

A surgical dressing of the treated area is normally not required and should be avoided whenever possible.

The following information concerning this procedure will be documented in the eCRF:

- The correct distance within the indicated range was achieved prior to the start of illumination (yes/no)
- Panel number of used panels
- Illumination time: start and stop time
- In case of premature termination: reason for premature termination, remaining treatment time and applied light dose
- In case of interruption(s): frequency of interruption(s), total duration of interruption(s), reason for interruption(s)
- Pain intensity reported by the subject during illumination (according to NRS-11)
- Pain relieving measures taken prior to, during and post illumination (physical measures (e.g. cold compress, cooling, nebulized water) and/or concomitant medication)

8.5 Dosage schedule

One PDT session with the content of 3 tubes of BF-200 ALA will be applied according to the study design described in Section 6.1, Section 8.3, Section 8.4 and Figure 1.

8.6 Treatment assignment

This is a non-randomized, open-label study, i.e., all eligible subjects will receive active treatment.

8.7 Blinding, packaging, and labeling

This is an open-label study. i.e., blinding is not applicable..

8.7.1 Investigational medicinal product

The sponsor will ascertain that all study medication is manufactured and packaged in accordance with regulatory requirements and the principles of Good Manufacturing Practice (GMP).

Responsible for manufacturing and release of BF-200 ALA:

Biofrontera Pharma GmbH
Hemmelrather Weg 201
51377 Leverkusen
Germany

The appropriate number of tubes and cardboard boxes will be labeled in English according to the pre-defined distribution of identification numbers. The labels will include all information required by 21 CFR 312.6 (including the statement: “Caution: New Drug—Limited by Federal (or United States) law to investigational use”).

For each subject, a cardboard box is provided containing three tubes with BF-200 ALA. Each box is labeled with tear-off label and can be identified and assigned to a specific subject by a unique identification number.

In addition, each tube will be labeled accordingly. This label information must be documented in the appropriate space in the subject’s source data when the IMP is dispensed prior to PDT.

Additional statements may be printed on the label as required by local regulations.

The sponsor will maintain a complete record of batch numbers and expiry dates of the IMP and the labels of the IMP in the Trial Master File (TMF).

8.7.2 Investigational medical device

BF-RhodoLED® XL will be distributed, installed and maintained at the sites by technicians or other properly trained delegates of:

Biofrontera Inc.
120 Presidential Way, Suite 330
Woburn, MA 01801
USA

The appropriate number of lamps will be labeled in English as investigational device in accordance with 21 CFR 801.1 and 21 CFR 812.5. Labels will include:

- the name and place of business of the sponsor, manufacturer, and distributor
- the statement: “CAUTION Investigational device. Limited by Federal (or United States) law to investigational use”).
- and/or references to all relevant contraindications, hazards, adverse effects, interfering substances, warnings and precautions.

For the purpose of this study, the study sites will be provided with one BF-RhodoLED® XL lamp. It is exclusively intended to be used in conjunction with study medication within the scope of clinical trials conducted by Biofrontera. As the lamp will be installed at the site by a technician or delegate of Biofrontera, there will be no immediate packaging available. All labeling will be applied directly to the lamp.

8.8 Supplies and accountability

After the study protocol is approved or accepted by the Institutional Review Board(s) (IRB(s)) and by FDA, the sponsor will initiate the study sites which includes installation of a BF-RhodoLED® XL lamp, and thereafter supply the study sites with study medication, together with all relevant documentation. The sponsor is responsible for delivery of the investigational products to the study sites.

The investigator will inventory and acknowledge receipt of all shipments of the IMP and IMD. The investigator is responsible for maintaining documentation showing the amount of investigational products provided to the study site and the used IMP for each study subject. Discrepancies in accountability of the investigational products must be explained and documented. The monitor is responsible to verify the investigator's documentation on receipt, use, and return of the investigational products. The monitor will check drug and medical device accountability at the study sites on an ongoing basis during the study. At the end of the study, all remaining study medication or empty tubes must be returned to the drug supplier acting on behalf of Biofrontera Pharma GmbH for disposal. The monitor will prepare a final report of accountability of the investigational products for filing in the investigator site file (ISF).

After the last subject completed the treatment and no further trials are planned, all lamps will be returned to Biofrontera Inc. Receipt and return of BF-RhodoLED® XL will be acknowledged and documented accordingly.

8.9 Compliance

The application of study medication will be administered/supervised by the investigator or subinvestigator. Any delegation of this responsibility should follow the guidelines stated in Section 15.2.

The study medication will never be handed out to the subjects, rendering individual compliance assessments unnecessary.

BF-RhodoLED® XL lamp will be exclusively operated by previously trained study personnel.

9 PRIOR AND CONCOMITANT MEDICAL CONDITIONS AND TREATMENTS

9.1 Prior and concomitant medical conditions

Medical history is an account of medical events that the subject has experienced in the past. The medical history will be recorded in the source data. However, only relevant medical history as judged by the investigator will be recorded in the eCRF. The investigator must document in the source data, which medical history is considered relevant for this study. For this study, transient amnestic episodes and TGA are considered relevant (28).

Diseases or illnesses including skin conditions present at the time of signing the informed consent are regarded as concomitant medical conditions and will be recorded in the eCRF.

Medical conditions first occurring or detected during the study, and worsening of a concomitant condition during the study, are to be regarded as AEs and must be documented in the AE section of the eCRF (see Section 11).

9.1.1 Medical skin history

At the screening visit relevant medical skin history as judged by the investigator should be documented in the eCRF. In case of AK, NMSC and melanoma history the following information will be documented in the eCRF additionally:

- Is this the first diagnosis of AK? If AK was diagnosed in the past, indicate date of first AK diagnosis.
- Were AK lesions diagnosed in the past located within the selected treatment area(s)? If previous AK events were treated in this treatment area(s), please indicate therapy and start date of therapy.
- Were there diagnoses of NMSC (e.g. BCC, SCC, Bowens disease) or melanoma in the past? If yes, report indication and first diagnosis and the total number of diagnosed lesions (1, 2-5, > 5) since first diagnosis. In case, such a lesion was diagnosed in the past, did the lesion occur within the selected treatment area(s)?

For other relevant skin history the information about indication and date of first diagnosis is sufficient.

9.2 Prior and concomitant medications/treatments

Any medication taken by a subject or treatments the subject is undergoing that are not related to any study-specific procedures (PDT with IMP), starting with the time of signing the informed consent until the end-of-study are considered concomitant medications or treatments. The use of required concomitant medications or treatments, which are known not to interfere with the IMP or to mask its effect, is unrestricted and may be continued during the study.

The following treatments are examples for permitted treatments in the designated time periods to alleviate pain and discomfort (please consider the information provided in the respective PIs). Other treatments are also allowed as long as they are not explicitly forbidden in Table 4:

- Prior to illumination
  - Acetaminophen (e.g. Tylenol®), ibuprofen up to 1200 mg per day, aspirin up to 3750 mg per day, ice gel/spray and/or application or injection of a local, fast-acting anesthetic, such as xylocaine or lidocaine.
- During illumination
  - In cases where the pain is regarded as unbearable by the subject, the illumination may be interrupted and/or cooling with an air stream and/or nebulized water may be offered.
  - Severe cases of pain might require to briefly interrupt illumination, e.g. to inject or apply a local, fast-acting anesthetic, such as xylocaine or lidocaine or to cool briefly with cooling packages.
- Treatment of pain and discomfort post illumination
  - Cooling the illuminated area(s) with wet or refrigerated compresses
  - Analgesic treatment with acetaminophen (e.g. Tylenol®) or NSAIDs (ibuprofen up to 1200 mg per day / aspirin up to 3750 mg per day)
  - Application of an analgesic cream

All concomitant medications/treatments or relevant concomitant medications/treatments taken/underwent during the study, must be documented in the eCRF along with the indication, route of administration, single dose, frequency of administration, as well as start and stop date of administration. The subject should confer with the investigator prior to the use of new medication until the end of the study.

The following concomitant treatments/procedures are not permitted:

- Any therapy such as cryosurgery, laser therapy, electrodessication, surgical removal of lesions, curettage, or treatment with chemical peels such as trichloroacetic acid inside or in close proximity (< 10 cm distance) to the treatment field 4 weeks prior to screening until end-of-study. Lesions may be treated with these methods if the distance to the treatment field is more than 10 cm.
- A list of forbidden, concomitant medication is provided in Table 4.

If the investigator, at any time in the study, suspects a lesion inside or outside the treatment field to have progressed into a manifest malignancy, they should refer the subject for standard medical treatment, irrespective of whether or not this results in exclusion of the subject from the study.

Table 4: List of forbidden concomitant medication with designated time periods.

Medication	**Topical administration**		**Systemic administration**	
	start of restriction	forbidden until	start of restriction	forbidden until
ALA or ALA-esters (except IMP at Visit 2)	8 weeks prior to Visit 1	end-of-study	12 weeks prior to Visit 1	end-of-study

Medication	**Topical administration**		**Systemic administration**	
	start of restriction	forbidden until	start of restriction	forbidden until
Cytotoxic drugs/ Cytostatic drugs	8 weeks prior to Visit 1 inside or in close proximity (< 10 cm distance) to the treatment field	end-of-study inside or in close proximity (< 10 cm distance) to the treatment field	6 months prior to Visit 1	end-of-study
Immunosuppressive therapies	8 weeks prior to Visit 1 inside or in close proximity (< 10 cm distance) to the treatment field	end-of-study inside or in close proximity (< 10 cm distance) to the treatment field	12 weeks prior to Visit 1	end-of-study
	7 days prior to PDT inside and outside the treatment field	7 days post PDT inside and outside the treatment field		
Interferon	---	---	6 weeks prior to Visit 1	end-of-study
Glucocorticosteroids	(allowed)	(allowed)	6 weeks prior to Visit 1[a]	end-of-study[a]
NSAIDs (others than listed below)	7 days prior to PDT	7 days post PDT	7 days prior to PDT	7 days post PDT
Acetylsalicylic acid > 3750 mg/day	---	---	7 days prior to PDT	7 days post PDT
Ibuprofen > 1200 mg/day	---	---	7 days prior to PDT	7 days post PDT
Diclofenac	7 days prior to PDT within illumination area(s)[b]	7 days post to PDT within illumination area(s)[b]	> 100 mg/day; 7 days prior to PDT	> 100 mg/day; 7 days post PDT

Medication	**Topical administration**		**Systemic administration**	
	start of restriction	forbidden until	start of restriction	forbidden until
Hypericin or drugs with phototoxic/ photoallergic potential[c]	4 weeks prior to Visit 1 inside or in close proximity (< 10 cm distance) to the treatment field	end-of-study inside or in close proximity (< 10 cm distance) to the treatment field	8 weeks prior to Visit 1	end-of-study
Investigational drugs	8 weeks prior to Visit 1	end-of-study	8 weeks prior to Visit 1	end-of-study
Drugs known to have major organ toxicity	---	---	8 weeks prior to Visit 1	end-of-study
Medication that influence coagulation (e.g. anticoagulants, anti-platelet drugs)	---	---	Visit 1 (may be used throughout the study if taken in a stable dose prior to study)	end-of-study (may be used throughout the study if taken in a stable dose prior to study)
EMLA® cream	On day of PDT inside or in close proximity (< 10 cm distance) to the treatment field	On day of PDT inside or in close proximity (< 10 cm distance) to the treatment field	---	---

[a] Not for inhaled glucocorticosteroids.
[b] Topical use of diclofenac up to 2.5 % may be used outside illumination area(s) throughout the study.
[c] Start of therapy with any photosensitizer or systemically-acting drugs with phototoxic or photoallergic potential, such as psoralenes, tetracyclines, nalidixic acid, furosemide, amiodarone, phenothiacines, chinolones, fibrates, or phytotherapy with St. John's wort, arnica, or valerian or topically applied phototoxic substances like tar, pitch, psoralenes or some dyes like thiazide, methylene blue, toluidine blue, eosin, rose bengal, or acridine within 4 weeks for topical administration or 8 weeks for systemic administration prior to screening. Subjects may, however, be eligible if such medication was taken longer than 4 weeks (topical) or 8 weeks (systemic) prior to screening without evidence of an actual phototoxic/photoallergic reaction.

10 STUDY PROCEDURES AND SCHEDULE

All data obtained from subjects, e.g. assessments, questionnaires and examination results, should be sufficiently documented in source.

10.1 Description of study days

Table 1 summarizes the study schedule.

10.1.1 Screening visit (≤ 14 days prior to PDT)

Potential subjects will be evaluated to determine if they fulfill the inclusion and exclusion criteria (see Sections 7.3 and 7.4).

Each subject will be assigned a six-digit subject number (consisting of a three-digit site number and a three-digit subject screening number) in the chronological order of enrollment within each site (e.g. 801-001). For this purpose, the next higher subject number is always assigned. This number will be documented and will be used to identify the subject. New subjects must always be assigned a new subject number.

The following procedures will be performed at Visit 1 (screening) and recorded in the eCRF:

- Obtain informed consent prior to any study-related procedures
- Assign subject number
- Obtain demographic data
- Document concomitant medical conditions and relevant medical history
- Document medical skin history (including NMSC (such as BCC, SCC or Bowens disease), melanoma, AK and other skin diseases)
- Document concomitant medications/treatments
- Document body measures
- Measure vital signs
- Physical examination
- Neurological assessments
- Check inclusion and exclusion criteria
- Assess skin type according to Fitzpatrick, 1988 (32)
- Select the treatment field and assess AK target lesions (size, number, location and clinical severity assessment according to Olsen et al., 1991 (33)). In case of severe AK lesions, a biopsy must be taken for confirmation of diagnosis.
- Generate graphic templates of the treatment field and location of AK target lesions on provided cartoon. The location of the treatment field and the AK lesions within in the treatment field as well as any AK lesions in close proximity (< 10 cm distance) to the treatment field should marked on a grid foil for re-identification during the course of the study.

- Clinical laboratory tests (including routine hematology and blood chemistry, serum pregnancy test for females of reproductive potential, and urinalysis). Please document if the subject was in a fasted state or not.
- Documentation of (S)AEs.
- Instruct subject about forbidden concomitant medications/treatments (see Section 9.2 and Table 4).

10.1.2 Visit 2/ Baseline/ Treatment (PDT)

The following procedures will be performed at Visit 2 and recorded in the eCRF:

- Re-evaluation of inclusion and exclusion criteria for confirmation of subject's eligibility
- Evaluation of dosing day exclusion criterion
- Neurological assessments prior to PDT and 60 (±10) min after end of illumination
- Skin assessment regarding new lesions (AK, NMSC, and melanoma) inside or in close proximity (< 10 cm distance) to the treatment field. NOTE: Occurrence of NMSC and melanoma will lead to exclusion of the subject
- Pregnancy test (urine) for females of reproductive potential prior to PDT
- Measurement of vital signs after subject's arrival at the site, within 10 min before start of illumination, within 10 min after end of illumination and 60 (±10) min after end of illumination
- Preparation of the treatment field and administration of study medication (3 tubes) should be applied to a total area of approx. 60 cm^2), and after drying of the gel application of a light-blocking, occlusive dressing according to treatment description in Section 8.3
- Illumination of the treatment field with the BF-RhodoLED® XL lamp until a total light dose of 37 J/cm^2 is achieved (according to treatment description in Section 8.4). In case of a discontinuous treatment field all patches must be within one illumination area (see Section 8.1.2)
- Assessment of application site pain during illumination via NRS-11
- Documentation of (S)AEs including application site skin reactions, application site discomfort, and new lesions. Application site skin reactions and application site discomfort should be assessed directly after illumination (within 10 min) and should be re-assessed 60 (±10) min after end of illumination (occurrence and severity).
- Documentation of concomitant medications/treatments including medications/treatments for pain management that might be required prior to, during or post illumination (see Section 9.2 and Table 4)
- Inform subjects to avoid sunlight, prolonged or intense light (e.g., tanning beds, sun lamps) on the treatment field for approximately 48 hours following treatment whether exposed to illumination or not

- Explanation and handout of subject diary to document AEs, their impact on the subject's daily life, and concomitant medication until the end of the study

10.1.3 Visit 3 Safety Interim Visit (7 (± 2) days post PDT)

The following procedures will be performed at Visit 3 and recorded in the eCRF:

- Measurement of vital signs
- Skin assessment regarding new lesions (AK, NMSC, and melanoma) inside or in close proximity (< 10 cm distance) to the treatment field since the last visit
- Documentation of concomitant medications/treatments (please see also listing of allowed and restricted medications in Section 9.2) with consideration of subject's diary
- Documentation of (S)AEs, including application site skin reactions and application site discomfort, and new lesions with consideration of subject's diary

10.1.4 Visit 4 Safety Interim Visit (14 (± 2) days post PDT)

The following procedures will be performed at Visit 4 and recorded in the eCRF:

- Measurement of vital signs
- Skin assessment regarding new lesions (AK, NMSC, and melanoma) inside or in close proximity (< 10 cm distance) to the treatment field since the last visit
- Documentation of concomitant medications/treatments (please see also listing of allowed and restricted medications in Section 9.2) with consideration of subject's diary
- Documentation of (S)AEs, including application site skin reactions and application site discomfort, and new lesions with consideration of subject's diary

10.1.5 Visit 5 Final Visit (28 (± 7) day post PDT)

The following procedures will be performed at Visit 5 and recorded in the eCRF:

- Measurement of vital signs
- Physical examination
- Collection of blood and urine samples for safety laboratory tests including serum pregnancy test for females with reproductive potential and urinalysis
- Skin assessment regarding new lesions (AK, NMSC, and melanoma) inside or in close proximity (< 10 cm distance) to the treatment field since the last visit
- Documentation of concomitant medications/treatments (please see also listing of allowed and restricted medications in Section 9.2) with consideration of subject's diary
- Documentation of (S)AEs, including application site skin reactions and application site discomfort, and new lesions with consideration of subject's diary

- Collection of subject diary

10.1.6 Unscheduled visit

In case of unexpected safety assessments unscheduled visits can be performed.

10.2 Assessments

10.2.1 Evaluation of demographic data

The following information will be obtained as demographic data from all participants at screening visit:

- Sex
- Age
- Race
- Ethnicity

10.2.2 Body measures

The following information will be obtained as body measures from all participants at screening visit:

- Height (in)
- Weight (lb)

10.2.3 Clinical criteria for diagnosis of AK

Lesions will be considered AK if they present clinically as rough, crusted, flesh-colored to reddish-brown papules, or with an adherent scale in a field of sun-damaged skin (34–36).

AK lesion severity will be evaluated according to the Olsen Severity Grading (33) as follows:

- **No AK/grade 0** i.e. no AK lesion present, neither visible nor palpable
- **Mild/grade 1** AK lesions should present flat, pink maculae without signs of hyperkeratosis and erythema. The lesions should be slightly palpable, with AK better felt than seen.
- **Moderate/grade 2** AK lesions should present as pink to reddish papules and erythematous plaques with hyperkeratotic surface. These AK lesions should be moderately thick and can be easily seen and felt.
- **Severe/grade 3** AK lesions should present as very thick plaques with hyperkeratotic surface. These AK lesions should be very thick and/or obvious.

Additionally, a biopsy must be obtained for every severe AK lesion to confirm the diagnosis of AK at the screening visit.

10.2.4 Assessment of AK target lesions and documentation of new lesions

In this clinical trial, at least 8 AK lesions of mild to moderate intensity (according to Olsen et al., 1991) with a minimal diameter of 4 mm must be present in the treatment field. All lesions located within the treatment field including AK lesions <4 mm as well as severe AK lesions, will be treated with field-directed PDT. Lesions included in the study should be distinguishable and entirely located within the treatment field, with a minimal distance of 1 cm between the lesion margin and the border of the treatment field. However, no distance restrictions between lesions will be applied.

All AK target lesions within the treatment field have to be counted and location (treatment area) has to be documented at Visit 1. In addition, the severity of the AK target lesions ≥4 mm and their size should be recorded by measuring the diameters (for non-circular lesions, the largest diameter and the corresponding perpendicular diameter will be measured). AK target lesions ≥4 mm should also be numbered. AK target lesions <4 mm should only be counted. Total lesion area of all lesions ≥4 mm in the treatment field will be automatically calculated in the eCRF.

The treatment field and the location of AK target lesions should be clearly sketched in the provided cartoon. The location of the treatment field and the AK target lesions in the treatment field should also be marked on a grid foil. Furthermore, at Visit 1 any AK lesions in close proximity (< 10 cm distance) to the treatment field must be plotted on a grid foil, if applicable, for identification of new AK lesions during the course of the study. At Visit 2 new AK lesions inside or in close proximity (< 10 cm distance) to the treatment field must be documented on the grid foil, if applicable. These new AK lesions must be documented as AEs and will be treated, if located within the treatment field, but will not be considered as AK target lesions. NOTE: Occurrence of NMSC and melanoma will lead to exclusion of the subject. At further visits all new lesions (AK, NMSC, and melanoma) inside or in close proximity (< 10 cm distance) to the treatment field must be drawn in the grid foil and documented as AEs.

10.2.5 Biopsy

A 2 mm punch biopsy will be taken from every severe AK lesion at the screening visit to confirm the diagnosis of AK. The biopsies will be histopathologically evaluated by a central dermatopathological laboratory.

Containers with fixation solution and shipping material will be provided by the central laboratory to the study centers.

The following laboratory is responsible for evaluating the biopsies:

[redacted]

10.2.6 Assessment of skin type

Subjects' skin type will be assessed at the screening visit using the six-level Fitzpatrick Skin Type Rating Scale (32). Further details are provided in Appendix 19A.

10.2.7 Safety

Safety measurements will be performed at the time points given in the study schedule (see Table 1).

Physical examination

The physical examination will involve head, neck, skin, lymph nodes, thorax including heart and lungs, abdomen, and musculoskeletal, peripheral vascular and nervous system status.

The outcome of the physical examination should be documented for each of these body systems. In the eCRF, only abnormal findings that are considered clinically significant are required to be reported. Clinically significant findings will be documented in the medical history (Visit 1) or afterwards as AEs.

Neurological Assessments

The following assessments serve mainly as an orientation to exclude gross neurological defects, e.g. a potential amnestic episode. Abnormal findings that are considered clinically significant will be documented in the medical history (Visit 1) or afterwards as AEs.

I Memory test – Part A

Three different picture sets (set A, set B and set C) will be provided. For each assessment timepoint a different set should be used. The subject should be presented with 3 different pictures from a specific set before the neurological investigation, which they should memorize.

II Neurological investigations

Investigation of the pupils (equality), coordination (finger-nose test), gait (balance), and sensitivity (cheeks, arms, legs).

III Memory test – Part B

The following questions will be asked to the subject:

- Can you tell me your date of birth, first and last name?
- What day of the week is it today?
- When did you arrive at the site today?
- Why are you here?
- Do you remember the PDT? (only at Visit 2 after PDT)

After the neurological investigations and answering the questions, all 5 pictures of the set will be presented to the subject who will be asked to identify the 3 pictures presented at the beginning of the examination.

Vital signs

Blood pressure (systolic and diastolic) and pulse rate will be measured after 5 min rest in supine position. Measurement of body temperature (°F).

Safety laboratory

Blood and urine sampling for clinical safety analysis can be performed in a nonfasted state. However, fasting state must be documented in source data. Fasting is defined as abstinence from food and beverage consumption (other than water) for at least 8 hours.

The following central laboratory is responsible for blood safety laboratory assessments:

[redacted]

- **Blood**

An approximately 3 ml EDTA (ethylenediaminetetraacetic acid) blood sample, and an approximately 7.5 ml serum sample will be collected. The total blood loss for safety laboratory examinations will be approximately 21 ml.

- *Clinical chemistry parameters*

  Glucose, creatinine, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), alkaline phosphatase (AP), gamma glutamyl transferase (GGT), potassium, sodium, calcium, total protein, albumin

- *Hematology parameters*

  Hemoglobin, hematocrit, red blood cell count, leukocyte count (white blood cells (WBC)) with differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count.

- **Urine**

An approximately 30 ml urine sample will be collected .The following parameters will be measured:

- *Urinalysis parameters*

  Glucose, bilirubin, ketones, specific gravity, blood, pH, protein, urobilinogen, nitrite, leucocytes.

Urinalysis will be performed at the investigational site from a sample of fresh mid-stream urine using a dipstick.

Pregnancy test in females of reproductive potential

A serum pregnancy test (β-human chorionic gonadotropin (β-hCG) test) will be performed at screening (Visit 1) and 28 days after the PDT (Visit 5). At PDT-visit (Visit 2), a urine dip-stick pregnancy test will be performed.

Adverse events

During the study, all (S)AEs have to be recorded as outlined in Section 11. If possible, each subject should be assessed by the same investigator/staff personnel throughout the study.

- **Application site reactions**

The term application site reaction encompasses all reactions occurring in the treatment field after starting PDT treatment and can be subclassified into the more specific categories application site discomfort and application site skin reactions.

- **Application site discomfort**

At Visit 2, application site discomfort during and after PDT, and at Visit 3 to Visit 5 application site discomfort after PDT will be assessed asking non-leading questions like "Have you noticed anything in the treatment surrounding areas since we last saw you?" Any signs or symptoms reported by the subject that correspond to the application site discomfort categories as outlined below should be assessed as described in Section 11.1.1.

Application site discomfort categories are for example:

- Burning
- Hyperaesthesia
- Pain
- Paraesthesia
- Pruritus
- Stinging
- Warmth
- Other

- **Application site skin reactions**

Application site skin reactions will be evaluated by the investigator (or delegate) during and after PDT at Visit 2 and at Visit 3 to Visit 5. The AE severity grading should be used (see Section 11.1.1).

The application site skin reaction categories listed below will be checked by visual inspection of the respective subject's treatment field (and documented on (S)AE eCRF page).

Application site skin reaction categories are for example:

- Discharge
- Erosion
- Erythema
- Exfoliation

- Fissure
- Induration
- Oedema
- Scabbing
- Skin flaking
- Ulceration
- Vesicles
- Other

- **Assessment of pain at the application site during illumination**

  At Visit 2, subjects will assess the pain experienced **during** illumination using an 11-point Numeric Rating Scale (NRS-11) ranging from 0 (no pain at all) to 10 (worst possible pain). This score should reflect the subject's respective maximum pain during illumination.

  Pain during illumination is not documented as separate AE, as it is considered as resulting from the intensity of other modalities, e.g. burning, stinging. These modalities (i.e. burning, stinging, itching) are documented and pain is rated via NRS-11. However, documenting pain as individual, additional AE is considered a double documentation. If pain is not related to illumination (e.g. neuropathic pain, headache) this is to be documented as AE nevertheless.

- **New lesions**

Any new lesions (AK, NMSC such as BCC, SCC or Bowens disease, and melanoma) inside or in close proximity (< 10 cm distance) to the treatment field have to be reported (see Section 10.2.4).

11 ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. This includes any unfavorable and unintended sign, symptom, syndrome, or illness that develops or worsens during the clinical study whether or not related to the investigational products and the study procedures.

For the purpose of the study, clinically significant abnormal results of diagnostic procedures including abnormal laboratory findings (e.g. requiring unscheduled diagnostic procedures or treatment measures or resulting in withdrawal from the study) discovered at screening will be related to medical history or are considered to be AEs if they are detected post screening. Any AEs first occurred or worsened in severity post treatment are considered as treatment-emergent adverse event (TEAE).

The severity of AEs should be assigned to one of the following categories:

- **Mild**: For example, an AE which is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: For example, an AE which is sufficiently discomforting to interfere with normal everyday activities.
- **Severe**: For example, an AE which is incapacitating and prevents normal everyday activities.

Worsening of a sign or symptom of the condition under treatment will be recorded as AE and if this worsening matches any criterion for an “SAE”, it must be recorded as such (see Section 11.1.2).

Examples of AEs include one of the following or a combination of two or more of these factors:

- A new sign, symptom, illness, or syndrome.
- Worsening of a concomitant or pre-existing condition.
- An effect of the IMP or concomitant medication.
- An effect of the IMD, if applicable
- An effect of an invasive procedure required by the protocol.
- An accident or injury.

AEs can be categorized as “non-serious” and “serious” (see Section 11.1.2).

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required is an AE, if it occurs or is detected during the study period. Planned surgical measures and the condition(s) leading to these measures are not AEs, if the condition(s) was (were) known before the study period (see

Section 9.1) and do not worsen during the study. In the latter case, the condition should be reported as medical history.

11.1.2 Serious adverse events

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death.
- Is life-threatening.

  "Life-threatening" means that the subject was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.

  This means that hospital inpatient admission or prolongation of hospital stay were required for the treatment of the AE, or that they occurred as a consequence of the event.
- Results in persistent or significant disability or incapacity.

  "Persistent or significant disability or incapacity" means a permanent or significant and substantial disruption of a person's ability to carry out normal life functions".
- Is a congenital anomaly or birth defect.
- Is an important medical event.

  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred.

  Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require interventions to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasia, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

  A diagnosis of a second cancer during a treatment should be considered as medically important.

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

11.1.3 Alert terms and other reasons for expedited reporting to Pharmacovigilance

No particular AEs are subject to reporting as alert terms in this study.

For details on known adverse reactions see Ameluz® PI (28) and corresponding IB.

Although not regarded as an SAE, any pregnancy in a subject occurring during treatment with the investigational products must be reported to the sponsor immediately. Information related to the pregnancy must be given on a "Pregnancy report form" that will be provided by the sponsor. This information must be provided regardless of the decision to withdraw the subject from the study or discontinue the treatment.

11.1.4 Investigational medicinal product complaints

Complaints associated with the IMP quality must be reported to the sponsor.

11.1.5 Investigational medical device complaints

All AEs reported in previous studies were not directly related to the PDT lamp e. g. BF-RhodoLED® but rather to the medication or PDT. Therefore, we do not expect any AEs affecting subjects or third persons (e.g. study personnel) that relate directly to BF-RhodoLED® XL also referred to as Adverse Devise Effects (ADEs), provided that it is properly used as described in the user manual.

Nevertheless, if occurring ADEs as well as technical complaints associated with the medical device BF-RhodoLED® XL must be reported to the sponsor and IRB (in cases of (U)SADEs)

ADEs reported by the treated subject must be reported via the eCRF.

11.2 Period of AE collection

Collection of AEs starts with signing the informed consent documents until the end of the study. AEs will be discriminated as pre-treatment adverse events (PTAEs) and TEAEs.

- AEs developing between signing the ICF and IMP application at Visit 2 will be considered as PTAEs and documented as an AE.
- TEAEs are defined as all AEs or SAEs with onset or worsening after treatment with IMP up to Visit 5
- If the investigator detects an SAE in a subject after end of study, and considers the event possibly related to prior study treatment or procedures, he/she should report this event to the pharmacovigilance department of the sponsor (see Section 11.3.1).

11.3 Documentation and reporting of adverse events by investigator

All AEs as well as any SAE that occur throughout the study must be documented in accordance with the instructions for the completion of (S)AE reports in clinical studies. If possible, AEs should be assigned to be either unrelated (corresponding to unrelated or unlikely related) or related (corresponding to probably, possibly or definitely related) to the IMP or the IMD, or both, as this will be important for evaluation of the safety of BF-200 ALA or the PDT lamp.

The following approach will be taken for documentation:

- **All AEs** during the study (whether serious or non-serious) must be documented.
- If the severity category of an AE changes, the date of change and the new severity category must be documented.
- If the AE is serious (see Section 11.1.2), the investigator must complete, in addition to the "Adverse Event" page in the eCRF, a "Serious Adverse Event/Expedited Report from a Clinical Trial for Combination products" (SAE report) form at the time the investigator became aware of the SAE. This form must be marked as "initial" and be sent immediately (within 24 h) to the sponsor's Pharmacovigilance department by email or fax (according to Biofrontera's Standard Operating Procedure (SOP)). SAEs must be identified as such in eCRF by stating the applicable SAE criteria that were met.
- When a "significant overdose" of IMP occurs without an AE or in other situations where the sponsor requires an expedited report without an AE (see Section 11.1.3), this information should be provided by the investigator via the "SAE report" form. It should be clearly stated that no AE was observed. In this case, there is no need to complete the "Adverse Event" page in the eCRF.
- The following details regarding AEs are required:
  - confirmed medical diagnosis or symptoms (if applicable)
  - location (treatment area(s))
  - category: general, application site skin reaction, application site discomfort or new lesion
  - time frame (by providing start/stop date and time)
  - severity and date of change of the respective severity category if applicable (see Section 11.1.1). On the first day of AE occurrence only the maximum severity has to be documented.
  - outcome (recovered/resolved, recovering/resolving; recovering with sequelae, not recovered/not resolved, fatal, unknown)
  - action taken (with reference to concomitant medications/treatments)
  - seriousness criteria (if applicable), and
  - if the AE is related to IMP only, IMD only, or both (cannot be ambiguously assigned to one of both).
- **For new lesions**: inside or in close proximity (< 10 cm distance) to the treatment field
- The causality/relatedness of AEs has to be assessed:
  - UNRELATED: AEs that are judged to be clearly and incontrovertibly due to a cause other than the IMP/IMD and study procedure (concomitant disease etc.).
  - UNLIKELY RELATED: the temporal sequence is atypical, and the AE does not follow a known pattern of response to IMP/IMD another causative factor is present but causal role of the study drug cannot be excluded.

- POSSIBLY RELATED: either an event that is temporally associated with the use of the IMP/IMD or a known pharmacological effect/associated reaction, which is also recognized with another concomitant therapy/disease or other external cause.
- PROBABLY RELATED: appropriate temporal association, known pharmacological effect, recognized to be an associated IMP/IMD reaction and for which no other possible cause is evident.
- DEFINITELY RELATED: the reaction has occurred with this IMP/IMD previously (i.e. positive re-challenge) and there is an appropriate temporal relationship between therapy and reaction; and the reaction follows a known or expected response pattern to the suspected drug.

The investigator should use medical judgment to determine whether he/she assumes a reasonable causal relationship, including into his/her evaluation all relevant factors and factual evidence such as

- temporal course and latency
- results from re-challenge
- pattern of the reaction
- known pharmacological properties of the product
- and alternative explanations (e.g. other drugs, medical history, concomitant diseases).

Every attempt should be made to describe the AE in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded as separate AEs unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be documented as separate events. In the case of SAEs or SARs, respectively, component signs and symptoms may be recorded in addition to a diagnosis if they further clarify the clinical picture. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

All subjects who have AEs, whether considered associated with the use of the IMP and/or the IMD or not, should be monitored to determine the outcome. The clinical course of the AE will be followed up according to standard of care, even after the end of the study, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate the follow-up. Should the AE result in death, a full pathologist's report should be supplied, if possible.

11.3.1 Immediate reporting

11.3.1.1 Reporting of SAEs to sponsor

SAEs observed throughout the study must be documented on an "SAE report" form in accordance with instructions for completing the "SAE report" form. This form and the instructions will be provided in the investigator file and must be completed and supplied immediately (within 24 h) to the sponsor (21CFR§ 312.32, 21CFR§ 312.64).

Any SAE that occurs throughout the study, whether or not related to the IMP or the medical device, must be reported by the investigator within 24 h by fax, or by e-mail, to the following contact data:

Email: [redacted]
Fax: [redacted]

The initial report must be as complete as possible, including details of the current disease and (serious) AE, and an assessment of the causal relationship between the event and the IMP or IMD or study procedures.

Information not available at the time of the initial report (e.g. an end date for the AE or laboratory values received after the report) must be documented on an "SAE report" form, with the box "Follow-up"/"Final report".

The instructions for completing the "SAE report" form give more detailed guidance on the reporting of SAEs, and AEs initially reported as non-serious that become serious. In the latter situation, when a non-serious event becomes serious, details must be forwarded immediately (within 24 h) to the sponsor on an "SAE report" form.

Note:

For regulatory reporting purposes, events which are assessed by the sponsor as "unrelated" or "unlikely related" to the study medication will be considered as having no reasonable causal relation and will not be reported on an expedited basis.

Events assessed by the sponsor as "possibly, probably or definitely related" will be considered as having a plausible causal relation to the study medication and will be reported if they are also considered unexpected and serious.

The sponsor will ensure that all legal reporting requirements to the competent authorities and the IRB(s) are met (see Section 11.4.2).

11.3.1.2 Reporting of pregnancies to sponsor

Pregnancies occurring during a subject's participation in the study, although not typically considered SAEs, must be notified to the sponsor within the same timelines as an SAE (within 24 h after becoming aware of the pregnancy) on a pregnancy notification form. Further treatment will be addressed on a case-by-case basis with the treating physician and the investigator.

Any pregnancy should be followed up until completion. If relevant, the development of the newborn will be monitored for an appropriate time post-delivery.

The pharmacovigilance department of the sponsor or designee has to be notified by fax or e-mail.

11.3.1.3 Reporting of USADEs to the sponsor and to IRB

Events which can be clearly assigned to the IMD and which are assessed by the investigator as "possibly, probably or definitely related" to the IMD and which are both serious and unanticipated will be considered as unanticipated serious adverse device effect (USADE). A report of any USADE occurring during an investigation shall be submitted to the reviewing

IRB and the sponsor within 10 working days after the investigator first learns of the effect (21 CFR §812.150).

In case a serious and unexpected event cannot be clearly assigned to the IMD, it should be treated as an SAE (see Section 11.1.2).

Note: Reporting of USADEs to the sponsor is equal to SAE reporting described in Section 11.3.1.1.

11.3.1.4 Expedited reporting of adverse events to IRB

The investigator will promptly forward IND safety reports received from sponsor (see Section 11.4.2) and report all unanticipated problems involving risk to human subjects or others, and changes in the research activity to the IRB. The sponsor may submit IND safety reports directly to the IRB on the investigator's behalf. Please refer to section 11.4.2.

11.3.2 Unblinding

This is an open-label study, i.e., unblinding is not applicable.

11.4 Documentation and reporting of adverse events by sponsor

11.4.1 Determination of expectedness, Reference Safety Information

Expectedness of serious AEs will be determined by the sponsor according to the designated Reference Safety Information (RSI). Any updates or substantial amendments will be considered accordingly. The RSI for the investigational products will be included in the current IB.

Unexpected: An AE or suspected adverse reaction is considered unexpected if it is not listed in the RSI or is not listed with the specificity or severity that has been observed. Unexpected, as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the RSI as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.4.2 Expedited reporting of adverse events to competent authorities and investigators

The sponsor will report all serious and unexpected AEs, which are judged by the sponsor as having a reasonable suspected causal relationship (unexpected serious suspected adverse reaction) as IND safety reports to the FDA and all participating investigators according to applicable law.

The sponsor will also report USADEs to the FDA, all reviewing IRBs and to all investigators.

The sponsor will submit IND safety reports directly to the IRB on the investigator's behalf, e.g. when the investigator submits to a central IRB, to avoid multiple submissions to the IRB. In these cases, the investigator receives confirmation that the report has been sent to the IRB by the sponsor.

11.4.3 Periodic reporting of adverse events by sponsor

A summary of all Investigational New Drug (IND) safety reports will be included in the progress report submitted annually to the competent authorities within 60 days of the international anniversary date of the product (14 June, in agreement with authorities). The same report will also be submitted to the IRB(s) to ensure a continuing review of the project.

11.4.3.1 Development safety update report (DSUR)

The sponsor will prepare and submit annual safety reports to competent authorities and concerned ethics committees.

11.5 Continuous risk assessment

The sponsor's pharmacovigilance department will apply appropriate monitoring measures to continuously survey the benefit risk ratio of the IMP, the IMD and study procedures.

12 WITHDRAWALS

12.1 Withdrawal of subjects

Subjects must be withdrawn from study (i.e. from any further study procedure) for the following reasons:

- At their own request (withdrawal of informed consent)
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being
- Upon sponsor request

In all cases, the reason for and date of withdrawal must be documented. Subjects can withdraw consent at any time of the study without being obliged to specify a reason for their withdrawal. In case of an AE causing the withdrawal of consent, the AE has to be documented as cause of withdrawal.

In case of withdrawal after IMP administration the subject should be encouraged to come to a final visit for the conduct of safety assessments (physical examination, vital signs, safety laboratory including serum pregnancy test, if applicable, AEs and concomitant medication) as soon as possible.

In case of withdrawal before IMP administration, a final visit is not necessary. The subject will be considered as a drop-out. For subjects who are withdrawn before IMP administration only the date of informed consent, demographics and date and reason for withdrawal and (S)AEs, if applicable, have to be reported in the eCRF. The data will be listed separately from data of treated subjects.

A subject will be considered lost-to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the site. The investigator must make every effort to contact subjects lost to follow-up. Attempts to contact these subjects must be documented in the subject's records (e.g. times and dates of attempted telephone contact, e-mails or copies of letters send to the subject). At least three attempts should be performed and documented.

Discontinuation date is the date on which the investigator decides that no further attempt will be made to contact the subject and the subject is declared as lost-to follow-up.

12.2 Replacement of subjects

Subjects who discontinue will not be replaced.

12.3 Withdrawal of samples

Not applicable.

13 EMERGENCY PROCEDURES

13.1 Emergency sponsor contact

In emergency situations, the investigator should contact the sponsor by phone at the number given below, if that is regarded as necessary:

[redacted] (Biofrontera contact person in the USA)

13.2 Emergency identification of investigational medicinal products

In this open-label study, all eligible subjects will receive one active treatment. For this reason, special emergency identification procedures are not applicable for this trial.

13.3 Emergency treatment

There is no substance-specific treatment for adverse reactions. For treatment of PDT associated pain and discomfort please see Section 9.2.

During and after a subject's participation in the trial, the investigator or institution should ensure that adequate medical care is provided to a subject for any AEs, including clinically significant laboratory values, related to the trial. The investigator or institution should inform a subject when medical care is needed for intercurrent disease(es) of which the investigator becomes aware.

14 STATISTICAL PROCEDURES

14.1 General considerations

The principal features of the statistical analysis are described in this section. Technical details of the statistical analyses will be specified in a statistical analysis plan (SAP). The SAP will be finalized prior to the First-subject-first-visit for the final analysis of the study. The recommendations of the ICH E9 'Note for Guidance on Statistical Principles for Clinical Trials' including the addendum R1 to ICH E9 will be taken into account.

Unless otherwise stated, continuous data will be summarized by means of descriptive statistics, i.e. number of subjects, mean, standard deviation (SD), median, quartiles and range (minimum and maximum). Categorical variables will be summarized by absolute and relative frequencies (percentages) of subjects by category. Missing values will not be included in the calculation of percentages.

Eligible subjects who withdraw from study participation before IMP administration will be considered as dropouts.

The demographic data from screening failures and dropouts prior to IMP administration are entered into the clinical database and will not be passed through the data cleaning process. Their data are listed separately from data of treated subjects.

Statistical analyses will be conducted using SAS version 9.4 or higher (SAS Institute, 2010).

14.2 Analysis variables

Study objective

The objective of the study is to evaluate the safety and tolerability of BF-200 ALA PDT, utilizing BF-RhodoLED® XL illumination, in the treatment of mild to severe AK on the face and scalp in an expanded field-directed treatment.

The endpoints of the study are:

- Frequency and severity of adverse events (AEs), serious AEs (SAEs), and treatment-emergent adverse events (TEAEs). TEAEs are defined as all AEs with onset or worsening after treatment with IMP up to Visit 5
- Duration of TEAEs including the breakdown of severity category (mild, moderate, severe)
- Assessment of new lesions (AK, NMSC such as BCC, SCC or Bowens disease, and melanoma) if they occur inside the treatment field
- Assessment of new lesions (AK, NMSC such as BCC, SCC or Bowens disease, and melanoma) if they occur around the treatment field at a distance of < 10 cm
- Application site skin reactions during and post PDT, assessed by the investigator
- Application site discomfort during and post PDT, reported by the subjects
- Application site pain during illumination, as assessed by the subjects using an 11-point numeric rating scale

- Changes in vital signs
- Safety laboratory data
- Physical examination data
- Neurological assessments

14.3 Analysis sets

Any decision for exclusion of individual subjects from an analysis population will be made before database lock in a data review meeting. Documentation concerning which subjects are to be excluded from an analysis population will be prepared and reported, i.e., as data review minutes.

- Consented set: All subjects who provided informed consent to participate in the study.
- Safety analysis set (SAF): This set will include all subjects who undergo at least one of the following treatment procedures: preparation of the treatment field, application of BF-200 ALA, or illumination. The SAF is the analysis set for all safety analyses.

14.4 Statistical methods

The planned analyses are of exploratory nature without any formal statistical hypotheses. All measured variables and derived parameters of subjects who are treated will be listed and, if appropriate, tabulated in summaries. For categorical variables, frequency counts and percentages will be used to summarize the results. Missing values will not be included in the calculation of percentages.

Descriptive statistics of continuous variables will be provided including number of observations, arithmetic mean, standard deviation (SD), median, quartiles as well as minimum and maximum.

14.4.1 Disposition of subjects and exposure

Descriptive analysis of subjects will be presented overall and per study site.

The number of subjects consented, treated, completed the study, prematurely discontinued from the study (with reason) and the number of screening failures will be displayed.

Details of IMP administration and PDT procedure will be tabulated.

14.4.2 Demographics and background characteristics

All variables concerning demographic and background characteristics will be summarized to describe the study population. Data will be presented for all subjects in the SAF.

Concomitant medications will be coded according to Anatomical Therapeutic Chemical Classification System (ATC) and number and frequency of subjects with previous or concomitant medication will be summarized.

14.4.3 Evaluation of the Safety Endpoints

Safety analyses

All safety endpoints will be analyzed descriptively and in an exploratory way. These safety analyses will be performed for the safety set. Selected safety analyses will be conducted overall and stratified by age groups, sex, skin type, and treatment area.

AEs will be coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA) version available at the day of database closure. The analysis will focus on the TEAEs. TEAEs will be summarized and tabulated according to primary system organ class and preferred term. TEAEs leading to death and TEAEs resulting in discontinuation of study will be tabulated using frequency tables.

The mean total duration of TEAEs including the breakdown of severity category (mild. moderate, severe) will be presented overall and by treatment area.

A listing of subjects with AEs will be provided for all subjects in the SAF.

The frequency of application site skin reactions and of application site discomfort will be presented overall, and per treatment area. The mean pain score (NRS-11) and the respective confidence intervals (CIs), and the range will be presented overall and by treatment area.

All laboratory values will be classified as normal or abnormal according to the laboratory's normal ranges and indicated as clinically significant or non-clinically significant by the investigator. Frequency tables for clinically significant findings will be provided. Laboratory values that are out of range and considered clinically significant will be additionally documented in the medical history (Visit 1) or as AEs (28 days after the PDT, Visit 5) and listed as such.

The analyses of variables for vital signs will focus on

A) the evaluation of the change from baseline (Visit 2, first measurement after the subject arrived at the site) to values on subsequent clinical visits and
B) The evaluation of the change on Visit 2 from baseline (first measurement after the subject arrived at the site) to values obtained prior and after illumination (until 60 min post illumination).

Descriptive analysis (number of subjects, mean, median and SD, minimum, maximum) of the time course and of changes from baseline to post baseline time points will be presented.

Physical examinations will include the following body systems: head, neck, skin, lymph nodes, thorax including heart and lung, abdomen, and musculoskeletal, peripheral vascular and nervous system.

Abnormal findings that are considered clinically significant will be additionally documented in the medical history (Visit 1) or as AEs at Visit 5 and listed as such.

In addition, neurological assessments will be performed at Visit 1, and at Visit 2 prior to PDT and 60 min after end of illumination.

Abnormal findings that are considered clinically significant will be additionally documented in the medical history (Visit 1) or as AEs at Visit 2 and listed as such.

Details of further analyses will be specified in the statistical analysis plan (SAP).

14.5 Handling of missing data

Missing data of safety variables will not be replaced. Further details on the handling of missing data will be specified in the SAP.

14.6 Interim analysis

No formal interim analysis will be performed.

14.7 Sample size justification

No sample size calculation was conducted.

14.8 Major Protocol Deviations

Not applicable. No per protocol set is defined in this study.

15 ETHICAL AND LEGAL ASPECTS

15.1 Good clinical practice

This study is to be conducted according to globally accepted standards of GCP (as defined in the ICH E6 (R2) Guideline for GCP), in agreement with the Declaration of Helsinki in its current version and in keeping with local regulations.

15.2 Delegation of investigator duties

The investigator should ensure that all persons contributing to the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions.

The investigator should immediately report any changes in study personnel to the sponsor. Any regulatory requirement regarding a change in site personnel has to be met. Besides that, the investigator should maintain a list of subinvestigators and other appropriately qualified persons to whom they have delegated significant trial-related duties.

If required by local regulations, the investigator should designate a deputy investigator with appropriate qualifications being able to fully replace the investigator in cases of absence.

15.3 Subject information, informed consent and HIPAA form

Every trial participant will receive a complete and comprehensive explanation of the significance, nature, extent, and possible risks of the trial. To this end, a detailed, written subject information sheet will be made available. In addition, an investigator/subinvestigator will carry out an oral information session during which the subjects will be given ample time and opportunity to clarify remaining questions.

Afterwards, the subject or their legal representative and the investigator/subinvestigator will sign the informed consent form (ICF). To grant direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, the subject/legal representative will also sign an agreement. Depending on the local legal requirements this agreement can be part of the ICF or a separate form, such as the HIPAA form. The original signed ICF and, if applicable, HIPAA forms will be archived in the ISF. The subject will receive a copy of these documents. The investigator will acknowledge instruction of every subject in accordance with the clinical study protocol (CSP) and the existence of a signed consent and HIPAA form.

Before valid consent has been obtained the subject will not undergo any study related procedures. The investigator should inform the subject’s primary physician about the subject’s participation in the trial if the subject agrees to this.

During the course of the trial, ICF may need to be updated and thus, requires re-consenting of subjects. The investigator /subinvestigator will inform every active trial participant in a timely manner and obtain updated ICF in line with above mentioned obligations.

15.4 Confidentiality

To ensure confidentiality the subject’s data will be collected for the clinical data base and analysis in a strictly pseudonymous form, i.e. using a subject number instead of the subject’s

name. The subject number will also be used for SAE reporting purposes. On supporting documents of an SAE report, such as hospital reports or laboratory reports, the subject's name and if required by regulations the physician's name has to be obliterated.

The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

Subject identity and personal data will be safeguarded according to national requirements on data protection.

The sponsor adheres to data protection regulations.

15.5 Protocol deviations

Protocol deviation have to be documented and explained by the investigator and/or the sponsor. Major protocol deviations have to be escalated to the sponsor. If there is a legal requirement, the investigator needs to report major protocol deviations to the responsible ethics committee (EC)/IRB.

The sponsor is obliged to report serious breaches (severe violations of GCP regulations as well as all events that affect to a significant degree, the safety or physical or mental health of the subjects of the trial or the scientific value of the trial) to the IRB(s) and the applicable authorities.

15.6 Protocol amendments

The investigators cannot alter the protocol without the sponsor's approval. If the sponsor amends the protocol all principal investigators need to agree to adhere to the amended protocol.

In case of protocol changes that might affect the subjects' safety and well-being or the validity and integrity of the study data, the amendment is deemed substantial. Minor changes to the protocol, such as administrative changes, correction of typos and inconsistencies etc. stipulate a non-substantial amendment.

15.7 Approval of the clinical study protocol and amendments

Prior to the start of the study, the CSP, subject information leaflet and ICF, and any other appropriate documents will be submitted to the IRB(s) in charge. If applicable, the documents will also be submitted to the authorities, in accordance with local legal requirements.

All ethical and legal requirements must be met before the sites can start enrolling subjects.

A protocol amendment has to be submitted to the IEC/IRB and, if required, to the regulatory authority(ies). In case of a non-substantial amendment these bodies only will be notified but they need to approve any substantial amendment to the protocol before it can be implemented. Amendments must be evaluated to determine whether the subject information leaflet and informed consent form should also be revised.

The investigator must keep a record of all communication with the IRB(s) and, if applicable, between a Coordinating Investigator and the IRB(s). This also applies to any communication between the investigator (or Coordinating Investigator, if applicable) and the authorities.

15.8 Ongoing information for ethics committee/institutional review board

Periodic reports (e.g. annually) will be generated and submitted regarding to the requirements of the respective IRB or any applicable law(s) for IRB continuing review.

15.9 Closure of the study

Upon study completion or premature termination, each investigational site will be closed.

Completion or premature termination of the study will be reported to the regulatory agency and to the IRB if required by local regulation or by the IRB(s).

Furthermore, the sponsor has the right to close a study site at any time. As far as possible, premature closure should occur after mutual consultation.

Study materials must be returned, disposed of, or retained as directed by the sponsor.

15.10 Record retention

At the close-out visit the monitor will inform the sites about the required archiving period. The investigator must obtain approval in writing from the sponsor prior to destruction of any records and must document any change of ownership.

Within the United Stated of America the investigator has a legal obligation to retain records required to be maintained under 21 CFR §312.62 for a period of 2 years, following the date a marketing application is approved for the drug and the indication for which it is being approved. In case no application is to be filed or if the application is not approved for such indication, records will be kept for two years after the investigation is discontinued and FDA is notified.

This regulation applies to:

- Adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual PDT such as:
  - Case report forms and supporting data.
  - Signed and dated consent forms.
  - Medical records including e.g. progress notes of the physician and nurse.
  - The case history of each subject shall document that informed consent was obtained prior to participation in the study.
- Records documenting disposition of the IMP and IMD (including dates, quantity, use and return to the sponsor) if the investigation is terminated, suspended, discontinued or completed.

15.11 Liability and insurance

Liability and insurance provisions for subjects will be arranged according to legal requirements. If required by legal requirements, the subjects will receive a copy of the general conditions of insurance. Liability and insurance provisions for investigators participating in this study will be defined in a separate agreement, if applicable.

15.12 Financial disclosure

Prior to the start of the study, the investigator will disclose to the sponsor any proprietary or financial interests he or she might hold in the IMP, the IMD or the sponsor company as outlined in the financial disclosure forms (e.g. Form FDA 3454 or FDA 3455). By signing the financial disclosure form the investigator is also obliged to inform the sponsor about any changes up to one year after study completion/termination.

Where required by regulation, the sponsor will also submit the financial arrangements for the study to the regulatory authorities and if applicable to the IRB(s). Similar information will be provided by each subinvestigator to whom the investigator delegates significant study-related responsibilities.

16 QUALITY CONTROL, QUALITY ASSURANCE, AND INSPECTIONS

Quality control mechanisms are implemented on a functional level and quality assurance audits will be done according to GCP (ICH Topic E6 (R2) GCP guideline) and the applicable regulatory requirements. Direct access to the on-site study documentation and medical records must be ensured.

16.1 Study monitoring and source data verification

Monitoring is the act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s). The frequency of monitoring and co-monitoring visits, and the degree of source data verification are defined in the monitoring plan. Monitoring will be done by on-site or remote visits. In addition to the monitoring visits, frequent communications (letter or email, telephone, and fax) by the clinical monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

The results of monitoring visits will be documented in monitoring reports. Issues arising will be escalated and dealt with in a timely manner. The escalation process is defined in the respective SOPs of the sponsor or contract research organization (CRO), if applicable.

Study closeout will be performed by the clinical monitor upon closure of the study.

16.2 Site audits

Audits can be conducted at any time during or after the trial to assure the validity and integrity of the study data, the protection of the right, safety and well-being of the subjects and the adherence to the protocol, to ICH-GCP, ISO 14155 (if applicable) and to the applicable legal requirements. On-site audits will be conducted by an independent auditor from the respective or the sponsor or delegate. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

16.3 Site Inspections

Domestic and foreign regulatory authority(ies) may conduct an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial. For this, the investigator/institution has to give access to all source documents, eCRFs, and other study documentation for an inspection. The investigator should inform the sponsor as soon as possible about any announced inspection. Site personnel should fully comply with inspection procedures.

17 DOCUMENTATION AND USE OF STUDY FINDINGS

17.1 Documentation of study findings

This study will be performed using an eCRF. The investigators and study site staff will receive system documentation, training, and support for the use of the eCRF.

All protocol-required information collected during the study must be entered by the investigator, or a designated representative, in the eCRF as soon as possible, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data. All data entry, modification or deletion will be recorded automatically in an electronic audit trail, indicating the individual subject, original value, the new value, the reason for change, who made the change, and when the change was made. All data changes will be clearly indicated with a means to locate prior values. The system will be secured to prevent unauthorized access to the data or the system. This will include the requirement for a user identification and password to enter or change data. The investigator will maintain a list of individuals who are authorized to enter or correct data and their system identification.

All electronic data entered by the site (including an electronic audit trail) as well as computer hardware and software (for accessing the data) will be maintained or made available at the site in compliance with applicable record retention regulations. The computerized system is able to generate accurate and complete copies of records in both human-readable and electronic form for inspection, review, and copying by regulatory authorities, the IRB(s), and auditors authorized by the sponsor.

A source data location list will be prepared and updated during the study. It will specify which types of source data are available and where they are stored (e. g. electronic or paper subject files etc.), and which data may be entered directly into the eCRF. This list will be filed in both the TMF and the investigator study file and updated as necessary. The sites can establish appropriate work sheets or record the source data directly in subjects' notes. Source data entries have to be signed and dated by the respective investigator or delegated person in compliance with the delegation log in which responsibilities and duties of the study performance are laid down. In addition, all changes and additional entries have to be made visible and signed and dated by the respective study team member.

The investigator, or designated subinvestigator, following review of the data in the eCRF, will confirm the validity of each subject's data by electronic signature. The sponsor will retain the original eCRF data and audit trail. A copy of all eCRFs completed by the site will be provided to the concerned investigator.

17.2 Use of study findings

All information concerning the product as well as any matter concerning the operation of the sponsor, such as clinical indications for the drug or medical device, the drug formula, methods of manufacture and other scientific data relating to it, that have been provided by the sponsor and are unpublished, are confidential and must remain the sole property of the sponsor. The investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the sponsor is obtained.

The sponsor has full ownership of the eCRFs completed as part of the study.

By signing the CSP, the investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. The authorities will be notified of the investigator's name, address, qualifications, and extent of involvement.

The sponsor will ensure that a final report on the study is prepared.

As required by local regulation or by the IRB(s), a summary of the clinical study will be submitted by the sponsor to the regulatory authorities and by the sponsor or investigator to the IRB(s).

The Coordinating Investigator of a multi-center trial or the Investigator in a single-center trial will be required to sign a statement in the clinical study report in which he or she confirms that, to the best of his or her knowledge, it accurately describes the conduct and results of the study.

All materials, documents, and information supplied by the sponsor to the investigator, and all materials, documents, and information prepared or developed in the course of the study to be performed under this protocol, shall be the sole and exclusive property of the sponsor.

Scientific publication of the study results may be planned mutually between the sponsor and the Investigator. Details of the publication policy will be specified in the investigator contracts.

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19 APPENDICES

Appendix A: Fitzpatrick's Skin Type Test according to Fitzpatrick (1988)

APPENDIX A

Fitzpatrick´s Skin Type Test

Fitzpatrick´s Skin Type according to Fitzpatrick, 1988 (32)

Skin type is often categorized according to the Fitzpatrick skin type scale, which ranges from very fair (skin type I) to very dark (skin type VI). The 2 main factors that influence the skin type are:

- Genetic disposition.
- Reaction to sun exposure and tanning habits.

Skin type is determined genetically and is one of the many aspects of a subject´s overall appearance, which also includes color of eyes, hair, etc. The way the skin reacts to sun exposure is another important factor in correctly assessing the skin type. Recent tanning (sun bathing, artificial tanning or tanning creams) have a major impact on the evaluation of skin color.

Please use to following questionnaires to assess subject´s skin type.

Genetic disposition					
Score	**0**	**1**	**2**	**3**	**4**
What is the color of your eyes?	Light blue, Gray, Green	Blue, Gray or Green	Blue	Dark Brown	Brownish Black
What is the natural color of your hair?	Sandy Red	Blond	Chestnut/ Dark Blond	Dark Brown	Black
What is the color of your skin (non exposed areas)?	Reddish	Very Pale	Pale with Beige tint	Light Brown	Dark Brown
Do you have freckles on unexposed areas?	Many	Several	Few	Incidental	None
Total score for genetic disposition: _____					

Fitzpatrick's Skin Type Test

(cont.)

Reaction to sun exposure					
Score	**0**	**1**	**2**	**3**	**4**
What happens when you stay in the sun too long?	Painful redness, blistering, peeling	Blistering followed by peeling	Burns sometimes followed by peeling	Rare burns	Never had burns
To what degree do you turn brown?	Hardly or not at all	Light color tan	Reasonable tan	Tan very easy	Turn dark brown quickly
Do you turn brown within several hours after sun exposure?	Never	Seldom	Sometimes	Often	Always
How does your face react to the sun?	Very sensitive	Sensitive	Normal	Very resistant	Never had a problem
Total score for reaction to sun exposure: _____					

Tanning habits					
Score	**0**	**1**	**2**	**3**	**4**
When did you last expose your body to sun (or artificial sunlamp/tanning cream)?	More than 3 months ago	2-3 months ago	1-2 months ago	Less than a month ago	Less than 2 weeks ago
Did you expose the area to be treated to the sun?	Never	Hardly ever	Sometimes	Often	Always
Total score for tanning habits: _____					

Add up the total scores of each of the three sections for calculation of subject's skin type score.

Fitzpatrick skin type will be assessed according to skin type score as follows:

Skin Type Score	Fitzpatrick Skin Type
0 – 7	I
8 – 16	II
17 – 24	III
25 – 30	IV
>30	V – VI