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Study ALA-AK-CT015,

NCT04319159

An open-label Phase I study to evaluate the pharmacokinetics of 5-aminolevulinic acid and protoporphyrin IX in human plasma under maximal use conditions after topical application of 3 tubes of BF-200 ALA 10% gel for photodynamic therapy (PDT) in subjects suffering from actinic keratosis

TITLE PAGE

CLINICAL STUDY PROTOCOL

An open-label Phase I study to evaluate the pharmacokinetics of 5-aminolevulinic acid and protoporphyrin IX in human plasma under maximal use conditions after topical application of 3 tubes of BF-200 ALA 10% gel for photodynamic therapy (PDT) in subjects suffering from actinic keratosis

Version 2.0

ALA-AK-CT015

Test Product:	BF-200 ALA (Ameluz®) [in combination with BF-RhodoLED®]
Indication:	Mild to severe actinic keratosis
Study Design:	non-randomized, open-label
Study Identifier:	ALA-AK-CT015, IND 115412, NCT: tbd
Study Phase:	Phase I study (in diseased subjects)
Investigator:	Janet C. DuBois, MD DermResearch, Inc. 8140 N. Mopac, Bldg. 3, Suite 120 Austin, TX 78759 (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	*17-Jan-2020*

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

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 and
- 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. SUSARs, related to treatment with the investigational product.

Sponsor

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 consent to the statistical part of the clinical trial protocol which is in compliance to current ICH guidelines.

Date: Signature: _____

Name (block letters): _____

Date: Signature: _____

Name (block letters): _____

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2 PROTOCOL OUTLINE

Title

An open-label Phase I study to evaluate the pharmacokinetics of 5-aminolevulinic acid and protoporphyrin IX in human plasma under maximal use conditions after topical application of 3 tubes of BF-200 ALA 10% gel for photodynamic therapy (PDT) in subjects suffering from actinic keratosis

Study no: ALA-AK-CT015 IND no: IND 115412 NTC:	Clinical Phase: I (in diseased subjects)

Study design: non-randomized, open-label

Study purpose and objectives

To assess the pharmacokinetics (PK) of the parent drug 5-aminolevulinic acid (ALA) and its active metabolite protoporphyrin IX (PpIX) during photodynamic therapy applying 3 tubes of BF-200 ALA 10 % gel (Ameluz®) in combination with the BF-RhodoLED® lamp in the systemic circulation of diseased individuals presenting with actinic keratosis (AK) on the face/scalp or in the periphery (neck/trunk/extremities) along with subjects' safety/tolerability during and after treatment. Disease severity and drug dose are supposed to represent conditions of maximal use in line with the Guidance for Industry on Topically Applied Active Ingredients (May 2019; docket no. 2019-09692) provided by the Food and Drug Administration (FDA).

Primary objectives

- Assessment of baseline-adjusted plasma concentration-time curves for ALA after a single PDT treatment applying 3 tubes of BF-200 ALA in conjunction with the BF-RhodoLED® under maximal use conditions in subjects with mild to severe actinic keratosis.
- Assessment of baseline-adjusted plasma concentration-time curves for PpIX after a single PDT treatment applying 3 tubes of BF-200 ALA in conjunction with the BF-RhodoLED® under maximal use conditions in subjects with mild to severe actinic keratosis.

Secondary objectives

- Evaluation of baseline-adjusted pharmacokinetic parameters of ALA.
- Evaluation of baseline-adjusted pharmacokinetic parameters of PpIX.
- Assessment of safety and tolerability of PDT with BF-200 ALA under maximal use conditions

Tertiary objectives

- Evaluation of unadjusted plasma concentration-time curve for ALA and evaluation of unadjusted pharmacokinetic parameters of ALA.
- Evaluation of unadjusted plasma concentration-time curve for PpIX and evaluation of unadjusted pharmacokinetic parameters of PpIX.

Investigators / study sites

One Phase I unit in the United States of America (US) will participate in this study where all study visits and procedures will be conducted. Subjects will be screened and upon eligibility subjected to PDT and PK blood sampling. Study site will consider the two strata (face/scalp versus periphery (neck/trunk/extremities)) for enrolment.

Investigational medicinal product (IMP) and medical device

IMP: BF-200 ALA

- **Description:** BF-200 ALA is a gel formulation of 10 % 5-aminolevulinic acid hydrochloride, corresponding to 7.8 % 5-aminolevulinic acid (ALA). It is FDA-approved and marketed in the US as Ameluz® for the lesion-directed and field-directed treatment of AK of mild to moderate severity on the face and scalp, in combination with BF-RhodoLED® lamp. The IMP will be packed in tubes, containing 2 g each (medication is identical to the marketed formulation).
- **Route of administration**: topical, field-directed treatment in a film of 1 mm thickness over treatment field(s) of approximately 60 cm^2 in total.
- **Dose**: Three tubes, each containing 2 g gel. Each tube contains 156 mg ALA, resulting in a total exposure of 468 mg ALA (free base).

Investigational medical device (IMD): BF-RhodoLED®

The study treatment requires illumination of treatment fields with the BF-RhodoLED® lamp (red light with emission at ~635 nm). The applied light dose of ~37 J/cm² will be achieved with a 10 min illumination. Please refer to the BF-RhodoLED® user manual for detailed lamp operating and safety instructions.

Subjects and lesions

Eligible subjects will be of all genders, between 18 and 85 years of age and suffering from at least 12 clinically confirmed AK lesions of mild to severe severity (according to Olsen et al., 1991) with a diameter of ≥ 4 mm each, either in the face/scalp (including forehead, excluding eyes, nostrils, ears, and mouth) or on neck/trunk/extremities. AK lesions must be located in one or several treatment fields with a combined area of approximately 60 cm^2. Treatment fields may be discontinuous, but up to 2 illumination areas with the BF-RhodoLED® lamp (6 cm x16 cm each) should be sufficient to illuminate the treatment fields.

Number of subjects

32 subjects (16 subjects in each stratum)

Study Duration and Dates

Screening of subjects, including diagnosis and safety analyses, will be conducted at Visit 1. The study will include two further visits (Visit 2 where the photodynamic therapy (PDT) is performed with PK blood sampling and Visit 3 for final safety assessment). The time interval between Visit 1 (screening) and Visit 2 (treatment) will be no longer than 14 days but can be extended for up to additional 14 days in case a dosing day criterion is met.

At Visit 2, three tubes of BF-200 ALA will be applied to each eligible subject. After three hours of incubation, subjects will receive PDT illumination with the BF-RhodoLED® lamp. In terms of the PDT procedure (preparation of treatment field(s), drug application, incubation, illumination), the treatment will be done according to the labels of BF-200 ALA and BF-RhodoLED® with the exceptions that 3 tubes are applied per subject and the

periphery is treated in addition to the approved treatment of head and scalp. Blood samples will be taken from subjects starting 0.5 h prior to BF-200 ALA application and then for up to 10 h afterwards. Subjects will be called by telephone for safety assessment 7 (± 3) days post Visit 2. The final Visit 3, 28 (± 7) days after Visit 2, will entail safety assessment.

Recruitment period	approx. 6 months
FSFV	approx. Feb 2020
LSFV	approx. Aug 2020
LSLV/end of study	approx. Oct 2020

Sample size

The suggested sample size for the study is 32 subjects, stratified into two groups of 16 subjects each. One of the groups will receive PDT applying 3 tubes of BF-200 ALA on the face/scalp, the other group will receive PDT applying 3 tubes of BF-200 ALA on the neck/trunk/extremities. A previous PK Phase I study under maximal use conditions in AK subjects with 1 tube of BF-200 ALA (ALA-AK-CT006) had revealed homogeneous baseline-adjusted levels of ALA and PpIX in 12 subjects, with a coefficient of variation of 53-73% in the key pharmacokinetic parameters after drug application. As statistical evaluation of PK and safety is intended to be performed as descriptive statistics only, no calculation of predictive power is required.

Inclusion and exclusion criteria

Inclusion criteria

1. Subjects with at least 12 distinctive and clinically confirmed mild to severe AK lesions (according to Olsen et al., 1991) with a diameter of ≥ 4 mm each, on either the face/scalp (including forehead, excluding eyes, nostrils, ears, and mouth) or the neck/trunk/extremities, within treatment field(s) of about 60 cm² in total. Treatment field(s) may be discontinuous but must be within 2 illumination areas of the BF-RhodoLED® lamp (6 cm x 16 cm each).
2. All genders 18 - 85 years of age (inclusive).
3. Willingness and ability of the subject to provide informed consent and to sign the Health Insurance Portability and Accountability Act (HIPAA) form. A study-specific informed consent form and HIPAA form must be obtained in writing for all subjects prior to starting any study procedures.
4. Willingness and ability to comply with study procedures, particularly willingness to receive one PDT with up to two illumination devices simultaneously.
5. Subjects with good general health and subjects with clinically stable medical conditions will be permitted to be included in the study.
6. Subjects receiving any drugs affecting coagulation (e.g. anticoagulants, anti-platelet drugs) should be on a stable dose.
7. Acceptance to abstain from extensive sunbathing and the use of a solarium during the clinical study.
8. Women of child-bearing potential must have a negative serum pregnancy test and must use an adequate and highly effective or two effective methods of contraception throughout the study.

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 within illumination areas (reassessment of subjects is allowed once if the sunburn is expected to resolve within the screening period. Reassessment can be done on the day of the actual treatment).
4. Clinically significant medical conditions making implementation of the protocol or interpretation of the study results difficult or impairing subjects' safety such as:
   a. Presence of porphyria or known photodermatoses
   b. Known diagnosis of human immunodeficiency virus (HIV) based on clinical history
   c. Metastatic tumor or tumor with high probability of metastasis
   d. Infiltrating skin neoplasia (suspected or known).
   e. Unstable cardiovascular disease (New York Heart Association [NYHA] class III, IV)
   f. Unstable hematologic (including Myelodysplastic syndrome), hepatic, renal, neurologic, or endocrine condition
   g. Unstable collagen-vascular condition
   h. Unstable gastrointestinal condition
   i. Immunosuppressive condition
   j. Presence of clinically significant inherited or acquired coagulation defect
5. Clinical diagnosis of atopic dermatitis, Bowen's disease, BCC, eczema, psoriasis, rosacea, squamous cell carcinoma (SCC), other malignant or benign tumors in the treatment field(s), or other possible confounding skin conditions (e.g. wounds, irritations, bleeding or skin infections) within or in close proximity (< 5 cm distance) to treatment field(s). (Reassessment of subjects is allowed once if wounds, irritations, bleeding or skin infections are expected to resolve within the screening period. Reassessment can be done on the day of actual treatment.)
6. Presence of strong pigmentation or tattoos or any other abnormality that may impact lesion assessment or light penetration in the treatment field(s).
7. More than moderate smoker (e.g. > 10 cigarettes/day or equivalent).
8. Suspicion of drug or alcohol abuse. For the purpose of this study, alcohol abuse is defined as more than moderate alcohol consumption (> 1 drink/day for women and > 2 drinks/day for men).
9. Physical treatment of malignant or benign tumors of the skin within the treatment field(s) and at a distance of < 5 cm to the treatment field(s) during the last 4 weeks prior to screening.

10. Any therapy such as cryotherapy, laser therapy, electrodessication, surgical removal of lesions, curettage, or treatment with chemical peels such as trichloroacetic acid within the treatment field(s), or within a radius less than 5 cm away from the treatment field(s) 4 weeks prior to screening.
11. Any topical medical treatment of the skin within the designated time period below:
    a. Topical treatment with ALA or methyl-aminolevulinate (MAL) or an investigational drug in- and outside the treatment field(s) within 8 weeks prior to screening.
    b. Topical treatment with immunomodulatory/immunosuppressive anti-inflammatory, or cytotoxic agents inside the treatment field(s) or within a radius less than 5 cm away from the treatment field(s) within 8 weeks prior to screening.
    c. Start of topical administration of medication with hypericin or other drugs with phototoxic or photoallergic potential in- and outside the treatment field(s) within 8 weeks prior to screening. Subjects may, however, be eligible if such medication was applied for more than 8 weeks prior to screening visit without evidence of an actual phototoxic/photoallergic reaction.
12. Any use of the below specified systemic treatments within the designated periods:
    a. Use of cytotoxic drugs within 24 weeks, immunomodulators or immunosuppressive therapies or use of ALA or ALA-esters (e.g. MAL) within 12 weeks, investigational drugs or drugs known to have major organ toxicity within 8 weeks, interferon or corticosteroids (oral or injectable) within 6 weeks prior to screening.
    b. 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 or applied for more than 8 weeks prior to screening visit without evidence of an actual phototoxic/photoallergic reaction.
13. Laboratory values outside the reference range that are clinically significant in the opinion of the investigator (e.g., suggesting an unknown disease and requiring further clinical evaluation according to investigator), especially aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (gamma-GT).
14. Impaired renal function (Glomerular filtration rate below 50 mL/min/1.73m² estimated by Modification of Diet in Renal Disease equation (MDRD)).
15. Positive test for HIV antibodies, Hepatitis B-virus surface antigen (HBsAg) or positive Anti-hepatitis C-virus antibody (Anti-HCV) test.
16. Significant blood donation or blood loss (≥ 500 mL) within three months prior to Visit 2.
17. Breast-feeding women.

18. Subject unlikely to comply with the protocol, e.g. inability to return for visits, unlikely to complete the study, or inappropriate in the opinion of the investigator.
19. Prior participation in the study (participation is defined as having been screened).
20. A member of study staff or sponsor staff directly involved in the conduct of the protocol or a close relative thereof.
21. Simultaneous participation in a further clinical study.

Reassessment of subjects is allowed once if sunburn, wounds, irritations, bleeding or skin infections detected at Visit 1 are expected to resolve within the screening period. Reassessment can be done on the day of the actual treatment.

Dosing day exclusion criteria:

1. Febrile or infectious illness within 7 days prior to Visit 2.
2. Subjects with sunburn, wounds, irritations, bleeding or other confounding skin conditions within illumination areas at Visit 2.
3. Use of topical NSAIDs inside and outside the treatment field(s) or systemic intake of NSAIDs within 7 days prior to Visit 2.

In case a subject meets one of the dosing day exclusion criteria, Visit 2 can be rescheduled once within 14 days. Meeting any of the dosing day exclusion criteria on the rescheduled visit will lead to discontinuation from the trial.

Procedures

- Screening
  - Assessment of eligibility along inclusion/exclusion criteria including vital signs, and physical examination
  - Blood sampling for safety laboratory and PK-baseline parameters
- PDT
  - Field-directed application of BF-200 ALA on face/scalp or trunk/neck/extremities (3 x 2 g BF-200 ALA) subsequent to degreasing and lesion preparation on a total skin area of about 60 cm², which may be discontinuous, as long as it can be covered by two illumination areas of BF-RhodoLED® lamp (6 cm x 16 cm).
  - Occlusive, light-blocking dressing of treatment fields during incubation with BF-200 ALA.
  - PDT-illumination is performed 3 h after topical application according to label. If two illumination areas are needed, two BF-RhodoLED® lamps are used simultaneously. Thus, for the entire 60 cm² treatment only one illumination step is performed.
  - For further treatment details refer to the Prescribing Information of Ameluz® and/or the user manual of BF-RhodoLED®.
- Blood sampling (approx. 10 mL/sample) for ALA and PpIX
  - At screening (Visit 1), together with the blood for the safety laboratory evaluation

- On the treatment day (Visit 2) at the following timepoints (in relation to BF-200 ALA application): -0.5; 0*; 0.5; 1; 1.5; 2; 2.5; 3**; 3.5; 4; 5; 6; 8; 10 hours;
  *: Prior to topical application
  **: Prior to illumination
- Safety assessments
  - Immediately following PDT, treatment-emergent adverse events (TEAEs) including application site skin reactions, discomfort, and pain (using an 11-point Numeric Rating Scale (NRS-11)) will be assessed
  - Subjects will be called by telephone on day 7 (±3) post PDT to assess the safety profile of the treatment
  - At Visit 3, 28 (±7) days post PDT, assessment of TEAEs including application site skin reactions and discomfort, vital signs, physical examination, and blood sampling for safety laboratory

Criteria of evaluation

Pharmacokinetics
Primary endpoints
- Baseline-adjusted plasma concentrations of ALA for obtaining baseline-adjusted plasma concentration-time curves
- Baseline-adjusted plasma concentrations of PpIX for obtaining baseline-adjusted plasma concentration-time curves

Secondary endpoints
- Baseline-adjusted AUC_{0-t}, baseline-adjusted $AUC_{0-\infty}$, baseline-adjusted C_{max}, T_{max}, $T_{1/2}$, and λ_Z for ALA (if data permit)
- Baseline-adjusted AUC_{0-t}, baseline-adjusted $AUC_{0-\infty}$, baseline-adjusted C_{max}, T_{max}, $T_{1/2}$, and λ_Z for PpIX (if data permit)

Safety
- Local and overall tolerability, pain assessment (NRS-11), safety laboratory, physical examination, and vital signs

Tertiary endpoints
- Unadjusted plasma concentration-time curve for ALA and pharmacokinetic parameters of ALA: unadjusted AUC_{0-t}, unadjusted $AUC_{0-\infty}$, unadjusted C_{max}, T_{max}, $T_{1/2}$, and λ_Z if data permit
  Unadjusted plasma concentration-time curve for PpIX and pharmacokinetic parameters of PpIX: unadjusted AUC_{0-t}, unadjusted $AUC_{0-\infty}$, unadjusted C_{max}, T_{max}, $T_{1/2}$, and λ_Z if data permit

Statistical methods

- **Pharmacokinetics**
  Individual plasma concentrations and baseline-adjusted plasma concentrations of ALA and PpIX will be listed and summarized. Graphical displays will be provided as appropriate. If data permit, calculation of pharmacokinetic parameters will be performed on baseline-adjusted (and unadjusted) plasma concentration data of ALA

and PpIX. The results will be listed and summarized as appropriate. Data will be analyzed overall and according to strata. • **Safety** Safety results will be listed and summarized using descriptive statistics. Data will be analyzed overall and according to strata.
Bioanalytics • Bioanalyses of ALA and PpIX in plasma will be performed using internally standardized liquid chromatography tandem mass spectrometry methods.
End of study Last subject last visit

Table 1: Study schedule

	All subjects			
	Visit 1	**Visit 2[a]**	**Phone call**	**Visit 3**
	Screening	**PDT/baseline**		**EoS**
	≤ 14 days prior to PDT	**Day 0**	**7 days (± 3 days) post PDT**	**28 days (± 7 days) post PDT**
Clinic visit	X	X		X
Informed consent/HIPAA	X			
Assign subject number	X			
Demographics	X			
Inclusion/ exclusion criteria	X	X[a,b]		
Skin type assessment [c]	X			
AK history	X			
Concomitant diseases/relevant medical history	X			
Selection of treatment fields and assessment of target lesions (size, number, location, and clinical assessment according to Olsen[d])	X			
Generation of template of AK treatment field(s) on grid foil; sketching of treatment field(s) and suggested illumination area(s) into cartoon	X			
Instruction of subjects of concomitant medication permitted/forbidden within 7 days before and after PDT	X	X		
General physical examination	X			X
Vital signs (HR, BP)	X	X		X
Clinical laboratory tests (routine hematology, blood chemistry, serum pregnancy test (in WOCBP), and urinalysis)	X[e]			X
Hepatitis and HIV serology, examination of coagulation parameters and eGFR	X			
Urine pregnancy test in WOCBP		X		
Blood sampling for ALA and PpIX analysis[f]	X	X		
Application of BF-200 ALA and PDT with BF-RhodoLED® (including preparation of treatment field(s))		X		
Assessment of application site pain during PDT via 11-point pain questionnaire (NRS-11)		X		
(S)AEs	X	X	X	X
Concomitant medications/ treatments	X	X	X	X
eCRF entry	X	X	X	X

AE: Adverse Event; AK: Actinic Keratosis; ALA: 5-aminolevulinic acid; BP: Blood Pressure; HR: Heart Rate; eCRF: electronic case report form; HIV: Human Immunodeficiency Virus; EoS: End of study; NRS; 11-point Numeric Rating Scale; PDT; Photodynamic Therapy; PpIX: Protoporphyrin IX; SAE: Serious Adverse Event; WOCBP: Women of Childbearing Potential

[a] Visit 2 can be rescheduled within 2 weeks after the scheduled date if at least one of the dosing day exclusion criteria is met.

[b] Re-check of eligibility and check of dosing day exclusion criteria.

[c] Skin type will be evaluated according to Fitzpatrick criteria (Fitzpatrick 1988).

[d] Lesions will be evaluated according to Olsen criteria (Olsen et al., 1991).

[e] In case the subjects come to the screening visit in a fasted state, blood and urine sampling will be performed. In case the subject is not fasted, blood and urine sampling will be postponed 1-2 days.

[f] Blood sampling time points (at Visit 1: one baseline sample and at Visit 2: 14 samples in total (timepoints in relation to BF-200 ALA application: -0.5; 0; 0.5; 1; 1.5; 2; 2.5; 3; 3.5; 4; 5; 6; 8; 10 h)).

3 ABBREVIATIONS AND DEFINITIONS

β-hCG	Human chorionic gonadotropine
5-FU	5-Fluorouracil
ADE	Adverse device event
AE	Adverse event
AK	Actinic keratosis
ALA	5-aminolevulinic acid
ALT	Alanine aminotransferase
ASS	Acetylsalicylic acid
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the curve
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
CV	Coefficient of variation
DSUR	Development safety update report
EC	Ethics committee
eCRF	Electronic case report form
EDTA	Ethylendiaminetetraacetic acid
EMA	European Medicines Agency
EoS	End-of-Study
EU	European Union
FDA	Food and Drug Administration
g	Gram(s)

GCP	Good clinical practice
GmbH	Gesellschaft mit beschränkter Haftung, Ltd, limited liability company
GMP	Good manufacturing practice
HBsAg	Hepatitis B-virus surface antigen
HCV	Hepatitis C-virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
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® lamp (6 cm x 16 cm) 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
MAL	Methyl aminolevulinic acid
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
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
PK	Pharmacokinetic(s)
PpIX	Protoporphyrin IX
ROS	Reactive oxygen species
RSI	Reference safety information
SAE	Serious adverse event
SAF	Safety set
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SCC	Squamous cell carcinoma
SD	Standard deviation
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAEs	Treatment-emergent adverse events
Treatment area	Body area in which the treatment field is located
Treatment field	Area within the illumination area to which medicinal product was applied
USADE	Unanticipated serious adverse device effect
UV	Ultraviolet
WOCBP	Women of childbearing potential

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. Today, it is generally accepted that AK represents an early stage of a malignant condition (carcinoma in situ) that can progress into SCC. Between 0.025 % and 16 % of the AK lesions develop into SCC (2). Therefore, it is highly recommended to treat lesions of AK before they evolve to skin cancer. However, the line of progression from mild AK lesions to lesions of moderate or severe phenotype and further progression into SCC was counteracted by the finding that the clinical classification of lesions using the Olsen grade does not accurately match the histopathological classification according to Röwert-Huber (3). This reinforces the need to treat even AK lesions of mild clinical phenotype and cancerous fields as they could histopathologically present forms of early in situ SCC type II or in situ SCC type III already (3). In addition, epidemiological data have indicated that AK lesions, as an indicator for chronic sun damage, are a reliable marker for people who are most predisposed to the development of an invasive SCC (4).

Based on these observations, early and field-directed treatment is advised by recent guidelines and expert recommendations to address all AK severity grades, including subclinical manifestations (5–10). Photodynamic therapy (PDT) is one of several treatment options available for the field-directed treatment of cutaneous neoplasms and non-neoplastic lesions. It requires three components: a photosensitizer, light with sufficient energy at suitable wavelengths, and oxygen.

Kennedy et al. (11) discovered that the topical application of 5-aminolevulinic acid (ALA), an endogenous metabolite found in essentially all eukaryotic cells, as a prodrug is convenient for PDT of subjects with a variety of neoplastic and non-neoplastic cutaneous diseases. This precursor in the porphyrins' synthetic pathway is converted by the target cells to protoporphyrin IX (PpIX), an effective natural photosensitizer. Anomalous cells in dermal lesions seem to be metabolically different from normal cells resulting in a higher accumulation of PpIX. Eventually, these target cells will be selectively destroyed by events triggered by PDT (12–16).

PpIX can be activated by the absorption of energy at different wavelengths, ranging from blue to red light. PpIX shows a maximal excitation at around 410 nm (Soret band) with four smaller peaks in the visible range around 510, 530, 580, and 630 nm. Illumination with red light (e.g. by light emitting diode (LED) devices around 630 nm) may be advantageous for the treatment of deeper lesions because it penetrates tissue better when compared with light at shorter wavelengths. The use of LED devices results (as shown in several Phase III studies) in high clearance rates but is accompanied by a high frequency of adverse events (AE), in

particular transient application site reactions such as erythema, edema, irritation, pruritus, and pain.

In ALA PDT, luminous energy is transferred by the photosensitizer PpIX to oxygen, leading to the formation of reactive oxygen species (ROS), eventually causing cell death. The light-induced damage depends on the applied doses and incubation periods. Preneoplastic and neoplastic cells are eliminated, and the epidermis is regenerated after healing of the induced local inflammation. Since the penetration of ALA is mostly prevented by the basal membrane separating the epidermis from the dermis, no scar formation is observed.

Due to ALA PDT's mode of action, AEs are mainly local application site reactions such as erythema, pain, edema, and irritation which are transient and self-limiting, normally within 1-2 weeks.

Topically applied ALA is well tolerated in humans. Over the past 25 years, the use of ALA PDT was extended from the treatment of dermal lesions to the identification and eradication of neoplastic or preneoplastic cells in additional tissues/organs such as vagina, bladder, gastrointestinal tract, respiratory tract, and brain. For non-dermal indications, systemic applications of ALA are commonly used.

Biofrontera Bioscience GmbH has developed a nanoemulsion-based gel formulation of ALA (development code: BF-200 ALA; brand name: Ameluz®). 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 (17,18). 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. This is considered a relevant advantage, given the instability of ALA in aqueous formulations.

In the US, Ameluz® in combination with the red-light BF-RhodoLED® lamp has been approved for the lesion-directed 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.

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). In Israel, Ameluz® was granted marketing registration approval for the treatment of mild to moderate AK on the face and scalp in May 2016. Subsequently,

Biofrontera's illumination device BF-RhodoLED® was registered in Israel in May 2017 as well.

In a dose-finding clinical study (ALA-AK-CT001) in vivo pharmacokinetics of BF-200 ALA were investigated. ALA and PpIX serum levels and ALA urine levels were measured before, 3 and 24 hours after administration of BF-200 ALA for PDT. None of the post dose levels were increased in comparison to the naturally occurring pre-dose levels, suggesting the absence of relevant systemic absorption after topical administration.

Further pharmacokinetic data with BF-200 ALA were collected in one previous pharmacokinetics (PK) Phase I study (ALA-AK-CT006). This maximal use study, in which one tube of BF-200 ALA was applied to subjects suffering from at least 10 mild to moderate AKs in a 20 cm² skin area on the face or forehead, no systemic elevation of PpIX levels was observed. A slight and transient elevation of systemic ALA levels was well below the daily rate of ALA synthesis. Taking into consideration the available data from the scientific literature, the elevation in the concentration of ALA is not expected to yield any noticeable clinical effect and thus regarded as uncritical for the subjects (19–22). Systemic absorption of ALA after application of a dose of 7.8 mg ALA/cm² to treatment fields >20 cm² has not been investigated so far.

A recent European study (ALA-AK-CT010) compared the efficacy of BF-200 ALA with placebo for the field-directed treatment of AK located on extremities and trunk/neck (periphery) with PDT when using the BF RhodoLED® lamp. This study demonstrated significant efficacy on extremities, trunk and neck that compare favorably with other treatment options. Thus, it can be assumed that Ameluz® in conjunction with BF-RhodoLED® may provide a new, safe and effective treatment option for mild to moderate AK on the extremities, trunk and neck as well.

The Marketing Authorization Holder (Biofrontera Bioscience GmbH) intends to perform a Phase I study to obtain pharmacokinetic profiles of ALA and its metabolite PpIX in a single PDT applying 3 tubes of BF-200 ALA (458 mg ALA in total) in conjunction with the BF-RhodoLED® lamp in diseased subjects presenting with AK on the face and scalp as well as the periphery under maximal use conditions.

4.2 Study rationale

Given that extension of fields with chronic actinic sun damage can exceed the usually treated area size of 20-25 cm² (23), particularly when also taking AK in the periphery into consideration, safe and efficient options for the treatment of these expanded AK areas are needed.

FDA-approved treatment options for field-directed AK treatment comprise formulations containing ingenol mebutate or diclofenac/hyaluronic acid (3 %/2.5 %), most of which require repeated applications for up to several months or lead to side effects related to cytotoxic and/or inflammatory reactions induced by the treatment that may last for the entire treatment period or even longer.

Compared with other methods like surgery, abrasion, cryotherapy, and alternative topical treatments, use of PDT is advantageous especially due to the high selectivity of the treatment, but also based on the short treatment period that can be entirely controlled by the physician,

and the excellent cosmetic results (24). 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 cryotherapy, 5-fluorouracil, imiquimod, ingenol mebutate or diclofenac/ hyaluronic acid, has shown that ALA PDT using BF-200 ALA was the most efficacious treatment option (25).

Today, besides Ameluz®, one further PDT product containing ALA is available in the US market. Levulan® Kerastick® contains ALA at a concentration of 20 % and is provided as a 2-component system. Consequently, ALA has to be dissolved immediately before use. By label, use of Levulan® Kerastick® is restricted to lesion-directed treatment of minimally to moderately thick AKs located on the face and scalp as well as on upper extremities. Thus, Ameluz® is the only PDT product available in the US market which has been approved for the field-directed treatment of AKs.

So far, availability of clinical data for the treatment of large AK areas is limited. However, several studies for treatment of AK areas >20 cm² using ALA PDT have indicated good efficacy and tolerability (26–29). Therefore, PDT may represent an adequate option for the treatment of extended cancerous fields preventing long treatment duration with sequential treatment sessions.

For these reasons, this exploratory study aims at obtaining pharmacokinetic profiles of ALA and its metabolite PpIX after a single PDT treatment with BF-200 ALA in subjects with actinic keratosis in an expanded treatment field of 60 cm² located on the face/scalp or in the periphery, applying approx. 458 mg ALA in total (7.8 mg ALA/cm²). In addition, subjects' safety/tolerability during and after treatment will be assessed.

4.3 Risk/benefit analysis

This open-label Phase I study will include diseased subjects presenting with at least 12 AK lesions with diameter of ≥ 4 mm within the 60 cm^2 treatment field. All participants will receive active BF-200 ALA treatment - already marketed for the treatment of AK in the US, EU, Switzerland and Israel under the brand name Ameluz® - in combination with conventional red-light PDT illumination.

Clinical efficacy and safety of BF-200 ALA in combination with conventional red-light PDT 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) (30–32). Additionally, one confirmatory intra-individual study (ALA-AK-CT010) with 50 subjects was performed for the assessment of clinical efficacy and safety of BF-200 ALA for the treatment of AKs located on extremities or trunk/neck. In these pivotal clinical trials, complete clearance of subjects 12 weeks after the first PDT with BF-200 ALA was shown to be up to 61.8 % and total lesion clearance was up to 84.2 % (30–32). Thus, we expect that a comparable percentage of participating subjects will benefit from the single PDT treatment which will be administered in the current study.

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) and lasted for 1 to 4 days in most cases; 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 type of illumination used for PDT and correlates with the higher clearance rate achieved by the use of narrow spectrum lamps, e.g. BF-RhodoLED®. In rare cases, adverse reactions may require interruption or discontinuation of the illumination.

Common adverse effects of PDT with BF-200 ALA include headache and reactions at the application site, such as abnormal sensation, increased sensitivity to pain, discomfort, erosion, and discharge. More detailed information on known adverse reactions is provided in the prescribing information (PI) for Ameluz® (19). 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 more extended treatment fields will be similar to those known from treatment of AK lesions as well as cancerous fields described previously. Nonetheless, an appropriate form of pain management has to be considered as PDT pain may be related to the size of the treatment field(s) (33). For this reason, pain management will be performed according to established guidelines (34,35) but restrictions for co-medication 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® will be handled by appropriately trained study personnel. For maximal comparability to previous studies, up to two BF-RhodoLED® lamps will be used simultaneously, such that the light dose of 37 J/cm^2 will be applied to the entire 60 cm^2 treatment field in 10 min.

5 STUDY OBJECTIVES

5.1 Primary objectives

The primary objectives of the study are:

- Assessment of baseline-adjusted plasma concentration-time curves for ALA after a single PDT treatment applying 3 tubes of BF-200 ALA in conjunction with the BF-RhodoLED® under maximal use conditions in subjects with mild to severe actinic keratosis.
- Assessment of baseline-adjusted plasma concentration-time curves for PpIX after a single PDT treatment applying 3 tubes of BF-200 ALA in conjunction with the BF-RhodoLED® under maximal use conditions in subjects with mild to severe actinic keratosis.

Data will be analyzed overall and according to strata (treatment area: face/scalp or periphery (neck/trunk/extremities)).

5.2 Secondary objectives

The secondary objective of this study is to calculate pharmacokinetic parameters based on baseline-adjusted plasma concentration data of ALA and PpIX (if data permits) and to evaluate the safety and tolerability of PDT with BF-200 ALA under maximal use conditions.

Pharmacokinetics:

The secondary objectives of the study regarding pharmacokinetics include:

- Evaluation of baseline-adjusted pharmacokinetic parameters of ALA.
- Evaluation of baseline-adjusted pharmacokinetic parameters of PpIX.

Safety:

The secondary objectives of the study regarding safety include:

- Assessment of safety and tolerability of PDT with BF-200 ALA under maximal use conditions

All secondary parameters will be analyzed descriptively and in an exploratory way overall and according to strata.

5.3 Tertiary objectives

To compensate for situations in which baseline-adjustment mathematically impairs calculation of PK parameters, the tertiary objective of this study is to calculate unadjusted PK parameters of ALA and PpIX as well.

The tertiary objectives include:

- Evaluation of unadjusted plasma concentration-time curve for ALA and evaluation of unadjusted pharmacokinetic parameters of ALA.
- Evaluation of unadjusted plasma concentration-time curve for PpIX and evaluation of unadjusted pharmacokinetic parameters of PpIX.

All tertiary parameters will be analyzed descriptively and in an exploratory way overall and according to strata.

6 STUDY DESIGN, DURATION AND DATES

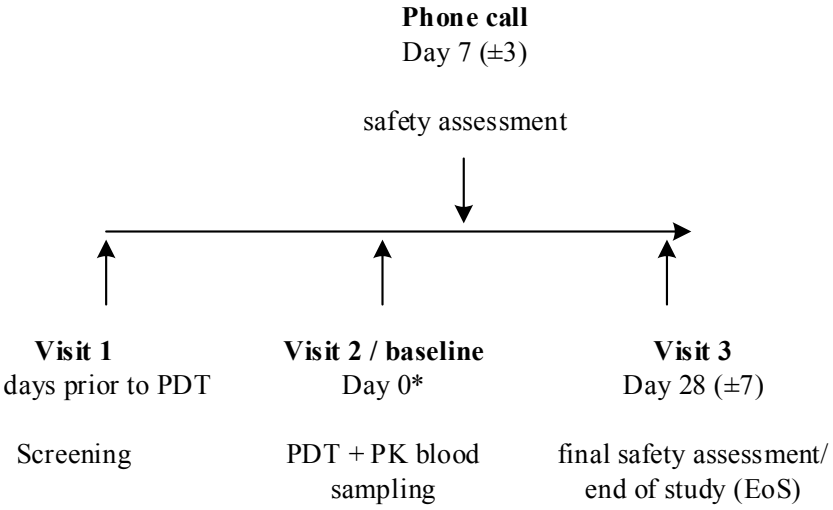
6.1 Study design

This protocol describes a non-randomized, open-label Phase I study that will be conducted in the US. All study visits and procedures will be conducted at one Phase I unit.

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**) and 1 baseline PK blood sample will be taken
- a baseline/treatment visit, at which eligible subjects will receive PDT with application of 3 tubes of BF-200 ALA, and 14 PK blood samples will be collected, starting 0.5 h prior to BF-200 ALA application and then for up to 10 h afterwards (**Visit 2**)
- a phone call for safety assessment at 7 (± 3) days post PDT
- a further clinic visit, 28 (± 7) days after treatment, at which safety and tolerability assessments will be performed (**Visit 3**)

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



* Visit 2 can be rescheduled within 2 weeks after the scheduled date if at least one of the dosing day exclusion criteria is met.

Figure 1: Summary of study visits

The PDT procedure (preparation of treatment field(s), drug application, incubation, illumination) will be performed according to the labels of BF-200 ALA and BF-RhodoLED® with the exceptions that 3 tubes of BF-200 ALA (totaling in 458 mg ALA) are applied per subject and the treatment will be performed on scalp/face or in the periphery (neck/trunk/ extremities).

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

For each subject the duration of trial participation is expected to be approximately 42-63 days (including the screening period) and the overall study duration is estimated to be about 9 months. Subject recruitment is estimated to start approx. in February 2020 (first subject first visit) and to end approx. in August 2020 (6 months recruitment). 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 treatment area is a body region to be treated with PDT. The following treatment areas will be investigated:

- Face/scalp: the whole face (except the upper and lower eyelids, the lip area (not past the vermilion border) and the nostrils) and the bald scalp
- Periphery: any part of the extremities and/or trunk/neck excluding the genitalia (minimal distance of about 1 cm)

Definition of illumination area:

The illumination area is the area effectively illuminated by one BF-RhodoLED® lamp (6 cm x 16 cm) in one illumination session. In this study, up to two illumination areas can be illuminated simultaneously using two BF-RhodoLED® lamps.

Definition of treatment field(s)

The treatment field is defined as the field to which medicinal product is applied.

In this study, at least 12 distinctive AK lesions (each with a diameter of ≥ 4 mm) within one or several treatment field(s) located either within the treatment area face/scalp or within the treatment area periphery will be treated with PDT.

The treatment field(s) may be discontinuous and several patches within the same treatment area can be combined to form a total area of approximately 60 cm^2. In case of discontinuous treatment field(s), all patches must be located within up to two illumination areas of the BF-RhodoLED® lamp (6 cm x 16 cm each). Lesions included in the study should be entirely located within the treatment field(s), leaving a minimal distance of ≥ 0.5 cm of the lesion margin to the treatment field border.

The location of all treatment field(s) and suggested illumination area(s) should be clearly marked in the graphic templates (cartoon and grid foil) for re-identification during the course of the study. The investigator will also describe treatment field(s), illumination area(s) and lesions in source data and the electronic case report form (eCRF).

7 SELECTION OF SUBJECTS

7.1 Number of subjects

The suggested sample size for the study is 32 subjects, stratified into 2 groups of 16 subjects each. Based on the results of a previous PK study, a group size of 12 subjects is considered to be sufficient for proper pharmacokinetic evaluation which is also in agreement with FDA guidance (36). In order to compensate for potential drop-outs of subjects as well as potentially higher variability of data due to combined investigation of two treatment areas, the stratum size was adapted from 12 to 16 subjects. For this reason, the sample size of 32 subjects is considered to be adequate for pharmacokinetic evaluation in this PK study.

7.2 Recruitment arrangements

Subjects will be screened at the Phase I unit and, if eligible, subjected to PDT and PK blood sampling. The study site will be responsible for obtaining equal stratum size and has to stop recruitment once 16 subjects for one stratum have been treated.

7.3 Inclusion criteria

Eligible subjects must meet the following criteria:

1. Subjects with at least 12 distinctive and clinically confirmed mild to severe AK lesions (according to Olsen et al. 1991 (37)) with a diameter of ≥ 4 mm each, on either the face/scalp (including forehead, excluding eyes, nostrils, ears, and mouth) or the neck/trunk/extremities, within treatment field(s) of about 60 cm² in total. Treatment field(s) may be discontinuous but must be within 2 illumination areas of the BF-RhodoLED® lamp (6 cm x 16 cm each).
2. All genders 18-85 years of age (inclusive).
3. Willingness and ability of the subject to provide informed consent and to sign the Health Insurance Portability and Accountability Act (HIPAA) form. A study-specific informed consent form and HIPAA form must be obtained in writing for all subjects prior to starting any study procedures.
4. Willingness and ability to comply with study procedures, particularly willingness to receive one PDT with up to two illumination devices simultaneously.
5. Subjects with good general health and subjects with clinically stable medical conditions will be permitted to be included in the study.
6. Subjects receiving any drugs affecting coagulation (e.g. anticoagulants, anti-platelet drugs) should be on a stable dose.
7. Acceptance to abstain from extensive sunbathing and the use of solarium during the clinical study.
8. Women of child-bearing potential must have a negative serum pregnancy test and must use an adequate and highly effective or two effective methods of contraception 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 within illumination areas (reassessment of subjects is allowed once if the sunburn is expected to resolve within the screening period. Reassessment can be done on the day of the actual treatment.).
4. Clinically significant medical conditions making implementation of the protocol or interpretation of the study results difficult or impairing subjects' safety such as:
    a. Presence of porphyria or known photodermatoses
    b. Known diagnosis of human immunodeficiency virus (HIV) based on clinical history
    c. Metastatic tumor or tumor with high probability of metastasis
    d. Infiltrating skin neoplasia (suspected or known)
    e. Unstable cardiovascular disease (New York Heart Association [NYHA] class III, IV)
    f. Unstable hematologic (including Myelodysplastic syndrome), hepatic, renal, neurologic, or endocrine condition
    g. Unstable collagen-vascular condition
    h. Unstable gastrointestinal condition
    i. Immunosuppressive condition
    j. Presence of clinically significant inherited or acquired coagulation defect
5. Clinical diagnosis of atopic dermatitis, Bowen's disease, BCC, eczema, psoriasis, rosacea, SCC, other malignant or benign tumors in the treatment field(s), or other possible confounding skin conditions (e.g. wounds, irritations, bleeding or skin infections) within or in close proximity (< 5 cm distance) to treatment field(s). (Reassessment of subjects is allowed once if wounds, irritations, bleeding or skin infections are expected to resolve within the screening period. Reassessment can be done on the day of the actual treatment.)
6. Presence of strong pigmentation, tattoos or any other abnormality that may impact lesion assessment or light penetration in the treatment field(s).
7. More than moderate smoker (e.g. > 10 cigarettes/day or equivalent).
8. Suspicion of drug or alcohol abuse. For the purpose of this study, alcohol abuse is defined as more than moderate alcohol consumption (> 1 drink/day for women and > 2 drinks/day for men).

9. Physical treatment of malignant or benign tumors of the skin within the treatment field(s) and at a distance of < 5 cm to the treatment field(s) during the last 4 weeks prior to screening.
10. Any therapy such as cryotherapy, laser therapy, electrodessication, surgical removal of lesions, curettage, or treatment with chemical peels such as trichloroacetic acid within the treatment field(s), or within a radius less than 5 cm away from the treatment field(s) 4 weeks prior to screening.
11. Any topical medical treatment of the skin within the designated time period below:
    a. Topical treatment with ALA or methyl-aminolevulinate (MAL) or an investigational drug in- and outside the treatment field(s) within 8 weeks prior to screening.
    b. Topical treatment with immunomodulatory/immunosuppressive anti-inflammatory, or cytotoxic agents inside the treatment field(s) or within a radius less than 5 cm away from the treatment field(s) within 8 weeks prior to screening.
    c. Start of topical administration of medication with hypericin or other drugs with phototoxic or photoallergic potential in- and outside the treatment field(s) within 8 weeks prior to screening. Subjects may, however, be eligible if such medication was applied for more than 8 weeks prior to screening visit without evidence of an actual phototoxic/photoallergic reaction.
12. Any use of the below specified systemic treatments within the designated periods:
    a. Use of cytotoxic drugs within 24 weeks, immunomodulators or immunosuppressive therapies or use of ALA or ALA-esters (e.g. MAL) within 12 weeks, investigational drugs or drugs known to have major organ toxicity within 8 weeks, interferon or corticosteroids (oral or injectable) within 6 weeks prior to screening.
    b. 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 or applied for more than 8 weeks prior to screening visit without evidence of an actual phototoxic/photoallergic reaction.
13. Laboratory values outside the reference range that are clinically significant in the opinion of the investigator (e.g., suggesting an unknown disease and requiring further clinical evaluation according to investigator), especially aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (gamma-GT).
14. Impaired renal function (Glomerular filtration rate below 50 mL/min/1.73m² estimated by Modification of Diet in Renal Disease equation (MDRD)).
15. Positive test for HIV antibodies, Hepatitis B-virus surface antigen (HBsAg) or positive Anti-hepatitis C-virus antibody (Anti-HCV) test.

16. Significant blood donation or blood loss (≥ 500 mL) within three months prior to Visit 2.
17. Breast-feeding women.
18. Subject unlikely to comply with the protocol, e.g. inability to return for visits, unlikely to complete the study, or inappropriate in the opinion of the investigator.
19. Prior participation in the study (participation is defined as having been screened).
20. A member of study site staff or sponsor staff directly involved in the conduct of the protocol or a close relative thereof.
21. Simultaneous participation in a further clinical study.

Reassessment of subjects is allowed once if sunburn, wounds, irritations, bleeding or skin infections detected at Visit 1 are expected to resolve within the screening period. Reassessment can be done on the day of the actual treatment.

Dosing day exclusion criteria:

1. Febrile or infectious illness within 7 days prior to Visit 2.
2. Subjects with sunburn, wounds, irritations, bleeding or other confounding skin conditions within illumination areas at Visit 2.
3. Use of topical NSAIDs inside and outside the treatment field(s) or systemic intake of NSAIDs within 7 days prior to Visit 2.

In case a subject meets one of the dosing day exclusion criteria, Visit 2 can be rescheduled once within 14 days. Meeting any of the dosing day exclusion criteria on the rescheduled visit will lead to discontinuation of the trial.

7.5 Screening failures

All subjects whose eligibility cannot be confirmed at Visit 2 will be considered as screening failures if eligibility cannot be achieved and Visit 2 rescheduled within 2 weeks.

Subjects assessed as screening failures will not be treated at Visit 2.

7.6 Subjects of reproductive potential

Female subjects of childbearing 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 clinical 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. The further treatment of AK lesions should be addressed on a case-by-case basis with the treating physician and the investigator.

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.

8 STUDY TREATMENT

8.1 Details of investigational products

8.1.1 Investigational Medicinal Product

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

The composition is 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 1.2.

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 treatment totaling in 458 mg ALA. The quantity provided is sufficient to cover the 60 cm^2 skin area of the treatment field(s) with a 1 mm thick layer.

8.1.2 Investigational Medical Device

The Class III device BF-RhodoLED® (in this document also referred to as investigational medical device, IMD) 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® is manufactured in compliance with ISO 13485 standards by:

Biofrontera Pharma GmbH
Hemmelrather Weg 201
51377 Leverkusen
Germany

BF-RhodoLED® utilizes 128 LEDs and lenses (arranged in a rectangle) to emit a uniform, bundled, visible red light with a typical peak wavelength at approximately 635 nm and a half bandwidth of 20 nm. The total area illuminated by the lamp is 8 cm x 18 cm with an effective illumination area of 6 cm x 16 cm. The optimum treatment distance is 5-8 cm. 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 distance of 5-8 cm. Therefore, it must be confirmed and documented that the specified illumination time and distance between the lamp and the treatment field(s) have been met. Otherwise, reasons for not meeting the requirements must be provided. The lamp is programmed to automatically provide a total illumination time of 10 min. In case of necessary interruptions, e.g. due to unbearable pain or repositioning of the subject, the lamp will continue until the required illumination time is achieved.

For the purpose of this study, the study site will be equipped with at least two BF-RhodoLED® lamps. 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 parameters of LED lamp used

	Recommendation
Wave length (λ_{em})	approx. 635 nm
Light dose (energy)	approx. 37 J/cm²
Intensity	Max. 77 mW/cm^2
Illumination time	10 min
Distance skin-lamp	5-8 cm

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

8.2 Storage

At the study site, 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. 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 site 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® study lamps must be stored inaccessible to unauthorized persons.

8.3 Application of BF-200 ALA

Treatment field(s) will be localized and documented as described in Section 6.3. A treatment field does not necessarily have to be continuous, but (discontinuous) treatment field(s) should cover a total area of approximately 60 cm^2 and must allow illumination in a single step (see Section 7.3 and 8.4).

AK lesions located outside the specified treatment field(s) will not be considered for treatment in this study. For treatment of these AK lesions, subjects will be referred to a licensed dermatologist after the end of the clinical trial for follow up care.

Treatment field(s) should be prepared for drug application by degreasing (using ethanol or isopropanol), removal of all scabs and crusts, and if appropriate roughening of the surface, (e.g. by mild debridement for the removal of crusts) within 1 h before application of the study medication. Care should be taken to avoid bleedings. Therefore, special care has to be taken when screened subjects report non-significant acquired or inherited coagulation defects and/or receive treatment with e.g.100 mg acetylsalicylic acid (e.g. ASS) per day or warfarin.

After this preparation, 3 tubes of BF-200 ALA will be administered to the entire 60 cm^2 treatment field(s), covering the skin with a film of approximately 1 mm thickness. 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), in the nostrils or near genitalia (keep a distance of about 1cm). In case of accidental contact of BF-200 ALA with the eyes or mucous membranes, rinsing with water for at least 5 min will be performed.

The gel will be allowed to dry for approximately 10 min, before an occlusive, light-blocking dressing (e.g. TegadermTM dressing plus aluminum foil) will be placed over the treatment field(s). The subject should stay in an environment with comfortable temperature during incubation time. It is particularly important to ascertain that extremities will not be cold during the 3 h incubation. After the incubation time of 3 h ± 10 min, the occlusive, light-blocking dressing will be removed and the remaining gel should be wiped off.

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

- preparation of treatment field(s) including lesions within one hour prior to dosing
- occurrence of bleedings in the application area
- unique IMP number (on subject package and allocated tubes)

- time of IMP application and removal
- application of occlusive, light-blocking dressing

8.4 Illumination with BF-RhodoLED®

After removal of remaining gel, the entire treatment field(s) will be illuminated using BF-RhodoLED®, until a total light dose of approximately 37 J/cm^2 is achieved. During illumination, the lamp(s) will be positioned at a distance of 5-8 cm from the skin surface as indicated in the user manual.

In case of discontinuous treatment field(s) that may not be covered by the 96 cm² (6 cm x 16 cm) illumination field of a singular device, two BF-RhodoLED® lamps are used simultaneously, such that for the entire 60 cm² surface only one illumination step is performed.

The calibration of the lamp ensures that the skin area illuminated receives a total light dose of 37 J/cm^2 (an illumination time of 10 min) at a distance of 5-8 cm. Therefore, it must be confirmed and documented that the specified illumination time and distance between the lamp and the treatment field(s) have been met. Otherwise, reasons for not meeting the requirements must be provided. The lamp is programmed to automatically provide a total illumination time of 10 min. In case of necessary interruptions, e.g. due to unbearable pain, the lamp will continue until the required illumination time is achieved.

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

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® can be derived from the user manual.

Discomfort and pain during PDT 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 spectrum, subjects may have the feeling of being burned. The latter is caused by a generally harmless, but in some subjects very unpleasant, biochemical reaction during PDT which may be enhanced by a strong psychological component.

As pain experienced during PDT will be evaluated by all subjects after the treatment, the PDT should be started without measures to relieve pain. In cases where the pain is regarded as unbearable by the subject, pain relieving measures as outlined in Section 9.2 may be applied.

The subject should be informed about restrictions defined in Table 4 and in Section 9.2.

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

Although a nearly complete loss of PpIX by photobleaching is assumed to occur during PDT, subjects should avoid exposure to intensive sun light for about 48 h since new PpIX may accumulate from remaining ALA. 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.

8.5 Dosage schedule

A single PDT session will be applied according to the study design described in Section 6.1, Section 8.3 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
D-51377 Leverkusen
Germany

The appropriate number of tubes and card board boxes will be labeled in English according to the pre-defined distribution of treatment 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 card box is provided containing three tubes with BF-200 ALA. Each box is labeled with a 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® will be distributed and assembled/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 manufacturer, packer, 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 Phase I unit will be provided with at least two BF-RhodoLED® lamps. 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 assembled on 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 was approved or accepted by the Institutional Review Board(s) (IRB(s)) and by FDA, the sponsor will initiate the study site which includes installation of at least two BF-RhodoLED® lamps, and thereafter supply the study site with study medication, together with all relevant documentation. The sponsor is responsible for delivery of the investigational products to the study site.

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 Phase I unit 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 disassembled by a technician and returned to Biofrontera Inc. Receipt and return of BF-RhodoLED® 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 but applied by study personnel, rendering individual compliance assessments unnecessary.

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

9 PRIOR AND CONCOMITANT ILLNESSES AND TREATMENTS

9.1 Prior and concomitant illnesses

Additional diseases present at the time of signing the informed consent are regarded as concomitant diseases and must be documented in the eCRF. Relevant past diseases must also be documented in source data and in the medical history section of the eCRF.

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

9.2 Prior and concomitant treatments

Any medication taken by a subject at study entry or treatments the subject is undergoing throughout the study that are not related to any study-specific procedures (PDT with IMP), are considered concomitant treatments. The use of required concomitant treatments, which are known not to interfere with the IMP or to mask their effect, is unrestricted and may be continued during the study.

Inflammation triggered by the photodynamic reaction is an important part of the therapeutic principle and is intended. Therefore, intake of systemic anti-inflammatory drugs must be stopped prior to PDT, especially systemic corticosteroids and antiphlogistics (NSAIDs) (see Section 7.4 and below).

Nevertheless, the following treatments are permitted in the designated trial periods to alleviate pain and discomfort:

- During PDT
    - In cases where the pain is regarded as unbearable by the subject, the PDT may be interrupted and/or cooling with an air stream or nebulized water may be offered.
    - Severe cases of pain might require to briefly interrupt illumination, e.g. to inject a local, fast-acting anesthetic, such as xylocaine or to cool briefly with cooling packages.
- Treatment of pain and discomfort after PDT
    - Cooling the illuminated area(s) with wet or refrigerated compresses
    - Analgesic treatment with acetaminophen (e.g. Tylenol®)

Cooling compresses and acetaminophen (e.g. Tylenol®) should be offered by the study staff to all subjects after PDT for the purpose of pain management.

Further treatments are also allowed for the management of pain and discomfort but should be used as a second line treatment option:

- Topical corticosteroids
- Topical diclofenac up to 2.5 % outside the treatment field(s)

All concomitant treatments underwent/taken during the study must be documented in source data and on the appropriate pages of the eCRF along with the indication, single dose, route of administration, 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 during the course of the study.

The following concomitant treatments/procedures are <u>not permitted</u>:

- Any therapy such as cryotherapy, laser therapy, electrodessication, surgical removal of lesions, curettage, or treatment with chemical peels such as trichloroacetic acid within the treatment field(s), or within a radius less than 5 cm away from the treatment field(s) 4 weeks prior to screening and throughout the study. Non-target lesions may be treated with these methods if the distance to the treatment field is more than 5 cm.
- A list of forbidden, concomitant medication is provided in Table 4.

If the investigator, at any time in the study, suspects a lesion within or outside the treatment field(s) 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[a]**		**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
Cytotoxic drugs	8 weeks prior to Visit 1 (within treatment field(s))[b]	end of study (within treatment field(s))[b]	24 weeks prior to Visit 1	end of study
Immunomodulators/ immunosuppressive therapies	8 weeks prior to Visit 1 (within treatment field(s))[b]	end of study (within treatment field(s))[b]	12 weeks prior to Visit 1	end of study
	7 days prior to PDT (within and outside treatment field(s))	end of study (within and outside treatment field(s))		
Interferon	---	---	6 weeks prior to Visit 1	end of study
Corticosteroids	(allowed)	(allowed)	6 weeks prior to Visit 1[d]	end of study[d]
NSAIDs	7 days prior to PDT[c]	7 days post PDT[c]	7 days prior to PDT	7 days post PDT
Acetylsalicylic acid > 100 mg/day	---	---	7 days prior to PDT	7 days post PDT
Ibuprofen > 200 mg/day	---	---	7 days prior to PDT	7 days post PDT

Medication	**Topical administration**[a]		**Systemic administration**	
	start of restriction	forbidden until	start of restriction	forbidden until
Diclofenac (> 2.5 %)	8 weeks prior to Visit 1 (within treatment field(s))[b]	end of study (within treatment field(s))[b]	7 days prior to PDT	7 days post PDT
Hypericin or drugs with phototoxic/ photoallergic potential[e]	8 weeks prior to Visit 1	end of study	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 dose stable prior to study)	end of study (may be used throughout the study if taken in a dose stable prior to study)
EMLA® cream	Visit 2 (within treatment field(s))[b]	7 days post PDT (within treatment field(s))[b]	---	---

[a] Within and outside the treatment field(s).
[b] Restriction is limited to the use within treatment field(s) and surrounding skin areas within a radius less than 5 cm away from the treatment field(s).
[c] Topical use of diclofenac up to 2.5 % may be used outside treatment field(s) throughout the study.
[d] For oral or injectable corticosteroids.
[e] 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 8 weeks prior to screening. Subjects may, however, be eligible if such medication was taken in 8 weeks prior to screening without evidence of an actual phototoxic/photoallergic reaction. These medications must not be newly prescribed within 8 weeks prior to screening. If such a prescription becomes unavoidable for medical reasons in between Visit 2 and Visit 3, the study participation of the affected subject should be continued regularly.

10 STUDY PROCEDURES AND SCHEDULE

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

NOTE: In case the subjects come to the screening visit in a fasted state, blood and urine sampling will be performed. In case the subject is not fasted, blood and urine sampling will be postponed 1-2 days.

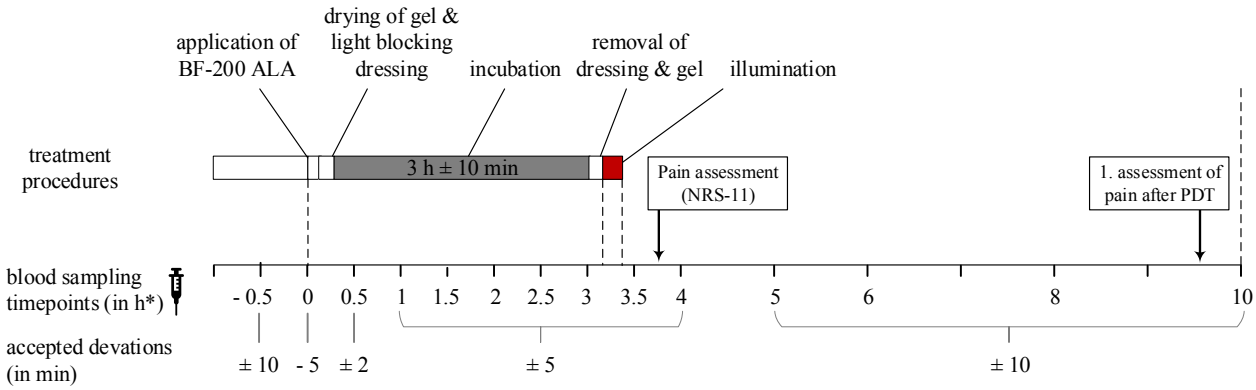
- Obtain informed consent prior to any study-related procedures.
- Assign subject number
- Document concomitant diseases and relevant medical history
- Document AK history
- Obtain demographic data
- Check inclusion and exclusion criteria
- Assess skin type according to Fitzpatrick, 1988 (38)
- Select treatment field(s) and assess target lesions (size, number, location and clinical assessment according to Olsen et al., 1991 (37))
- Generate template of AK treatment field(s) on provided grid foil and sketch treatment field(s) and suggested illumination area(s) into cartoon (to be kept in the subject file)
- General physical examination
- Measure vital signs (HR, BP)
- Fasting clinical laboratory tests (including routine hematology, blood chemistry, serum pregnancy tests, coagulation parameters, eGFR and urinalysis)
- Hepatitis and HIV serology.
- Blood sampling for ALA and PpIX baseline levels
- Documentation of (S)AEs.
- Instruct subject about forbidden concomitant treatments (see Section 9.2).

10.1.2 Visit 2/Baseline (PDT)

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

- Reevaluation of inclusion and exclusion criteria for confirmation of subject's eligibility
- Evaluation of dosing day exclusion criteria

- Explanation of allowed/forbidden medication 7 days after PDT to subjects (see Section 9.2 and Table 4)
- Measurement of vital signs (HR and BP) prior to PDT
- Pregnancy test (urine) for females of reproductive potential prior to PDT
- Blood sampling for ALA and PpIX analysis: In total, 14 blood samples will be collected at the time points defined below (Figure 2)
- Preparation of treatment field(s) and application of BF-200 ALA and occlusive, light-blocking dressing according to treatment description in Section 8.3
- Date and time of study drug application and removal will be recorded in source data and in the eCRF
- Illumination of treatment field(s) with the BF-RhodoLED® lamp until a total light dose of 37 J/cm² is achieved (according to treatment description in Section 8.4). In case of discontinuous treatment field(s), two BF-RhodoLED® lamps are used simultaneously, such that for the entire 60 cm² surface only one illumination step is performed
- Duration of illumination and distance between the BF-RhodoLED® lamp and the treatment field(s) will be documented in source data and in the eCRF. Otherwise, reasons for not meeting the requirements must be given. The duration, reason, and frequency of any interruptions must be recorded in the subject's source data and the eCRF. Pain relieving measures should be documented accordingly, if applicable
- Documentation of concomitant medications/treatments (e.g. for pain management) that might be required during or after PDT (see Section 9.2 and Table 4)
- Assessment of application site pain during PDT via NRS-11 (should be performed in between the blood sampling time points 3.5 h and 4 h after application of BF-200 ALA)
- (S)AEs including application site skin reactions, application site discomfort, pain during and post PDT, and new lesions in the treatment field(s) (assessment of pain after PDT should be performed as described in Section 10.2.7 before discharge of the subject)
- Reinform subjects about restrictions to intensive UV-radiation for 48 h (please see also Section 8.4 for detailed information)



*Blood sampling time points are specified in hours relating to the time point of BF-200 ALA application. Timepoint 0 is defined as the start of the application of BF-200 ALA.

Figure 2: Time points for PK blood sampling at Visit 2.

10.1.3 Phone call (7 (± 3) days post PDT)

The aim of this safety telephone call is to achieve an overall impression on the tolerability of the photodynamic treatment with BF-200 ALA and to evaluate the subject‘s health condition since the PDT session. Using non-leading questions like “How did you feel since your photodynamic treatment session,” the investigator or delegated persons will evaluate any discomfort the subject may be experiencing. Any reported AE or concomitant treatment will be recorded in the source data and the eCRF.

The following information will be collected during the phone call and recorded in the eCRF:

- Documentation of (S)AEs and concomitant medication, application site skin reactions, and application site discomfort

10.1.4 Visit 3 (Tolerability & safety assessment 28 (± 7) days after PDT)

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

- General physical examination
- Measurement of vital signs (HR, BP)
- Fasting clinical laboratory tests (including routine hematology, blood chemistry, and urinalysis) (In case the subject is not fasted, blood and urine sampling will be postponed 1-2 days.)
- Serum pregnancy tests for female subjects of reproductive potential
- Documentation of concomitant medications/treatments (please see also listing of allowed and restricted medications in Section 9.2)
- Documentation of (S)AEs, including application site skin reactions and application site discomfort, and new lesions in the treatment field(s)

10.2 Assessments

10.2.1 Evaluation of demographic data

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

- Gender
- Age
- Race
- Ethnicity
- Height
- Weight
- BMI

10.2.2 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 (39–41).

AK lesion severity will be evaluated according to the Olsen Severity Grading (37) 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.

10.2.3 Assessment of target lesions

In this clinical trial, AK lesions of mild to severe intensity (according to Olsen et al., 1991 (37)), of which at least 12 lesions are of a diameter of ≥ 4 mm at screening, will be treated with (field-directed) PDT. AK lesions should be distinguishable; however, no distance restrictions between lesions will be applied.

All lesions within the treatment field(s) have to be counted. For circular or almost circular lesions with a diameter of ≥ 4 mm its location, (e.g. upper arm, forehead), severity and size (diameters) must be documented. For non-circular lesions, the largest diameter and the corresponding perpendicular diameter will be measured and the mean diameter will be calculated and documented.

Furthermore, for smaller actinic lesions (< 4 mm) in the treatment field(s) only the total number has to be documented.

10.2.4 Assessment of AK history

Subject's AK history will be assessed at the screening visit. The following information will be documented in the eCRF:

- Is this the first diagnosis of AK?
- Date of first AK diagnosis, if applicable
- Were AK lesions diagnosed in the past located in the same region or in the proximity of the region which will be treated at Visit 2?

10.2.5 Assessment of skin type

Subjects' skin type will be assessed at the screening visit using the six-level Fitzpatrick Skin Type Rating Scale (38). Further details are provided in Appendix A.

10.2.6 Pharmacokinetics

Sample collection and sample handling

For assessment of ALA and PpIX baseline plasma concentrations, the first of three pre-dose blood samples will be taken at Visit 1. All remaining blood samples for pharmacokinetic analyses will be collected at Visit 2 at the time points depicted in Figure 2 and in Table 5.

Timing of blood samples for pharmacokinetic analysis has priority over any other scheduled activities. Time windows for accepted deviations for pharmacokinetic sampling are also given in Table 5. Deviations outside these windows will be considered as protocol deviations.

Approximately 10 mL of blood per sample will be taken using lithium heparin tubes. The combined blood loss for pharmacokinetics sample analyses will be approximately 150 mL per subject.

Details on sample collection, handling and processing will be provided in a separate document.

Table 5: Accepted deviations for pharmacokinetic sampling

Nominal time of blood sampling	Accepted deviations
Predose (Visit 1)	Not applicable
Predose (-0.5 h)	± 10 min
Predose (0 h)	Must be within 5 min before dosing
0.5 h	± 2 min
1 h, 1.5 h, 2 h, 2.5 h, 3 h, 3.5 h, 4 h	± 5 min
5 h, 6 h, 8 h, 10 h	± 10 min

Bioanalytical measurements

The concentrations of ALA and PpIX in plasma will be measured by an analytical laboratory using validated internally standardized liquid chromatography-tandem mass spectrometry methods. Incurred sample re-analysis will be performed. The methods will be validated according to FDA and EMA guidelines, before pharmacokinetic analysis of study samples.

For PK analysis, the arithmetic mean of the ALA and PpIX plasma concentrations estimated based on the three predose samples (Visit 1, -0.5 h and 0 h predose at Visit 2) will be used as ALA respectively PpIX baseline concentration.

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

The following laboratory is responsible for bioanalytical measurements (sample transfer will be via [redacted]):

[redacted]

10.2.7 Safety

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

Physical examination

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

Vital signs

Blood pressure (systolic and diastolic) and pulse rate will be measured after 5 min rest in supine position.

Safety laboratory

Blood and urine sampling for clinical safety analysis, except for the urine dip-stick pregnancy test, will be performed when the subject is in a fasted state. 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 safety laboratory assessments:

[redacted]

Blood

An approximately 3 mL EDTA (ethylenediaminetetraacetic acid) blood sample, a 2.7 mL sodium citrate blood sample, a 5 mL serum sample and a 7.5 mL serum sample will be collected at Visit 1 and approximately 3 mL EDTA blood and a 7.5 mL serum sample at Visit 3. Serology examinations and pregnancy test will be performed to ensure the safety of the subjects before treatment. The total blood loss for safety laboratory examinations will be approximately 28.7 mL.

- *Serology parameters*[1]

  HIV-1/2 antibodies, HBsAg, and Anti-HCV.

- *Coagulation parameters*[1]

  International normalized ratio, prothrombin time, and activated partial prothrombin time.

- *Clinical chemistry parameters*

  Blood urea nitrogen, creatinine, cholesterol, alkaline phosphatase, total bilirubin, ALT, AST, gamma-GT, low-density lipoprotein, high-density lipoprotein, triglycerides, albumin, phosphorus, total protein, uric acid, sodium, potassium, calcium, chloride, glucose, lactate dehydrogenase, bicarbonate and creatine phosphokinase.

- *Hematology parameters*

  Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), hemoglobin, hematocrit, red blood cell count, white blood cell count with differential count (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count.

  [1] Only at Visit 1

Urine

An approximately 30 mL urine sample will be collected at Visit 1 and at Visit 3. The following parameters will be measured:

- *Urinalysis parameters*

  Leukocytes, nitrite, pH, protein, glucose, ketone, urobilinogen, bilirubin, blood (hemoglobin and erythrocytes). Microscopic examination of the sediment will be performed if considered necessary.

Pregnancy test in females of childbearing potential

A serum pregnancy test (β-human chorionic gonadotropin (β-hCG) test) will be performed at screening (Visit 1) and Visit 3. 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.

Assessment of pain at the application site during PDT

At Visit 2, subjects will assess the pain experienced **during PDT** 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 PDT (see Appendix B). Importantly, pain during PDT has to be documented in pain eCRF (as result of NRS-11) and also as AE (see 11.1.1).

For documentation on the AE eCRF page, the NRS-11 result indicated by the subject should be transformed as follows: pain 1-3 = mild, 4-7 = moderate, 8-10 = severe.

Application site reactions

The term application site reaction encompasses all reactions occuring in the treatment field(s) 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 the phone call and Visit 3 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:

- Burning
- Pain
- Itching
- Stinging
- Warmth
- Others

Application site skin reactions

Application site skin reactions in the treatment field(s) will be evaluated separately by the investigator (or equally qualified physicians) in source and on the AE eCRF page at the clinical visit after PDT (Visit 3). The AE intensity grading should be used (see section 11.1.1). In addition to the investigator assessments of application site skin reactions during and after PDT at Visit 2 and after PDT at Visit 3 subjects will be asked for application site skin reactions during the phone call.

The application site skin reaction categories listed below will be checked by visual inspection of the respective subject's treatment field(s) by a designated member of the study team during Visit 2 and Visit 3 (and documented in source data and on AE eCRF page). Intensity assessment will follow the AE intensity grading (see section 11.1.1).

- Erythema
- Edema
- Induration
- Vesicles
- Erosion
- Ulceration
- Scaling/flaking
- Scabbing/crusting
- Discharge/exudate
- Others

At the phone call, application site skin reactions will be assessed by asking for AEs using non-leading questions as described above. Application site skin reactions will be recorded as reported by the subject and as assessed by the investigator (as AE) in source data and in the eCRF.

10.3 General and dietary restrictions

The consumption of alcoholic beverages should be moderate. In this study, moderate alcohol consumption is defined in accordance to the "Dietary Guidelines for Americans 2015-2020" (42) as drinking up to 1 drink per day for women and up to two drinks per day for men. One alcoholic drink-equivalent is defined as containing 14 grams (0.6 fl oz) of pure alcohol. Subjects should not smoke more than 10 cigarettes/day or equivalent. The use of certain concomitant medications is restricted. For further information see Sections 7 and 9.

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).

Maximum severity 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 illness.
- 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 were 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 (19) 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 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® also referred to as Medical Device 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® 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 and on the AE log.

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 AEs and TEAEs.

- AEs developing between signing the ICF until Visit 2 with a suspected causal relationship to any study procedures will be considered and documented as an AE.
- Collection of TEAEs extends from Visit 2 (baseline) until end of the study at Visit 3.
- If the investigators detect an SAE in a subject after end of study, and considers the event possibly related to prior study treatment or procedures, they 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 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** (whether serious or non-serious) must be documented throughout the study.
- 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 "SAE report" form at the time the SAE is detected. 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), the investigator should only complete a "Serious Adverse Event/Expedited Report from a Clinical Trial for Combination products" form. It should be clearly stated that no adverse event was observed. Instructions on where to send this form will be provided. 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 (inside/outside treatment field(s))
  - time frame (by providing start/stop date and time)
  - intensity (see Section 11.1.1)
  - outcome
  - seriousness criteria (if applicable), and
  - if the AE is related to IMP only, IMD only, or cannot be ambiguously assigned to one of both.
- 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 (concurrent illness 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/illness 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 accepted standards of medical practice, 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 illness 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.

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

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

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.

11.3.1.2 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.

11.3.1.3 Reporting of expeditable 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.

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 IB 'ALA-AK-CT015-IB' in section 7.2.

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 Reporting of expeditable 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 (suspected unexpected serious adverse reaction - SUSAR) 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.

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 safety 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.

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.

As far as possible, all examinations scheduled for the final study day should be performed on all subjects who receive the IMP but who do not complete the study according to protocol.

For subjects that may not be treated due to screening failures or who decide to terminate the study prior to treatment, at least the following parameters must be documented in the eCRF: date of informed consent, demographics and date and reason for withdrawal.

12.2 Replacement of subjects

Subjects who discontinue will not be replaced.

12.3 Withdrawal of samples

In the data review meeting criteria for withdrawal of PK samples will be defined on case-by-case basis.

13 EMERGENCY PROCEDURES

13.1 Emergency sponsor contact

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

[redacted]

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 illness(es) of which the investigator becomes aware.

14 STATISTICAL PROCEDURES

Subjects who withdraw from study participation before administration of PDT (including treatment field preparation) are considered screening failures. The demographic data, date of informed consent as well as date and reason for withdrawal from screening failures 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. A detailed overview of statistical procedures is provided in the SAP. The SAP will encompass demographics, PK and safety analysis.

14.1 Analysis variables

The primary endpoints for pharmacokinetics are the

- Baseline-adjusted plasma concentrations of ALA for obtaining baseline-adjusted plasma concentration-time curves
- Baseline-adjusted plasma concentrations of PpIX for obtaining baseline-adjusted plasma concentration-time curves

Secondary endpoints are the

- Baseline-adjusted AUC_{0-t}, baseline-adjusted $AUC_{0-\infty}$, baseline-adjusted C_{max}, T_{max}, $T_{1/2}$, and λ_Z for ALA (if data permit)
- Baseline-adjusted AUC_{0-t}, baseline-adjusted $AUC_{0-\infty}$, baseline-adjusted C_{max}, T_{max}, $T_{1/2}$, and λ_Z for PpIX (if data permit)
- Assessment of safety and tolerability of PDT with BF-200 ALA under maximal use conditions, including:
    - Frequency and severity of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs). TEAEs are defined as all AEs with onset or worsening after treatment with the investigational medicinal product and device.
    - Overall tolerability.
    - Application site skin reactions in the treatment field(s) during and post PDT.
    - Application site discomfort during and after illumination reported by the subjects.
    - Application site pain during PDT on an 11-point Numeric Rating Scale (NRS-11).
    - Vital signs data.
    - Safety laboratory data if clinically significant deviations occur.
    - Data from the physical examinations if clinically significant findings occur.

Tertiary endpoints are the

- Unadjusted plasma concentration-time curve for ALA and pharmacokinetic parameters of ALA: unadjusted AUC_{0-t}, unadjusted $AUC_{0-\infty}$, unadjusted C_{max}, T_{max}, $T_{1/2}$, and λ_Z if data permit

- Unadjusted plasma concentration-time curve for PpIX and pharmacokinetic parameters of PpIX: unadjusted AUC_{0-t}, unadjusted $AUC_{0-\infty}$, unadjusted C_{max}, T_{max}, $T_{1/2}$, and λ_Z if data permit

All pharmacokinetic characteristics (AUC_{0-t},$AUC_{0-\infty}$, $T_{1/2}$ and λ_z) will be derived from baseline-adjusted as well as unadjusted plasma concentrations of ALA and PpIX as described above.

The pharmacokinetic parameters for ALA and PpIX will be derived from plasma using noncompartmental methods and are listed in Table 6. Values < LLOQ and negative values after baseline adjustment are set to zero and disregarded when displaying data on a logarithmic scale.

Table 6: List of pharmacokinetic parameters

Parameter	Description
C_{max}	Observed maximum baseline-adjusted or unadjusted plasma concentration
AUC_{0-t}	Area under the baseline-adjusted as well as unadjusted plasma concentration-time curve from time zero to the last sampling time point at which the concentration was at or above lower limit of quantification (LLOQ); t(last) is defined as the last value > 0 after baseline adjustment. AUC_{0-t} will be calculated according to the linear trapezoidal formula
$AUC_{0-\infty}$	Area under the baseline-adjusted as well as unadjusted plasma concentration-time data extrapolated to infinity ($AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$)
$\%AUC_{t-\infty}$	Proportion of extrapolated part ($\%AUC_{t-\infty}$) $(1- [AUC_{0-t}/AUC_{0-\infty}])\bullet 100$
t_{max}	time to reach C_{max}
$t_{1/2,\lambda z}$	apparent terminal half-life, calculated by $\ln 2/\lambda_z$
λ_z	Terminal rate constant λ_z denotes the terminal rate constant estimated by linear regression analysis from a range of concentrations in the terminal phase estimated for each treatment and subject by log-linear regression from the linear portion of the logarithmic transformed concentration-time plot. The algorithm will start with the last 3 points with quantifiable concentrations and increases the number of involved points by 1 until the time point after C_{max} restricted on time points after removing of the BF-200 ALA gel. For each regression an adjusted R^2 will be computed: Adjusted $R^2 = 1 - \frac{(1-R^2)\cdot(n-1)}{n-2}$, where n denotes the number of data points ($n \geq 3$). The regression with the largest adjusted $R^2 > 0.8$ will be selected for the estimation of λ_z using WinNonlin option "BestFit".

14.2 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.

Enrolled set

All subjects enrolled in this study i.e. that provided informed consent to participate in the study.

Treated set

All subjects that received IMP treatment (including subjects whose PDT treatment was terminated for any reason without illumination). This set is the analysis set for the summary of subject discontinuation.

Safety set

The safety set (SAF) will include all subjects who undergo at least one of the following treatment procedures: preparation of the treatment field(s), application of BF-200 ALA, or illumination. The SAF is the analysis set for all safety analyses.

Pharmacokinetic sets

The pharmacokinetic sets are defined for each of the two analytes separately. The pharmacokinetic set per analyte includes all subjects who have at least one evaluable pre-dose and post dose pharmacokinetic sample (i.e., samples taken after the application of BF-200 ALA) for the respective analyte. A post dose sample is regarded evaluable if the plasma concentration is at or above LLOQ.

As plasma concentration data of ALA and PpIX are considered separately, e.g., a subject can be in the pharmacokinetic set for evaluation of PpIX but not for evaluation of ALA.

Subjects who develop bleeding during preparation of the treatment area are not to be excluded from the pharmacokinetic set.

14.3 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.

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

Descriptive statistics of pharmacokinetic parameters and plasma concentrations for ALA and PpIX additionally included the geometric mean, geometric SD, and geometric CV. If a zero occurs in a sample, the corresponding geometric mean and geometric SD will be computed, omitting this value.

The PK data will be presented for all subjects in the respective PK sets. Selected data may be presented excluding outliers as well. Safety data will refer to the SAF set.

Disposition of subjects and exposure

Descriptive analysis of subjects in each analysis set such as the enrolled set, the treated set, the SAF, the pharmacokinetic set for ALA and PpIX, respectively, will be presented. Premature discontinuation from the study and completion of the study will be summarized. Reasons for discontinuation will be tabulated.

PDT details (e.g. incubation time of the IMP, duration of illumination, interruptions/pauses, interferences) and sampling time points for PK blood samples will be presented overall and by strata.

Demographics and background characteristics

All variables concerning demographic and background characteristics will be summarized to describe the study population.

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.

Safety analyses

All safety endpoints will be analyzed descriptively and in an exploratory way. These safety analyses will be performed for the safety set. Safety analyses will be conducted overall and according to strata.

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 if a reasonable number of AEs of this type are observed.

A listing of subjects with AEs will be provided for all AEs reported and all subjects enrolled.

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

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 siginificant by the investigator. Out of range laboratory values that are considered clinically significant will be documented in the medical history (Visit 1) or as AEs (Visit 3) and listed as such.

The analyses of variables for vital signs will focus on the evaluation of the change from baseline to the scheduled time point after baseline. Descriptive analysis (number of subjects, mean, median and SD, minimum, maximum) of the time course and of changes from baseline to post baseline time point will be presented.

General physical examinations will include the following body systems: head and neck, skin, lymph nodes, thorax including heart and lung, abdomen, and musculoskeletal, peripheral vascular and nervous system. All clinically significant abnormal physical findings will be listed. Details of further analyses will be specified in the statistical analysis plan (SAP).

Pharmocokinetics

Descriptive statistics of unadjusted and baseline-adjusted plasma concentrations for ALA and PpIX by nominal blood sampling time will be provided.

The following graphics will be provided for ALA and PpIX:

- Geometric mean concentrations (unadjusted and baseline-adjusted) will be given on linear and logarithmic concentration scale.
- Individual concentrations (unadjusted and baseline-adjusted) will be provided overall for each subject on linear and logarithmic concentration scale (by-patient plot).
- Individual concentrations (unadjusted and baseline-adjusted) will be provided according to strata for each subject on linear and logarithmic concentration scale (by-patient plot).

For unadjusted concentrations, the mean overall baseline concentration will be presented as a dotted line in the overall graphic, and the respective average baseline of all subjects will be presented in the corresponding by-patient plots.

Descriptive statistics of calculated PK parameter for ALA and PpIX will be provided overall and according to strata.

14.4 Handling of missing data

Missing data of safety or pharmacokinetics variables will not be replaced. Details on the handling of missing data will be specified in the SAP.

14.5 Interim analysis

No formal interim analysis will be performed.

14.6 Sample size justification

Thirty-two (32) subjects will be included in this study, stratified into two groups of 16 subjects each. One of the groups will receive PDT applying 3 tubes of BF-200 ALA in the face/scalp, the other group will receive PDT applying 3 tubes of BF-200 ALA on the neck/trunk/extremities.

A previous PK Phase I study under maximal use conditions in AK subjects with 1 tube of BF-200 ALA (ALA-AK-CT006) had revealed homogeneous baseline-adjusted levels of ALA and PpIX in 12 subjects, with a CV of 53-73% in the key pharmacokinetic parameters after drug application. As statistical evaluation of PK and safety is intended to be performed as descriptive statistics only, no calculation of predictive power is required.

Based on the results of a previous PK study (ALA-AK-CT006), a group size of 12 subjects is considered to be sufficient for proper pharmacokinetic evaluation and in agreement with the findings from the pilot study. In order to compensate for potential drop-outs of subjects as well as potentially higher variability of data due to combined investigation of two treatment

areas, stratum size was adapted from 12 to 16 subjects. A drop-out rate of 25% (4 of 16 patients) was assumed taking into account the complex nature of the study procedures comprising PDT treatment with three tubes and up to two illuminations, and frequent blood sampling on one single day. For this reason, the sample size of 32 subjects is considered to be adequate for pharmacokinetic evaluation in this PK 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 and informed consent

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 administered IMP and 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 onsite visits. In addition to the monitoring visits, frequent communications (letter, 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 contract research organization (CRO) or sponsor.

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 quality assurance unit of the CRO or the sponsor or by a contracted auditor. 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 investigator 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. Site documentation will identify the software and hardware systems used to create, modify, maintain, archive, retrieve, or transmit data.

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 B: NRS-11 for pain during PDT

APPENDIX A

Fitzpatrick´s Skin Type Test

Fitzpatrick´s Skin Type according to Fitzpatrick, 1988 (38)

One of the important parameters for the success of your treatment is the correct typing of your skin.

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 skin type and the treatment program devised by your doctor are:

- Genetic disposition -Skin types I to III should add one level when you have blood relatives with darker skin type IV or higher.
- Reaction to sun exposure and tanning habits.

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

So, please help us determine your skin type to assist us in your treatment.

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: _____					

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

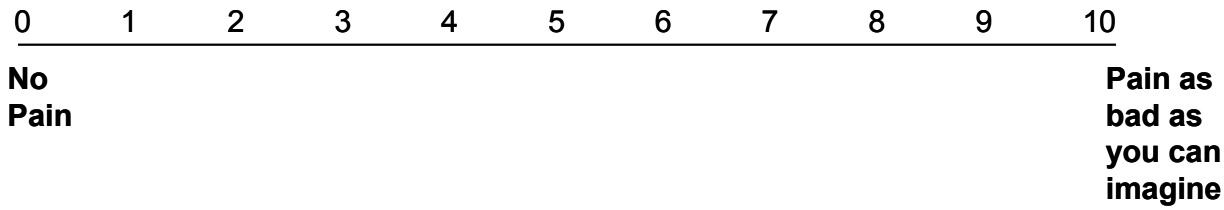
Skin Type Score	Fitzpatrick Skin Type
0 – 7	I
8 – 16	II
17 – 24	III
25 – 30	IV
>30	V – VI

APPENDIX B

Numeric rating pain scale for pain during photodynamic therapy

Pain sensation during photodynamic therapy (PDT) will be assessed using the 11-point numeric rating pain scale, shown below:

Please rate your pain intensity by circling the number that best describes your maximum pain during PDT.



To be transferred into the 4-point scale if applicable 0= none, 1-3 = mild, 4-7 = moderate, 8-10 = severe.