COVER PAGE

CLINICAL STUDY PROTOCOL

Study ALA-AK-CT019

NCT05662202

A randomized, double-blind, vehicle-controlled, multicenter Phase III study to evaluate the safety, tolerability, and efficacy of BF-200 ALA (Ameluz®) in the field-directed treatment of actinic keratosis on the extremities and neck/trunk with photodynamic therapy (PDT) using the BF-RhodoLED® XL or BF-RhodoLED® lamp.

Document date: 31 May 2023

TITLE PAGE

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Version 3.0

ALA-AK-CT019

Test Product:	BF-200 ALA (Ameluz®) [in combination with the BF-RhodoLED® XL or BF-RhodoLED®]
Indication:	Actinic keratosis
Study Design:	Multicenter, randomized, parallel group, double-blind
Study Identifier:	IND 115412
Study Phase:	Phase III study
Coordinating Investigator(s):	Nathalie C. Zeitouni, MD Southwest Skin Specialists, LLC d/b/a Medical Dermatology Specialists 1331 N. 7th Street, Suite 250 Phoenix, AZ 85006, USA e-mail: PPD
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Sponsor's Signatoree:	PPD e-mail: PPD Tel.: PPD, Fax: PPD
Date of issue	31-May-2023

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

DECLARATIONS OF SPONSOR AND INVESTIGATORS

Declaration of sponsor and coordinating investigator

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

- the current risk-benefit evaluation of the investigational medicinal product in conjunction with an investigational device (combination 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., suspected unexpected serious adverse reactions / unanticipated serious adverse device effects, related to treatment with the investigational product.

Sponsor

Date: _____ Signature: _____

Name (block letters):_____

Coordinating Investigator

Date: _____ Signature: _____

Name (block letters):_____

Declaration of investigator

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

1 TABLE OF CONTENTS

Title page **1**
Declarations of sponsor and investigators **2**
Declaration of sponsor and coordinating investigator 2
Declaration of investigator 3
Declaration of biostatistician 4
1 Table of contents **5**
1.1 List of Tables 10
1.2 List of Figures 10
2 Abbreviations and Definitions **11**
2.1 Abbreviations 11
2.2 Definitions 14
3 Protocol Outline **16**
4 Introduction and study rationale **31**
4.1 Introduction 31
4.2 Selection of drugs and dosages 32
4.3 Study rationale 33
4.4 Risk/benefit analysis 34
5 Study objectives and key endpoints **36**
5.1 Objectives 36
5.2 Key Endpoints 36
5.2.1 Primary endpoint 36
5.2.2 Key secondary endpoints 36
6 Investigational plan **37**
6.1 Overview of study design 38
6.2 Study duration and end-of-study definition 38
6.3 Study population 38
6.3.1 Number of Subjects 38
6.3.2 Recruitment arrangements 39
6.3.3 Inclusion criteria 39
6.3.4 Exclusion criteria 40
6.3.5 Dosing day exclusion criterion 41

6.3.6 Screening Failures 42
6.3.7 Subjects of reproductive potential 42
6.3.8 Randomization: Treatment assignment and blinding 42
7 Study treatment 44
7.1 Investigational Medicinal Product 44
7.1.1 Details 44
7.1.2 Storage 45
7.2 Investigational Medical Device 45
7.2.1 Details 46
7.2.2 Storage 47
7.2.3 Illumination profile 47
7.3 Application of Investigational Medicinal Product 48
7.4 Application and Handling of Investigational Medical Device 49
8 Study Procedures 51
8.1 Study treatment phase 51
8.1.1 Visit 1: Screening visit (≤ 4 weeks prior to PDT-1) 51
8.1.2 Visit 2: Baseline/ Treatment (PDT-1) 52
8.1.3 Phone call 1 (1 week (± 2 days) post PDT-1) 53
8.1.4 Visit 3: Interim assessment (4 weeks (± 1 week) post PDT-1) 53
8.1.5 Visit 4 (12 weeks (± 1 week) post PDT-1): Final assessment of complete responders / re-treatment (PDT-2) for non- or partial responders 53
8.1.6 Phone call 2 (1 week (± 2 days) post PDT-2) 55
8.1.7 Visit 5: Interim Assessment (4 weeks (± 1 week) post PDT-2) 55
8.1.8 Visit 6: Final assessment of non- or partial responders (12 weeks (± 1 week) post PDT-2) 55
8.2 Follow-up phase (FUP) 56
8.3 Unscheduled visits 57
8.4 Prior and concomitant medical conditions and treatment 57
8.4.1 Prior and concomitant medical conditions 57
8.4.1.1 Medical skin history 57
8.4.2 Prior and concomitant treatment 58
8.5 Withdrawals 61
8.5.1 Withdrawals of subjects 61

8.5.2 Replacement of subjects 62
8.5.3 Withdrawal of samples 62
9 Study evaluations and assessments 63
9.1 Demographic data 63
9.2 Body measures 63
9.3 Assessment of skin type 63
9.4 Assessment of AK 63
Selection of the treatment field 63
Baseline assessment of AK lesions inside the treatment field 64
Generation of templates (Grid foil, cartoon) 64
Clearance status of AK 64
9.4.1 Clinical criteria for diagnosis 64
9.4.2 Biopsy 65
9.4.2.1 Histopathological evaluation of AK 65
9.5 Assessment of esthetic appearance by investigator 66
9.6 Assessments of satisfaction regarding PDT treatment and esthetic outcome by subject 66
9.7 Safety 67
9.7.1 Physical examination 67
9.7.2 Vital signs 67
9.7.3 Safety laboratory 67
9.7.3.1 Blood 67
9.7.3.2 Urine 68
9.7.4 Pregnancy test in females of reproductive potential 68
9.7.5 Adverse events 68
9.7.5.1 Application site reactions 68
9.7.5.2 Documentation of new lesions 72
10 Safety Management 73
10.1 Definitions 73
10.1.1 Adverse events 73
10.1.2 Serious adverse events 74
10.1.3 Alert terms and other reasons for expedited reporting to Pharmacovigilance 75
10.1.3.1 Transient Amnestic Episodes 75

10.1.3.2 Contact Dermatitis 75
10.1.4 Investigational medicinal product complaints 76
10.1.5 Investigational medical device complaints 76
10.2 Period AE collection 76
10.3 Documentation and reporting of adverse events by investigator 76
10.3.1 Immediate Reporting 78
10.3.1.1 Reporting of SAEs and AESIs to sponsor 78
10.3.1.2 Reporting of pregnancies to sponsor 79
10.3.1.3 Reporting of USADEs to the sponsor and to IRB 80
10.3.1.4 Expedited reporting of adverse events to IRB 80
10.3.2 Unblinding 80
10.4 Documentation and reporting of adverse events by sponsor 80
10.4.1 Determination of expectedness, Reference Safety Information 80
10.4.2 Expedited reporting of AEs to competent authorities and investigators 81
10.4.3 Periodic reporting of AEs by sponsor 81
10.4.3.1 Development safety update report (DSUR) 81
10.5 Continuous risk assessment 81
10.6 Emergency procedures 81
10.6.1 Emergency sponsor contact 81
10.6.2 Emergency identification of investigational medicinal products 81
10.6.3 Emergency treatment 82
11 Statistical Procedures 83
11.1 Endpoints 83
11.2 Analysis sets 86
11.2.1 Protocol Deviations leading to exclusion from PPS 87
11.3 Estimands 87
11.4 Statistical methods 88
11.4.1 Disposition of subjects and exposure 88
11.4.2 Demographics and background characteristics 88
11.4.3 Evaluation of efficacy endpoints 89
11.4.4 Evaluation of safety endpoints 90
11.5 Handling of missing data 91
11.6 Interim analysis 91

11.7 Sample size justification 91
12 Study administration 93
12.1 Treatment assignment methods 93
12.1.1 Randomization: Generation of randomization sequence 93
12.2 Packaging and labeling 93
12.2.1 Investigational medicinal product 93
12.2.2 Investigational medical device 94
12.3 Supplies and accountability 95
12.4 Compliance 95
12.5 Ethical and legal aspects 95
12.5.1 Good clinical practice (GCP) 95
12.5.2 Delegation of investigator duties 96
12.5.3 Subject information and informed consent and HIPAA form 96
12.5.4 Confidentiality 96
12.5.5 Protocol and GCP violations 97
12.5.6 Protocol amendments 97
12.5.7 Approval of the clinical study protocol and amendments 97
12.5.8 Ongoing information for ethics committee/ institutional review board 98
12.5.9 Closure of the study 98
12.5.10 Record retention 98
12.5.11 Liability and insurance 98
12.5.12 Financial disclosure 99
12.6 Quality control and Quality assurance audit 99
12.6.1 Study monitoring and source data verification 99
12.6.2 Site audits 99
12.6.3 Site inspections 100
13 Documentation and use of study findings 101
13.1 Documentation of study findings 101
13.2 Use of study findings 101
14 References 103
15 Appendices 107
Appendix A 108
Appendix B 111

Appendix C 114

1.1 List of Tables

Table 1: Study schedule 26
Table 2: Composition and manufacturer of study medication 45
Table 3: Key light parameters of the BF-RhodoLED® and BF-RhodoLED® XL 46
Table 4: List of forbidden concomitant medication with designated time periods. 59
Table 5: Clinical evaluation of AK according to Olsen (1) 65
Table 6: Histological evaluation according to KIN classification 66
Table 7: Category descriptors with a 4-point scale for Application Site Reactions 69
Table 8: Reading Criteria for the Patch testing according to the Guidelines of the International Contact Dermatitis Research Group (49) 115

1.2 List of Figures

Figure 1: Summary of study visits 38
Figure 2: Illumination profile. 47
Figure 3: Treatment sequence including IMP application, placement of occlusive dressing, incubation of IMP and illumination at Visit 2 and Visit 4, if applicable 48

2 ABBREVIATIONS AND DEFINITIONS

2.1 Abbreviations

β-hCG	β-human chorionic gonadotropin
ADE	Adverse device effect
AE	Adverse event
AESI	Adverse event of special interest
AK	Actinic keratosis
ALA	5-aminolevulinic acid
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
BCC	Basal cell carcinoma
BD	Bowen's disease
BF	Biofrontera
BF-200 ALA	Nanoemulsion gel formulation containing 7.8 % ALA (development name for Ameluz®) for topical use
BP	Blood pressure
CFR	Code of Federal Regulations
CI	Confidence interval
CRO	Contract Research Organization
CS	Clinically significant
CSP	Clinical study protocol
DCF	Data clarification form
DSUR	Development safety update report
EC	Ethics committee
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EoS	End-of-Study
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration

FU	Follow-up
FUP	Follow-up phase
FWER	Family wise error rate
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GmbH	Gesellschaft mit beschränkter Haftung, Ltd, limited liability company
GMP	Good manufacturing practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's brochure
ICE	Intercurrent event
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMD	Investigational medical device
IMP	Investigational medicinal product
IND	Investigational new drug
IP	Investigational product
IRB	Institutional review board
ISF	Investigator site file
ISO	International Organisation for Standardization
KIN	Keratinocytic intraepidermal neoplasia
LDH	Lactate dehydrogenase
LED	Light-emitting diode
LSLV-TP	Last subject last visit of the treatment phase
LSLV-FU	Last subject last visit of the follow-up phase
MAL	Methyl aminolevulinic acid
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New drug application
NMSC	Non-melanoma skin cancer
NRS-11	Numeric Rating Scale (11-point pain rating scale)
NSAID	Non-steroidal anti-inflammatory drugs
PDT	Photodynamic therapy
PI	Prescribing Information

PpIX	Protoporphyrin IX
PPS	Per-protocol set
PR	Pulse rate
PTAEs	Pre-treatment adverse events
QPPV	Qualified person for pharmacovigilance
RSI	Reference safety information
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SCC	Squamous cell carcinoma
SD	Standard deviation
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
TMF	Trial Master File
TP	Treatment phase
US	United States of America
USADE	Unanticipated serious adverse device effect
UV	Ultraviolet
WBC	White blood cells

2.2 Definitions

Enrolled

A subject is defined as enrolled when informed consent has been given.

End of study (EoS)

Last Subject Last Visit of the follow-up phase (LSLV-FU).

Total light dose

Total light dose in this study is 37 J/cm^2.

Treatment area:

The region of the body in which the treatment field is located, distinguishing between

- **Extremities,** including subareas hands, upper/lower arms, feet, upper/lower legs
- **Neck/trunk,** including subareas neck, shoulder, upper/lower back, upper chest, abdomen

Illumination area:

The area effectively illuminated by one BF-RhodoLED® XL lamp (maximal area, 5 panels used: 23 cm x 29 cm (667 cm^2, curved shape) or [redacted] (flat shape)) or by one BF-RhodoLED® (6 cm x 16 cm (96 cm²)) in one illumination session. Illumination of the entire treatment field using BF-RhodoLED® might require consecutive illumination in up to three illumination sessions.

Treatment field:

The part of the skin to which the investigational medicinal product (IMP) is applied.

The treatment field must contain 4 – 15 mild to moderate (according to Olsen (1)) clinically confirmed actinic keratosis (AK) target lesions on the extremities or neck/trunk. In addition, non-target AK lesions may be present in the treatment field, including up to two severe AK lesions ≥ 4 mm. All AK target lesions and, if applicable, severe AK lesions ≥ 4 mm located in the treatment field should be clearly distinguishable, without restrictions on the distance between lesions, and should have a minimal distance of 1 cm to the border of the treatment field. The treatment field may be continuous or in several patches. The treatment field should be selected to treat a skin area of approx. either 80 cm², 160 cm² or 240 cm² in each subject.

In case of a discontinuous treatment field, all patches must be located within one effective illumination area of the BF-RhodoLED® XL or within up to three effective illumination areas of the BF-RhodoLED®.

Illumination profile:

The illumination profile used in this study applies the total light dose of approx. 37 J/cm² [redacted]

[redacted]. For the BF-RhodoLED® XL this profile requires approx. [redacted] min if the light-emitting diode (LED) panels are arranged in curved shape, and approx. [redacted] min if the panels are arranged in flat shape. For BF-RhodoLED® this profile requires approx. [redacted] min.

AK target lesions

AK lesions of mild to moderate severity (according to Olsen (1)) with a diameter of ≥ 4 mm at baseline located inside the treatment field. For non-circular lesions, all diameters have to be at least 4 mm.

Non-target AK lesions

AK lesions of mild to moderate severity (according to Olsen (1)) with a diameter of < 4 mm and any severe AK lesion(s) inside the treatment field.

Complete responders

Subjects who present complete clearance of all AK target lesions 12 weeks after the last PDT according to clinical assessment (i.e., Olsen Grade = 0 for all AK target lesions (according to Olsen (1)).

Non-target AK lesions will not be considered for complete clearance status.

Non- and partial responders

Subjects with remaining AK target lesions according to clinical assessment (Grade ≠ 0, according to Olsen (1)) at Visit 4 or Visit 6. Subjects with remaining AK target lesions 12 weeks after PDT-1 (Visit 4) will be re-treated during Visit 4 and final assessment for response will be at Visit 6.

New lesions

New preneoplastic or neoplastic lesions including AK, non-melanoma skin cancer (NMSC) such as basal cell carcinoma (BCC), squamous cell carcinoma (SCC) or Bowen's disease (BD), and melanoma that occur inside the treatment field.

3 PROTOCOL OUTLINE

Title

A randomized, double-blind, vehicle-controlled, multicenter Phase III study to evaluate the safety, tolerability, and efficacy of BF-200 ALA (Ameluz®) in the field-directed treatment of actinic keratosis on the extremities and neck/trunk with photodynamic therapy (PDT) using the BF-RhodoLED® XL or BF-RhodoLED® lamp.

Study no: ALA-AK-CT019 Clinical Phase: III

Study Design

This is a Phase III, multicenter, randomized, parallel group, double-blind study comparing BF-200 ALA with vehicle in the treatment of actinic keratosis (AK) located on extremities or neck/trunk with PDT when using a RhodoLED lamp (BF-RhodoLED® XL or BF-RhodoLED®). Each subject will receive PDT with either BF-200 ALA or vehicle for inter-individual comparison. Allocation of IMP to subjects will be randomized at a ratio of 4:1.

Investigators / study sites

Multiple sites in the United States of America (US) will participate in this study. Each site should randomize between 5 and 25 subjects. No site should randomize more than 25 subjects unless prior approval of the sponsor is obtained. The maximum number should in no case exceed 30 subjects.

Number of subjects

It is planned to randomize approx. 165 subjects to either BF-200 ALA or vehicle.

Subjects and lesions

Subjects of all sexes and of age 18 years and older will be enrolled.

Presence of 4 – 15 mild to moderate (according to Olsen) clinically confirmed AK target lesions with a diameter of ≥ 4 mm within the treatment field on the extremities or neck/trunk. In addition, non-target AK lesions may be present in the treatment field, including up to two severe AK lesions ≥ 4 mm. For each severe AK lesion ≥ 4 mm, a biopsy must be taken at screening (Visit 1) for confirmation of diagnosis. The treatment field may be continuous or in several patches, totaling approx. either 80 cm^2, 160 cm^2 or 240 cm^2 (1 to 3 entire tubes of IMP) in each subject and must be located within one effective illumination area of the BF-RhodoLED® XL or within up to three effective illumination areas of the BF-RhodoLED®.

Definitions

- "Illumination area" is the area effectively illuminated by a RhodoLED lamp (BF-RhodoLED® XL lamp or BF-RhodoLED®) in one illumination session
- "Treatment field" is the part of the skin to which IMP is applied
- "Treatment area" describes the region of the body in which the treatment field is located, distinguishing between extremities (including subareas hands, upper/lower arms, feet, upper/lower legs) and neck/trunk (including subareas neck, shoulder, upper/lower back, upper chest, abdomen)

- "AK target lesions" are AK lesions of mild to moderate severity (according to Olsen et al. 1991) with a diameter of ≥ 4 mm at baseline located inside the treatment field. For non-circular lesions, all diameters have to be at least 4 mm.
- "Non-target AK lesions" are AK lesions of mild to moderate severity and a diameter of < 4 mm and any severe AK lesion(s) inside the treatment field.
- "Complete responders" are defined as subjects who present complete clearance of all AK target lesions 12 weeks after the last PDT according to clinical assessment (i.e., Olsen Grade = 0 for all AK target lesions (according to Olsen et al. 1991).

Investigational products (IP)

Investigational medicinal product (IMP)

BF-200 ALA or vehicle (matching placebo to BF-200 ALA).

BF-200 ALA is a gel formulation of 10 % 5-aminolevulinic acid hydrochloride, corresponding to 7.8 % 5-aminolevulinic acid (ALA). It is approved as Ameluz® by the Food and Drug Administration (FDA) in combination with photodynamic therapy using BF-RhodoLED® lamp or RhodoLED® XL lamp and indicated for the lesion-directed and field-directed treatment of actinic keratoses (AK) of mild to moderate severity on the face and scalp. The vehicle is indistinguishable in color, appearance, smell, and texture from BF-200 ALA and contains all other ingredients except the active ingredient ALA. The IMP will be packed in tubes, containing 2 g each. The content of 1 to 3 entire tubes of IMP will be applied per subject per PDT (1 tube per 80 cm²).

Investigational medical device (IMD)

The study treatment requires combining the IMP with illumination of the treatment field with approx. 37 J/cm² of red-light at a peak wavelength of approx. 635 nm. In this study, the light-emitting diode (LED) device BF-RhodoLED® XL should preferably be used, but BF-RhodoLED® is allowed as an alternative. Both lamps are approved as equivalent light sources for PDT in combination with Ameluz®, but the BF-RhodoLED® XL enables the illumination of a larger skin area. The illumination profile used in this study applies a total light dose of approx. 37 J/cm² [redacted]. In addition, the BF-RhodoLED® XL illumination panels can be used in two different shapes, either in a curved shape or in a flat shape. Depending on the shape, the total illumination duration is approx. [redacted] min or approx. [redacted] min. If the BF-RhodoLED® lamp is used, up to three consecutive illuminations may be necessary.

Study Duration and Dates

Duration of the study treatment phase per subject will be approx. 16 weeks for subjects requiring 1 PDT (until Visit 4) and approx. 28 weeks for subjects with 2 PDTs (until Visit 6). This will be followed by approx. 40 additional weeks until completion of the follow-up phase.

Within 4 weeks after the screening visit (Visit 1) and following confirmation of eligibility, subjects will be randomized and PDT-1 will be performed (baseline, Visit 2). A phone call 1

week after PDT-1 to assess transient side effects will be performed and an onsite assessment 4 weeks after PDT-1 (Visit 3) to assess safety and preliminary efficacy parameters. At Visit 4, 12 weeks after PDT-1, a final evaluation of safety and efficacy will be performed for complete responders, i.e., subjects with all AK target lesions clinically cleared.

Subjects with at least one remaining AK target lesion (non- or partial responders) at Visit 4 will receive a second PDT (PDT-2) on the same day, followed by a phone call and visits (Visit 5 and Visit 6) at the same intervals as after PDT-1. All subjects who are clinically not completely cleared 12 weeks after PDT-2 will receive further non-study treatment at the discretion of the investigator. All subjects will enter a follow-up phase starting approx. 12 weeks after the last PDT, entailing follow-up visits at 6 months (FU1) and 12 months (FU2) after the last PDT.

Results of the treatment phase (Visit 1 to Visit 4 or Visit 6) will be reported after Last Subject Last Visit of the treatment phase (LSLV-TP).

The results of the two follow-up visits will be analyzed and reported separately from the treatment phase. End of study (EoS) is defined as Last Subject Last Visit of the follow-up phase (LSLV-FU).

In-/exclusion criteria

Inclusion criteria

1. Willingness and ability of subjects to provide informed consent and sign the Health Insurance Portability and Accountability Act (HIPAA) form. A study-specific informed consent and HIPAA form must be obtained in writing prior to starting any study procedures.
2. 4 – 15 mild to moderate clinically confirmed AK lesions according to Olsen either on the extremities or on the neck/trunk with a diameter of ≥ 4 mm that must be present in the treatment field. In addition, non-target AK lesions may be present in the treatment field, including up to two severe AK lesions ≥ 4 mm. For each severe AK lesion (≥ 4 mm), a biopsy must be taken for confirmation of diagnosis. The treatment field (continuous or in several patches) totaling approx. either 80 cm^2, 160 cm^2 or 240 cm^2 must be within one effective illumination area of the BF-RhodoLED® XL but may require up to three illuminations with the BF-RhodoLED®. All AK target lesions and, if applicable, severe AK lesions ≥ 4 mm located in the treatment field should be clearly distinguishable, without restrictions on the distance between lesions, and should have a minimal distance of 1 cm to the border of the treatment field.
3. All sexes, ≥ 18 years of age.
4. Willingness to undergo a 2 mm punch biopsy for each (up to two) severe AK lesion of ≥ 4 mm, if applicable, at the screening visit.
5. Willingness and ability to comply with study procedures, particularly willingness to receive up to 2 PDTs within approx. 12 weeks.
6. Subjects with good general health or with clinically stable medical conditions will be permitted to be included in the study.
7. Willingness to stop the use of moisturizers and any other non-medical topical treatments within the treatment field at least 24 h prior to the next clinical visit.

8. Acceptance to abstain from extensive sunbathing and the use of a solarium or tanning beds during the treatment phase.
9. For female subjects with reproductive potential: Negative serum pregnancy test.
10. For female subjects with reproductive potential: Effective contraception at screening visit and throughout the treatment phase of the study (until Visit 4 or Visit 6).

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

a. Topical treatment with ALA or ALA esters (e.g., methyl aminolevulinic acid (MAL)) inside the treatment field within 3 months.

b. Topical treatment with immunomodulatory, cytostatic, or cytotoxic drugs inside or in close proximity (< 10 cm distance) to the treatment field within 3 months.

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

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

Reassessment of subjects is allowed once in case exclusion criterion 3 is met and eligibility can be achieved within 4 weeks. Reassessment can be done on the day of the actual treatment.

Dosing day exclusion criterion

At Visit 2 (baseline, PDT-1)

Subjects with sunburn or other possibly confounding skin conditions (e.g., wounds, irritations, bleeding or skin infections) inside or in close proximity (< 2 cm distance) to the treatment field. Reassessment of subjects is allowed once if the sunburn or other confounding skin conditions is/are expected to resolve within 2 weeks.

At Visit 4 (PDT-2)

Subjects with sunburn or other possibly confounding skin conditions (e.g., wounds, irritations, bleeding or skin infections) inside or in close proximity (< 2 cm distance) to the treatment field. Rescheduling of PDT-2 can be performed once at the earliest possibility after resolution, but rescheduling should not exceed 2 weeks.

Treatment

Subjects will be randomized (stratified by the treatment areas extremities or neck/trunk) for treatment with PDT with either BF-200 ALA (Ameluz®, test group) or vehicle (control group). The IMP is packed in tubes, each containing 2 g gel. A pack of 6 tubes will be assigned to each subject to allow treatment with 1 to 3 tubes per PDT. For each PDT, IMP will be homogenously applied to the assigned treatment field (approx. either 80 cm^2, 160 cm^2 or 240 cm^2; 1 tube per 80 cm^2). Each tube must be applied in its entirety.

The treatment field should be prepared for IMP application by degreasing (using ethanol or isopropanol) and removal of scabs and crusts, and if appropriate roughening of the surface (e.g., by mild debridement). Care should be taken to avoid bleeding. The assigned IMP (1 to 3 tubes) will then be applied to the entire treatment field, including all AK target lesions. All AK target lesions and, if applicable, severe AK lesions ≥ 4 mm located in the treatment field should have a minimal distance of 1 cm to the border of the treatment field. The medication will be allowed to dry and covered with Tegaderm® for approx. 3 h. The subject should stay in a well-tempered environment during the incubation time. It is particularly important to ascertain that extremities will not be cold during the 3 h incubation. Thereafter, the Tegaderm® and any remnants of the applied study medication will be removed and illumination with approx. 37 J/cm^2 will be administered using preferably the BF-RhodoLED® XL or, alternatively, BF-RhodoLED®. Subjects with incomplete response will receive a 2nd identical PDT approx. 12 weeks after PDT-1. For all subjects, the final assessment will be performed 12 weeks after the last PDT (Visit 4 or Visit 6, end-of-treatment phase of the study).

Primary objective

The primary objective of the study is to compare the efficacy of BF-200 ALA PDT with vehicle PDT, utilizing illumination with a RhodoLED lamp, in the treatment of mild to moderate actinic keratosis on the extremities or neck/trunk in terms of overall subject complete response (complete clearance of all AK target lesions) in the treatment phase.

The primary endpoint is the overall subject complete response rate 12 weeks after the last PDT, defined as the percentage of subjects with all AK target lesions clinically cleared 12 weeks after the last PDT. The primary estimand will use the treatment-policy strategy and compare the treatment effect in subjects independent of a) the use of medications in a temporal relation to PDT which might influence the efficacy of the treatment, b) refusal of 2nd treatment e.g., due to pain, c) any other type of treatment discontinuation, or d) postponement of PDT-2.

The primary endpoint will additionally be analyzed descriptively and in an exploratory way stratified by demographics, skin type class (I-III and IV-VI), study sites, and AK baseline parameters (e.g., AK target lesion number per subject at baseline, maximal AK target lesion severity at baseline, size of the treatment field, and treatment area).

Secondary objective

The secondary objective of the study is to evaluate secondary efficacy parameters and safety and tolerability in the treatment phase.

Efficacy:

Key secondary endpoints:

The key secondary endpoints are:

1) Overall subject complete response rate 12 weeks after the last PDT, defined as the percentage of subjects with all AK target lesions clinically cleared 12 weeks after the last PDT, for subjects with lesions treated on extremities

2) Overall subject complete response rate 12 weeks after the last PDT, defined as the percentage of subjects with all AK target lesions clinically cleared 12 weeks after the last PDT, for subjects with lesions treated on neck/trunk

Key secondary endpoints will additionally be analyzed descriptively and in an exploratory way stratified by AK baseline parameters (e.g., AK target lesion number per subject at baseline, maximal AK target lesion severity at baseline, size of the treatment field, and treatment area).

Further secondary endpoints of the treatment phase regarding efficacy are:

- Percentage of clinically cleared individual AK target lesions in relation to total number of AK target lesions at baseline (Visit 2) assessed 12 weeks after the last PDT, overall and stratified by treatment area and AK severity at baseline (according to Olsen et al., 1991).
- Percentage of clinically cleared individual severe AK lesions in relation to total number of severe AK lesions at baseline (according to Olsen et al., 1991; Visit 2) assessed 12 weeks after the last PDT, overall and stratified by treatment area.
- Subject complete response rate, 12 weeks after PDT-1, defined as the percentage of subjects with all AK target lesions clinically cleared, overall and stratified by AK baseline parameters (e.g., AK target lesion number per subject at baseline, maximal AK target lesion severity at baseline, size of the treatment field, and treatment area).
- Percentage of clinically cleared individual AK target lesions in relation to total number of AK target lesions at baseline (Visit 2) assessed 12 weeks after PDT-1, overall and stratified by treatment area and AK severity at baseline (according to Olsen et al., 1991).
- Percentage of clinically cleared individual severe AK lesions in relation to total number of severe AK lesions at baseline (according to Olsen et al., 1991; Visit 2) assessed 12 weeks after PDT-1, overall and stratified by treatment area.
- The esthetic appearance 12 weeks after the last PDT as assessed by the investigator, overall and stratified by treatment area.
- The esthetic outcome 12 weeks after the last PDT as assessed by the subject, overall and stratified by treatment area.
- Satisfaction with PDT treatment 12 weeks after the last PDT as assessed by the subject, overall and stratified by treatment area.

Safety and tolerability:

The secondary endpoints/variables of the treatment phase regarding safety and tolerability are:

- Frequency and extent of adverse events (AEs), adverse events of special interest (AESIs), serious AEs (SAEs), and treatment-emergent adverse events (TEAEs), overall and stratified by demographics, skin type class (I – III and IV – VI), size of the treatment field, and treatment area. TEAEs (including application site skin reactions and discomfort) are defined as all AEs with onset or worsening after treatment with IMP up to 12 weeks after the last PDT
- Assessment of new lesions (AK, non-melanoma skin cancer [NMSC, including BCC, SCC, or BD] or melanoma) inside the treatment field
- Assessment of application site reactions according to a 4-point scale
- Application site pain during illumination, reported by the subjects assessed on an 11-point numeric rating scale, overall and stratified by size of the treatment field and treatment area
- Vital signs data
- Safety laboratory data
- Physical examination data

Tertiary objective

The tertiary objective of the study is to evaluate efficacy, safety, and tolerability parameters in the follow-up phase.

Efficacy:

The tertiary endpoints of the follow-up phase regarding efficacy are:

- Subject recurrence rate defined as the percentage of subjects with all AK target lesions clinically cleared 12 weeks after the last PDT presenting with at least one recurrent lesion during follow-up, stratified by demographics, study sites, AK baseline parameters (e.g., AK target lesion number per subject at baseline, maximal AK target lesion severity at baseline, size of the treatment field, and treatment area).
- Percentage of AK target lesions showing recurrence in follow-up in relation to total number of clinically cleared AK target lesions 12 weeks after last PDT, overall and stratified by treatment area and AK severity at baseline (according to Olsen et al., 1991).
- Percentage of severe AK lesions showing recurrence in follow-up in relation to total number of clinically cleared severe AK lesions 12 weeks after last PDT, overall and stratified by treatment area.
- The esthetic appearance at follow-up visits as assessed by the investigator, overall and stratified by treatment area.

- The esthetic outcome at follow-up visits as assessed by the subject, overall and stratified by treatment area.
- Satisfaction with PDT treatment at follow-up visits as assessed by the subject, overall and stratified by treatment area.

Safety:
The tertiary endpoints of the follow-up phase regarding safety are:

- Any relevant AE (including AEs or conditions affecting skin health in the treatment field which may impair proper assessment of the recurrence rate of the treated AK lesions, or other clinically relevant events at the investigator's discretion) as well as any SAE that has occurred since the end-of-treatment visit (Visit 4 or Visit 6) overall and stratified by demographics and treatment area.
- Assessment of new lesions (AK, NMSC or melanoma) inside the treatment field

Sample size calculation

It is planned to randomize approx. 165 subjects.

This sample size will ensure a power of more than 90 % at a significance level of 0.0025 (alpha, one-sided) according to a one-sided Z-test with pooled variance, in order to demonstrate a statistically significant difference in response rates between subjects treated with BF-200 ALA or vehicle in the full analysis set (FAS). The sample size assumes 10 % non-evaluable responses.

The ratio of BF-200 ALA to vehicle will be 4:1.

Statistics

The main statistical analysis will be performed as soon as the 12-week post last PDT data are available for analysis. Additional data from the follow-up phase (6 months and 12 months after the last PDT) will be analyzed and reported separately from the report of the treatment phase of the study. Statistical testing will be applied to compare active treatment vs vehicle.

The primary efficacy variable will be tested for the following hypothesis:

The primary null hypothesis (H_0, one-sided) is that the overall complete subject response rate assessed 12 weeks after the last PDT for subjects treated with BF-200 ALA is lower or equal to that of subjects treated with vehicle. The primary alternative hypothesis (H1, one-sided) is that the overall complete subject response rate assessed 12 weeks after the last PDT for subjects treated with BF-200 ALA is greater than the response rate for subjects treated with vehicle. A one-sided Cochran-Mantel-Haenszel test with stratification factor treatment area (extremities vs neck/trunk) will be used to test the primary hypothesis on a significance level of 0.0025 (one-sided, 0.25 %).
The primary analysis will be performed on the FAS. The analysis will be repeated on the per-protocol set (PPS) as supplementary analysis.

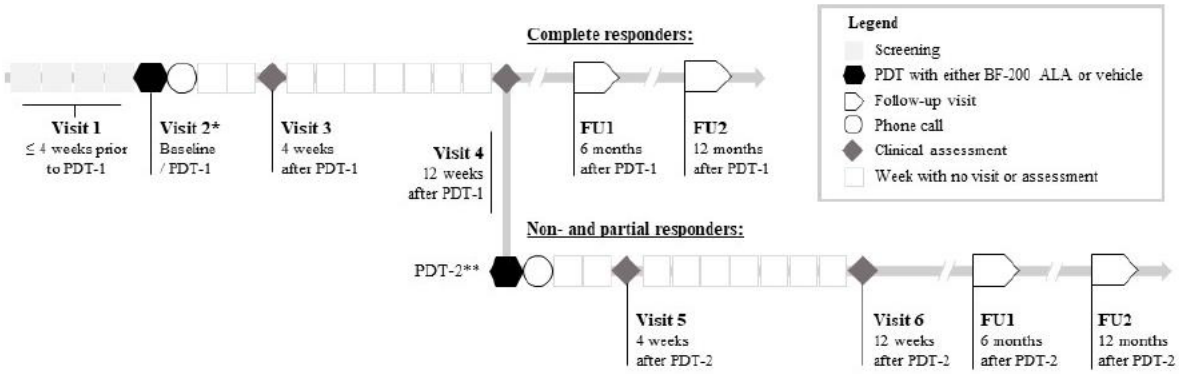
Key secondary efficacy variables, the primary efficacy variable for subgroups of subjects with lesions on 1) extremities or in 2) neck/trunk, respectively, will be analyzed with confirmatory

statistics, using a hierarchical testing procedure, whereas further secondary efficacy variables will be tested descriptively and in an exploratory manner.

The analyses on (key) secondary efficacy endpoints will be performed on the FAS. Confirmatory hypothesis testing of key secondary variables will be done only after the test of the primary efficacy variable is passed and will be done strictly in the given order (extremities followed by neck/trunk) to ensure the Family Wise Error Rate (FWER). The analysis of selected secondary endpoints will be repeated on the PPS as supplementary analysis.

Safety endpoints will be analyzed using the safety analysis dataset (SAF).

Schedule – study overview



* Visit 2 can be rescheduled once after the scheduled date if the dosing day exclusion criterion is expected to resolve within 2 weeks.

** Rescheduling is allowed once if the dosing day exclusion criterion is met, but rescheduling should not exceed 2 weeks.

Table 1: Study schedule

	All subjects (first treatment)					Re-treated subjects only[a]			All subjects	
	Visit 1	**Visit 2**	**Phone call 1**	**Visit 3**	**Visit 4**	**Phone call 2**	**Visit 5**	**Visit 6**	**Follow-up phase**	
	Screening	**PDT-1**			**PDT-2[a]**				**FU1**	**FU2**
	≤ 4 weeks prior to PDT-1	Baseline/ treatment	1 week (± 2 days) post PDT-1	4 weeks (± 1 week) post PDT-1	12 weeks (± 1 week) post PDT-1	1 week (± 2 days) post PDT-2	4 weeks (± 1 week) post PDT-2	12 weeks (± 1 week) post PDT-2	6 months (± 0.5 month) post last PDT	12 months (± 1 month) post last PDT
Clinical visit*	X	X		X	X		X	X	X	X
Obtain Informed consent	X									
Assignment of subject number	X									
Demographics	X									
Inclusion/ exclusion criteria	X[b]	X[c,d]								
Dosing day exclusion criterion		X[e]			X[a,f]					
Concomitant medical conditions/relevant medical history (excluding medical skin history)	X									
Medical skin history	X									
Skin type assessment	X									
Body measures	X									
Vital signs (PR, BP)	X	X		X	X		X	X		
Physical examination	X				X[g]			X		
Selection of the treatment field	X									
Assessment of AK target lesions and severe AK lesions ≥ 4 mm inside the treatment field: size, number, location, severity	X	X								
Generation of templates (Grid foil, cartoon) for re-identification of AK lesions inside the treatment field, including non-target AK lesions	X	X								

	All subjects (first treatment)					Re-treated subjects only[a]			All subjects	
	Visit 1	**Visit 2**	**Phone call 1**	**Visit 3**	**Visit 4**	**Phone call 2**	**Visit 5**	**Visit 6**	**Follow-up phase**	
	Screening	**PDT-1**			**PDT-2[a]**				**FU1**	**FU2**
	≤ 4 weeks prior to PDT-1	Baseline/ treatment	1 week (± 2 days) post PDT-1	4 weeks (± 1 week) post PDT-1	12 weeks (± 1 week) post PDT-1	1 week (± 2 days) post PDT-2	4 weeks (± 1 week) post PDT-2	12 weeks (± 1 week) post PDT-2	6 months (± 0.5 month) post last PDT	12 months (± 1 month) post last PDT
Punch biopsy of each (up to two) severe AK lesion ≥ 4 mm	X									
Assessment of AK target lesions and severe AK lesions ≥ 4 mm: clearance status, severity				X	X		X	X	X	X
Skin assessment regarding new lesions (AK, NMSC and melanoma) inside the treatment field[h]		X[d]		X	X		X	X	X	X
(S)AEs	X	X	X	X	X	X	X	X		
Assessment of application site reactions using 4-point scale		X[i]	X	X	X[i]	X	X	X		
Concomitant medications/ treatments	X	X	X	X	X	X	X	X		
Clinical laboratory tests including serum pregnancy test, if applicable[j]	X				X[g]			X		
Explanation of allowed/ forbidden medication before and after PDT to subjects	X	X		X	X[a]		X			
Inform subjects about restrictions to exposure to sunlight, prolonged or intense light for 48 h after IMP application		X			X[a]					
Urine pregnancy test[k]		X			X[a]					
Randomization and assignment of randomization number		X								

	All subjects (first treatment)					Re-treated subjects only[a]			All subjects	
	Visit 1	**Visit 2**	**Phone call 1**	**Visit 3**	**Visit 4**	**Phone call 2**	**Visit 5**	**Visit 6**	**Follow-up phase**	
	Screening	**PDT-1**			**PDT-2[a]**				**FU1**	**FU2**
	≤ 4 weeks prior to PDT-1	Baseline/ treatment	1 week (± 2 days) post PDT-1	4 weeks (± 1 week) post PDT-1	12 weeks (± 1 week) post PDT-1	1 week (± 2 days) post PDT-2	4 weeks (± 1 week) post PDT-2	12 weeks (± 1 week) post PDT-2	6 months (± 0.5 month) post last PDT	12 months (± 1 month) post last PDT
Field-directed application of IMP and illumination with BF-RhodoLED® (XL) (including preparation of treatment field)		X			X[a]					
Assessment of application site pain during illumination via NRS-11		X			X[a]					
Esthetic appearance of the treated skin area assessed by investigator					X[g]			X	X	X
Assessments of satisfaction regarding PDT treatment and esthetic outcome by subject					X[g]			X	X	X
Lesion-directed treatment of remaining non-target AK lesions and new lesions inside to the treatment field according to standard of care at the discretion of the investigator after assessments					X[g]			X	X	X
Lesion-directed treatment of remaining AK target lesions according to standard of care at the discretion of the investigator after assessments								X	X[l]	X[l]
Optional biopsy of a lesion at the discretion of the investigator					X[g]			X		

	All subjects (first treatment)					Re-treated subjects only[a]			All subjects	
	Visit 1	**Visit 2**	**Phone call 1**	**Visit 3**	**Visit 4**	**Phone call 2**	**Visit 5**	**Visit 6**	**Follow-up phase**	
	Screening	**PDT-1**			**PDT-2[a]**				**FU1**	**FU2**
	≤ 4 weeks prior to PDT-1	Baseline/ treatment	1 week (± 2 days) post PDT-1	4 weeks (± 1 week) post PDT-1	12 weeks (± 1 week) post PDT-1	1 week (± 2 days) post PDT-2	4 weeks (± 1 week) post PDT-2	12 weeks (± 1 week) post PDT-2	6 months (± 0.5 month) post last PDT	12 months (± 1 month) post last PDT
Lesion-directed treatment of recurrent AK lesions[m] according to standard of care at the discretion of the investigator after assessments									X	X
Relevant concomitant medications/treatments[n]									X	X
Any relevant AE (application site AEs or conditions affecting skin health in the treatment field which might impair proper assessment of the recurrence rate of the treated target lesions, or other clinically relevant events at the investigator's discretion), all SAEs									X	X

	All subjects (first treatment)					Re-treated subjects only[a]			All subjects	
	Visit 1	**Visit 2**	**Phone call 1**	**Visit 3**	**Visit 4**	**Phone call 2**	**Visit 5**	**Visit 6**	**Follow-up phase**	
	Screening	**PDT-1**			**PDT-2[a]**				**FU1**	**FU2**
	≤ 4 weeks prior to PDT-1	Baseline/ treatment	1 week (± 2 days) post PDT-1	4 weeks (± 1 week) post PDT-1	12 weeks (± 1 week) post PDT-1	1 week (± 2 days) post PDT-2	4 weeks (± 1 week) post PDT-2	12 weeks (± 1 week) post PDT-2	6 months (± 0.5 month) post last PDT	12 months (± 1 month) post last PDT

AE: Adverse event; AK: Actinic keratosis; BCC: Basal cell carcinoma; BP: Blood pressure; FU: Follow-up; IMP: Investigational medicinal product; BD: Bowen's disease; NMSC: Non-melanoma skin cancer; NRS: Numeric rating scale; PDT: Photodynamic therapy; PR: Pulse rate; SCC: squamous cell carcinoma; SAE: serious adverse event
a Only for subjects with partially responding or non-responding lesions as defined at Visit 4 requiring a second PDT.
b Reassessment of subjects is allowed once in case exclusion criterion 3 is met, and eligibility can be achieved within 4 weeks
c Re-check of eligibility.
d Occurrence of skin diseases inside or in close proximity (< 2 cm distance) to the treatment field as specified in exclusion criterion 5 will lead to exclusion of the subject. New AK lesions ≥ 4 mm inside the treatment field will not be considered as new lesions, but will be documented as AK target lesions. New severe AK lesions ≥ 4 mm occurring at Visit 2 must be excluded from the treatment field. If this is not possible, the patient is not eligible.
e Visit 2 can be rescheduled within 2 weeks after the scheduled date if the dosing day exclusion criterion is met.
f Visit 4 can be rescheduled within 2 weeks for subjects with non or partial responding lesions if the dosing day exclusion criterion is met.
g Only for complete responders as defined at Visit 4.
h Any AK lesion, NMSC (such as BCC, SCC, BD) and melanoma have to be reported as (S)AEs if they occur inside to the treatment field.
i Assessment performed prior to IMP application, prior to illumination and 10 ± 2 min after illumination at Visit 2 and at Visit 4 for partial or non-responders.
j Clinical laboratory tests will include routine hematology, blood chemistry, and urinalysis.
k All female participants of reproductive potential will undergo a pregnancy test.
l Including AK target lesions as well as severe AK lesions with a diameter ≥ 4 mm.
m If not performed during Visit 6 or FU1, respectively.
n Relevant concomitant medications/treatments are defined as medication/treatments administered for relevant AEs and/or all SAEs during FUP
* Unscheduled visits may be performed for safety reasons.

4 INTRODUCTION AND STUDY RATIONALE

4.1 Introduction

(Solar) actinic keratosis (AK) is the most common neoplasia of the skin. It predominantly occurs in fair-skinned individuals over the age of 50 on the head, bald scalp, neck, dorsal arms and hands and lower extremities. The affected body sites represent chronically sun-exposed skin areas, leading to the assumption that AK is the result of accumulated ultraviolet (UV) irradiation damage in keratinocytes. Although damaged areas are not always clinically conspicuous, affected subjects eventually show lesions of different sizes characterized by rough, scaly, and erythematous patches or plaques. Epidermal changes can include hyperkeratosis, parakeratosis, dyskeratosis, acanthosis, or keratinocyte atypia. The entire area of sun-exposed skin affected by both clinical and subclinical actinic keratosis is described as cancerized field (2).

Clinically, AK lesion severity can be graded based on the overall appearance and thickness described by Olsen et al. (1). Histologically, they can be graded using a classification system based on the extent of atypical keratinocytes described by Röwert-Huber et al (3). Cockerell attempted to combine the clinical and histological classification systems (4).

The occurrence of AK lesions indicates an elevated risk of developing skin cancer. Today, it is generally accepted that AK represents an early stage of a malignant condition (carcinoma *in situ*) that can progress to SCC (5,6). Between 0.025 % and 16 % of the AK lesions develop into SCC (7), however no prediction can be made about which AK lesions may transform. Initially, a sequence of progression from mild to moderate or severe AK lesions and subsequent progression to SCC was assumed. This was challenged by the following observations:

1) The poor alignment of clinical classification using Olsen with the histopathological classification according to Röwert-Huber or Cockerell (8)
2) AKs progression to SCC on average within about 24 months after coming into existence (9)
3) The finding that SCC arises more frequently from mild lesions than from more serious lesions according to Olsen grading (10)

Hence, the need to also treat AK lesions of mild clinical phenotype and even cancerous fields was reinforced, as both represent a high risk of progression to SCC. Thus, recent guidelines and expert recommendations advise early and field-directed treatment to address all AK severity grades, including subclinical manifestations (6,11–16). A variety of treatment options for AK aim at the physical destruction, removal or remission of atypical keratinocytes while ensuring an acceptable cosmetic outcome for the patients. In the United States of America (US), the Food and Drug Administration (FDA)-approved treatment options for field-directed treatment of AK on the face and scalp include formulations containing diclofenac/hyaluronic acid (3 %/2.5 %), imiquimod cream (3.75 %), tirbanibulin ointment 1 %, or topical 5-fluorouracil. These treatment modalities require repeated applications for up to several

months or can lead to side effects related to erosive and/or inflammatory reactions that may last for the entire treatment period or even longer (17–20).

Among these options, photodynamic therapy (PDT) has several advantages. Photodynamic therapy (PDT) is a non-invasive treatment eliciting cell death (phototoxicity) in neoplastic cells. In short, phototoxicity results from molecular oxygen being released from a photosensitizing agent during a light-induced reaction. PDT is an effective and selective treatment performed over a short treatment period entirely controlled by the physician, if required. Most adverse reactions occur during illumination or shortly afterwards, and are generally of mild or moderate intensity, and last for 1 to 4 days in most cases; in some cases, however, adverse reactions can persist for 1 to 2 weeks or even longer (21). PDT has excellent cosmetic results (22).

In a network meta-analysis addressing the long-term efficacy (at least 12 months) for interventions for AK, PDT using the prodrug 5-aminolaevulinic acid (ALA) showed the most favorable risk ratio and thus most sustainable efficacy among all interventions (23). Another network meta-analysis on the relative clinical efficacy of 10 different treatment modalities for mild to moderate AK on the face and scalp showed that ALA-PDT in the formulation of BF-200 ALA was the most efficacious treatment option (24).

4.2 Selection of drugs and dosages

Biofrontera Bioscience GmbH (BF) developed a nanoemulsion-based gel formulation of 5-aminolevulinic acid (ALA) (BF-200 ALA; brand name: Ameluz®) used for PDT. ALA is the prodrug of the photosensitizer protoporphyrin IX (PpIX), which initiates the phototoxic cascade upon light activation. BF-200 ALA gel contains 10 % ALA hydrochloride (ALA HCl) in a nanoemulsion formulation which improves skin penetration and cellular uptake of ALA due to its amphiphilic component (25,26). The improved chemical, pharmaceutical and physical properties of BF-200 ALA allow a reduction of the concentration of the active pharmaceutical ingredient, ALA, to 7.8 %. This formulation also significantly increases the shelf-life and in-use stability of ALA, which is a relevant advantage given the instability of ALA in aqueous formulations.

In addition, Biofrontera developed two light emitting diode (LED) lamps to be used in combination with Ameluz®: BF-RhodoLED® and BF-RhodoLED® XL (marketed as RhodoLED® XL). These lamps were optimized to deliver light at a wavelength matching the peak excitation of PpIX in cells 0 – 6 mm below the tissue surface. Compared to the BF-RhodoLED®, the BF-RhodoLED® XL enables the illumination of a larger skin area. The BF-RhodoLED® XL has 5 LED panels which can be positioned either flat or in a curved shape.

In the EU, the European Medicines Agency (EMA) granted a centralized Marketing Authorization for Ameluz® for the treatment of mild to moderate AK on the face/scalp and field cancerization with conventional PDT or daylight PDT and for the treatment of mild to moderate AK in the periphery (i.e. extremities and neck/trunk) using narrow spectrum red light (EU/1/11/740/001). Ameluz® furthermore received marketing approval in Switzerland for the treatment of mild to moderate AK on the face/scalp and field cancerization with conventional PDT and daylight PDT and is approved for the treatment of AK in the periphery

(Swissmedic number: 65693). In the US, Ameluz® in combination with BF-RhodoLED® or RhodoLED® XL is approved for the lesion- and field-directed PDT of AK of mild to moderate severity on the face/scalp by the FDA (NDA 208081).

Ameluz® is also approved for the treatment of superficial and/ or nodular basal cell carcinoma (BCC) unsuitable for surgical treatment in the EU and in Switzerland. A vehicle-controlled Phase III study is currently ongoing to demonstrate efficacy and safety for the treatment of superficial BCC in the US to extend marketing authorization. For further information on marketing authorization please refer to the investigator's brochure (IB).

Today, in addition to Ameluz®, one other PDT product containing ALA is available on the US market: Levulan® Kerastick® in combination with the BLU-U® lamp (27). Levulan® Kerastick® contains ALA at a concentration of 20 %, provided as a 2-component system to allow its dissolution only 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 (27). Thus, Ameluz® is the only PDT product available on the US market which has been approved for the field-directed treatment of AKs.

Clinical efficacy and safety of BF-200 ALA in combination with conventional red-light illumination for the treatment of mild to moderate AK on the face and scalp were previously examined in one dose-finding study and three confirmatory studies. These studies encompassed a total of 885 randomized subjects, of which 462 subjects (2674 lesions) were exposed to BF-200 ALA (28). All subjects received up to 1 tube (2 g) of BF-200 ALA. In these pivotal clinical trials, complete response of subjects 12 weeks after the last PDT with BF-200 ALA was shown to be up to 90.9 % and total lesion response was up to 94.3 % (29–32).

At the current time, the application of Ameluz® is restricted to areas of 20 – 25 cm², referring to one tube (21). However, the size of fields with chronic actinic sun damage frequently exceeds the approved area (33). Thus, an open label safety study under maximal use conditions was conducted in the US. This Phase I study (ALA-AK-CT015) was performed to evaluate systemic exposure after application of three tubes of BF-200 ALA (corresponding to 468 mg of ALA) in subjects with AK on the face/scalp and on extremities/neck/trunk (34). The study showed that ALA plasma concentrations rose transiently to a maximum concentration of about 2.5 to 3.3 times above baseline (note that ALA is endogenously synthesized as an intermediary product in heme biosynthesis). The maximum concentration was reached about 3 hours and returned to baseline within 10 hours after BF-200 ALA application. In addition, the results of the study indicated that a comparably low proportion of the topical 5-ALA was absorbed systemically. The pharmacokinetic (PK) parameters were comparable to the results of a previous PK study, where only one tube of BF-200 ALA was applied (34), pointing towards a safe and tolerable use of a higher dose.

4.3 Study rationale

Currently, the safety and tolerability of 3 tubes of BF-200 ALA in combination with the BF-RhodoLED® XL for the field-directed treatment of mild to severe AK located on the face and

scalp is being evaluated in an expanded treatment field of 60 cm², resulting in a thickness of 1 mm (ALA-AK-CT018).

Published data further suggests that PDT with BF-200 ALA is also safe and effective for treatment of AK if applied thinner than 1 mm (35,36). This, in conjunction with the PK data described above as well as the possibilities of the expanded illumination field especially of the BF-RhodoLED® XL, enables the investigation of treatment fields of 80 to 240 cm^2.

This Phase III study is designed to confirm the safety, tolerability, and efficacy of BF-200 ALA (Ameluz®) in combination with a RhodoLED lamp (BF-RhodoLED® XL or BF-RhodoLED®) for the field-directed treatment of 4 – 15 mild to moderate AK target lesions ≥ 4 mm located on extremities or neck/trunk. The treatment field may be continuous or in several patches, totaling approx. either 80 cm², 160 cm² or 240 cm² in each subject and must be located within one effective illumination area of the BF-RhodoLED® XL or within a maximum of three effective illumination areas of the BF-RhodoLED®. The size of the treatment field requires applying the content of up to 3 tubes of BF-200 ALA per PDT (1 tube per 80 cm^2). In this study, the BF-RhodoLED® XL should preferably be used, but BF-RhodoLED® is allowed as an alternative.

4.4 Risk/benefit analysis

This Phase III study will include subjects presenting with 4 – 15 mild to moderate AK lesions of ≥ 4 mm within the treatment field. The treatment field may be continuous or in several patches, totaling approx. 80 cm², 160 cm² or 240 cm². Subjects will receive either active BF-200 ALA treatment - already marketed under the brand name Ameluz® - or a BF-200 vehicle without the active ingredient in combination with conventional red-light illumination.

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. Subjects treated with a higher dose (6 g / 3 tubes of BF-200 ALA) within an enlarged treatment field of 60 cm² experienced more severe application site reactions (mainly pain, erythema) when treated on the face and scalp which was not reported for subjects treated in the periphery. In most cases the symptoms lasted for 1 to 4 days; however, in some cases, they persisted for 1 to 2 weeks or even longer (21,34).

It is known that the intensity of adverse events (AEs) depends on the applied light spectrum used for PDT and correlates with the higher response rate achieved by narrow spectrum lamps, emitting around 635 nm, e.g., BF-RhodoLED®. In some cases, adverse reactions may require interruption or discontinuation of the illumination. The illumination profile used in this study applies the total light dose of approx. 37 J/cm² [redacted]. This profile was developed to ease discomfort during illumination based on published evidence (37–40).

Common adverse reactions of PDT with BF-200 ALA include headache and application site reactions, such as erythema, pain/burning, irritation, edema, pruritus, exfoliation, scab, induration, vesicles. More detailed information on known adverse reactions is provided in the prescribing information (PI) for Ameluz® (21). 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 will be similar to those described previously. If required, pain management will be performed according to established guidelines (41,42) but restrictions for co-medications/treatments described in this protocol must be taken into consideration.

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

5 STUDY OBJECTIVES AND KEY ENDPOINTS

5.1 Objectives

The primary objective of the study is to compare the efficacy of BF-200 ALA PDT with vehicle PDT, utilizing illumination with a RhodoLED lamp, in the treatment of mild to moderate AK on the extremities or the neck/trunk in terms of overall subject complete response in the treatment phase.

The secondary objective of the study is to evaluate secondary efficacy parameters and safety and tolerability in the treatment phase.

The tertiary objective of the study is to evaluate efficacy, safety and tolerability parameters in the follow-up phase.

5.2 Key Endpoints

5.2.1 Primary endpoint

The primary endpoint is the overall subject complete response rate 12 weeks after the last PDT, defined as the percentage of subjects with all AK target lesions clinically cleared 12 weeks after the last PDT.

The primary endpoint will additionally be analyzed descriptively and in an exploratory way stratified by demographics, skin type class (I – III and IV – VI), study sites, and AK baseline parameters (e.g., AK target lesion number per subject at baseline, maximal AK target lesion severity at baseline, size of the treatment field, and treatment area).

5.2.2 Key secondary endpoints

Efficacy:

The key secondary endpoints are:

1) Overall subject complete response rate 12 weeks after the last PDT, defined as the percentage of subjects with all AK target lesions clinically cleared 12 weeks after the last PDT, for subjects with lesions treated on extremities
2) Overall subject complete response rate 12 weeks after the last PDT, defined as the percentage of subjects with all AK target lesions clinically cleared 12 weeks after the last PDT, for subjects with lesions treated on neck/trunk

Key secondary endpoints will additionally be analyzed descriptively and in an exploratory way stratified by AK baseline (e.g., AK target lesion number per subject at baseline, maximal AK target lesion severity at baseline, size of the treatment field, and treatment area).

For further secondary endpoints and tertiary endpoints please refer to Section 11.1.

6 INVESTIGATIONAL PLAN

This protocol describes a Phase III, multicenter, randomized, parallel group, double-blind (with respect to the investigational medicinal product (IMP)) study that will be conducted in the US.

The clinical study will comprise:

1) Study treatment phase (TP)

- Visit 1: Screening visit; at which eligibility of subjects for study participation will be assessed
- Visit 2: Baseline/ Treatment visit (PDT-1), at which eligible subjects will be randomized to receive PDT either with BF-200 ALA or vehicle
- Phone call 1: for safety assessment 1 week post PDT-1
- Visit 3: Interim assessment, clinic visit 4 weeks post PDT-1, at which safety, tolerability, and efficacy will be preliminarily assessed
- Visit 4: 12 weeks post PDT-1
    - Final assessment of complete responders
    - Re-treatment (PDT-2) for non- or partial responders
- For subjects receiving PDT-2: visits at the same intervals as after PDT-1 (Phone call 2, Visit 5, Visit 6). All partial or non-responding subjects 12 weeks after the second PDT (Visit 6) will receive further treatment at the discretion of the investigator.

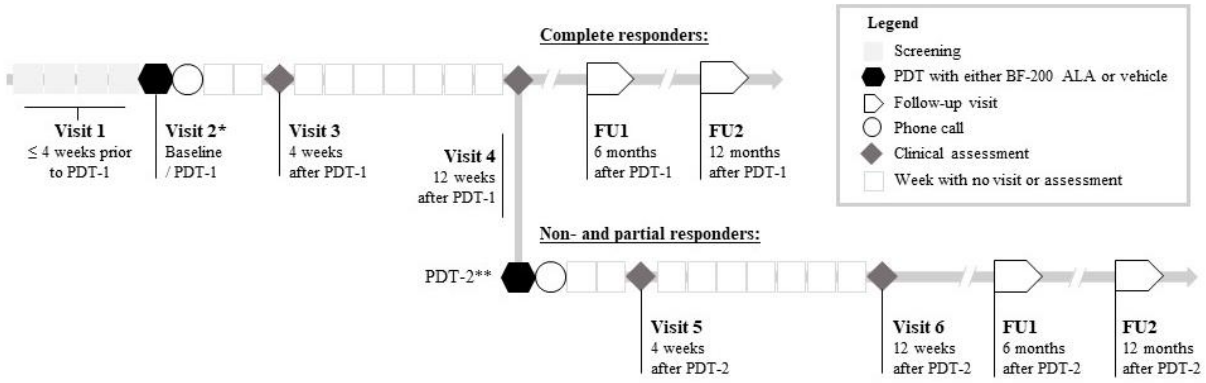
Results of the treatment phase (Visit 1 to Visit 4 or Visit 6) will be reported after Last Subject Last Visit of the treatment phase (LSLV-TP).

2) Follow-up phase (FUP)

- After completion of the treatment phase, all subjects will enter a follow-up phase, entailing follow-up visits 6 months (FU1) and 12 months (FU2) after the last PDT.

The results of the two follow-up visits will be analyzed and reported separately from the treatment phase. End of study is defined in Section 6.2. Figure 1 illustrates an overview of the study design. An overview of scheduled assessments is provided in Table 1.

6.1 Overview of study design



* Visit 2 can be rescheduled once after the scheduled date if the dosing day exclusion criterion is expected to resolve within 2 weeks (see Section 6.3.5)

** Rescheduling is allowed once if the dosing day exclusion criterion is met, but rescheduling should not exceed 2 weeks.

Figure 1: Summary of study visits

6.2 Study duration and end-of-study definition

Duration of the study treatment phase per subject will be approx. 16 weeks for subjects requiring 1 PDT (until Visit 4) and approx. 28 weeks for subjects with 2 PDTs (until Visit 6). This will be followed by approx. 40 additional weeks until completion of the follow-up phase. The overall study duration is estimated to be about 28 months (including an approx. 12 months recruitment phase and the follow-up phase). The duration of the overall study or the subject recruitment period may vary.

End of study (EoS) is defined as Last Subject Last Visit of the follow-up phase (LSLV-FU).

6.3 Study population

The target population of this trial are subjects suffering from AK. As AK is a neoplasia affecting mostly 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 UV light. Thus, incidence and severity increase among others with age and AK rarely occurs in minors (6). The study population will therefore consist of subjects of all sexes ≥ 18 years of age with 4 – 15 mild to moderate clinically confirmed AK lesions according to Olsen (1), either on the extremities or on the neck/trunk.

6.3.1 Number of Subjects

The suggested sample size for the study is 165 subjects (see Section 11.7).

6.3.2 Recruitment arrangements

Multiple sites in the United States of America (US) will participate in this study.

Each site should randomize between 5 and 25 subjects. No site should randomize more than 25 subjects unless prior approval of the sponsor is obtained. The maximum number should in no case exceed 30 subjects.

Subjects will be screened at the study sites and if eligible, randomized. For specifications on treatment assignment, please refer to Section 6.3.8.

Recruitment will be competitive within the limits described above.

6.3.3 Inclusion criteria

To be eligible subjects must meet the following criteria:

1. Willingness and ability of subjects to provide informed consent and sign the Health Insurance Portability and Accountability Act (HIPAA) form. A study-specific informed consent and HIPAA form must be obtained in writing prior to starting any study procedures.
2. 4 – 15 mild to moderate clinically confirmed AK lesions according to Olsen either on the extremities or on the neck/trunk with a diameter of ≥ 4 mm that must be present in the treatment field. In addition, non-target AK lesions may be present in the treatment field, including up to two severe AK lesions ≥ 4 mm. For each severe AK lesion (≥ 4 mm), a biopsy must be taken for confirmation of diagnosis. The treatment field (continuous or in several patches) totaling approx. either 80 cm², 160 cm² or 240 cm^2 must be within one effective illumination area of the BF-RhodoLED® XL but may require up to three illuminations with the BF-RhodoLED®. All AK target lesions and, if applicable, severe AK lesions ≥ 4 mm located in the treatment field should be clearly distinguishable, without restrictions on the distance between lesions, and should have a minimal distance of 1 cm to the border of the treatment field.
3. All sexes, ≥ 18 years of age.
4. Willingness to undergo a 2 mm punch biopsy for each (up to two) severe AK lesion ≥ 4 mm, if applicable, at the screening visit.
5. Willingness and ability to comply with study procedures, particularly willingness to receive up to 2 PDTs within approximately 12 weeks.
6. Subjects with good general health or with clinically stable medical conditions will be permitted to be included in the study.
7. Willingness to stop the use of moisturizers and any other non-medical topical treatments within the treatment field at least 24 h prior to the next clinical visit.
8. Acceptance to abstain from extensive sunbathing and the use of a solarium or tanning beds during the treatment phase.
9. For female subjects with reproductive potential: Negative serum pregnancy test.
10. For female subjects with reproductive potential: Effective contraception at screening visit and throughout the treatment phase of the study (until Visit 4 or Visit 6).

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

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

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

Reassessment of subjects is allowed once in case exclusion criterion 3 is met and eligibility can be achieved within 4 weeks. Reassessment can be done on the day of the actual treatment.

6.3.5 Dosing day exclusion criterion

At Visit 2 (baseline, PDT-1)

Subjects with sunburn or other possibly confounding skin conditions (e.g., wounds, irritations, bleeding, or skin infections) inside or in close proximity (< 2 cm distance) to the treatment field. Reassessment of subjects is allowed once if the sunburn or other confounding skin conditions is/are expected to resolve within 2 weeks.

At Visit 4 (PDT-2)

Subjects with sunburn or other possibly confounding skin conditions (e.g., wounds, irritations, bleeding, or skin infections) inside or in close proximity (< 2 cm distance) to the treatment field. Rescheduling of PDT-2 can be performed once at the earliest possibility after resolution, but rescheduling should not exceed 2 weeks.

6.3.6 Screening Failures

All subjects whose eligibility cannot be confirmed at Visit 1 and /or Visit 2 will be considered as screening failures. Reassessment of subjects is allowed as described in Section 6.3.5.

Subjects assessed as screening failures will not be treated. Only date of informed consent, demographics, date and reason for screen fail as well as (S)AEs, if applicable, have to be reported in the electronic Case Report Form (eCRF).

6.3.7 Subjects of reproductive potential

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

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

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

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

If pregnancy occurs, the investigator must contact the sponsor immediately for further instructions and must be followed up until the outcome of the pregnancy is known. Both the detection and the outcome of the pregnancy must be reported to the sponsor on special forms. Please also refer to Sections 8.5. and 10.3.1.2.

6.3.8 Randomization: Treatment assignment and blinding

The IMP will be administered exclusively to subjects matching the eligibility criteria and for whom the written informed consent is available (see Sections 6.3 and 12.5.3).

Subjects will be randomized for treatment with PDT with either BF-200 ALA (Ameluz®, test group) or vehicle (control group). The ratio of BF-200 ALA to vehicle will be 4:1.

Eligible subjects will be assigned a unique 4-digit randomization number in the applicable stratum (either extremities or neck/trunk). For this purpose, the investigator will use the patient pack with the next higher randomization number of the applicable stratum. The outer carton of the patient pack will have different colors to facilitate the assignment to strata (extremities = white; neck/trunk = blue), see Section 12.2.1. The randomization number will be documented in source and in the eCRF.

The randomization schedule and the allocation to treatment groups (with respect to the IMP) will not be known by the sponsor until completion of the treatment phase of the study, except in case of an emergency (see Section 10.6.2). The randomization schedule and the allocation to treatment groups (with respect to IMP) will remain unknown to the investigator until completion of the follow-up phase.

Subjects withdrawn from the study retain their subject number and their randomization number, if already assigned. New eligible subjects must always be assigned a new subject number and, if applicable, a new randomization number.

7 STUDY TREATMENT

A maximum of two PDT sessions with the content of 1 to 3 entire tubes of IMP each will be applied according to the study design described in Section 6, Section 7.3, Section 7.4 and Figure 1.

The treatment field will be localized and documented as described in Sections 9.4 and 6.3.3. A treatment field does not necessarily have to be continuous, but a (discontinuous) treatment field should cover a total area of approx. either 80 cm², 160 cm² or 240 cm². In case of a discontinuous treatment field, all patches must be located within one effective illumination area of the BF-RhodoLED® XL or within a maximum of three effective illumination areas of the BF-RhodoLED® (see Sections 2.2, 6.3.3 and 7.4).

AK lesions located outside the specified treatment field will not be considered for treatment in this study. For treatment of these AK lesions, subjects will receive standard of care at the discretion of the investigator, considering requirements described in Section 8.4. Most preferably, treatment of these lesions should be performed after final assessments at the end of the treatment phase (Visit 4 or Visit 6).

7.1 Investigational Medicinal Product

The drug component of the IMP will be BF-200 ALA, a topical gel formulation of 7.8 % ALA. The comparator is the vehicle of BF-200 ALA, without the active ingredient ALA, and thus is indistinguishable in in color, appearance, smell, and texture.

7.1.1 Details

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

The quantitative composition of the vehicle is very similar to that of BF-200 ALA, except for the absence of the active ingredient, and slightly increased contents of xanthan gum to adjust the viscosity, and water. Furthermore, pH is adjusted.

The compositions are shown in Table 2.

Table 2: Composition and manufacturer of study medication

Drug	BF-200 ALA	Vehicle
Brand name:	Ameluz®	Not applicable
Chemical name:	5-amino-4-oxopentanoat hydrochloride	Not applicable
International non-proprietary name:	ALA hydrochloride	Not applicable
Formulation:	BF-200 ALA containing 7.8 % ALA in a lecithin-based nanoemulsion gel with preservatives (sodium benzoate) and xanthan gum in purified water	Lecithin-based nanoemulsion gel similar to BF-200 ALA but without ALA
Manufacturer:	Biofrontera Pharma GmbH Hemmelrather Weg 201 51377 Leverkusen, Germany	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.

For further details on the IMP, please refer to the current Investigator's Brochure (IB).

7.1.2 Storage

At the study sites, study medication has to be stored at 2 °C to 8 °C (36 °F – 46 °F) (rounded) in a temperature-controlled cabinet, located in an area inaccessible by unauthorized persons. Temperature records (minimal-actual-maximal or electronic records) should be taken on a daily basis except for weekends and holidays if manually recorded.

Deviations (e.g., temperature measures outside the range of 1.5 °C to 8.4 °C (35.5 °F – 46.4 °F) or problems to store BF-200 ALA appropriately after delivery at study site) have to be immediately reported to the monitor and the sponsor. For these specific events, study medication must not be used unless sponsor's release was given.

Used study medication can be stored at room temperature.

7.2 Investigational Medical Device

The Class III devices BF-RhodoLED® and BF-RhodoLED® XL (in this document also referred to as investigational medical devices, IMDs) emit red light at a typical peak wavelength of approx. 635 nm. Both lamps are programmed to automatically provide a total light dose of approx. 37 J/cm^2.

Both lamps are approved as equivalent light sources for PDT in combination with Ameluz®, but the BF-RhodoLED® XL enables the illumination of a larger skin area. In this study, the

light-emitting diode (LED) device BF-RhodoLED® XL should preferably be used, but BF-RhodoLED® is allowed as an alternative.

7.2.1 Details

BF-RhodoLED® XL

The BF-RhodoLED® XL utilizes 225 LEDs (45 per panel arranged in a rectangle) to emit a uniform, visible red light. The lamp is equipped with 5 LED panels.

The maximal effective illumination area (all 5 panels) is

- Curved shape: 23 cm x 29 cm (667 cm²)
- Flat shape: [redacted] CCI

In this study, at least 3 adjacent panels have to be used for illumination with the BF-RhodoLED® XL lamp.

The calibration of the lamp ensures that the skin area illuminated receives the total light dose at a treatment distance between 11 – 14 cm. Each LED panel is equipped with a distance sensor. If the correct distance is achieved, it will be indicated a by a green light for each panel on the control unit and the panel lights up with a low light intensity. The low light intensity will allow for correct adjustment of each LED panel regarding distance and treatment field.

The recommended conditions for illumination with the BF-RhodoLED® XL are shown in Table 3.

BF-RhodoLED®

The BF-RhodoLED® utilizes 128 LEDs and lenses (arranged in a rectangle) to emit a uniform, bundled, visible red light. The effective illumination area is 6 cm x 16 cm (96 cm^2). The calibration of the lamp ensures that the skin area illuminated receives a total light dose of approx. 37 J/cm^2 when maintaining a distance of 5 – 8 cm. The recommended conditions for illumination with the LED lamps are shown in Table 3.

Table 3: Key light parameters of the BF-RhodoLED® and BF-RhodoLED® XL

	Recommendation	
	BF-RhodoLED® XL	**BF-RhodoLED®**
Peak wavelength (λ_{em})	approx. 635 nm	approx. 635 nm
Light dose (energy)	approx. 37 J/cm²	approx. 37 J/cm²
Typical irradiance	61 (± 20 %) mW/cm^2	max. 77 mW/cm^2
Typical illumination time	approx. CC min (curved shape) or approx. CC min (flat shape)	approx. CC min
Typical distance skin-lamp	12.5 cm (± 1.5 cm) / 4.9 in (± 0.6 in) (range 11 – 14 cm / 4.3 – 5.5 in)	Range 5 – 8 cm approx. 2.0 – 3.1 in

For the purpose of this study, the study sites will be provided with one BF-RhodoLED® XL or up to two BF-RhodoLED® lamps (see Section 12.2.2). All site personnel handling the lamps will be instructed properly on the handling and usage of the lamps, according to the user manuals.

More details, including further handling and operating instructions as well as a list of warnings and precautions when handling the LED lamps are provided in the user manuals.

7.2.2 Storage

The RhodoLED lamps must be stored inaccessible to unauthorized persons.

7.2.3 Illumination profile

The illumination profile used in this study applies the total light dose of approx. 37 J/cm² [redacted] CCI (Figure 2):

Figure 2: Illumination profile.

The total duration of illumination varies depending on the type and configuration of the lamp. For the BF-RhodoLED® XL, the illumination time is approx. CC min in curved shape and approx. CC min in flat shape. For BF-RhodoLED®, the illumination time is approx. CC min.

In case of necessary manual interruptions, e.g., due to unbearable pain or repositioning of the subject, the lamp will automatically continue illumination until the total light dose of approx. 37 J/cm^2 is achieved.

More details on the illumination profile are provided in the user manuals of the RhodoLED lamps.

7.3 Application of Investigational Medicinal Product

The treatment field should be prepared for IMP application by degreasing (using ethanol or isopropanol), removal of scabs and crusts, and, if appropriate, gentle roughening of the surface, (e.g., by mild debridement). Care should be taken to avoid bleeding, especially in subjects with non-significant acquired or inherited coagulation defects and/or subjects who receive medication that influences coagulation (see Table 4).

After this preparation, the content of 1 to 3 tubes of the assigned study medication will be administered to the entire treatment field, covering the skin homogenously with a thin film (1 tube per 80 cm^2). Each tube (2 g) must be applied in its entirety. All AK target lesions and, if applicable, severe AK lesions ≥ 4 mm located in the treatment field should have a minimal distance of 1 cm to the border of the treatment field. The application will be performed using glove-protected fingertips or a spatula. In case of accidental contact of study medication with the eyes or mucous membranes, rinsing with water for at least 5 min will be performed.

The application of IMP is regarded as start of treatment. The IMP will be allowed to dry for approx. 10 min, before an occlusive dressing (e.g., Tegaderm™ dressing) will be placed over the treatment field. 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 dressing will be removed, and the remaining gel should be wiped off.

To adhere to appropriate incubation times, it should be considered if the treatment field is illuminated once with the BF-RhodoLED® XL or by up to three consecutive illuminations with the BF-RhodoLED®. In case of consecutive illuminations, the application and incubation of the IMP should also be performed consecutively at an interval of approx. 20 min.

The incubation time starts when the occlusive dressing is placed and ends with removal of the IMP. Figure 3 illustrates the treatment procedure.

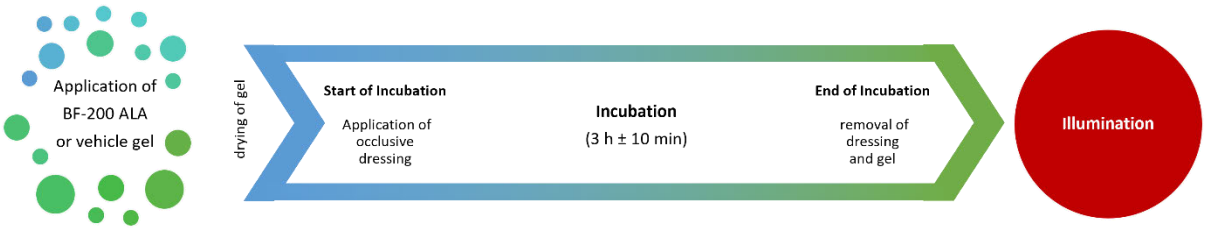


Figure 3: Treatment sequence including IMP application, placement of occlusive dressing, incubation of IMP and illumination at Visit 2 and Visit 4, if applicable.

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

- Preparation of treatment field including lesions according to protocol
- Occurrence of bleedings in the application area
- Number of tubes used
- Application of IMP according to protocol
- IMP application start time (in case of consecutive applications: for each application)
- Incubation time: start and stop time (in case of consecutive incubations: for each incubation)

7.4 Application and Handling of Investigational Medical Device

After removal of remaining gel, the entire treatment field will be illuminated using a RhodoLED lamp until the total light dose is achieved. In case of a discontinuous treatment field, all patches must be covered by one illumination area of the BF-RhodoLED® XL or a maximum of three illuminations areas of the BF-RhodoLED®. Please also refer to Section 7.2, 7.3 and 12.2.2. In case a second PDT will be performed, the same RhodoLED lamp type (either BF-RhodoLED® XL or BF-RhodoLED®) should be used.

During illumination, subjects and medical personnel must wear suitable protective eye goggles, even if illumination is performed in areas where little light reaches the subject's eyes. Healthy untreated skin surrounding the AK lesions does not need protection during illumination.

Discomfort and pain during illumination are caused by the intended phototoxic reaction. Although the emitted light is in the visible red spectrum and has no emission in the (heat-transmitting) infrared spectrum, submitted energy to the skin may create a warming sensation. A transient biochemical reaction during illumination involves the activation of heat sensitive nerve endings in the skin. Firstly, this may cause discomfort, intensified by a strong psychological component, including the feeling of being burned (43). Secondly, pain might also be experienced during illumination. Investigators may consider using pain relieving measures during or post illumination considering the requirements outlined in Section 8.4.2. However, pain will be evaluated by all subjects after the illumination.

Although illumination is assumed to cause nearly complete loss of protoporphyrin IX (PpIX) by photobleaching, new PpIX may accumulate from remaining ALA. Thus, additional light exposure may enhance the typical side effects of PDT. Subjects should not expose themselves to intensive UV-radiation (solarium, sunbathing, etc.) during the treatment phase (see also Section 6.3.5, 8.1.2 and 8.1.5) to avoid UV induced post inflammatory hyperpigmentation of the healing tissue.

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

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

- BF-RhodoLED lamp model
- In case the BF-RhodoLED® XL lamp is used: number of panels, shape (curved or flat), preset length of illumination profile
- In case BF-RhodoLED® is used: number of illumination sessions
- Start time of illumination session (in case BF-RhodoLED® is used: for each illumination session)
- Confirmation and documentation that the specified distance between the lamp and the treatment field(s) have been met prior to illumination. Otherwise, reasons for not meeting the requirements must be provided.
- In case of premature termination: reason for premature termination, remaining illumination time, applied light dose
- In case of interruption(s) not foreseen in the regular illumination profile: number of interruption(s) and reason for interruption(s)
- Pain intensity during illumination reported by the subject (according to Numeric Rating Scale (NRS-11)
- Pain relieving measures taken during or post illumination (physical measures (e.g., cold compress, cooling, nebulized water) and/or concomitant medication)

8 STUDY PROCEDURES

All data obtained from subjects, e.g., assessments, questionnaires, and examination results, should be sufficiently documented in source. Study procedures and schedule are summarized in Table 1.

8.1 Study treatment phase

8.1.1 Visit 1: Screening visit (≤ 4 weeks prior to PDT-1)

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

- Obtain informed consent prior to any study-related procedures, see Section 12.5.3.
- Assign subject number: This number will be documented and will be used to identify the subject. It is a five-digit subject number (consisting of a three-digit site number and a two-digit subject screening number), assigned in the chronological order of enrollment within each site (e.g., 901 – 01). New subjects must always be assigned a new subject number (next higher number).
- Obtain demographic data, see Section 9.1
- Document concomitant medical conditions and relevant medical history, see Section 8.4.1.
- Document medical skin history, see Section 8.4.1.1
- Document concomitant medications/treatments, see Section 8.4.2
- Perform and document body measures see Section 9.2
- Perform and document physical examination, see Section 9.7.1
- Measure and document vital signs, see Section 9.7.2
- Check inclusion and exclusion criteria, see Sections 6.3.3 and 6.3.4.
- Assess skin type according to Fitzpatrick, 1988 (44) (see Section 9.3 and Appendix A in Section 15).
- Select treatment field and assess AK target lesions and severe lesions ≥ 4 mm (size, number, location, and clinical severity), as described in Section 9.4. For each (up to two) severe AK lesion (≥ 4 mm), a biopsy must be taken for confirmation of diagnosis.
- Generate graphic templates of the treatment field and the location of AK lesions within that treatment field as described in Section 9.4.
- Clinical laboratory tests, see Section 9.7.3, including serum pregnancy test, if applicable (see Section 9.7.4).
- Document (S)AEs, see Section 9.7.5.

- Instruct subject about forbidden concomitant medications/treatments (see Section 8.4.2, Table 4).

8.1.2 Visit 2: Baseline/ Treatment (PDT-1)

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

- Re-evaluate inclusion and exclusion criteria for confirmation of subject's eligibility, see Sections 6.3.3 and 6.3.4. NOTE: Occurrence of skin diseases inside or in close proximity (< 2 cm distance) to the treatment field as specified in exclusion criterion 5 will lead to exclusion of the subject. New severe AK lesions ≥ 4 mm occurring at Visit 2 must be excluded from the treatment field. If this is not possible, the patient is not eligible (see Section 9.7.5.2).
- Evaluate dosing day exclusion criterion, see Section 6.3.5.
- Measure and document vital signs, see Section 9.7.2.
- Assess AK target lesions and severe lesions ≥ 4 mm (size, number, location, and clinical severity), as described in Section 9.4.
- Update of graphic templates (grid foil and cartoon), if applicable (see Section 9.4).
- Urine pregnancy test, if applicable, see Section 9.7.4.
- Randomization and assignment of randomization number, see Section 6.3.8.
- Prepare the treatment field and apply study medication as described in Section 7.3.
- Illumination of the treatment field as described in Section 7.4.
- Assess application site pain during illumination via NRS-11, see Section 9.7.5.
- Document (S)AEs (see Section 9.7.5), including application site skin reactions and application site discomfort (see Section 9.7.5.1).
- Document application site reactions according to 4-point scale (Table 7) at the timepoints described in Section 9.7.5.1.
- Document new lesions inside the treatment field as described in Section 9.7.5.2.
- Document concomitant medications/treatments including medications/treatments for pain management that might be required during or post illumination, see Section 8.4.2, Table 4.
- Instruct subject about forbidden concomitant medication/treatments, see Section 8.4.2, Table 4.
- Inform subjects to avoid sunlight, prolonged or intense light (e.g., tanning beds, sun lamps) on the treatment field for approx. 48 hours following treatment whether exposed to illumination or not.

8.1.3 Phone call 1 (1 week (± 2 days) post PDT-1)

The aim of this safety telephone call is to achieve an overall impression on the tolerability of the PDT with study medication 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. In addition, previous (S)AEs should be followed-up.

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

- Document (S)AEs (Section 9.7.5) including application site skin reactions and application site discomfort (Section 9.7.5.1).
- Document application site reactions according to 4-point scale, see Section 9.7.5.1, Table 7 and lay language script in Appendix B in Section 15.
- Document concomitant medications/treatments, see Section 8.4.2, Table 4.

8.1.4 Visit 3: Interim assessment (4 weeks (± 1 week) post PDT-1)

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

- Measure and document vital signs, see Section 9.7.2.
- Assess AK target lesions and severe lesions ≥ 4 mm at baseline (clearance status (cleared/non-cleared)) and clinical severity as described in Section 9.4.
- Document (S)AEs (see Section 9.7.5), including application site skin reactions and application site discomfort (see Section 9.7.5.1).
- Document application site reactions according to 4-point scale, see Section 9.7.5.1, Table 7.
- Document new lesions inside the treatment field as described in Section 9.7.5.2.
- Document concomitant medications/treatments, see Section 8.4.2, Table 4.
- Instruct subject about forbidden concomitant medication/treatments, see Section 8.4.2, Table 4.

8.1.5 Visit 4 (12 weeks (± 1 week) post PDT-1): Final assessment of complete responders / re-treatment (PDT-2) for non- or partial responders

Visit 4 is the end-of-treatment phase for all subjects who are complete responders. All subjects who are non- or partial responders will be re-treated during this visit (PDT-2). For definitions of complete and non- or partial responders see Section 2.2.

The following procedures will be performed at clinical Visit 4 and recorded in the eCRF **(all subjects)**:

- Assess AK target lesions and severe lesions ≥ 4 mm at baseline (clearance status (cleared/non-cleared)) and clinical severity as described in Section 9.4.

- Measure and document vital signs, see Section 9.7.2.
- Document (S)AEs (see Section 9.7.5), including application site skin reactions and application site discomfort (see Section 9.7.5.1).
- Document new lesions inside the treatment field as described in Section 9.7.5.2.
- Document concomitant medications/treatments, see Section 8.4.2, Table 4.

Complete responders

The following procedures will be performed and recorded in the eCRF in addition to the procedures listed for all subjects:

- Perform and document physical examination, see Section 9.7.1
- Clinical laboratory tests, see Section 9.7.3, including serum pregnancy test, if applicable (see Section 9.7.4).
- Document application site reactions according to 4-point scale, see Section 9.7.5.1, Table 7.
- Assessment of the esthetic appearance in the treatment field by the investigator, see Section 9.5.
- Assessments of satisfaction regarding PDT treatment and esthetic outcome by subject, see Section 9.6.
- Lesion-directed treatment of remaining non-target AK lesions and new lesions inside the treatment field according to standard of care at the discretion of the investigator, if applicable, after assessments. Indicate start date and chosen therapy.
- Optional biopsy of a lesion at the discretion of the investigator, see Section 9.4.2.

Subjects will be asked to return for the first follow-up visit in approx. 3 months (6 months post last PDT (PDT-1)).

Non- or partial responders

The following procedures will be performed and recorded in the eCRF in addition to the procedures listed for all subjects:

- Evaluate dosing day exclusion criterion, see Section 6.3.5.
- Urine pregnancy test, if applicable, see Section 9.7.4.
- Prepare the treatment field and apply study medication as described in Section 7.3.
- Illumination of the treatment field as described in Section 7.4.
- Assess application site pain during illumination via NRS-11, see Section 9.7.5.

- Document concomitant medications/treatments including medications/treatments for pain management that might be required during or post illumination, see Section 8.4.2, Table 4.
- Document application site reactions according to 4-point scale (Table 7) at the timepoints described in Section 9.7.5.1.
- Instruct subject about forbidden concomitant medication/treatments, see Section 8.4.2, Table 4.
- Re-inform subjects to avoid sunlight, prolonged or intense light (e.g., tanning beds, sun lamps) on the treatment field for approx. 48 hours following treatment whether exposed to illumination or not.

Only non- or partial responders at Visit 4 will receive Phone call 2, Visit 5, and Visit 6.

8.1.6 Phone call 2 (1 week (± 2 days) post PDT-2)

Only non- or partial responders at Visit 4 receive Phone call 2. The same procedures described for Phone call 1 apply to Phone call 2 and are described in Section 8.1.3.

8.1.7 Visit 5: Interim Assessment (4 weeks (± 1 week) post PDT-2)

Only non- or partial responders at Visit 4 will receive Visit 5. The same procedures described for Visit 3 apply to Visit 5 and are described in Section 8.1.4.

8.1.8 Visit 6: Final assessment of non- or partial responders (12 weeks (± 1 week) post PDT-2)

Visit 6 is the end-of-treatment phase for all subjects who were non- or partial responders at Visit 4.

The following procedures will be performed at Visit 6 and recorded in the eCRF:

- Assess AK target lesions and severe lesions ≥ 4 mm at baseline (clearance status (cleared/non-cleared)) and clinical severity as described in Section 9.4.
- Measure and document vital signs, see Section 9.7.2.
- Perform and document physical examination, see Section 9.7.1
- Document concomitant medications/treatments, see Section 8.4.2, Table 4.
- Document (S)AEs (see Section 9.7.5) including application site skin reactions and application site discomfort (see Section 9.7.5.1).
- Document application site reactions according to 4-point scale, see Section 9.7.5.1, Table 7.
- Document new lesions inside the treatment field as described in Section 9.7.5.2.
- Clinical laboratory tests, see Section 9.7.3, including serum pregnancy test, if applicable (see Section 9.7.4).

- Assessment of the esthetic appearance in the treatment field by the investigator, see Section 9.5.
- Assessments of satisfaction regarding PDT treatment and esthetic outcome by subject, see Section 9.6.
- Lesion-directed treatment of remaining lesions (target or non-target AK lesions) and/ or new lesions inside the treatment field according to standard of care at the discretion of the investigator, if applicable, after assessments. Indicate start date and chosen therapy.
- Optional biopsy of a lesion at the discretion of the investigator, see Section 9.4.2.

Subjects will be asked to return for the first follow-up visit in 3 months (6 months post last PDT (PDT-2)).

8.2 Follow-up phase (FUP)

All subjects who participate in this clinical trial will be followed-up for one year post their last PDT to assess

- the long-term treatment effect with respect to recurrences of AK target lesions
- the clearance status of severe AK lesions with a diameter ≥ 4 mm at baseline
- the esthetic appearance within the treatment field.

At **FU1 (6 months ± 0.5 month post last PDT)**

and **FU2 (12 months ± 1 month post last PDT)**

the following procedures will be performed and recorded in the eCRF:

- Assessment of AK target lesions and severe lesions ≥ 4 mm at baseline, which were clinically cleared (Olsen Grade = 0) 12 weeks after last PDT (clearance status (still cleared/recurrent) and clinical severity, if applicable), as described in Section 9.4.
- Documentation of relevant AEs (as defined in Section 9.7.5) and serious AEs (SAEs).
- Document new lesions inside the treatment field as described in Section 9.7.5.2.
- Documentation of relevant concomitant medications/treatments as defined in Section 8.4.2.
- Assessment of the esthetic appearance in the treatment field by the investigator, see Section 9.5.
- Assessments of satisfaction regarding PDT treatment and esthetic outcome by subject, see Section 9.6.
- Lesion-directed treatment of still remaining AK lesions (target and non-target AK lesions) inside the treatment field, recurrent AK target lesions, and recurrent severe

AK lesions with a diameter ≥ 4 mm at baseline, and new lesions according to standard of care at the discretion of the investigator, if applicable, after assessments. Indicate start date and chosen therapy.

Subjects presenting at FU1 will be asked to return for the second follow-up visit in 6 months (12 months after last PDT).

The results of the follow-up procedures will be analyzed and reported separately; they are not part of the treatment phase report.

8.3 Unscheduled visits

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

8.4 Prior and concomitant medical conditions and treatment

8.4.1 Prior and concomitant medical conditions

Medical history is the record of all medical events the subject has experienced. The medical history will be recorded in the source data. In the eCRF, only relevant medical history as judged by the investigator will be recorded. The investigator must document in the source data, which medical history is considered relevant for this study.

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

Medical conditions first occurring or detected during the study, and worsening of a concomitant condition during the study, are to be regarded as AEs and must be documented in the AE section of the eCRF (see Section 10).

8.4.1.1 Medical skin history

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

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

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

8.4.2 Prior and concomitant treatment

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

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

All (relevant) concomitant medications/treatments taken/underwent during the treatment phase or follow-up phase, respectively, must be documented in the eCRF along with:

- indication
- single dose
- frequency of administration
- route of administration
- start and stop date of administration

The subject should confer with the investigator prior to the use of new medication until the end of the treatment phase.

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

- During illumination
    - The illumination may be interrupted and/or cooling with an air stream and/or nebulized water may be offered. Furthermore, the illumination area can be briefly cooled with e.g., cooling packages.
- Treatment of pain and discomfort post illumination
    - Cooling the illuminated area(s) with e.g., cooling packages
    - Analgesic treatment with acetaminophen (e.g., Tylenol®) or non-steroidal anti-inflammatory drugs (NSAIDs; ibuprofen up to 1200 mg per day / acetylsalicylic acid up to 3750 mg per day)
    - Application of an analgesic cream

The following concomitant treatments/procedures are not permitted:

- Any prophylactic analgesic treatment prior to illumination.
- Any physical therapy such as cryotherapy, laser therapy, electrodessication, microdermabrasion, surgical removal of lesions, curettage, or treatment with chemical

peels such as trichloroacetic acid inside or in close proximity (< 10 cm distance) to the treatment field within 4 weeks prior to screening. Lesions may be treated with these methods if the distance to the treatment field is ≥ 10 cm.

- Field-directed treatments inside or in close proximity (< 10 cm distance) to the treatment field except IMP are forbidden during the entire study. Lesion-directed treatments inside or in close proximity (< 10 cm distance) to the treatment field are allowed after final assessment at the last visit of the treatment phase and during the follow-up phase.
- A list of forbidden, concomitant medication is provided in Table 4.

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

Medication	**Topical administration**		**Systemic administration**	
	start of restriction	forbidden until	start of restriction	forbidden until
ALA or ALA esters (except IMP at Visit 2 and Visit 4)	3 months prior to Visit 1 inside the treatment field	end-of-treatment phase	12 weeks prior to Visit 1	end-of-treatment phase
Cytotoxic drugs/ Cytostatic drugs	3 months prior to Visit 1 inside or in close proximity (< 10 cm distance) to the treatment field	end-of-treatment phase inside or in close proximity (< 10 cm distance) to the treatment field	6 months prior to Visit 1	end-of-treatment phase
Immuno-modulatory therapies	3 months prior to Visit 1 inside or in close proximity (< 10 cm distance) to the treatment field	end-of-treatment phase inside or in close proximity (< 10 cm distance) to the treatment field	12 weeks prior to Visit 1 for immuno-suppressive therapies	end-of-treatment phase for immuno-suppressive therapies
	7 days prior to PDT inside and outside the treatment field	7 days post PDT inside and outside the treatment field		
Interferon	---	---	6 weeks prior to Visit 1	end-of-treatment phase
Glucocortico-steroids[a]	(allowed)	(allowed)	6 weeks prior to Visit 1	end-of-treatment phase
NSAIDs (others than listed below)	7 days prior to PDT	7 days post PDT	7 days prior to PDT	7 days post PDT
Acetylsalicylic acid > 3750 mg/day[b]	---	---	7 days prior to PDT	7 days post PDT

Medication	**Topical administration**		**Systemic administration**	
	start of restriction	forbidden until	start of restriction	forbidden until
Ibuprofen > 1200 mg/day[b]	---	---	7 days prior to PDT	7 days post PDT
Diclofenac	7 days prior to PDT within illumination area[c]	7 days post PDT within illumination area[c]	> 100 mg/day; 7 days prior to PDT	> 100 mg/day; 7 days post PDT
Hypericin or drugs with phototoxic/ photoallergic potential[d]	4 weeks prior to Visit 1 inside or in close proximity (< 10 cm distance) to the treatment field	end-of-treatment phase inside or in close proximity (< 10 cm distance) to the treatment field	8 weeks prior to Visit 1	end-of-treatment phase
Investigational drugs	8 weeks prior to Visit 1	end-of-treatment phase	8 weeks prior to Visit 1	end-of-treatment phase
Drugs known to have major organ toxicity	---	---	8 weeks prior to Visit 1	end-of-treatment phase
Medication that influences coagulation (e.g., anticoagulants, anti-platelet drugs)	---	---	Visit 1 (may be used throughout the study if taken in a stable dose prior to study)	end-of-treatment phase (may be used throughout the study if taken in a stable dose prior to study)
EMLA® cream	On day of PDT inside or in close proximity (< 10 cm distance) to the treatment field	On day of PDT inside or in close proximity (< 10 cm distance) to the treatment field until end of illumination	---	---

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

8.5 Withdrawals

8.5.1 Withdrawals 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, e.g.
    - when the occurrence of a severe (local) AE is considered harmful
    - when a lesion inside or outside the treatment field is suspicious to have progressed to a manifest malignancy. In addition, subjects should be referred to standard medical treatment (see Section 8.4.2)
- If subject was unblinded by the investigator, e.g., due to medical reasons (emergency unblinding)
- Upon sponsor request
- Treatment of lesions with a forbidden medication or procedure (please refer to Section 8.4.2) which has a significant impact on the evaluation of study objectives

Subjects must be withdrawn from further treatment for the following reasons:

- In case of pregnancy during the treatment phase (before last PDT) no further PDT treatment will be performed, and the subject may continue to participate in the study to enable safety and efficacy assessments. In addition, the subject will be followed-up for the outcome of the pregnancy (see Section 6.3.7).
- In case of confirmed contact dermatitis during the treatment phase (before last PDT) no further PDT treatment will be performed, and the subject may continue to participate in the study to enable safety and efficacy assessments.

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

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

A subject will be considered lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the site. The investigator must make every effort to contact

subjects lost to follow-up. Attempts to contact these subjects must be documented in the subject's records (e.g., times and dates of attempted telephone contact, e-mails or copies of letters send to the subject). At least three attempts should be performed and documented. Discontinuation date is the date on which the investigator decides that no further attempt will be made to contact the subject and the subject is declared as lost-to follow-up.

Subjects withdrawn from the study retain their subject number and their randomization number, if already assigned.

8.5.2 Replacement of subjects

Randomized subjects who discontinue will not be replaced.

8.5.3 Withdrawal of samples

Not applicable.

9 STUDY EVALUATIONS AND ASSESSMENTS

9.1 Demographic data

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

- Sex
- Age
- Race
- Ethnicity

9.2 Body measures

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

- Height (in)
- Weight (lb)

9.3 Assessment of skin type

Subjects' skin type will be assessed at the screening visit using the six-level Fitzpatrick Skin Type Rating Scale (44). Further details are provided in the Appendix A in Section 15.

9.4 Assessment 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 (45–47).

Selection of the treatment field

In this clinical trial, 4 – 15 AK target lesions (i.e. mild to moderate severity (according to Olsen (1), see Section 9.4.1, Table 5: Clinical evaluation of AK according to Olsen (1)) and a diameter ≥ 4 mm located inside the treatment field) will be treated with field-directed PDT. In addition, smaller AK lesions of mild to moderate severity and severe AK lesions can be present in the treatment field and will be co-treated. All AK target lesions and, if applicable, severe AK lesions ≥ 4 mm located in the treatment field should have a minimal distance of 1 cm to the border of the treatment field. However, no distance restrictions between lesions will be applied.

The treatment fields should be selected to treat a skin area of approx. either 80 cm², 160 cm² or 240 cm². The purpose of defining these size categories is to ensure that the IMP is applied at a controlled thickness (1 entire tube/ 80 cm² resulting in a thickness of approx. 0.25 mm). The size of the treatment field should be documented in the eCRF.

Baseline assessment of AK lesions inside the treatment field

All AK target lesions and all (up to two) severe AK lesions ≥ 4 mm within the treatment field have to be counted, and the severity (according to Olsen (1)) and location (treatment area and subarea) have to be documented at Visit 1 and Visit 2. In addition, the size of these lesions should be recorded by measuring the diameters (for non-circular lesions, the largest diameter and the corresponding perpendicular diameter will be measured). For non-circular lesions, all diameters have to be at least 4 mm.

Additionally, a biopsy must be obtained for every (up to two) severe AK lesion ≥ 4 mm to confirm the diagnosis of AK at the screening visit (see Section 9.4.2).

Generation of templates (Grid foil, cartoon)

Grid foil and cartoon templates are prepared at Visit 1 and Visit 2 for re-identification of lesions during the course of the study. Landmarks can be indicated on the grid foil and in the cartoon for guidance.

The treatment field and the location of all AK target lesions as well as severe lesions ≥ 4 mm should be clearly sketched in the provided cartoon and on the grid foil. These lesions must also be numbered consistently on the cartoon and on the grid foil.

In addition, all AK lesions < 4 mm inside the treatment field must be plotted on the grid foil, if applicable.

In case of any updates or changes at Visit 2, the grid foil should be copied. Each copy should be signed and dated by the investigator.

All new lesions (AK, NMSC and melanoma) inside the treatment field must be documented as described in Section 9.7.5.2.

Clearance status of AK

The lesion clearance status (cleared/non-cleared) and severity for AK target lesions and severe AK lesions ≥ 4 mm must be documented, beginning at Visit 3.

During the follow-up visits the clearance status of AK target lesions and severe AK lesions (≥ 4 mm at baseline) which were clinically cleared at Visit 4 or Visit 6 (Olsen Grade = 0) should be indicated as still cleared or recurrent. Severity of recurrent lesions (according to Olsen (1)) should be indicated. Once a lesion is assessed as recurrent it stays recurrent for the subsequent visits even if it is treated. This is also applicable for recurrent lesions that were treated between the visits. The clearance status and the severity must be entered at the next visit.

9.4.1 Clinical criteria for diagnosis

AK lesion severity will be evaluated as follows:

Table 5: Clinical evaluation of AK according to Olsen (1)

Stage	Grading	Criteria
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.

9.4.2 Biopsy

a) A 2 mm punch biopsy must be taken from each (up to two) severe AK lesion at the screening visit to confirm the diagnosis of AK. Note: If the outcome confirms that exclusion criterion 5 is met, this will lead to exclusion of the subject. The outcome is required to be documented in the eCRF.

b) At the last regular visit of a patient (Visit 4 for complete responders after the first PDT or Visit 6 for re-treated patients) an optional biopsy can be taken at the discretion of the investigator. This should be performed if there is any evidence that a certain lesion is not AK, shows an untypical behaviour or requires further evaluation in the opinion of the investigator. The sponsor provides the necessary material for this optional biopsy.

The biopsies will be histopathologically evaluated based on the classification KIN (keratinocytic intraepidermal neoplasia) I – III according to Cockerell (4), see Section 9.4.2.1. Containers with fixation solution and shipping material will be provided by the central laboratory.

The following central laboratory is responsible for evaluating the biopsies:

UCSF Dermatopathology and Oral Pathology Service
1701 Divisadero Street, Suite 280
San Francisco, CA 94115

9.4.2.1 Histopathological evaluation of AK

Each biopsy from severe (up to two) AK lesions ≥ 4 mm as well as each optional biopsy of remaining suspicious lesions (see Section 9.4.2) will be primarily assessed based on the classification KIN I – III according to Cockerell (4,47,48).

Table 6: Histological evaluation according to KIN classification

Stage	Criteria
KIN I	Clinical: flat, pink macule or patch on solar damaged skin; background mottling; no roughness or hyperkeratosis
	Histological: focal atypia of basal keratinocytes of the **lower one third** of the epidermis
KIN II	Clinical: pink to red papule or plaque with rough, hyperkeratotic surface; variable induration.
	Histological: focal atypia of **at least the lower two thirds** of the epidermis; focal hyperkeratosis, alternating orthokeratosis and parakeratosis with sparing of acrotrichia and acrosyringia; prominent acanthosis and buds of keratinocytes into the upper papillary dermis; may see some involvement of upper acrotrichia and acrosyringia.
KIN III	Clinical: red, scaly indurated plaques on sun-damaged skin; may be pigmented.
	Histological: diffuse atypical keratinocytic proliferation involving the **full thickness of the epidermis** diffusely; parakeratosis, acanthosis, papillomatosis, involvement of adnexal structures.

9.5 Assessment of esthetic appearance by investigator

The investigator or delegate will assess and record the esthetic appearance of the skin in the treatment field at the end-of-treatment phase (Visit 4 or Visit 6) and at each follow-up visit using a 4-point scale:

0 = very good: The appearance has considerably improved compared to baseline

1 = good: The appearance has improved compared to baseline

2 = satisfactory: The appearance is comparable to baseline

3 = unsatisfactory: The appearance has worsened compared to baseline

9.6 Assessments of satisfaction regarding PDT treatment and esthetic outcome by subject

The esthetic outcome of the treated skin area and the satisfaction with PDT treatment will be assessed by the subjects at their final visit of the treatment phase (Visit 4 or Visit 6) and at each follow-up visit and recorded.

The subjects will be asked to rate the esthetic outcome of the treated skin area as follows:

0 = very good

1 = good

2 = satisfactory

3 = unsatisfactory

Further, subjects will be asked

- if they would choose PDT treatment in the future in case of recurrence or similar diseases (yes/no).
- how they would rate the PDT treatment in comparison with other treatment modalities, if applicable (better than/similar to/worse than). The treatment modalities used as comparators (e.g. topical treatments, cryotherapy) should be documented, if applicable.

9.7 Safety

Safety measurements will be performed at the time points given in Table 1.

9.7.1 Physical examination

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

The outcome of the physical examination should be documented for each of these body systems. In the eCRF, only abnormal findings that are considered clinically significant are required to be reported. Clinically significant findings will be documented in the medical history (Visit 1) or afterwards as AEs (see Sections 10.1 and 10.3).

Note: In case an assessment of the skin shows AK lesions, only AK lesions outside the treatment field have to be documented.

9.7.2 Vital signs

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

9.7.3 Safety laboratory

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

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

ACM Global Laboratories
160 Elmgrove Park
Rochester, NY 14624

9.7.3.1 Blood

An approx. 3 ml EDTA (ethylenediaminetetraacetic acid) blood sample, and an approx. 7.5 ml serum sample will be collected at screening (Visit 1) and 12 weeks after the last PDT (Visit 4 or Visit 6). The total blood loss for safety laboratory examinations will be approx. 21 ml.

- *Clinical chemistry parameters*

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

- *Hematology parameters*

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

9.7.3.2 Urine

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

- *Urinalysis parameters*

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

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

9.7.4 Pregnancy test in females of reproductive potential

A serum pregnancy test (β-human chorionic gonadotropin (β-hCG) test) will be performed at screening (Visit 1) and 12 weeks after the last PDT (Visit 4 or Visit 6).

A urine dipstick pregnancy test will be performed at PDT-visits (Visit 2 and Visit 4, if applicable).

9.7.5 Adverse events

During the treatment phase, all (S)AEs have to be recorded as outlined in Section 10. If possible, each subject should be assessed by the same investigator/staff personnel throughout the study. During the follow-up phase, only relevant AEs (application site AEs or conditions affecting skin health in the treatment field which might impair proper assessment of the recurrence rate of the treated AK lesions, or other clinically relevant events at the investigator's discretion) and all SAEs (see Section 10.1.2) have to be reported. In addition, previous (S)AEs should be followed-up.

9.7.5.1 Application site reactions

Application site reactions include all reactions occurring in the treatment field after starting treatment. They can be classified as application site discomfort or application site skin reactions.

The investigator or delegates will evaluate any discomfort the subject may be experiencing by using non-leading questions like "How did you feel since your photodynamic treatment

session?". Application site reactions should be documented as (S)AEs on the (S)AE eCRF page. The AE severity grading should be used (see Section 10.1).

- **Application site discomfort**

At all clinical visits and during the phone calls of the treatment phase (except Visit 1), application site discomfort post PDT will be assessed. In addition, application site discomfort during PDT will be assessed at Visit 2 and Visit 4, if applicable.

Any signs or symptoms reported by the subject should be assessed by the investigator.

Application site discomfort might involve burning, irritation, paraesthesia, or pruritus (21).

- **Application site skin reactions**

Application site skin reactions will be evaluated by the investigator (or delegate) at all clinical visits of the treatment phase (except Visit 1).

During the phone call(s), application site skin reactions will be reported by the subject and assessed by the investigator.

Application site skin reactions might involve discharge, erosion, erythema, exfoliation, induration, edema, scabbing, pustules, bleeding, or vesicles (21).

- **Application site reactions according to 4-point scale**

In addition, the following application site reactions will be assessed using the 4-point scale provided in Table 7 and documented separately in the eCRF at all clinical visits and for the phone calls of the treatment phase (except Visit 1).

Subjects will be asked for application site discomfort at the clinical visits and for application site discomfort and for application site skin reactions during the phone calls. A script in lay language is provided in Appendix B (Section 15) for guidance.

Application site skin reactions will be evaluated by the investigator (or delegate) at the clinical visits.

Note: Severity grading according to 4-point scale is different from AE severity grading as defined in Section 10.1.1.

Table 7: Category descriptors with a 4-point scale for Application Site Reactions

Category	Grading	Criteria
Application Site Discomfort		
burning	Grade 0 = None	no perceptible burning in the treatment field
	Grade 1 = Mild	minimal, barely perceptible -tolerable and little discomfort
	Grade 2 = Moderate	barely perceptible tolerable, but causes some discomfort
	Grade 3 = Severe	very uncomfortable or intolerable
hyperalgesia	Grade 0 = None	no perceptible hyperalgesia in the treatment field
	Grade 1 = Mild	minimal, barely perceptible - tolerable and little discomfort

	Grade 2 = Moderate	tolerable, but causes some discomfort
	Grade 3 = Severe	very uncomfortable or intolerable
irritation	Grade 0 = None	no perceptible irritation in the treatment field
	Grade 1 = Mild	minimal, barely perceptible - tolerable and little discomfort
	Grade 2 = Moderate	tolerable, but causes some discomfort
	Grade 3 = Severe	very uncomfortable or intolerable
paraesthesia	Grade 0 = None	no perceptible paraesthesia in the treatment field
	Grade 1 = Mild	minimal, barely perceptible -tolerable and little discomfort
	Grade 2 = Moderate	tolerable, but causes some discomfort
	Grade 3 = Severe	very uncomfortable or intolerable
pruritus	Grade 0 = None	no perceptible pruritus in the treatment field
	Grade 1 = Mild	minimal, barely perceptible -tolerable and little discomfort
	Grade 2 = Moderate	tolerable, but causes some discomfort
	Grade 3 = Severe	very uncomfortable or intolerable
Application Site Skin Reaction		
bleeding	Grade 0 = None	no bleeding in the treatment field
	Grade 1 = Mild	bleeding at up to and including 25% of the lesions
	Grade 2 = Moderate	bleeding at more than 25% of the lesions up to and including 75% of the lesions
	Grade 3 = Severe	bleeding at more than 75% of lesions or any bleeding at non-lesion skin area of the treatment field
discharge	Grade 0 = None	no visible discharge in the treatment field
	Grade 1 = Mild	discharge at up to and including 25% of the lesions
	Grade 2 = Moderate	discharge at more than 25% of the lesions up to and including 75% of the lesions
	Grade 3 = Severe	discharge at more than 75% of lesions or any discharge at non-lesion skin area of the treatment field
edema	Grade 0 = None	no visible edema in the treatment field
	Grade 1 = Mild	scant, rare edema to easily seen edema, minimally palpable, involving up to 1/3 of the treatment area
	Grade 2 = Moderate	easily seen edema and typically palpable, involving between 1/3 to 2/3 of the treatment area
	Grade 3 = Severe	easily seen edema, indurated in some areas, involving over 2/3 of the treatment area
erosion	Grade 0 = None	no visible erosion in the treatment field
	Grade 1 = Mild	up to four areas of erosion 3 mm diameter or less in size OR a single area larger than 3 mm diameter in size
	Grade 2 = Moderate	more than a single area of erosion larger than 3 mm diameter in size or more than four areas of 3 mm diameter or less in size
	Grade 3 = Severe	any degree of erosion than (Grade 2) above

erythema	Grade 0 = None	no visible erythema in the treatment field
	Grade 1 = Mild	barely perceptible to predominantly minimal erythema (pink) in the treated area with or without a few isolated areas of more intense erythema
	Grade 2 = Moderate	predominantly moderate erythema (red) in the treated area with or without a few isolated areas of intense erythema (bright red)
	Grade 3 = Severe	predominantly intense erythema (bright red) in the treated area with or without a few isolated areas of very intense (fiery red) erythema
exfoliation	Grade 0 = None	no visible exfoliation in the treatment field
	Grade 1 = Mild	barely perceptible to limited areas of fine peeling in up to 1/3 of the treatment area
	Grade 2 = Moderate	fine peeling involving 1/3 to 2/3 of the treatment area or limited areas of coarser peeling
	Grade 3 = Severe	coarser peeling involving more than 2/3 of the treatment area or limited areas of very coarse peeling
induration	Grade 0 = None	no perceptible induration in the treatment field
	Grade 1 = Mild	minimal, barely perceptible - tolerable and little discomfort
	Grade 2 = Moderate	tolerable, but causes some discomfort
	Grade 3 = Severe	very uncomfortable or intolerable
pustules	Grade 0 = None	no visible pustules in the treatment field
	Grade 1 = Mild	a single area larger than 3 mm diameter in size covered with pustules OR up to four areas of 3 mm diameter or less in size
	Grade 2 = Moderate	more than a single area larger than 3 mm diameter in size covered with pustules OR more than four areas of 3 mm diameter or less in size
	Grade 3 = Severe	any degree of pustules greater than (Grade 2) above
scabbing	Grade 0 = None	no scabbing in the treatment field
	Grade 1 = Mild	barely perceptible scabbing to limited areas of fine scabbing in up to 1/3 of the treatment area
	Grade 2 = Moderate	fine scabbing involving 1/3 to 2/3 of the treatment area or limited areas of coarser scabbing
	Grade 3 = Severe	coarser scaling involving more than 2/3 of the treatment area or limited areas of very coarse scabbing
vesicles	Grade 0 = None	no visible vesicles in the treatment field
	Grade 1 = Mild	a single area larger than 3 mm diameter in size covered with vesicles OR up to four areas of 3 mm diameter or less in size
	Grade 2 = Moderate	more than a single area larger than 3 mm diameter in size covered with vesicles OR more than four areas of 3 mm diameter or less in size
	Grade 3 = Severe	any degree of vesiculation than (Grade 2) above

Application site reactions assessment using the 4-point scale must be performed at the following time points:

- On the day of PDT (Visit 2 or Visit 4)
  - Prior to IMP application (prior to lesion preparation)
  - Prior to illumination (after IMP incubation, once the dressing is removed and the remaining IMP is wiped off)
  - 10 min (± 2 min) after end of illumination
- 1 week after PDT (Phone Call)
- 4 weeks after PDT (Visit 3 or Visit 5)
- 12 weeks after PDT (Visit 4 or Visit 6)

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

At Visit 2 (PDT-1) and Visit 4 (PDT-2 for non- or partial responders), subjects will assess the pain experienced during illumination using an 11-point Numeric Rating Scale (NRS-11). The NRS-11 ranges from 0, no pain at all, to 10, pain as bad as you can imagine. This score should reflect the subject's respective maximum pain during illumination and will be assessed retrospectively directly after (last) illumination.

Pain during illumination is considered as resulting from the intensity of other modalities, e.g., burning, stinging. These modalities (i.e., burning, stinging, itching) are documented as AEs. As pain is rated via NRS-11, it will not be documented as separate AE to avoid double documentation.

If pain is not related to illumination (e.g., neuropathic pain, headache) this is to be documented as AE, nevertheless.

9.7.5.2 Documentation of new lesions

Any new lesions (AK, NMSC such as BCC, SCC or Bowen's disease, and melanoma) inside the treatment field have to be reported as AE (see Section 10.3).

All new lesions inside the treatment field occurring after Visit 2 must be indicated on the grid foil. In case of any updates, a new copy of the grid foil should be taken, and each copy should be signed and dated by the investigator.

New AK lesions ≥ 4 mm inside the treatment field at Visit 2 will not be considered as new lesions but will be documented as AK target lesions. New severe AK lesions ≥ 4 mm occurring at Visit 2 must be excluded from the treatment field. If this is not possible, the patient is not eligible.

Any new lesions meeting exclusion criterion 5 at Visit 2 will lead to exclusion of the subject (see Section 6.3.4).

10 SAFETY MANAGEMENT

10.1 Definitions

10.1.1 Adverse events

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

For details on known adverse reactions see Ameluz® PI (21) and current IB.

For the purpose of the study, clinically significant abnormal results of diagnostic procedures including abnormal laboratory findings discovered at screening will be related to medical history (see Section 8.4). If clinically significant abnormal results are detected post screening, they are considered to be AEs. This also refers to events requiring unscheduled diagnostic procedures or treatment measures or events resulting in withdrawal from the study. Any AE with onset or worsening after treatment with IMP up to 12 weeks after the last PDT is considered as treatment-emergent adverse event (TEAE).

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

- An unfavorable and unintended new sign, symptom, illness, or syndrome
- Worsening (change in nature, severity, or frequency) of a concomitant or pre-existing condition
- An unfavorable effect of the IMP or concomitant medication
- An unfavorable effect of the IMD, if applicable
- An unfavorable effect of an invasive procedure required by the protocol
- An accident or injury
- Drug interactions

Surgical procedures are not AEs but therapeutic measures. The condition for which the surgery is required is an AE, if it occurs or is detected during the study. In case of planned surgical measures for conditions known before the study period (see Section 8.4.1) and do not worsen during the study (medical history), reporting an (S)AE is not justified.

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.

Application site reactions, must be documented as AEs with the severity scale described above. In addition, application site reactions are to be assessed according to the Application Site Reactions form with the 4-point scale described in Table 7.

AEs can be categorized as “non-serious” and “serious” (see Section 10.1.2).

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.

10.1.2 Serious adverse events

An AE is considered “serious” if, in the view of either the investigator or sponsor, it

- Results in death.
- Is life-threatening.
  “Life-threatening” means that the subject was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
  This means that hospital inpatient admission or prolongation of hospital stay were required for the treatment of the AE, or that they occurred as a consequence of the event.
- Results in persistent or significant disability or incapacity.
  “Persistent or significant disability or incapacity” means a permanent or significant and substantial disruption of a person’s ability to carry out normal life”.
- Results in 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 cancer during a treatment should be considered as medically important.

10.1.3 Alert terms and other reasons for expedited reporting to Pharmacovigilance

Two Adverse Events of Special Interest (AESIs) have been defined for this study: Transient Amnestic Episodes and Contact Dermatitis.

10.1.3.1 Transient Amnestic Episodes

Rare cases of transient amnestic episodes have been reported during post-marketing use of Ameluz® in combination with photodynamic therapy. As these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

To collect more data on this rare adverse event, the transient amnestic episode is defined as an AESI for which expedited reporting to pharmacovigilance is required. Thus, if a patient develops any form of amnesia/ loss of memory after treatment, this must be notified to the sponsor within the same timelines as an SAE (within 24 h after becoming aware) on the “SAE reporting form” that will be provided by the sponsor. The immediate reporting is required even if the event is non-serious. For further details on reporting please refer to Section 10.3.1.1. The patient should be referred to a neurologist for further evaluation and confirmation of the diagnosis.

10.1.3.2 Contact Dermatitis

Rare cases of allergic dermatitis have been reported during post-marketing use of Ameluz® in combination with photodynamic therapy. As these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

To collect more data on this rare adverse event and to confirm allergic skin reaction following treatment with the IMP, a suspicion of contact dermatitis is defined as an AESI for which expedited reporting to pharmacovigilance is required. Thus, if there is suspicion that a patient developed any form of local allergic reactions to the IMP, this must be notified to the sponsor within the same timelines as an SAE (within 24 h after becoming aware) on the “SAE reporting form” that will be provided by the sponsor. The immediate reporting is required even if the event is non-serious. For further details on reporting please refer to Section 10.3.1.1.

If the investigator suspects contact dermatitis to the IMP, this needs to be confirmed or infirmed by using a standardized patch test. The reading of the test will be done according to the guidelines from the International Contact Dermatitis Research Group (49). Patch testing will be performed 6 – 8 weeks after the suspicion of contact dermatitis has been reported to the sponsor. The sponsor will provide the relevant site with the material necessary for re-testing using patch tests (e.g. IMP). Instructions on performing the patch test are described in Appendix C in Section 15.

For details on known adverse reactions see Ameluz® PI (21) and corresponding IB.

A pregnancy in a subject during treatment with the investigational products must be reported to the sponsor immediately. For further details on reporting please refer to Section 10.3.1.2.

10.1.4 Investigational medicinal product complaints

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

10.1.5 Investigational medical device complaints

All AEs reported in previous studies were not directly related to the PDT lamp (referred to as Adverse Device Effects (ADEs)), but rather to the IMP or PDT. Thus, no ADEs are expected affecting subjects or third persons (e.g., study personnel), provided the IMDs are properly used as described in the user manuals.

ADEs occurring in subjects which are classified as unanticipated serious adverse device effects USADEs have to be reported to Institutional Review Board (IRB) and to FDA.

Nevertheless, ADEs occurring in third persons as well as technical complaints associated with the IMDs must be reported to the sponsor.

ADEs reported by the treated subject must be reported via the AE section in the eCRF.

10.2 Period AE collection

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

- AEs developing between signing the informed consent form (ICF) and IMP application at Visit 2 will be considered as PTAEs and documented as an AE.
- TEAEs are defined as all AEs or SAEs that occur after IMP application at Visit 2 until end of the treatment phase, 12 weeks after the last PDT (either Visit 4 or Visit 6).
- Relevant AEs include application site AEs or conditions affecting skin health in the treatment field which might impair proper assessment of the recurrence rate of the treated AK lesions, or other clinically relevant events at the investigator’s discretion at visit FU1 and FU2.
- If the investigator detects an SAE in a subject after end of study, and considers the event possibly related to prior study treatment or procedures, he/she should report this event to the pharmacovigilance department of the sponsor (see Section 10.3.1).

10.3 Documentation and reporting of adverse events by investigator

AEs must be documented in accordance with the instructions for the completion of (S)AE reports in clinical studies.

The following approach will be taken for documentation:

- **All AEs** during the treatment phase and all **relevant AEs** during the follow-up phase (whether serious or non-serious) must be documented using the "Adverse Event" page in the eCRF in addition to source data.
- In addition to the above, if the AE is serious (see Section 10.1.2) or an AESI, further reporting obligations apply as described in Section 10.3.1.1. The first completed SAE report form must be marked as "initial". The applicable SAE criteria must be stated in the eCRF.
- 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 10.1.3), this information should be provided via the SAE report form. It should be clearly stated that no AE was observed. In this case, there is no need to complete the "Adverse Event" page in the eCRF.

The following details regarding AEs are required:

- confirmed medical diagnosis or symptoms (if applicable)
- category: general, application site skin reaction or application site discomfort or new lesion
- time frame (by providing start/stop date and time)
- severity (see Section 10.1)
- outcome (recovered/resolved, recovering/resolving; recovering with sequelae, not recovered/not resolved, fatal, unknown)
- action taken (with reference to concomitant medications/treatments)
- seriousness criteria (if applicable)
- AESI (yes/no),
- if the AE is related to IMP only, IMD only, or both (cannot be ambiguously assigned to one of both),
- in case of a suspicious contact dermatitis final evaluation of the patch test (see Section 10.1.3.2)

AEs should be assessed regarding relatedness to the IMP, IMD or both:

- **Unrelated:** AEs that are judged to be clearly and incontrovertibly not caused by the IMP/IMD and study procedure (concomitant disease etc.).
- **Unlikely related:** the temporal sequence is atypical, and the AE does not follow a known pattern of response to IMP/IMD another causative factor is present but causal role of the study drug cannot be excluded.
- **Possibly related:** either an event that is temporally associated with the use of the IMP/IMD or a known pharmacological effect/associated reaction, which is also recognized with another concomitant therapy/disease or other external cause.

- **Probably related:** appropriate temporal association, known pharmacological effect, recognized to be an associated IMP/IMD reaction and for which no other possible cause is evident.
- **Definitely related:** the reaction has occurred with this IMP/IMD previously (i.e., positive re-challenge) and there is an appropriate temporal relationship between therapy and reaction; and the reaction follows a known or expected response pattern to the suspected drug.

The investigator should medically judge a reasonable causal relationship by considering 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
- 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 the case of SAEs or serious adverse reactions (SARs), respectively, component signs and symptoms may be recorded in addition to a diagnosis if they further clarify the clinical picture.

If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

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

10.3.1 Immediate Reporting

10.3.1.1 Reporting of SAEs and AESIs to sponsor

SAEs or AESIs observed throughout the study must be documented on an "Serious Adverse Event/Expedited Report from a Clinical Trial for Combination products" ("SAE report") form in accordance with instructions for completing the "SAE report" form. This form and the instructions will be provided in the investigator site file and must be completed and supplied to the sponsor within 24 h after becoming aware of the SAE (21 CFR §312.32, 21 CFR §312.64) or AESI.

Any SAE or AESI 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

Email: PPD

Fax： PPD

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

Information not available at the time of the initial report (e.g., an end date for the AE or laboratory values received after the report) must be documented on an "SAE report" form, with the box "Follow-up"/"Final report". In case the pharmacovigilance department decides that further clarification is needed, it will be requested via the data clarification form (DCF).

The instructions for completing the "SAE report" form give more detailed guidance on the reporting of SAEs, AESIs and AEs initially reported as non-serious that become serious. If a non-serious event becomes serious, details must be forwarded immediately as described above.

Note:

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

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

The sponsor will ensure that all legal reporting requirements to the competent authorities and the IRB(s) are met (see Section 10.4.2).

10.3.1.2 Reporting of pregnancies to sponsor

Pregnancies occurring during a subject's participation in the study, although not typically considered SAEs, must be notified to the sponsor within the same timelines as an SAE (within 24 h after becoming aware of the pregnancy) on a "Pregnancy report form" that will be provided by the sponsor. This information must be provided regardless of withdrawal of the subject from the study or discontinuation of the treatment. No further study treatment will be performed. Further treatment will be arranged on a case-by-case basis with the treating physician and the investigator.

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

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

10.3.1.3 Reporting of USADEs to the sponsor and to IRB

ADEs 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 USADE (unanticipated serious ADEs). A report of any USADE occurring during an investigation shall be submitted to the reviewing IRB and the sponsor within 14 calendar days after the investigator gets aware of the effect (21 CFR §812.150). Investigators with local IRBs have to submit the required documents (safety package) to the IRB themselves, for investigators with a central IRB this will be submitted by pharmacovigilance service provider (spm²), and the investigator will be notified.

In case a serious and unexpected event cannot be clearly assigned to the IMD, it should be treated as an SAE (see Section 10.1.2).

Note: Reporting of SADEs to the sponsor is equal to SAE reporting described in Section 10.3.1.1.

10.3.1.4 Expedited reporting of adverse events to IRB

The investigator will promptly forward the Investigational New Drug (IND) safety reports received from sponsor (see Section 10.4.2) and report all unanticipated problems involving risk to subjects or others, and changes in the research activity to the IRB.

The sponsor may submit IND safety reports directly to the IRB on the investigator's behalf. Please refer to Section 10.4.2.

10.3.2 Unblinding

The process of unblinding is described in Section 10.6.2 and will lead to the subject's discontinuation of trial participation.

If applicable and required, treatment codes will be unblinded prior to submission to authorities and investigators by the sponsor's pharmacovigilance group, which is an independent entity within the sponsor.

10.4 Documentation and reporting of adverse events by sponsor

10.4.1 Determination of expectedness, Reference Safety Information

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

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

properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

10.4.2 Expedited reporting of AEs to competent authorities and investigators

The sponsor will report all serious and unexpected AEs with reasonable suspected causal relationship (SUSAR) as IND safety reports to the FDA and all participating investigators according to applicable law.

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

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

10.4.3 Periodic reporting of AEs by sponsor

A summary of all 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).

10.4.3.1 Development safety update report (DSUR)

The sponsor will prepare and submit annual safety reports to competent authorities and concerned ethics committees (EC), if applicable.

10.5 Continuous risk assessment

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

10.6 Emergency procedures

10.6.1 Emergency sponsor contact

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

PPD (Biofrontera contact person in the US)

10.6.2 Emergency identification of investigational medicinal products

There is no apparent reason to break the randomization code in the event of an adverse drug reaction. This is because subjects receive a topical treatment a maximum of two times with a 3-month interval each which is considered single application(s), and there is also no substance-specific treatment for adverse reactions. Therefore, special emergency identification procedures are not applicable to this trial.

In case of emergency the investigator can request unblinding of a specific randomization number via the eCRF system. The qualified person for pharmacovigilance (QPPV) as well as the responsible project manager at Biofrontera Bioscience GmbH will receive immediate notice from the system about the request. The QPPV will provide the investigator with the treatment allocation of the respective randomization number at earliest possibility.

If the unblinding (throughout the study) is performed by the investigator due to a medical requirement, the subject will discontinue trial participation.

10.6.3 Emergency treatment

There is no substance-specific treatment for adverse reactions. For treatment of PDT associated pain and discomfort please see Section 8.4.2.

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

11 STATISTICAL PROCEDURES

The principal features of the statistical analysis are described in this section. Technical details of the statistical analyses will be specified in statistical analysis plans (SAPs). The SAPs will be finalized prior to the database locks for the final analysis of the treatment phase and follow-up phase, respectively. The recommendations of the ICH E9 'Note for Guidance on Statistical Principles for Clinical Trials' including the addendum R1 to ICH E9 will be considered.

The main statistical analysis will be performed as soon as the 12-week post last PDT data are available for analysis. Additional data from the follow-up phase (6 months and 12 months after the last PDT) will be analyzed and reported separately.

Statistical testing will be applied to compare active treatment vs vehicle. A significance level of 0.0025 (one-sided, 0.25 %) will be applied for confirmative statistical testing procedures for the primary efficacy variable (Cochran-Mantel-Haenszel test adjusting for the treatment area) and the key secondary efficacy variables (chi-square test or the Fisher's exact test if the number of expected cells counts is lower than five for any outcome, respectively). Whereas further secondary efficacy variables will be tested descriptively and in an exploratory manner. A two-sided significance level of 0.05 (5 %) will be applied for any statistical testing procedures for all further secondary efficacy variables. Where appropriate, two-sided local 95 % Confidence Intervals (cIs) of differences between BF-200 ALA and vehicle will be presented. As the secondary endpoint analyses, including the calculation of cIs, are not confirmatory, an adjustment for multiplicity is necessary.

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

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

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

11.1 Endpoints

Primary objective

The primary objective of the study is to compare the efficacy of BF-200 ALA PDT with vehicle PDT, utilizing illumination with a RhodoLED lamp, in the treatment of mild to moderate AK on the extremities or the neck/trunk in terms of overall subject complete response in the treatment phase.

The primary endpoint is the overall subject complete response rate 12 weeks after the last PDT, defined as the percentage of subjects with all AK target lesions clinically cleared 12 weeks after the last PDT.

Secondary objective

The secondary objective of the study is to evaluate secondary efficacy parameters and safety and tolerability in the treatment phase.

Efficacy:

The key secondary endpoints are:

1) Overall subject complete response rate 12 weeks after the last PDT, defined as the percentage of subjects with all AK target lesions clinically cleared 12 weeks after the last PDT, for subjects with lesions treated on extremities

2) Overall subject complete response rate 12 weeks after the last PDT, defined as the percentage of subjects with all AK target lesions clinically cleared 12 weeks after the last PDT, for subjects with lesions treated on neck/trunk

Further secondary endpoints of the treatment phase regarding efficacy are:

- Percentage of clinically cleared individual AK target lesions in relation to total number of AK target lesions at baseline (Visit 2) assessed 12 weeks after the last PDT, overall and stratified by treatment area and AK severity at baseline (according to Olsen (1)).
- Percentage of clinically cleared individual severe AK lesions in relation to total number of severe AK lesions at baseline (according to Olsen (1); Visit 2) assessed 12 weeks after the last PDT, overall and stratified by treatment area.
- Subject complete response rate, 12 weeks after PDT-1, defined as the percentage of subjects with all AK target lesions clinically cleared, overall and stratified by AK baseline parameters (e.g., AK target lesion number per subject at baseline, maximal AK target lesion severity at baseline, size of the treatment field, and treatment area).
- Percentage of clinically cleared individual AK target lesions in relation to total number of AK target lesions at baseline (Visit 2) assessed 12 weeks after PDT-1, overall and stratified by treatment area and AK severity at baseline (according to Olsen (1)).
- Percentage of clinically cleared individual severe AK lesions in relation to total number of severe AK lesions at baseline (according to Olsen (1); Visit 2) assessed 12 weeks after PDT-1, overall and stratified by treatment area.
- The esthetic appearance 12 weeks after the last PDT as assessed by the investigator, overall and stratified by treatment area.
- The esthetic outcome 12 weeks after the last PDT as assessed by the subject, overall and stratified by treatment area.
- Satisfaction with PDT treatment 12 weeks after the last PDT as assessed by the subject, overall and stratified by treatment area.

Safety and tolerability:

- Frequency and extent of AEs, AESIs, SAEs, and treatment-emergent adverse events (TEAEs), overall and stratified by demographics, skin type class (I – III and IV – VI), size of the treatment field, and treatment area. TEAEs (including application site skin reactions and discomfort) are defined as all AEs with onset or worsening after treatment with IMP up to 12 weeks after the last PDT
- Assessment of new lesions (AK, non-melanoma skin cancer [NMSC, including BCC, SCC or BD] or melanoma) inside the treatment field
- Assessment of application site reactions according to a 4-point scale
- Application site pain during illumination, reported by the subjects assessed on an 11-point numeric rating scale, overall and stratified by size of the treatment field and treatment area
- Vital signs data
- Safety laboratory data
- Physical examination data

Tertiary objective

The tertiary objective of the study is to evaluate efficacy, safety and tolerability parameters in the follow-up phase.

Efficacy:

- Subject recurrence rate defined as the percentage of subjects with all AK target lesions clinically cleared 12 weeks after the last PDT presenting with at least one recurrent lesion during follow-up, stratified by demographics, study sites, AK baseline parameters (e.g., AK target lesion number per subject at baseline, maximal AK target lesion severity at baseline, size of the treatment field, and treatment area).
- Percentage of AK target lesions showing recurrence in follow-up in relation to total number of clinically cleared AK target lesions 12 weeks after last PDT, overall and stratified by treatment area and AK severity at baseline (according to Olsen (1)).
- Percentage of severe AK lesions showing recurrence in follow-up in relation to total number of clinically cleared severe AK lesions 12 weeks after last PDT, overall and stratified by treatment area.
- The esthetic appearance at follow-up visits as assessed by the investigator, overall and stratified by treatment area.
- The esthetic outcome at follow-up visits as assessed by the subject, overall and stratified by treatment area.

- Satisfaction with PDT treatment at follow-up visits as assessed by the subject, overall and stratified by treatment area.

Safety:

- Any relevant AE (including AEs or conditions affecting skin health in the treatment field which may impair proper assessment of the recurrence rate of the treated AK lesions, or other clinically relevant events at the investigator's discretion) as well as any SAE that has occurred since the end-of-treatment visit (Visit 4 or Visit 6) overall and stratified by demographics and treatment area.
- Assessment of new lesions (AK, NMSC or melanoma) inside the treatment field

11.2 Analysis sets

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

- Consented set: All subjects who provided informed consent to participate in the study.
- Randomized set: All subjects randomized to IMP irrespective of whether they received IMP or not. The randomized set is the analysis set for the summary of subject discontinuation.
- Safety analysis set (SAF): All subjects treated at least once with IMP (IMP application). The assignment of subjects to the treatment groups will be as actually treated. The SAF is the analysis set for all safety analysis.
- Full analysis set (FAS): All subjects randomized and treated at least once with PDT (IMP application and illumination). In accordance with the intent-to-treat-principle, the assignment of subjects to the treatment groups will be as randomized. The FAS will be the analysis set applied to the evaluation of primary efficacy endpoint, key secondary efficacy endpoints and further secondary efficacy endpoints.
- Per-protocol set (PPS): All subjects of the FAS without any major protocol deviations. The assignment of subjects to the treatment group will be as actually treated. The PPS will be used for supplementary analysis of the primary and key secondary efficacy endpoints and may also be used for selected analysis of further secondary efficacy endpoints.

Analysis sets for the Follow-up phase (FUP) include

- SAF-FUP: all subjects treated at least once with the IMP entering the FU period.
- FAS-FUP: all subjects from the FAS of the clinical observation period entering the FU period.
- PPS-FUP: all subjects from the PPS (without any major protocol deviations) of the clinical observation period entering the FU period.

11.2.1 Protocol Deviations leading to exclusion from PPS

The following protocol deviations will result in exclusion from the PPS:

- The treatment differs significantly from protocol (e.g., incubation time differs by more than 30 min from times indicated by the protocol; applied light dose differs by more than 20 %).
- No final assessment visit (Visit 4 or Visit 6)
- Missing AK lesion clearance status at final assessment visits (Visit 4 or Visit 6)
- Forbidden medication will be decided on a case-by-case basis
- Significant deviation from visit time window at Visit 4 or Visit 6
- Wrong or expired IMP applied

All other protocol deviations (including violation of timelines) will be handled on a case-by-case manner. The definition of major protocol deviations in the sense of being reportable to the IRB may deviate from the aforementioned criteria.

11.3 Estimands

The primary estimand will use the treatment-policy strategy and compare the treatment effect in subjects independent of the following possible intercurrent events

a) the use of medications in a temporal relation to PDT which might influence the efficacy of the treatment,
b) refusal of 2nd treatment e.g., due to pain,
c) any other type of treatment discontinuation, or
d) postponement of PDT-2.

The efficacy endpoints will be analyzed focusing on the primary estimand.

Every attempt will be made to obtain data 12 weeks after last PDT irrespective of intercurrent events.

Primary estimand is defined by:

- Treatment: The treatment intended for the evaluation to address the study objective is the randomized treatment (BF-200 ALA or vehicle) administered to subjects at Visit 2 (PDT-1) and at Visit 4 (PDT-2), in case of remaining lesions at Visit 4. Treatment includes approx. 3 h incubation period of the IMP and a subsequent illumination with IMD until application of approx. 37 J/cm².
- Population: The population targeted by the clinical questions will be represented by the entire trial population defined through inclusion / exclusion criteria (Full analysis set, i.e., subjects randomized and treated at least once with PDT (IMP application and illumination)). For further details on study population, see Section 6.3. A minimum of

4 to a maximum of 15 mild to moderate AK lesions with a diameter of ≥ 4 mm are required per subject to enable a profound assessment. No further demographic factors influencing AK development are considered.

- Variable: Treatment success [binary: yes/no], defined as subject being clinically completely cleared 12 weeks after the last PDT.
- Intercurrent event (ICE): The occurrence of all intercurrent events will be handled using the treatment-policy strategy according to ICH E9 (R1). All values will be used regardless of occurrence of the above mentioned intercurrent events up to 12 weeks after the last PDT. Before data base lock the occurrence of any other, not pre-defined ICE will be reviewed.
- Population-level summary: The difference in percentage of clinically completely cleared subjects 12 weeks after last PDT with BF-200 ALA vs vehicle.

The primary estimand targets to estimate the effect of initiating the treatment regimen in the population of interest and compares the benefit of the initially randomized treatments as they are taken. As the treatment-policy strategy is used for all types of intercurrent events, all available data will be used for the primary estimand, regardless of the use of medications in a temporal relation to PDT which might influence the efficacy of the treatment, the refusal of 2nd treatment due to pain, any other type of treatment discontinuation, or postponement of PDT-2.

The primary estimand is based on clinical assessments 12 weeks after the last PDT. For description of how to handle data missing on clinical visits 12 weeks after the last PDT please refer to Section 11.5.

This estimand will be applied for the key-secondary endpoints in the same manner.

11.4 Statistical methods

11.4.1 Disposition of subjects and exposure

Descriptive analysis of subjects in each analysis set such as the consented set, the randomized set, the SAF, the FAS, and the PPS will be presented overall, and by treatment group, per study site, and study period.

Premature discontinuation from the study and completion of the study periods will be summarized. Reasons for discontinuation will be tabulated.

The number and relative frequency of subjects treated and re-treated with PDT will be presented by treatment group.

11.4.2 Demographics and background characteristics

All variables concerning demographic and background characteristics will be summarized to describe the study population. Data will be presented for all subjects in the FAS. Selected data may also be presented for the SAF and PPS.

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

11.4.3 Evaluation of efficacy endpoints

Primary efficacy analysis

The primary efficacy variable will be tested for the following hypothesis:

The primary null hypothesis (H_0, one-sided) is that the overall complete subject response rate assessed 12 weeks after the last PDT for subjects treated with BF-200 ALA is lower or equal to that of subjects treated with vehicle.

The primary alternative hypothesis (H_1, one-sided) is that the overall complete subject response rate assessed 12 weeks after the last PDT for subjects treated with BF-200 ALA is greater than the response rate for subjects treated with vehicle.

A one-sided Cochran-Mantel-Haenszel test with stratification factor treatment area (extremities vs neck/trunk) will be used to test the primary hypothesis on a significance level of 0.0025 (one-sided, 0.25 %).

The primary analysis will be performed on the FAS. The analysis will be repeated on the per-protocol set (PPS) as supplementary analysis.

The primary endpoint will additionally be analyzed descriptively and in an exploratory way stratified by demographics, skin type class (I – III and IV – VI), study sites, and AK baseline parameters (e.g., AK target lesion number per subject at baseline, maximal AK target lesion severity at baseline, size of the treatment field, and treatment area).

Key secondary efficacy analysis

The key secondary efficacy variables will be tested for the following hypothesis:

The primary null hypothesis (H_0, one-sided) is that the overall complete subject response rate assessed 12 weeks after the last PDT for subjects treated with BF-200 ALA is lower or equal to that of subjects treated with vehicle on extremities or on neck/trunk, respectively.

The primary alternative hypothesis (H_1, one-sided) is that the overall complete subject response rate assessed 12 weeks after the last PDT for subjects treated with BF-200 ALA is greater than the response rate for subjects treated with vehicle on extremities or on neck/trunk, respectively.

A one-sided chi-square test will be used to test the key secondary hypotheses on a significance level of 0.0025 (one-sided, 0.25 %) using a hierarchical testing procedure: confirmatory hypothesis testing of key secondary variables will be done only after the test of the primary efficacy variable is passed and will be done strictly in the given order (extremities followed by neck/trunk) to ensure the Family Wise Error Rate (FWER). Confirmatory hypothesis testing in the pre-defined order will stop once the first non-significant test result is obtained. If the number of expected cells counts is lower than five for any outcome the Fisher's exact test will be used instead.

The analyses on key secondary efficacy endpoints will be performed on the FAS. The analysis will be repeated on the PPS as supplementary analysis.

Key secondary endpoints will additionally be analyzed descriptively and in an exploratory way stratified by AK baseline parameters (e.g., AK target lesion number per subject at baseline, maximal AK target lesion severity at baseline, size of the treatment field, and treatment area).

Secondary efficacy analysis

Further secondary efficacy endpoints will be analyzed descriptively and in an exploratory way. The analyses on secondary efficacy endpoints will be performed on the FAS.

The analysis of selected secondary endpoints will be repeated on the PPS as supplementary analysis.

Details of further analyses will be specified in the SAP.

11.4.4 Evaluation of safety endpoints

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

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

In addition, application site reactions will be analyzed according to 4-point scale provided in Table 7. A separate listing will be provided for all application site reactions reported and all subjects randomized.

The mean and the maximal pain score (NRS-11) and the respective CIs will be presented:

1) overall
2) by treatment area
3) by size of the treatment field

All laboratory values will be classified as normal or abnormal according to the laboratory's normal ranges. Only values considered clinically significant by the investigator will be documented in the eCRF (see Section 9.7.5) 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.

The physical examination will include the following body systems: head, neck, skin, lymph nodes, thorax including heart and lung, abdomen, and musculoskeletal, peripheral vascular and nervous system. Abnormal findings that are considered clinically significant will be documented in the medical history (Visit 1) or as AEs (12 weeks after the last PDT, Visit 4 or Visit 6) and listed as such.

Details of further analyses will be specified in the SAP.

11.5 Handling of missing data

The main efficacy endpoints are based on the overall subject complete response rate assessed clinically 12 weeks after the last PDT. If a subject dropped out before the planned visit 12 weeks after the last PDT, or the variable value on this is missing and results cannot be obtained, the results based on the last available visit with a non-missing variable value will be used for the analyses on the overall complete subject response.

If the outcome of a subject cannot be assessed, and the efficacy variable is completely missing, the subject will be counted as a non-responder. For subjects, who should have had a second PDT but were misleadingly classified as complete responders at Visit 5, the results from the first PDT will be used. For complete responders after the first PDT who by mistake received a second PDT, evaluations of the first PDT will also be considered.

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

11.6 Interim analysis

No formal interim analysis will be performed.

11.7 Sample size justification

The sample justification based on the results of study ALA-AK-CT010 „A randomized, double-blind, intra-individual, multi-center phase III study to evaluate the safety and efficacy of BF-200 ALA (Ameluz®) versus placebo in the treatment of mild to severe AK on extremities, neck/trunk with PDT when using the BF-RhodoLED® lamp."

- Overall subject complete response rate assessed 12 weeks after the last PDT (ALA-AK-CT010 - Table 4.2.1- FAS):
    - BF-200 ALA: N=49, cleared: N=33 (67.3 %)
    - Vehicle: N=49, cleared: N= 6 (12.2 %)
- Overall subject complete response rate assessed 12 weeks after the last PDT by treatment area (ALA-AK-CT010 - Table 4.2.2- FAS):
  Extremities:
    - BF-200 ALA: N=39, cleared: N=24 (61.5 %)
    - Vehicle: N=39, cleared: N= 3 (7.7 %)

  Neck/trunk:

- BF-200 ALA: N=10, cleared: N= 9 (90.0 %)
- Vehicle: N=10, cleared: N= 3 (30.0 %)

For the current study, the same treatment areas are selected as in the forementioned study and the same marketed formulation (Ameluz®) and illumination conditions will be used (635 nm, approx. 37 J/cm²). The treatment field is expanded to 80 – 240 cm² and the number of AK lesions might be slightly higher. Thus, a higher amount of Ameluz® is necessary (1 to 3 tubes instead of 1 tube).

A stratified randomization by treatment area (extremities vs neck/trunk) will be used. As the distribution of subjects with AK lesions for those two treatment areas cannot be exactly determined, and the effect especially in the treatment area neck/trunk is not robust due to low numbers of subjects with lesions in this treatment area in study CT010, an overall difference in response rates of 38 % is assumed for the sample size calculation.

It is planned to randomize 165 subjects (BF-200 ALA PDT vs. vehicle PDT, ratio 4:1). This sample size will ensure a power of more than 90 % at a significance level of 0.0025 (alpha, one-sided) according to a one-sided Z-test with pooled variance, in order to demonstrate a statistically significant difference in response rates between subjects treated with BF-200 ALA or vehicle in the full analysis set (FAS). The sample size includes about 10 % (15 subjects) non-evaluable responses.

This estimate is based on the following assumptions:

- Inter-individual (2-arm, parallel) BF-200 ALA versus vehicle
- 4 – 15 mild to moderate AK target lesions
- Ratio 4:1 (BF-200 ALA to vehicle)
- Proportion of subjects with response in BF-200 ALA treated group: 0.5
- Proportion of subjects with response in vehicle treated group: 0.12
- Alpha: 0.0025 (one-sided)
- Power 90 %
- Primary endpoint: Subject complete response assessed 12 weeks after the last PDT

12 STUDY ADMINISTRATION

12.1 Treatment assignment methods

Information on the treatment assignment can be found in Section 6.3.8.

Randomization numbers will be blocked to facilitate attainment of a homogeneous distribution of treatment groups. The block size will not be revealed but a detailed description of the randomization including block size will be provided in a separate randomization plan (not provided to sites). The randomization procedure will ensure a stratification of randomization by site.

For the number of subjects per site refer to Section 6.3.

12.1.1 Randomization: Generation of randomization sequence

The randomization schedule(s) will be generated using SAS version 9.4 or higher (SAS Institute, 2010). The randomization schedule will link sequential numbers to treatment codes. A sealed randomization schedule will be kept at FGK GmbH in a locked environment accessible by the management board and unblinded persons of FGK only, which are separate from the study team. Copies of the randomization schedule will furthermore be delivered to the drug supplier responsible for packaging and labeling of the IMP, a Biofrontera representative responsible for the release of study medication, and to QPPV to provide information about specific randomization numbers to the investigator, whenever required. All these individuals are separate from the study team.

12.2 Packaging and labeling

12.2.1 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 IMP (BF-200 ALA and vehicle):

Biofrontera Pharma GmbH
Hemmelrather Weg 201
51377 Leverkusen
Germany

The appropriate number of tubes and cardboard boxes will be labeled in English according to the pre-defined distribution of randomization 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 patient pack is provided containing 6 tubes containing 2 g BF-200 ALA or vehicle, 3 tubes for PDT-1 and, if applicable, 3 tubes for PDT-2. Each box is labeled with 6

tear-off labels and can be identified and assigned to a specific subject by a unique randomization number.

The label of the outer carton and of the patient pack will be printed on a white or blue background, depending on the treatment area (extremities or neck/trunk) they are assigned to (extremities = white; neck/trunk = blue).

In addition, each tube will be labeled accordingly. The label of the tubes will be printed on a white background. 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 all IMP and the labels of the IMP in the Trial Master File (TMF).

12.2.2 Investigational medical device

Both RhodoLED lamps used in this study are manufactured by an ISO 13485:2016 certified manufacturer:

Biofrontera Pharma GmbH
Hemmelrather Weg 201
51377 Leverkusen
Germany

The RhodoLED lamps will be distributed, installed, and maintained at the sites on behalf of Biofrontera Bioscience by technicians or other properly trained delegates of:

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

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

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

For the purpose of this study, the study sites will be provided with one BF-RhodoLED® XL or up to 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(s) will be installed at the site by a technician or delegate of Biofrontera, there will be no immediate packaging available. All labeling will be applied directly to the lamp.

12.3 Supplies and accountability

After the study protocol is approved or accepted by the IRB(s) and by FDA and the IRB site specific approval is obtained, the sponsor will initiate the study site. The sponsor is responsible for provision of the IMP, IMD and relevant documentation to the study sites.

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

The investigator will inventory and acknowledge receipt of all shipments of the IMP and installation of the IMD. The investigator is responsible for maintaining documentation showing the number of investigational products provided to the study site and the used IMP for each study subject. Discrepancies in accountability of the investigational products must be explained and documented. The monitor is responsible to verify the investigator's documentation on receipt, use, and return of the investigational products. The monitor will check drug and medical device accountability at the study sites on an ongoing basis during the study. At the end of the study, all remaining study medication or empty tubes must be returned to the drug supplier acting on behalf of Biofrontera Pharma GmbH for disposal if not explicitly agreed otherwise. The monitor will prepare a final report of accountability of the investigational products for filing in the investigator site file (ISF).

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

12.4 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 12.5.2.

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

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

12.5 Ethical and legal aspects

12.5.1 Good clinical practice (GCP)

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

12.5.2 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.

12.5.3 Subject information and informed consent and HIPAA form

Every trial participant will receive a complete and comprehensive explanation of the significance, nature, extent, and possible risks of the trial. To this end, a detailed, written subject information leaflet 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 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, may 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.

12.5.4 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.

12.5.5 Protocol and GCP violations

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

The sponsor is obliged to report unanticipated problems (i.e., 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.

12.5.6 Protocol amendments

The investigators must not 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.

12.5.7 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 EC/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.

12.5.8 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.

12.5.9 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.

12.5.10 Record retention

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

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

This regulation applies to:

- Adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual PDT such as:
    - Case report forms and supporting data.
    - Signed and dated consent forms. The case history of each subject shall document that informed consent was obtained prior to participation in the study.
    - Medical records including progress notes of the physician and nurse.
- 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.

12.5.11 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.

12.5.12 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.

12.6 Quality control and Quality assurance audit

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

12.6.1 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, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s). The frequency of monitoring and co-monitoring visits, and the degree of source data verification are defined in the monitoring plan. Monitoring will be done by on-site or remote visits. In addition to the monitoring visits, frequent communications (letter, email, telephone, and fax) by the clinical monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements.

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

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

12.6.2 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 delegate. Direct access to all necessary documents must be guaranteed by the investigator, who must provide support at all times for these activities.

12.6.3 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.

13 DOCUMENTATION AND USE OF STUDY FINDINGS

13.1 Documentation of study findings

This study will be performed using an eCRF. The investigators and study site staff will receive an eCRF completion guide, 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 within five (5) business days after the subjects' visits. An explanation should be given for all missing data. Every 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, and by whom and when the change was made. All data changes will be clearly indicated with the means to find previous values. The system will be secured to prevent unauthorized access to the data or the system. This will include the requirement for a user identification and password to enter or change data. The investigator will maintain a list of individuals who are authorized to enter or correct data and their system identification.

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

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

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

13.2 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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15 APPENDICES

A: Fitzpatrick Skin Type according to Fitzpatrick, 1988 (44).

B: Lay language script for Application Site Reactions Assessments during Phone Calls

C: Confirmation of Contact Dermatitis: Patch testing (according to Johansen et al., 2015 (49))

Appendix A

Fitzpatrick Skin Type Test

Fitzpatrick Skin Type according to Fitzpatrick, 1988 (44).

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 two main factors that influence the skin type are:

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

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

Please use the following questionnaires to assess the subject's skin type:

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

Fitzpatrick Skin Type Test

(cont.)

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

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

Add up the total scores of each of the three sections for the subject's Skin Type Score.

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

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

Appendix B

Lay language script for Application Site Reactions Assessments during Phone Calls

(Note: This script is intended as a guide to assess application site reactions according to Table 7. You may adapt the wording to your personal preference. Questions regarding application site reactions should be asked after asking about adverse events with non-leading questions, see sections 8.1.3 and 8.1.6. If subjects are unable to answer a specific question they should be encouraged to describe the appearance/feeling of their skin using their own words.)

"I will now ask you several questions regarding reactions that may have happened on the area of the skin that received the study drug during your last visit. Please answer the questions with how the area feels and looks today.

I will begin by asking you questions regarding how your skin feels on this area.

Do you feel a sensation of burning?" *(burning)*

> *If patient answered yes*: "Would you say that the burning is 1 – barely perceptible, you almost don't feel it; 2 – it is uncomfortable but you can stand it; or 3 – it is very uncomfortable?"
>
> *If patient answered no: document 0, and move to the next question.*

"Do you feel like this area of your skin is more sensitive to pain?" *(hyperalgesia)*

> *If patient answered yes:* "Would you say that the increased pain sensitivity is 1 – barely perceptible, you almost don't feel it; 2 – it is uncomfortable but you can stand it; or 3 – it is very uncomfortable?"
>
> *If patient answered no: document 0, and move to the next question.*

"Do you feel like this area of your skin is irritated?" *(irritation)*

> *If patient answered yes:* "Would you say that the skin irritation is 1 – barely perceptible, you almost don't feel it; 2 – it is uncomfortable but you can stand it; or 3 – it is very uncomfortable?"
>
> *If patient answered no: document 0, and move to the next question.*

"Do you feel like this area of your skin is numb or do you feel tingling?" *(paraesthesia)*

> *If patient answered yes:* "Would you say that this sensation is 1 – barely perceptible, you almost don't feel it; 2 – it is uncomfortable but you can stand it; or 3 – it is very uncomfortable?"
>
> *If patient answered no: document 0, and move to the next question.*

"Do you feel like this area of your skin is itching?" *(pruritus)*

If patient answered yes: "Would you say that the itching is 1 – barely perceptible, you almost don't feel it; 2 – it is uncomfortable but you can stand it; or 3 – it is very uncomfortable?"

If patient answered no: document 0, and move to the next question.

The next questions will be related to how the skin looks like on the area where the study drug was applied. If you cannot see it, is there someone next to you who can help you answer the questions?

"Can you see any bleedings in the area?" *(bleeding)*

If patient answered yes: "How many of the small bumps, or spots, that were treated are bleeding? Do you see bleeding outside of these small bumps?"

If patient answered no: document 0. Otherwise document the severity based on the answer and move to the next question.

"Do you see any liquid coming out of the bumps/spots that were treated?" *(discharge)*

If patient answered yes: "How many of the small bumps, or spots, that were treated have liquid coming out? Do you see liquid coming out outside of these small bumps?"

If patient answered no: document 0. Otherwise document the severity based on the answer and move to the next question.

"Do you see or feel any swelling in the area that was treated?" *(edema)*

If patient answered yes: "How would you describe the swelling? Is it small, hard to see, or very apparent? Would you say that less than a third of the area is swollen, between a third and two-thirds are swollen or that more than two-thirds are swollen?"

If patient answered no: document 0. Otherwise document the severity based on the answer and move to the next question.

"Do you see loss of some or all of the outer skin layer in the area that was treated?" *(erosion)*

If patient answered yes: "How many areas do you see? How large are they (smaller or larger than half of a pea for example)?"

If patient answered no: document 0. Otherwise document the severity based on the answer and move to the next question.

Do you see a reddening of the skin in the area that was treated?" *(erythema)*

If patient answered yes: "Over the area, is the color of the skin mostly pink, red or bright red?"

If patient answered no: document 0. Otherwise document the severity based on the answer and move to the next question.

"Do you see a scaling of your skin in the area that was treated or does your skin look scaly in the area that was treated?" *(exfoliation)*

If patient answered yes: "How much of the area is scaling: less than a third of the area, between a third and two-thirds or more than two-thirds?"

If patient answered no: document 0. Otherwise document the severity based on the answer and move to the next question.

"Do you feel like this area of your skin is harder than usual?" *(induration)*

If patient answered yes: "Would you say that the skin hardening is 1 – barely perceptible, you almost don't feel it; 2 – it is uncomfortable but you can stand it; or 3 – it is very uncomfortable?"

If patient answered no: document 0, and move to the next question.

"Do you see some small, blister-likes sores filled with pus or whitish on the surface of your skin in the area that was treated?" *(pustules)*

If patient answered yes: "How many areas that are covered with these small, blister-likes sores do you see? How big are the areas (smaller or larger than half of a pea for example)?"

If patient answered no: document 0. Otherwise document the severity based on the answer and move to the next question.

"Do you see some crusting on the surface of your skin in the area that was treated?" *(scabbing)*

If patient answered yes: "Would you describe the crusting as thin or thick? How much of the area does it cover?"

If patient answered no: document 0. Otherwise document the severity based on the answer and move to the next question.

"Do you see some small blisters, filled with clear liquid, on the surface of your skin in the area that was treated?" *(vesicles)*

If patient answered yes: "How many areas that are covered with these small blisters do you see? How big are the areas (smaller or larger than half of a pea for example)?"

If patient answered no: document 0. Otherwise document the severity based on the answer and move to the next question.

Appendix C

Confirmation of Contact Dermatitis: Patch testing

(according to Johansen et al., 2015 (49))

Patch testing will be performed 6 – 8 weeks after the suspicion of contact dermatitis has been reported to the sponsor to confirm or infirm, an allergic reaction to the IMP.

Postpone the test if any of the following criteria is met:

- Severe or generalized active dermatitis
- Dermatitis on the site chosen for the application of the patch test
- Treatment with topical corticosteroid on the test site in the last 7 days
- Recent UV exposure of the test site

The procedure will be performed as follow:

- Use an aluminum coated Finn chambers (diameter 12 mm) for each sample; Note that each chamber should be clearly identified.
- To avoid photoreactions the applications should be performed under dimmed light conditions and the test fields should be shielded from light until the last reading. Please instruct the subject accordingly.
- About 45 µL of Ameluz® or vehicle, respectively of each sample (~40 mg/cm^2) is pipetted from the syringe into the chamber such that it fills the well of the disk but does not extrude when the patch is applied to the back.
- Directly apply the chambers on the patient's back, or suitable alternate location. A naïve body region, never previously exposed to the IMP, should be selected. Each panel should be applied starting at the bottom and working upwards, pressing each chamber in place and removing any air between the tape and the skin. Document the time.
- Leave the patches on for approximately 48 h.
- Mark the placement on the skin.
- Remove the patches and wipe the remaining gel.

Readings of the test will be done at the following timepoints after removing the patches:

- Approximately 30 min
- Approximately 24 – 48 h
- Approximately 72 – 120 h

Reading criteria:

The reading of the patch test reactions will be based on inspection and palpation of the morphology (erythema, infiltrate, papules, and vesicles) according to reading criteria recommended by the Guideline of the International Contact Dermatitis Research Group (49), see Table 8:

Table 8: Reading Criteria for the Patch testing according to the Guidelines of the International Contact Dermatitis Research Group (49)

Symbol	Morphology	Assessment
-	No reaction	Negative reaction
?+	Faint erythema only	Doubtful reaction
+	Erythema, infiltration, possibly papules	Weak positive reaction
++	Erythema, infiltration, papules, vesicles	Strong positive reaction
+++	Intense erythema, infiltrate, coalescing vesicles	Extreme positive reaction
IR	Various morphologies, e.g. soap effect, bulla, necrosis	Irritant reaction

Morphologically positive patch test reactions (+, ++, or +++) one day after removal, or later, are indicative of an allergic reaction. In addition, sharp-edged margins and fine wrinkling of the surface of the test area point towards irritant reactions whereas spreading beyond the application sites is indicative for a sensitization reaction.

Since vehicle and Ameluz® contain propylene glycol as an excipient, an irritant reaction is possible (see IB and (21))

Final evaluation:

Based on the readings, the investigator will evaluate the outcome of the test for each substance tested (Ameluz® or vehicle) as:

- negative (no allergy),
- equivocal, or
- positive (allergic contact dermatitis).

The date and time of patch application, the date and time of patch removal, the date and time of each reading timepoint and the final evaluation will be documented in the eCRF.