

COVER PAGE

CLINICAL STUDY PROTOCOL

Study ALA-ACV-CT014

NCT05080764

A Randomized, Double Blind, Vehicle-controlled, Multicenter Phase II Study to Evaluate the Safety and Efficacy of BF-200 ALA (Ameluz®) and BF-RhodoLED® in the Treatment of Moderate to Severe Acne Vulgaris in Adults With Photodynamic Therapy (PDT)

Document date: 09 Dec 2024

TITLE PAGE

CLINICAL STUDY PROTOCOL

A randomized, double blind, vehicle-controlled, multicenter Phase II study to evaluate the safety and efficacy of BF-200 ALA (Ameluz®) and BF-RhodoLED® in the treatment of moderate to severe Acne vulgaris in adults with photodynamic therapy (PDT).

Study number

ALA-ACV-CT014

Test Product:	BF-200 ALA (Ameluz®) [in combination with BF-RhodoLED®]
Indication:	Moderate to severe Acne vulgaris
Study Design:	Randomized, double blinded, vehicle-controlled, parallel group, multi-center
Study Identifier:	NCT05080764
IND Number:	115412
Study Phase:	Phase IIb study
Coordinating Investigator:	Mitchel P. Goldman, M.D Cosmetic Laser Dermatology 9339 Genesee Avenue, Suite 330 San Diego CA 92121 PPD
Sponsor:	Biofrontera Bioscience GmbH Hemmelrather Weg 201 51377 Leverkusen, Germany
Sponsor's Signatory:	PPD e-mail: PPD Tel.: PPD Fax: PPD
Date of issue	09-Dec-2024
Version	4.0

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

DECLARATIONS OF SPONSOR AND INVESTIGATORS

Declaration of sponsor and coordinating investigator

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

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

The investigator will be supplied with details of any significant or new findings, e. g. 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 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 the Clinical Research Organization (CRO) acting on behalf of the sponsor.

Date: _____ Signature: _____

Name (block letters): _____

Declaration of CRO Acting on behalf of sponsor

The undersigned hereby declare their consent to work in accordance with the moral, ethical, and scientific principles governing clinical research as described in the current version of the Declaration of Helsinki, and the International Council for Harmonisation guideline for Good Clinical Practice [ICH-GCP E6].

All work will be conducted according to the applicable local law(s) and regulation(s).

The undersigned confirm that they conduct the study as set out in this protocol.

CRO Representative

Date: _____ Signature: _____

Name (block letters): _____

Project Manager Clinical Trials

Date: _____ Signature: _____

Name (block letters): _____

Declaration of biostatistician

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

Company: _____

Date: _____ Signature: _____

Name (block letters): _____

1 TABLE OF CONTENTS

Declarations of sponsor and investigators.....	2
Declaration of sponsor and coordinating investigator.....	2
Declaration of investigator	3
Declaration of CRO Acting on behalf of sponsor	4
Declaration of biostatistician	5
1 Table of contents.....	6
1.1 List of in-text tables	10
1.2 List of in-text figures.....	10
2 Protocol outline.....	11
3 Abbreviations and definitions	25
4 Introduction and study rationale	28
4.1 Introduction	28
4.2 Study rationale	31
4.3 Risk-benefit analysis	31
5 Study objectives	33
5.1 Primary objective	33
5.2 Secondary objective	33
5.3 Follow-up Objective.....	35
6 Study design, duration and dates.....	35
6.1 Study design.....	35
6.2 Study duration, dates and end of study definition.....	37
7 Selection of Subjects.....	37
7.1 Number of subjects	37
7.2 Recruitment arrangements	37
7.3 Inclusion criteria.....	38
7.4 Exclusion criteria	38
7.5 Screening failures.....	41
7.6 Subjects of reproductive potential.....	41
8 Study treatment	43
8.1 Details of investigational products.....	43

8.1.1	Investigational Medicinal Products	43
8.1.2	Investigational Medical Device	44
8.2	Storage.....	45
8.3	Application of investigational medicinal products	45
8.4	Illumination with PDT lamp	46
8.5	Dosage schedule.....	47
8.6	Randomization and treatment assignment	47
8.7	Blinding, packaging, and labeling.....	48
8.7.1	Investigational Medicinal Product	48
8.7.2	Investigational Medical Device	49
8.8	Supplies and accountability	49
8.9	Compliance	50
9	Prior and concomitant medical conditions and treatments	51
9.1	Prior and concomitant medical conditions.....	51
9.2	Prior and concomitant medications/treatments	51
10	Study procedures and schedule.....	54
10.1	Description of study days.....	54
10.1.1	Visit 1/Screening (≤ 6 weeks prior to PDT-1).....	54
10.1.2	Visit 2/Baseline (PDT-1)	54
10.1.3	Phone call (1 week (± 2 days) post PDT-1).....	56
10.1.4	Visit 3 (tolerability & safety assessment, 4 (± 1) weeks post PDT-1).....	56
10.1.5	Visit 4a (tolerability & safety assessment, 8 (± 1) weeks post PDT-1), Final Visit.....	57
10.1.6	Phone call 2 (1 week (± 2 days) post PDT-2).....	58
10.1.7	Visit 4b (tolerability & safety assessment, 4 (± 1) weeks post PDT-2).....	58
10.1.8	Visit 5a (tolerability & safety assessment, 8 (± 1) weeks post PDT-2), Final Visit.....	59
10.1.9	Phone call 3 (1 week (± 2 days) post PDT-3).....	60
10.1.10	Visit 5b (tolerability & safety assessment, 4 (± 1) weeks post PDT-3).....	60
10.1.11	Visit 6 (tolerability & safety assessment, 8 (± 1) weeks post-PDT-3), Final Visit	60
10.2	Assessments	61
10.2.1	Evaluation of demographic data	61
10.2.2	Body Measures	61
10.2.3	Clinical criteria for diagnosis of acne vulgaris	61
10.2.4	Assessment of skin type.....	63
10.2.5	Acne scar assessment.....	63
10.2.6	Assessment of esthetic appearance and of subject satisfaction	64
10.2.7	Safety	65
11	Adverse events	68
11.1	Definitions.....	68

11.1.1	Adverse events	68
11.1.2	Serious adverse events	69
11.1.3	Alert terms and other reasons for expedited reporting to Pharmacovigilance...	70
11.1.4	Investigational medicinal product complaints	70
11.1.5	Investigational medical device complaints	70
11.2	Period of AE collection	70
11.3	Documentation and reporting of adverse events by investigator	71
11.3.1	Immediate Reporting	73
11.3.2	Unblinding	74
11.4	Documentation and reporting of adverse events by sponsor/ CRO	74
11.4.1	Determination of expectedness, Reference Safety Information	74
11.4.2	Reporting of SUSARs and USADEs to competent authorities and investigators by sponsor	75
11.4.3	Periodic reporting of adverse events by sponsor	75
11.5	Continuous risk assessment.....	75
12	Withdrawals.....	76
12.1	Withdrawal of subjects.....	76
12.2	Replacement of subjects.....	76
12.3	Withdrawal of samples.....	76
12.4	Withdrawal of pictures	76
13	Emergency procedures	77
13.1	Emergency CRO contact.....	77
13.2	Emergency identification of investigational medicinal products.....	77
13.3	Emergency treatment	77
14	Statistical procedures	78
14.1	General considerations	78
14.2	Analysis variables	79
14.3	Analysis sets.....	81
14.4	Estimands	82
14.5	Handling of missing data	84
14.5.1	Handling of photos with insufficient quality/missing analysis by Canfield algorithm	84
14.6	Statistical methods	84
14.6.1	Disposition of subjects and exposure.....	84
14.6.2	Demographic and background characteristics	84
14.6.3	Evaluation of the Co-Primary Efficacy Endpoints	85
14.6.4	Safety analysis	85
14.7	Interim analysis	86

14.8	Sample size justification	86
14.9	Major Protocol Deviations	87
15	Ethical and legal aspects	89
15.1	Good clinical practice	89
15.2	Delegation of investigator duties	89
15.3	Subject information, informed consent and HIPAA form	89
15.4	Confidentiality	90
15.5	Protocol deviations.....	90
15.6	Protocol amendments	90
15.7	Approval of the clinical study protocol and amendments.....	90
15.8	Ongoing information for the institutional review board	91
15.9	Closure of the study	91
15.10	Record retention	91
15.11	Liability and insurance	92
15.12	Financial disclosure.....	92
16	Quality control, quality assurance, and inspections.....	93
16.1	Study monitoring and source data verification	93
16.2	Site audits	93
16.3	Site Inspections	93
17	Documentation and use of study findings	94
17.1	Documentation of study findings	94
17.2	Use of study findings	94
	References	96
18	Appendices	100
18.1	APPENDIX A	101
18.2	APPENDIX B	104

1.1 List of in-text tables

Table 1: Study schedule	22
Table 2: Composition and manufacturer of study medication	43
Table 3: Key parameters of PDT lamp used	45
Table 4: List of forbidden concomitant medication with designated time periods.....	52
Table 5: Investigator's Global Assessment (IGA) severity 5 scale of acne vulgaris severity	62
Table 6: Modified Investigator's Global Assessment (mIGA) severity 5 scale of acne vulgaris severity – excluding comedones	62

1.2 List of in-text figures

Figure 1: Summary of study visits for responders and non-responders.	37
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2 PROTOCOL OUTLINE

Title A randomized, double blind, vehicle-controlled, multicenter Phase II study to evaluate the safety and efficacy of BF-200 ALA (Ameluz®) and BF-RhodoLED® in the treatment of moderate to severe Acne vulgaris in adults with photodynamic therapy (PDT).	
Study no: ALA-ACV-CT014	Clinical Phase: IIb
Study Design This is a Phase IIb, multicenter, randomized, parallel group, double blind study comparing BF-200 ALA with two incubation times with vehicle. Each subject will receive either BF-200 ALA or vehicle treatment for inter-individual comparison. Subjects will be randomized at a ratio of 2:2:1:1 to BF-200 ALA (1 hour incubation), BF-200 ALA (3 hours incubation), vehicle (1 hour incubation), and vehicle (3 hours incubation). The study will be conducted in a double blind (with respect to vehicle) manner.	
Investigators / study sites Multiple sites in the United States of America (US) will participate in this study. Each site should randomize between 12 and 24 subjects. No site should enroll more than 24 subjects unless prior approval of the sponsor is obtained. The maximum number should not exceed 36 subjects.	
Number of subjects It is planned to randomize 126 subjects to either BF-200 ALA or vehicle.	
Definitions • “illumination area” is the area effectively illuminated by one BF-RhodoLED® lamp • “treatment field” is the part of the skin to which IMP was applied	
Investigational products (IP) Investigational medicinal product (IMP) BF-200 ALA or placebo to BF-200 ALA (vehicle). BF-200 ALA is a gel formulation of 7.8% 5-aminolevulinic acid (ALA), corresponding to 10% ALA hydrochloride. It is Food and Drug Administration (FDA)-approved and marketed in the US as Ameluz® for the lesion-directed and field-directed treatment of actinic keratoses (AK) of mild to moderate severity on the face and scalp, as a combination product with BF-RhodoLED® lamp. The vehicle is indistinguishable from BF-200 ALA by appearance, texture or smell and contains all other ingredients except the active ingredient ALA. The IMP will be packed in tubes, containing 2 g each. Investigational medical device (IMD) The study treatment requires illumination of the treatment field with a BF-RhodoLED® lamp (red light with emission at ~635 nm, ~37 J/cm²). Please refer to the BF-RhodoLED® user manual for detailed lamp operating and safety instructions.	

Subjects and lesions

Subjects of all sexes and age 16 years and older, assigned to Fitzpatrick skin type I to VI, will be randomized.

Disease severity will be determined by (i) grading according to a 5-point Investigator Global Assessment (IGA) and modified IGA rating score (mIGA) and (ii) lesion counting. The results from these two investigator-based assessments will be the basis for the determination of subject eligibility and the calculation of the primary endpoint.

To be eligible, subjects should have an IGA of 3 (moderate) or 4 (severe) at screening (Visit 1). In addition, subjects must have at least 20 inflammatory and at least 20 non-inflammatory lesions on the face. The amount of nodular inflammatory lesions is limited to a maximum number of three. The eligibility (including IGA scores and lesion count) must be reconfirmed at Visit 2 by the investigator prior to randomization of the subject.

The acne severity, including lesion count and determination of IGA/mIGA scores, is assessed by the investigator at each study visit.

Investigator's Global Assessment (IGA) of acne vulgaris severity		
0	'Clear'	No acne lesions present. Residual hyperpigmentation and erythema may be present
1	'Almost clear'	A few scattered comedones and a few small papules
2	'Mild'	Easily recognizable; less than half the face is involved. Some comedones and some papules and pustules
3	'Moderate'	More than half the face is involved. Many comedones, papules and pustules. One nodule may be present
4	'Severe'	Entire face is involved, covered with comedones, numerous papules and pustules, and few nodules and cysts

Modified Investigator's Global Assessment (mIGA) severity 5 scale of acne vulgaris severity – excluding comedones:

Modified Investigator's Global Assessment (mIGA) severity 5 scale of acne vulgaris severity – excluding comedones		
0	'Clear'	Residual hyperpigmentation and erythema may be present (comedones not considered)
1	'Almost clear'	A few small papules (comedones not considered)
2	'Mild'	Easily recognizable; less than half the face is involved. Some papules and pustules (comedones not considered)
3	'Moderate'	More than half the face is involved. Many papules and pustules. One nodule may be present (comedones not considered)
4	'Severe'	Entire face is involved, covered with numerous papules and pustules, and few nodules and cysts (comedones not considered)

Study Duration and Dates

Duration of the study per subject: up to 17 weeks (1 PDT), up to 22 weeks (2 PDTs) or up to 27 weeks (3 PDTs) including an additional delay due to dosing day exclusion criteria and allowed ranges in the visit timelines.

Within 6 weeks after the screening visit (Visit 1) and following confirmation of eligibility, subjects will be randomized and receive PDT-1 (Visit 2).

At Visit 3, 4 weeks after PDT-1, the investigator will determine the subject's status. Subjects with no remaining inflammatory lesions (i.e. Responders) at Visit 3 do not receive further treatment and continue with Visit 4a, 8 weeks after PDT-1 for final safety and efficacy assessments.

Subjects with at least one remaining inflammatory lesion (i.e. Non-Responders) at Visit 3 receive PDT-2 during the visit and continue the study with Visit 4b. At Visit 4b, 4 weeks after Visit 3/PDT-2, the investigator will determine the subjects status. Responders at Visit 4b do not receive further treatment and continue with Visit 5a, 8 weeks after PDT-2 for final safety and efficacy assessments.

Non-responders at Visit 4b receive PDT-3 during the visit and will be re-assessed 4 and 8 weeks after PDT-3 (Visit 5b and Visit 6, respectively).

Phone calls will be performed 1 week after each PDT to assess subject's well-being, including transient application site effects.

End of study (EoS) is defined as database lock.

Sample size calculation

It is planned to randomize approximately 126 subjects with a ratio of 2:2:1:1 to BF-200 ALA (1 hour incubation), BF-200 ALA (3 hours incubation), vehicle (1 hour incubation), and vehicle (3 hours incubation). Statistical testing will be applied to compare both active treatment groups vs. vehicle.

This sample size will ensure a power of 80% with an alpha level set to 5% ($\alpha = 0.05$) using a one-sided Wilcoxon rank-sum test to demonstrate statistically significant superiority in the co-primary endpoint (1) "Relative change in the number of inflammatory lesions (percent change from baseline)", and a one-sided Fisher's Exact Test to demonstrate statistically significant superiority in the co-primary endpoint (2) "Treatment success defined by a minimum improvement of the mIGA score by 2 assessed 8 weeks after the last PDT and resulting in an mIGA score of 0 (clear) or 1 (almost clear)" in the full analysis set (FAS).

The power calculation assumes a relative change in the number of inflammatory lesions of 50 for BF-200 ALA, 20 for vehicle, and clearance rates of 75% for BF-200 ALA, and 40% for vehicle, respectively, 8 weeks after the last PDT. The sample size includes 12% non-evaluable responses.

Main in-/exclusion criteria

Inclusion criteria

1. Willingness and ability of the subject to provide informed consent and to sign the Health Insurance Portability and Accountability Act (HIPAA) form. A study-specific informed consent and HIPAA form must be obtained in writing prior to starting any

study procedures. Minors under 18 years of age must be accompanied by the parent(s) or legal guardian(s) at the time of consent signing. The parent(s) or legal guardian(s) must also provide informed consent/HIPAA for the subject.

2. Subjects with moderate to severe acne on the face (IGA ≥ 3).
3. Presence of ≥ 20 inflammatory and ≥ 20 non-inflammatory (open and closed comedones) Acne vulgaris lesions on the face (should be located within not more than 2 illumination areas) as assessed by investigator.
4. All sexes, ≥ 16 years of age.
5. Willingness and ability to comply with study procedures, particularly willingness to receive up to 3 PDTs within 8 to 10 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 topical facial treatments other than medical cleansers (i.e. face washes etc.) at least 14 days prior to randomization visit (Visit 2, baseline) and discontinue medical cleansers in the face at least 1 week prior to randomization visit (Visit 2, baseline) and thereafter until the end of study (use of soap is allowed but the product used should not be changed during the study).
8. Females of reproductive potential must have a negative serum pregnancy test and must use an adequate and highly effective or two effective methods of contraception throughout the study. (If hormonal contraception is used, the same product and dose should be taken for at least 6 months before the first treatment and throughout the entire study.)

Exclusion criteria:

1. Any known history of hypersensitivity to ALA, porphyrins or excipients of BF-200 ALA.
2. History of soy or peanut allergy.
3. Subjects with sunburn or other possible confounding skin conditions (e.g. wounds, irritations, bleeding or skin infections) within or in close proximity (< 5 cm distance) to treatment field. (Reassessment of subjects is allowed once if the sunburn or other confounding skin conditions is/are expected to resolve within the screening period. Reassessment can be done on the day of the actual treatment.)
4. Clinical diagnosis of atopic dermatitis and other cutaneous conditions (e.g. lupus erythematosus), Bowen's disease, BCC, eczema, psoriasis, acne conglobate, acne fulminans, or secondary acne (steroid-induced acne, perioral dermatitis, acne rosacea), squamous cell carcinoma, other malignant or benign tumors in the treatment field.
5. 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
6. Beard or other facial hair that might interfere with the study assessments unless subject agrees to be clean-shaven throughout the entire study period. (Reassessment of subjects is allowed once if assessment of acne lesions is impaired by facial hair at screening. Reassessment can be performed on the day of the actual treatment.).
7. Facial procedures such as dermabrasion, chemical or laser peels as well as exposure to UV radiation (other than sunlight) at least 4 weeks prior to randomization visit (Visit 2, baseline).
8. Presence of strong artificial pigmentation (e.g. tattoos) or any other abnormality that may impact lesion assessment or light penetration in the treatment field.
9. Suspicion of drug or alcohol abuse.
10. Any topical medication of the skin prior to screening as defined below:
- a. Topical treatment with ALA or ALA-esters (e.g. MAL) or an investigational drug in- and outside the treatment field within 8 weeks prior to screening.
 - b. Topical treatment with immunosuppressive, cytostatic or cytotoxic drugs inside the treatment field within 8 weeks prior to screening.
 - c. Start of a regular and continuous topical administration of medication with hypericin or other drugs with phototoxic or photoallergic potential inside the treatment field within 4 weeks prior to screening. Subjects may, however, be eligible if such medication was regularly applied for more than 4 weeks prior to screening visit without evidence of an actual phototoxic/photoallergic reaction or if such medication is only administered for a limited time (e.g. an antibiotic).
11. Any use of the below specified systemic treatments within the designated periods:
- a. Systemic acne therapy (oral antibiotics within 8 weeks or oral isotretinoin within 6 months or start with hormonal therapy for acne within 6 months prior to Visit 2).
 - b. Use of cytotoxic or cytostatic drugs within 6 months, or immunosuppressive therapies or use of ALA or ALA-esters (e.g. MAL) within 12 weeks, investigational drugs or drugs known to have major organ toxicity within 8 weeks, interferon or glucocorticosteroids (oral or injectable) within 6 weeks prior to screening.

- c. Start of long-term intake of medication with hypericin or systemically acting drugs with phototoxic or photoallergic potential within 8 weeks prior to screening. Subjects may, however, be screened and randomized if such medication was taken in or was regularly applied for more than 8 weeks prior to screening visit without evidence of an actual phototoxic/photoallergic reaction or if such a drug is only used for a limited time (e.g. an antibiotic).

- 12. Breast feeding women.
- 13. Subject 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.
- 14. Prior randomization in the study.
- 15. A member of study site staff or sponsor staff directly involved in the conduct of the protocol or a close relative thereof.
- 16. Simultaneous participation in a further clinical study.
- 17. Four or more nodular acne lesions in the face.
- 18. Unwillingness or inability to limit sun exposure for 48 hours post PDT treatment.

Re-assessment of subjects is allowed once in case exclusion criterion 3, 6 and/or 7 is met, and eligibility can be achieved within 2 weeks.

Dosing day exclusion criteria

- 1. Febrile or infectious disease within 7 days prior to PDT visits.
- 2. Subjects with sunburn, wounds, irritations, bleeding or other confounding skin conditions within illumination areas at PDT visits.
- 3. Application of topical glucocorticosteroids in- and outside the treatment field within 7 days prior to PDT visits.
- 4. Administration of (topical or systemic) medication with phototoxic/photoallergic potential for a limited time. After discontinuing the medication, a wash out period of the medications 5-fold half-life time should be applied prior to the next PDT.

In case a subject meets any dosing day exclusion criteria at a PDT visit (V2, V3 & V4b), this visit can be rescheduled once at the earliest possibility after resolution, but rescheduling should not exceed 2 weeks.

Treatment

Subjects will be randomized for treatment with PDT to vehicle (control group) or BF-200 ALA (Ameluz[®], test group) and the respective incubation time of either 1 or 3 hours. The randomization ratio will be 2:2:1:1 to BF-200 ALA (1 hour incubation), BF-200 ALA (3 hours incubation), vehicle (1 hour incubation), and vehicle (3 hours incubation). Thus, the chance of receiving verum will be ~66%. The IMP is packed in tubes, each containing 2 g gel. A pack of 3 tubes will be assigned to each subject to allow a maximum of 3 PDTs. For each PDT, the content of approximately 1 tube should be homogenously applied as a thin layer to the whole face, excluding the periocular area.

The treatment field will be vigorously cleansed with gauze soaked with ethanol or isopropanol for approximately 2 minutes to remove skin oils and is thereby lightly exfoliated. Care should be taken to avoid bleeding.

After this preparation, study medication will be homogenously applied as a thin layer to the treatment field. The application will be performed using glove-protected fingertips or a spatula. Care should be taken to avoid that the study medication is applied to the periocular area of 1 cm below the eyes or the area between the eyes and eyebrows including upper eyelid. The treatment field shall be such that it can be illuminated in two sessions.

After drug application, the subject should stay inside for 1 h + 5 min or 3 h + 10 min, respectively. Thereafter, any remnants of the IMP will be removed, and a 10 min illumination will be administered using the light emitting diode (LED) red light device BF-RhodoLED[®] according to the lamp's user manual. If two illumination sessions are performed consecutively, IMP should be applied to these regions with a 15 min time interval in order to ensure similar incubation times. Two additional PDTs may be conducted on a 4-week schedule if any inflammatory acne lesions remain until Visit 4b (according to investigator assessment).

Primary and main secondary objectives

The primary objective of the study is to compare the efficacy of BF-200 ALA PDT (containing 7.8% 5-aminolevulinic acid (ALA) as active ingredient) with vehicle PDT, utilizing BF-RhodoLED[®] illumination, in the treatment of moderate to severe Acne vulgaris on the face.

If not otherwise stated, the following endpoint calculations will be conducted based on the assessments performed by the investigator.

The co-primary efficacy variables are:

1. Relative change in the number of inflammatory lesions (percentage change from baseline) 8 weeks after the last PDT as assessed by investigator.
2. Treatment success defined by a minimum improvement of the mIGA score by at least 2 assessed 8 weeks after the last PDT and resulting in an mIGA score of 0 (clear) or 1 (almost clear).

The co-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) use or change of cleansers and soaps, c) refusal of 2nd or 3rd PDT treatment due to pain, d) any other type of treatment discontinuation, or e) postponement of 2nd or 3rd PDT.

The secondary objective of the study is to evaluate the safety and secondary efficacy parameters related to BF-200 ALA/BF-RhodoLED® PDT for the treatment of moderate to severe Acne vulgaris.

Secondary efficacy variables:

1. Absolute and/or percentage change from baseline in the number of lesions as assessed by investigator:
 - a. Inflammatory lesions – 4 weeks after the last PDT
 - b. Inflammatory lesions – 8 weeks after the last PDT
 - c. Non-inflammatory lesions – 4 weeks after the last PDT
 - d. Non-inflammatory lesions – 8 weeks after the last PDT
 - e. Inflammatory & non-inflammatory lesions – 4 weeks after the last PDT
 - f. Inflammatory & non-inflammatory lesions – 8 weeks after the last PDT
2. Absolute and percentage change from baseline in the number of lesions as assessed by investigator:
 - a. Inflammatory lesions – 4 weeks after PDT-1
 - b. Non-inflammatory lesions – 4 weeks after PDT-1
 - c. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-1
 - d. Inflammatory lesions – 4 weeks after PDT-2
 - e. Non-inflammatory lesions – 4 weeks after PDT-2
 - f. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-2
 - g. Inflammatory lesions – 4 weeks after PDT-3
 - h. Non-inflammatory lesions – 4 weeks after PDT-3
 - i. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-3
 - j. Inflammatory lesions – 8 weeks after PDT-3
 - k. Non-inflammatory lesions – 8 weeks after PDT-3
 - l. Inflammatory & non-inflammatory lesions – 8 weeks after PDT-3
3. Absolute and percentage change from baseline in the number of lesions as assessed by investigator, only for responders at Visit 3 /4 weeks after PDT-1:
 - a. Inflammatory lesions – 4 weeks after PDT-1
 - b. Inflammatory lesions – 8 weeks after PDT-1
 - c. Non-Inflammatory lesions – 4 weeks after PDT-1
 - d. Non-Inflammatory lesions – 8 weeks after PDT-1
 - e. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-1
 - f. Inflammatory & non-inflammatory lesions – 8 weeks after PDT-1
4. Absolute and percentage change from baseline in the number of lesions as assessed by investigator, only for responders at Visit 4b /4 weeks after PDT-2:
 - a. Inflammatory lesions – 4 weeks after PDT-2
 - b. Inflammatory lesions – 8 weeks after PDT-2
 - c. Non-Inflammatory lesions – 4 weeks after PDT-2
 - d. Non-Inflammatory lesions – 8 weeks after PDT-2
 - e. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-2
 - f. Inflammatory & non-inflammatory lesions – 8 weeks after PDT-2

5. Absolute and percentage change from baseline in the number of lesions as assessed by investigator, only for responders at Visit 5b /4 weeks after PDT-3
 - a. Inflammatory lesions – 4 weeks after PDT-3
 - b. Inflammatory lesions – 8 weeks after PDT-3
 - c. Non-Inflammatory lesions – 4 weeks after PDT-3
 - d. Non-Inflammatory lesions – 8 weeks after PDT-3
 - e. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-3
 - f. Inflammatory & non-inflammatory lesions – 8 weeks after PDT-3
6. Change in the number of nodules & cysts 8 weeks after the last PDT (absolute change and percentage change from baseline) as assessed by investigator.
7. Treatment success defined by a minimum improvement of the IGA by at least 2, 8 weeks after the last PDT.
8. Improvement of the IGA, 8 weeks after the last PDT.
9. Improvement of the mIGA, 8 weeks after the last PDT.
10. Improvement of scar severity and overall esthetic appearance 8 weeks after last PDT (assessed by investigator).
11. Subject satisfaction regarding esthetic outcome and treatment, 8 weeks after the last PDT.

Safety variables

Safety analysis variables include:

1. Frequency and severity of adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESI) and treatment-emergent adverse events (TEAEs). TEAEs are defined as all AEs with onset after first treatment with IMP up to the last visit of the subject (approximately 8 weeks post last PDT).
2. Application site skin reactions assessed by the investigators.
3. Application site discomfort reported by the subjects.
4. Pain during illumination, reported by the subjects (pain will be assessed on an 11-point numeric rating scale).
5. Vital signs data.
6. Safety laboratory data.
7. Physical examinations data.

Exploratory variables

1. Change in the number of inflammatory and/or non-inflammatory lesions (absolute change and/or percentage change from baseline) as assessed by the Canfield algorithm for:
 - a. Inflammatory lesions – 8 weeks after the last PDT
 - b. Non-inflammatory lesions – 8 weeks after the last PDT
 - c. Inflammatory & non-inflammatory lesions – 8 weeks after the last PDT
2. Treatment success defined by a minimum improvement of the PAS equivalent to an improvement of IGA by at least 2, assessed by the Canfield algorithm 8 weeks after the last PDT.
3. Treatment success defined by a minimum improvement of the mPAS equivalent to

an improvement of mIGA by at least 2, assessed by the Canfield algorithm 8 weeks after the last PDT.

Statistics

Statistical testing will be applied to compare both active treatment groups (incubation times 1 or 3 hours) vs. vehicle (both incubation times combined). Confirmatory hypothesis tests will be performed for the 2 co-primary endpoints, comparing 3 h incubation time BF-200 ALA vs. vehicle and 1 h incubation time BF-200 ALA vs. vehicle. The pairwise comparison will always start with the 3 h BF-200 ALA vs. vehicle comparison followed by 1 h BF-200 ALA vs. vehicle comparison. A hierarchical testing procedure will be used to ensure the family-wise error rate. Due to the Phase II type of this study, a one-sided significance level of 5% ($\alpha=0.05$) will be used.

The co-primary efficacy variables will be tested for the following hypotheses:

Relative change in the number of inflammatory lesions:

The first co-primary null hypothesis (H_{01} , one-sided) is that the relative change in the number of inflammatory lesions (percentage change from baseline taken at Visit 2) assessed 8 weeks after the last PDT in subjects treated with BF-200 ALA is not superior to subjects treated with vehicle. The first co-primary alternative hypothesis (H_{11} , one-sided) is that the relative change in the number of inflammatory lesions for subjects treated with BF-200 ALA is superior to subjects treated with vehicle. Two one-sided Wilcoxon rank-sum tests will be used to test the first co-primary hypothesis on a significance level of 5% ($\alpha=0.05$).

Improvement of mIGA:

The second co-primary null hypothesis (H_{02} , one-sided) is that BF-200 ALA is not superior to subjects treated with vehicle with respect to the success rate. Success is defined as at least a 2-grade improvement in the mIGA score, assessed 8 weeks after the last PDT, and resulting in an mIGA score of 0 (clear) or 1 (almost clear). The second co-primary alternative hypothesis (H_{12} , one-sided) is that the success rates for subjects treated with BF-200 ALA are superior to subjects treated with vehicle. Two one-sided Fisher's exact tests will be used to test the secondary co-primary hypothesis on a significance level of 5% ($\alpha=0.05$).

The primary analysis will be performed on the FAS dataset. The analysis will be repeated as supplementary analysis for the PPS dataset.

Secondary efficacy variables:

Secondary efficacy variables will be analyzed in an exploratory way. Where appropriate, secondary endpoints will be analyzed with two-sided statistical testing procedures using a significance level of 10% ($\alpha=0.1$). The analyses on secondary efficacy endpoints will be performed on the FAS dataset. Secondary endpoints 1 and 7 will also be analyzed on the PPS dataset.

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

Exploratory endpoints will be analyzed on all subjects from the FAS for whom corresponding data was collected.

Schedule - study overview

within 6 weeks prior to PDT-1 (Visit 1)	PDT-1 (baseline) (Visit 2)	1 week after PDT-1 <Phone>	4 weeks after PDT-1 (Visit 3)	8 weeks after PDT-1 (Visit 4a)
Screening	Randomization	Safety evaluation	Evaluation	Final Evaluation
	PDT-1		If number of inflammatory lesions = 0, the subject should be evaluated at 8 weeks post PDT-1 without 2 nd PDT	

If number of inflammatory lesions > 0,
the subject should receive 2nd PDT

PDT-2

PDT-2 (Visit 3)	1 week after PDT-2 <Phone>	4 weeks after PDT-2 (Visit 4b)	8 weeks after PDT-2 (Visit 5a)
PDT-2	Safety evaluation	Evaluation	Final Evaluation
		If number of inflammatory lesions = 0, the subject should be evaluated at 8 weeks post PDT-2 without 3 rd PDT	

If number of inflammatory lesions > 0,
the subject should receive 3rd PDT

PDT-3

PDT-3 (Visit 4b)	1 week after PDT-3 <Phone>	4 weeks after PDT-3 (Visit 5b)	8 weeks after PDT-3 (Visit 6)
PDT-3	Safety evaluation	Evaluation	Final Evaluation

Table 1: Study schedule

Assessment or activity	All subjects			Responder ^h after PDT-1		Non-responder ⁱ after PDT-1		Responder ^h after PDT-2		Non-responder ⁱ after PDT-2		All subjects that underwent PDT-3	
	Screening	PDT-1	Phone call 1	Clinic visits		PDT-2	Phone call 2	Clinic visits		PDT-3	Phone call 3	Clinic visits	
	Visit 1 (≤ 6 weeks prior to PDT-1)	Visit 2 (Baseline)	(1 week ± 2 days post- PDT- 1)	Visit 3 (4 weeks ± 1 week post- PDT-1)	Visit 4a (8 weeks ± 1 week post- PDT-1)	Visit 3 (4 weeks ± 1 week post-PDT- 1)	(1 week ± 2 days post- PDT-2)	Visit 4b (4 weeks ± 1 week post- PDT-2)	Visit 5a (8 weeks ± 1 week post- PDT-2)	Visit 4b (4 weeks ± 1 week post- PDT-2)	(1 week ± 2 days post- PDT-3)	Visit 5b (4 weeks ± 1 week post- PDT-3)	Visit 6 (8 weeks ± 1 week post- PDT-3)
Clinical visit *	X	X		X	X	X		X	X	X		X	X
Informed Consent/ HIPAA form	X												
Assign subject number	X												
Demographics	X												
Body measures	X												
Skin type assessment ^a	X												
Relevant medical history	X												
Inclusion / exclusion criteria ^b	X ^b	X ^b											
Randomization		X											
Clinical assessment of acne severity (IGA and mIGA, lesion counts (numbers of inflammatory and non- inflammatory lesions, cysts, nodules)) and acne scars ^c by investigator	X ^c	X ^c		X	X ^c	X		X	X ^c	X		X	X ^c
Generation of pictures with Canfield Visia-CR for centralized assessment by Canfield algorithm and	X	X		X	X	X		X	X	X		X	X

independent evaluator, if applicable													
Evaluation of dosing day criteria ^d and preparation of treatment field, application of IMP and illumination		X ^d				X ^d				X ^d			
Record date and time of study drug application and removal and illumination		X				X				X			
Confirm time of exposure, maximal light intensity, and distance between illumination source and treated lesions		X				X				X			
Application site skin reactions and discomfort during PDT		X				X				X			
Assessment of application site pain during illumination via 11-point pain questionnaire (NRS-11)		X				X				X			
Assessment of esthetic appearance by investigator and esthetic outcome and satisfaction with PDT by subject (by subject questionnaire)					X				X				X
General physical examination	X				X				X				X
Vital signs (HR, BP)	X	X		X	X	X		X	X	X		X	X
Clinical laboratory tests	X				X				X				X
Serum pregnancy test ^e	X				X				X				X
Urine pregnancy test ^{e,f}		X				X				X			
(S)AEs including application site reactions ^g	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/treatment and facial care products	X	X	X	X	X	X	X	X	X	X	X	X	X

Investigator will instruct subject about restrictions of precautions and medications prior and after PDT	X	X	X			X	X			X			
^a Skin type will be evaluated according to Fitzpatrick criteria (Fitzpatrick 1988) ^b Re-assessment of subjects is allowed once in case exclusion criterion 3, 6 and/or 7 is met, and eligibility can be achieved within 2 weeks. ^c Scar assessment at screening, baseline and 8 weeks after last PDT at the final Visit (Visit 4a, 5a, or 6) by the investigator. ^d In case a subject meets any dosing day exclusion criteria, this visit can be rescheduled once at the earliest possibility after resolution, but rescheduling should not exceed 2 weeks. ^e All female participants of reproductive potential will undergo a pregnancy test. ^f If positive, an additional serum test is possible. ^g In the context of this study, any adverse reactions arising from the IMP and/or medical device will be referred to as adverse events and will be documented as such. ^h Responders in terms of decision making regarding an additional PDT are defined as subjects with all inflammatory lesions cleared at Visit 3 or Visit 4b. ⁱ Non-responders are defined as subjects with remaining inflammatory lesion(s) at Visit 3 or at Visit 4b. These subjects will receive a second PDT at Visit 3 and depending on the lesion clearance a third PDT at Visit 4b. * Unscheduled visits may be performed for safety reasons.													

3 ABBREVIATIONS AND DEFINITIONS

β-hCG	β-human chorionic gonadotropin
ACV	Acne Vulgaris
ADE	Adverse device event
AE	Adverse event
AESI	Adverse Event of Special Interest
ALA	5-aminolevulinic acid
AK	Actinic keratosis
ALT	Alanine aminotransferase
AP	Alkaline phosphatase
ASS	Acetylsalicylic acid
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
BCC	Basal cell carcinoma
BF	Biofrontera
BF-200 ALA	Nanoemulsion gel formulation containing 7.8% ALA (development name for Ameluz®)
BF-RhodoLED®	PDT lamp
BP	Blood pressure
CA	California
C. acnes	Cutibacterium acnes
CFR	Code of Federal Regulations
cm	Centimeter(s)
CPIII	coproporphyrin III
CS	Clinically significant
CSP	Clinical Study Protocol
DSUR	Development safety update report
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EoS	End of Study
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
g	Gram(s)
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase
GmbH	Gesellschaft mit beschränkter Haftung, Ltd, limited liability company
GMP	Good manufacturing practice
h	Hour(s)
HCl	Hydrochloride

HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICE	Intercurrent events
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
(m)IGA	(modified) Investigator Global Assessment
Illumination area	Area effectively illuminated by one BF-RhodoLED®. One illumination area should cover approximately half of the face.
IMD	Investigational medical device
IMP	Investigational medicinal product
IND	Investigational New Drug
IP	Investigational Products
IPL	Intense pulsed laser
IRB	Institutional Review Board
ISF	Investigator Site File
J	Joule
LDH	Lactate dehydrogenase
LED	Light emitting diode
LSLV	Last Subject Last Visit
Ltd	Limited
MAL	Methyl-aminolevulinic acid
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
min	Minutes
mW	Milliwatt
NCS	Non-clinically significant
NCT	ClinicalTrials.gov registry number
NDA	New Drug Application
nm	Nanometer
Non-Responder	Non-Responders are defined as subjects with at least one remaining inflammatory lesion at Visit 3 or at Visit 4b.
NRS-11	11-point numeric rating scale
NSAID	Non-steroidal anti-inflammatory drug
(m)PAS	(modified) Parametric Acne Score (1)
pH	pH-value (grade of acidity)
PDT	Photodynamic therapy
PI	Prescribing Information
PpIX	Protoporphyrin IX
PPS	Per Protocol Set
PSU	Pilosebaceous unit
QPPV	Qualified Person for Pharmacovigilance

Responder	Responders are defined as subjects with no remaining inflammatory lesions at Visit 3 or at Visit 4b.
ROS	Reactive oxygen species
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SD	Standard deviation
SOP	Standard Operating Procedure
SUSAR	Suspected unexpected serious adverse reaction, equivalent to serious and unexpected suspected adverse reactions
TEAE	Treatment-emergent adverse event
TLR	Toll-like receptor
TMF	Trial Master File
Treatment field	Part of skin to which investigational product is applied, and which lies within the illumination areas
US, USA	United States (of America)
USADE	Unanticipated serious adverse device effect
UV	Ultraviolet
WBC	White blood cells (leukocyte count)
WHO	World Health Organization
WMA	World Medical Association

4 INTRODUCTION AND STUDY RATIONALE

4.1 Introduction

Acne vulgaris, commonly referred to as acne, is a common chronic inflammatory skin disease affecting nearly all adolescents and occasionally persists into adulthood (2). Acne, especially of moderate and severe intensity, often causes physical and psychological disturbances such as permanent scarring, psychological distress, decreased self-esteem, anxiety and depression (3–5). In 2015, it affected approximately 9.4% of the global population (6) and affects subjects with different racial/ethnic backgrounds (7). In the US, 40-50 million individuals suffer from this disease, with an 85% prevalence rate in those aged 12-24 years (8,9). The pathogenesis of acne is multi-factorial. Key factors are follicular hyperkeratosis, increased sebum production, microbial hyper-colonization of *Cutibacterium acnes* (*C. acnes*, formerly *Propionibacterium acnes*) and a complex inflammatory occurrence with participation of acquired and inherited immune defense (2,4,10,11). Neuroendocrine regulation, dietary and genetic factors also play a role in the development of acne. The pilosebaceous unit (PSU), consisting of hair follicle, sebaceous gland, erector pili muscles, a simple hair and the opening of the follicle to the skin surface (“pore”) (4,12,13), is also affected. These units are highly concentrated on the face, back and chest and thus, these body regions are the most prominent areas affected by acne (4,14). Acne is characterized by the formation of inflammatory (erythematous papules and pustules, nodules or cysts) and non-inflammatory (open and closed comedones, also called white- and blackheads) lesions (15–17). Several types of acne are known including acne vulgaris (4,10), but, to date, no standardized scales for grading acne severity exist. In 1990, the American Academy of Dermatology developed a classification system for primary acne vulgaris based on number, type and severity of lesions. This grading scale delineates 3 stages: mild, moderate and severe (18). Subjects with mild acne have few to several papules and pustules, but no nodules. Thus, a mild case of acne is primarily non-inflammatory and consists mainly of comedones. Moderate acne is characterized by the presence of several to many papules and pustules and a few to several nodules. Numerous or extensive papules and pustules, as well as many nodules are observed in severe acne (18). Accordingly, inflammatory lesions are observed in moderate and severe forms of acne. Acne is also classified by type of subsequent lesion: comedonal, papulopustular, and nodulocystic (18). Pustules and cysts are considered inflammatory acne. Furthermore, various individually defined Investigator Global Assessments (IGAs) are used for the classification of acne severity (19,20).

Treatment options for acne must be individualized taking into account previous therapies, acne severity, subject distress, compliance, and severity of scarring. Treatment options for acne include topical and systemic agents, physical therapies (light- and laser-based therapies) and PDT (2,4,21). Several studies indicate PDT as an emerging treatment option for acne (2,22) which is used to treat cutaneous neoplasms and non-neoplastic lesions.

Three components are required: a photosensitizer, light with a sufficient amount of energy at suitable wavelengths and oxygen.

In contrast to nonmelanoma skin cancer, the exact mechanisms by which PDT is effective against acne are still unclear. It is merely known that porphyrins accumulate into the

epidermis, hair follicles and selectively into the sebaceous glands (2,23). Further mechanisms suggest bacterial killing (*C. acnes*) which accumulate porphyrins in the presence of ALA, the downregulation of Toll-like receptors (TLR-2, TLR-4) in the sebaceous glands that trigger inflammation to bacteria, apoptosis of sebocytes, apoptotic phototoxic damage of sebaceous glands and increased keratinocyte shedding in the PSUs (16,22,24). Several studies indicate ALA-PDT combined with red light or intense pulsed laser (IPL) as more effective in treating acne than with the light source alone (23,25). One explanation could be the high intracellular levels of porphyrins (e.g. coproporphyrin III (CPIII) and protoporphyrin (Pp)IX) in *C. acnes*, resulting in significant PpIX accumulation in acne lesions upon addition of excessive ALA (21,24,25). Several studies assessed the efficacy of ALA-PDT with different light sources and incubation times, varying from 0.5 to 3 h (25–27). However, to date, the use of PDT with BF-200 ALA (Ameluz®) in combination with the PDT lamp for the treatment of acne lesions was not investigated in a clinical trial setting.

ALA is an endogenous metabolite found in essentially all eukaryotic cells. Kennedy et al. (26) discovered the topical application of ALA for PDT of subjects with a variety of neoplastic and non-neoplastic cutaneous diseases. This precursor in the porphyrins' synthetic pathway is converted by the target cells to PpIX, an effective natural photosensitizer. PpIX accumulates in the epidermis, follicles, and sebaceous glands due to excessive application of ALA (27).

The absorption of energy at different wavelengths activates PpIX, ranging from blue to red light. PpIX shows a maximal excitation at around 410 nm (Soret band) with 4 smaller peaks in the visible range around 510, 530, 580, and 630 nm. Illumination with red light (e.g. LED devices around 630 nm) may be advantageous for acne treatment because red light is more likely to damage sebaceous glands when compared to blue or pulsed light (24,28). The use of LED devices results (as shown in several Phase III studies) in high clearance rates in AK and BCC but is accompanied by a high frequency of adverse events (AEs). These mainly reflect the mode of action, in particular application site reactions such as erythema, edema, irritation, pruritus, and pain. For the treatment of acne, the same light dose as used in the treatment of AK or BCC lesions has been proven to be practicable and efficient in reducing inflammatory lesions. However, no visible effect in treating non-inflammatory lesions was observed. The observed adverse events are consistent with those, reported in AK and BCC studies (29–31).

In ALA-PDT, luminous energy is transferred by the PpIX to oxygen leading to the formation of reactive oxygen species (ROS) and finally causing immediate cell death. The light-induced damage depends on the applied doses and incubation periods. Preneoplastic and neoplastic cells are eliminated due to an altered metabolism, resulting in an increased PpIX accumulation. The epidermis is regenerated after healing of the induced local inflammation leading to a favorable cosmetic outcome. In acne lesions, it is assumed that the photosensitizer is absorbed into the PSUs and is preferentially taken up by sebocytes. Accordingly, sebaceous glands are damaged, and bacterial cell death is observed. As the penetration of ALA is mostly prevented by the basal membrane, separating the epidermis from the dermis, no scar formation is observed.

Due to ALA's mode of action, AEs are mainly local application site reactions such as erythema, pain, edema, and irritation. Most adverse reactions are of a transient and self-limiting nature and usually disappear within 1-2 weeks after the treatment. Exfoliation, post-

inflammatory hypopigmentation (especially in darker Fitzpatrick skin types), and crust formation were also observed (2,15,22,23,32).

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

Biofrontera Bioscience GmbH has developed a nanoemulsion-based gel formulation of 5-aminolevulinic acid (ALA) (development code: BF-200 ALA; brand name: Ameluz®) that is used in conjunction with photodynamic therapy (PDT). BF-200 ALA gel contains 10% 5-aminolevulinic acid hydrochloride, equivalent to 7.8% ALA in a nanoemulsion formulation which enhances stability and skin penetration (33,34). In the United States (US), Ameluz® in conjunction with the BF-RhodoLED® lamp (commonly referred to as PDT lamp) has been approved by the FDA on May 2016 (NDA 208081) for the lesion- and field-directed treatment of actinic keratosis (AK) of mild to moderate severity on the face and scalp with PDT. In October 2024, the previously approved dosage regimen of 1 tube of Ameluz® on an area of 20 cm² was increased to a maximum of 6 g Ameluz® (3 tubes) to be used on an area of 60 cm².

In the European Union (EU), a Community Marketing Authorization was granted for Ameluz® in December 2011 for the treatment of mild to moderate AK on the face and scalp (EU/1/11/740/001). In November 2012, the PDT lamp was CE-marked and subsequently launched in the European market. In September 2016 the approval was extended to the indication of field cancerization on face and scalp, and in January 2017 to the treatment of superficial and nodular basal cell carcinoma (BCC). In March 2018, the posology was extended to the treatment of mild to moderate AK and field cancerization with daylight PDT. On March 2020 the European marketing authorization was further extended for treatment of mild to moderate AK on the extremities. Additionally, Ameluz® received marketing approval in Switzerland for the treatment of mild to moderate AK on the face/ scalp and extremities/ neck & trunk with conventional PDT in November 2015 and 2022 and for the treatment with daylight PDT in September 2018. The treatment of field cancerization and BCC has been approved in May 2018 (Swissmedic number: 65693).

The Marketing Authorization Holder (Biofrontera Bioscience GmbH) intends to conduct a Phase IIb study to demonstrate the efficacy and safety profile of BF-200 ALA (Ameluz®) compared to vehicle in the treatment of moderate to severe Acne vulgaris located on the face with PDT utilizing BF-RhodoLED® illumination.

Today, besides Ameluz®, several PDT products containing ALA or derivatives are available on the market. Levulan® (registered in the US) contains ALA at a concentration of 20% and is provided as a 2-component system where ALA is dissolved immediately before use. In the US, Levulan® was used in several studies for the treatment of acne (23,35–38). Further acne IITs and US acne studies investigated Metvix® (not approved in the US) or other ALA formulations as a possible drug for acne treatment (11,16,30,39,40). Metvix® cream (registered in many European countries [including Germany] and Canada) contains the

prodrug methyl-aminolevulinate (MAL) at a concentration of 16.8% (corresponding to 21.3% MAL HCl), a chemically more stable derivative of ALA. The study results vary, depending on different concentrations and formulations of ALA or ALA esters.

4.2 Study rationale

The current study is intended to characterize the efficacy and safety profile of BF-200 ALA compared to vehicle in the treatment of moderate to severe acne vulgaris located on the face with PDT when using the PDT lamp for illumination.

Acne especially with moderate or severe severity is often paralleled with physical and psychological consequences such as permanent scarring, psychological distress, decreased self-esteem, anxiety and depression. Other psychiatric comorbidities of acne include eating disorders, especially anorexia nervosa and bulimia nervosa (3).

US guidelines recommend various acne treatments, including topical treatments, systemic agents, and physical modalities. However, some of these treatment options, e.g. retinoids (such as oral isotretinoin) are associated with many daunting adverse effects like teratogenicity (41). Thus, especially females of reproductive potential are in need of safer but yet effective treatments, because in 12% of females, acne continues to occur until age 44 (4). Systemic administration of antibiotics is often used as an alternative approach to treat moderate to severe acne. However, due to increasing numbers of antibiotic-resistant bacteria excessive use of antibiotics is already problematic and will become an even bigger problem in the future.

There is a significant medical need to develop novel alternatives to effectively and safely treat acne for which PDT holds great potential according to US guidelines (41). The general benefits of PDT comprise of a high efficacy with a beneficial safety profile along with an overall positive cosmetic outcome. Until today, several studies provide a favorable outcome for PDT applying ALA or MAL in the treatment of acne, primarily in the reduction of inflammatory lesions (10,23,42).

The current clinical study aims to demonstrate the efficacy and safety for treatment of moderate to severe acne medication by evaluating the improvement of acne severity after performing up to 3 PDT sessions assessed 8 weeks after the last treatment. Two different incubation times of study medication will be compared.

4.3 Risk-benefit analysis

This Phase IIb study will be conducted on subjects suffering from moderate to severe facial acne, presenting with ≥ 20 inflammatory and ≥ 20 non-inflammatory lesions. Due to the chosen ratio of study medications, ~66% of subjects will receive active BF-200 ALA treatment that is already marketed for the treatment of AK in the US and for AK and BCC in the EU and Switzerland under the brand name Ameluz® - 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, edema, pruritus, exfoliation, scab, induration, and vesicles. Most adverse reactions occurred during illumination or shortly afterwards. Symptoms were usually of mild or moderate intensity (investigator's assessment on a 4-point scale) and lasted for 1 to 4 days in most cases; however, in some cases, they persisted for 1 to 2 weeks or even longer. In studies evaluating the safety of treatment of expanded fields with numerous AK the overall mean duration of the majority of adverse reactions was ≤ 7 days, the mean duration was rarely longer than 14 days. It is known that the severity of adverse reactions depends on the type of illumination used for PDT and correlates with the higher clearance rate achieved by the use of narrow spectrum lamps, e.g. BF-RhodoLED[®]. In rare cases, adverse reactions may require interruption or discontinuation of the illumination.

Common adverse effects of PDT with BF-200 ALA/BF-RhodoLED[®] include headache and reactions at the application site, such as abnormal sensation, increased sensitivity to pain, discomfort, erosion, and discharge. More detailed information on known adverse reactions is provided in the corresponding investigator's brochure (IB) and the prescribing information (PI) for Ameluz[®] (43). This drug is contraindicated in subjects with known hypersensitivity to ALA, to porphyrins or to any excipients of BF-200 ALA which include soybean phosphatidylcholine, and in subjects with porphyria or photodermatoses.

Irrespective of the treatment outcome all subjects will be regularly monitored until 8 weeks after the last PDT. Pain management will be performed according to established guidelines but restrictions for co-medication described in this protocol must be taken into consideration (see [Section 9.2](#)) (42).

In this study, inclusion and exclusion criteria were defined to minimize possible risks and to ensure a uniform study population. BF-200 ALA and BF-RhodoLED[®] will be handled by appropriately trained study personnel. Incubation times of 1 or 3 hours will be compared to optimize the treatment procedure from a risk-benefit perspective to minimize the burden for the subject.

5 STUDY OBJECTIVES

5.1 Primary objective

The primary objective of the study is to compare the efficacy of BF-200 ALA PDT (containing 7.8% 5-aminolevulinic acid (ALA) as active ingredient) with vehicle PDT, utilizing BF-RhodoLED[®] illumination, in the treatment of moderate to severe Acne vulgaris on the face.

If not otherwise stated, the following endpoint calculations will be conducted based on the assessments performed by the investigator.

The pairwise comparison will always start with the 3 h BF-200 ALA vs. vehicle comparison followed by 1 h BF-200 ALA vs. vehicle comparison.

The co-primary efficacy variables are:

1. Relative change in the number of inflammatory lesions (percentage change from baseline) 8 weeks after the last PDT as assessed by investigator.
2. Treatment success defined by a minimum improvement of the mIGA score by at least 2 assessed 8 weeks after the last PDT and resulting in an mIGA score of 0 (clear) or 1 (almost clear).

5.2 Secondary objective

The secondary objective of the study is to evaluate the safety and secondary efficacy parameters related to BF-200 ALA/BF-RhodoLED[®] PDT for the treatment of moderate to severe Acne vulgaris.

Secondary efficacy variables:

1. Absolute and/or percentage change from baseline in the number of lesions as assessed by investigator:
 - a. Inflammatory lesions – 4 weeks after the last PDT
 - b. Inflammatory lesions – 8 weeks after the last PDT
 - c. Non-inflammatory lesions – 4 weeks after the last PDT
 - d. Non-inflammatory lesions – 8 weeks after the last PDT
 - e. Inflammatory & non-inflammatory lesions – 4 weeks after the last PDT
 - f. Inflammatory & non-inflammatory lesions – 8 weeks after the last PDT
2. Absolute and percentage change from baseline in the number of lesions as assessed by investigator:
 - a. Inflammatory lesions – 4 weeks after PDT-1
 - b. Non-inflammatory lesions – 4 weeks after PDT-1
 - c. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-1
 - d. Inflammatory lesions – 4 weeks after PDT-2
 - e. Non-inflammatory lesions – 4 weeks after PDT-2
 - f. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-2

- g. Inflammatory lesions – 4 weeks after PDT-3
 - h. Non-inflammatory lesions – 4 weeks after PDT-3
 - i. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-3
 - j. Inflammatory lesions – 8 weeks after PDT-3
 - k. Non-inflammatory lesions – 8 weeks after PDT-3
 - l. Inflammatory & non-inflammatory lesions – 8 weeks after PDT-3
3. Absolute and percentage change from baseline in the number of lesions as assessed by investigator, only for responders at Visit 3 /4 weeks after PDT-1:
- a. Inflammatory lesions – 4 weeks after PDT-1
 - b. Inflammatory lesions – 8 weeks after PDT-1
 - c. Non-Inflammatory lesions – 4 weeks after PDT-1
 - d. Non-Inflammatory lesions – 8 weeks after PDT-1
 - e. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-1
 - f. Inflammatory & non-inflammatory lesions – 8 weeks after PDT-1
4. Absolute and percentage change from baseline in the number of lesions as assessed by investigator, only for responders at Visit 4b /4 weeks after PDT-2:
- a. Inflammatory lesions – 4 weeks after PDT-2
 - b. Inflammatory lesions – 8 weeks after PDT-2
 - c. Non-Inflammatory lesions – 4 weeks after PDT-2
 - d. Non-Inflammatory lesions – 8 weeks after PDT-2
 - e. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-2
 - f. Inflammatory & non-inflammatory lesions – 8 weeks after PDT-2
5. Absolute and percentage change from baseline in the number of lesions as assessed by investigator, only for responders at Visit 5b /4 weeks after PDT-3:
- a. Inflammatory lesions – 4 weeks after PDT-3
 - b. Inflammatory lesions – 8 weeks after PDT-3
 - c. Non-Inflammatory lesions – 4 weeks after PDT-3
 - d. Non-Inflammatory lesions – 8 weeks after PDT-3
 - e. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-3
 - f. Inflammatory & non-inflammatory lesions – 8 weeks after PDT-3
6. Change in the number of nodules & cysts 8 weeks after the last PDT (absolute change and percentage change from baseline) as assessed by investigator.
7. Treatment success defined by a minimum improvement of the IGA by at least 2, 8 weeks after the last PDT.
8. Improvement of the IGA, 8 weeks after the last PDT.
9. Improvement of the mIGA, 8 weeks after the last PDT.
10. Improvement of scar severity and overall esthetic appearance 8 weeks after last PDT (assessed by investigator).

11. Subject satisfaction regarding esthetic outcome and treatment 8 weeks after the last PDT.

Safety variables:

Safety analysis variables include:

- Frequency and severity of adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESI) and treatment-emergent adverse events (TEAEs). TEAEs are defined as all AEs with onset after first treatment with IMP up to the last visit of the subject (approximately 8 weeks post last PDT).
- Application site skin reactions assessed by the investigators.
- Application site discomfort reported by the subjects.
- Pain during illumination reported by the subjects (pain will be assessed on an 11-point numeric rating scale).
- Vital signs data.
- Safety laboratory data.
- Physical examinations data.

Exploratory variables:

1. Change in the number of inflammatory and/or non-inflammatory lesions (absolute change and/or percentage change from baseline) as assessed by Canfield algorithm for:
 - a. Inflammatory lesions – 8 weeks after the last PDT
 - b. Non-inflammatory lesions – 8 weeks after the last PDT
 - c. Inflammatory & non-inflammatory lesions – 8 weeks after the last PDT
2. Treatment success defined by a minimum improvement of the PAS equivalent to an improvement of IGA by at least 2, assessed by the Canfield algorithm 8 weeks after the last PDT (see [Section 10.2.3](#)).
3. Treatment success defined by a minimum improvement of the mPAS equivalent to an improvement of mIGA by at least 2, assessed by the Canfield algorithm 8 weeks after the last PDT (see [Section 10.2.3](#)).

5.3 Follow-up Objective

Not applicable.

6 STUDY DESIGN, DURATION AND DATES

6.1 Study design

This protocol describes a randomized, parallel group, double blind (with respect to vehicle), multicenter Phase IIb study that will be conducted in the US.

The clinical study will consist of:

- A screening visit (within 6 weeks before treatment), at which eligibility of subjects for study participation will be assessed (**Visit 1**).
- A baseline and treatment visit, at which eligible subjects will receive PDT-1 with application of 1 tube of study medication (**Visit 2**).
- A phone call for safety assessment at 1 week (± 2 days) post PDT-1 (PC-1).
- A 2nd treatment visit (**Visit 3**) for subjects who have remaining inflammatory lesions at this visit (PDT-2) 4 weeks (± 1 week) after Visit 2 (non-responders).
- All subjects cleared (responders) at Visit 3 will undergo a final assessment at **Visit 4a**, 8 weeks (± 1 week) after PDT-1.
- Subjects who received a 2nd PDT, will receive a 2nd phone call (PC-2) for safety assessment 1 week (± 2 days) post PDT-2.
- A final treatment visit (**Visit 4b**) for subjects who have remaining inflammatory lesions at this visit (PDT-3) 4 weeks (± 1 week) after Visit 3 (non-responders).
- All subjects cleared at Visit 4b (responders) will undergo a final assessment at **Visit 5a**, 8 weeks (± 1 week) after PDT-2.
- Subjects who received a 3rd PDT will receive a 3rd phone call (PC-3) for safety assessment 1 week (± 2 days) after PDT-3, at which safety and tolerability assessments will be performed.
- PDT-3 will be followed by **Visit 5b** (4 weeks (± 1 week) after PDT-3) and **Visit 6** (8 weeks (± 1 week) after PDT-3) which will be the final visit for all subjects.

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

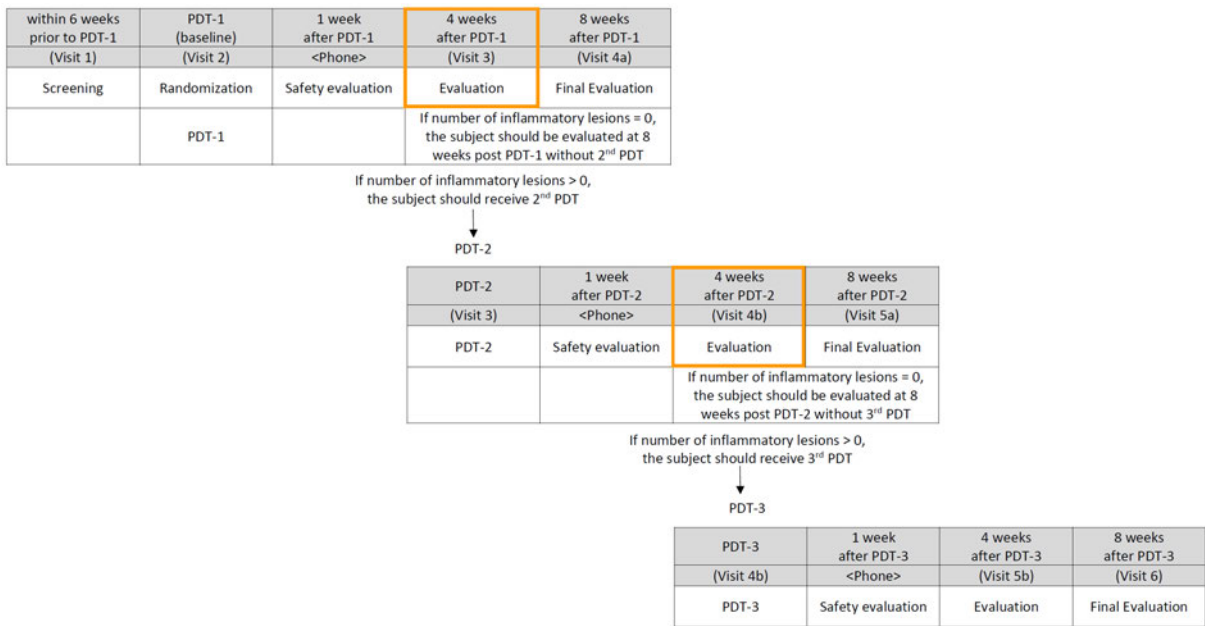


Figure 1: Summary of study visits for responders and non-responders.

The PDT procedure (preparation of treatment field, drug application, incubation, illumination) will be performed according to [Sections 8.3](#) and [8.4](#).

6.2 Study duration, dates and end of study definition

For each subject, the duration of trial participation is expected to be approximately 17 weeks (1 PDT), 22 weeks (2 PDTs) or 27 weeks (3 PDTs) (including screening period and an additional delay due to dosing day exclusion criteria and allowed range in the visit timelines). The duration of the overall study or the subject recruitment period may vary. End of study (EoS) is defined as database lock.

7 SELECTION OF SUBJECTS

7.1 Number of subjects

The suggested sample size for the study is 126 randomized subjects. Subjects will receive BF-200 ALA with a chance of ~66%. (see [Section 14.8](#) for more details).

7.2 Recruitment arrangements

Subjects will be screened at the study site and, if eligible, subjected to PDT. The study site has to stop recruitment once 24 subjects have been treated. After sponsor approval up to 36 subjects can be randomized.

Re-assessment of subjects is allowed once in case exclusion criterion 3, 6 or 7 is met, and eligibility can be achieved within 2 weeks.

7.3 Inclusion criteria

Subjects meeting all of the following criteria will be considered for enrollment in the study:

1. Willingness and ability of the subject to provide informed consent and to sign the Health Insurance Portability and Accountability Act (HIPAA) form. A study-specific informed consent and HIPAA form must be obtained in writing prior to starting any study procedures. Minors under 18 years of age must be accompanied by the parent(s) or legal guardian(s) at the time of consent signing. The parent(s) or legal guardian(s) must also provide informed consent/HIPAA for the subject.
2. Subjects with moderate to severe acne on the face (IGA ≥ 3).
3. Presence of ≥ 20 inflammatory and ≥ 20 non-inflammatory (open and closed comedones) Acne vulgaris lesions on the face (should be located within not more than 2 illumination areas) as assessed by investigator.
4. All sexes, ≥ 16 years of age.
5. Willingness and ability to comply with study procedures, particularly willingness to receive up to 3 PDTs within 8 to 10 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 topical facial treatments other than medical cleansers (i.e. face washes etc.) at least 14 days prior to randomization visit (Visit 2, baseline) and discontinue medical cleansers in the face at least 1 week prior to randomization visit (Visit 2, baseline) and thereafter until the end of study (use of soap is allowed but the product used should not be changed during the study)
8. Females of reproductive potential must have a negative serum pregnancy test and must use an adequate and highly effective or two effective methods of contraception throughout the study. (If hormonal contraception is used, the same product and dose should be taken for at least 6 months before the first treatment and throughout the entire study.)

7.4 Exclusion criteria

Subjects presenting with any of the following criteria will not be included in the study:

1. Any known history of hypersensitivity to ALA, porphyrins or excipients of BF-200 ALA.
2. History of soy or peanut allergy.
3. Subjects with sunburn or other possible confounding skin conditions (e.g. wounds, irritations, bleeding or skin infections) within or in close proximity (< 5 cm distance) to treatment field. (Reassessment of subjects is allowed once if the sunburn or other confounding skin conditions is/are expected to resolve within the screening period. Reassessment can be done on the day of the actual treatment.)

4. Clinical diagnosis of atopic dermatitis and other cutaneous conditions (e.g. lupus erythematosus), Bowen's disease, BCC, eczema, psoriasis, acne conglobate, acne fulminans, or secondary acne (steroid-induced acne, perioral dermatitis, acne rosacea), squamous cell carcinoma, other malignant or benign tumors in the treatment field.
5. 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
6. Beard or other facial hair that might interfere with the study assessments unless subject agrees to be clean-shaven throughout the entire study period. (Reassessment of subjects is allowed once if assessment of acne lesions is impaired by facial hair at screening. Reassessment can be performed on the day of the actual treatment).
7. Facial procedures such as dermabrasion, chemical or laser peels as well as exposure to UV radiation (other than sunlight) at least 4 weeks prior to randomization visit (Visit 2, baseline).
8. Presence of strong artificial pigmentation (e.g. tattoos) or any other abnormality that may impact lesion assessment or light penetration in the treatment field.
9. Suspicion of drug or alcohol abuse.
10. Any topical medication of the skin prior to screening as defined below:
 - a. Topical treatment with ALA or ALA-esters (e.g. MAL) or an investigational drug in- and outside the treatment field within 8 weeks prior to screening.
 - b. Topical treatment with immunosuppressive, cytostatic or cytotoxic drugs inside the treatment field within 8 weeks prior to screening.
 - c. Start of a regular and continuous topical administration of medication with hypericin or other drugs with phototoxic or photoallergic potential inside the treatment field within 4 weeks prior to screening. Subjects may, however, be eligible if such medication was regularly applied for more than 4 weeks prior to screening visit without evidence of an actual phototoxic/photoallergic

reaction or if such medication is only administered for a limited time (e.g. an antibiotic).

11. Any use of the below specified systemic treatments within the designated periods:

- a. Systemic acne therapy (oral antibiotics within 8 weeks or oral isotretinoin within 6 months or start with hormonal therapy for acne within 6 months prior to Visit 2).
- b. Use of cytotoxic or cytostatic drugs within 6 months, or immunosuppressive therapies or use of ALA or ALA-esters (e.g. MAL) within 12 weeks, investigational drugs or drugs known to have major organ toxicity within 8 weeks, interferon or glucocorticosteroids (oral or injectable) within 6 weeks prior to screening.
- c. Start of long-term intake of medication with hypericin or systemically acting drugs with phototoxic or photoallergic potential within 8 weeks prior to screening. Subjects may, however, be screened and randomized if such medication was taken in or was regularly applied for more than 8 weeks prior to screening visit without evidence of an actual phototoxic/photoallergic reaction or if such a drug is only used for a limited time (e.g. an antibiotic).

12. Breast feeding women.

13. Subject 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.

14. Prior randomization in the study.

15. A member of study site staff or sponsor staff directly involved in the conduct of the protocol or a close relative thereof.

16. Simultaneous participation in a further clinical study.

17. Four or more nodular acne lesions on the face.

18. Unwillingness or inability to limit sun exposure for 48 hours post PDT treatment.

Re-assessment of subjects is allowed once in case exclusion criterion 3, 6 and/or 7 is met, and eligibility can be achieved within 2 weeks.

Dosing day exclusion criteria

1. Febrile or infectious disease within 7 days prior to PDT visits.
2. Subjects with sunburn, wounds, irritations, bleeding or other confounding skin conditions within illumination areas at PDT visits.
3. Application of topical glucocorticosteroids in- and outside the treatment field within 7 days prior to PDT visits.
4. Administration of (topical or systemic) medication with phototoxic/photoallergic potential for a limited time. After discontinuing the medication, a wash out period of the medications 5-fold half-life time should be applied prior to the next PDT.

In case a subject meets any dosing day exclusion criteria at a PDT visit (V2, V3 & V4b), this visit can be rescheduled once at the earliest possibility after resolution, but rescheduling should not exceed 2 weeks.

7.5 Screening failures

All subjects whose eligibility cannot be confirmed at Visit 2 will be considered as screening failures. In case a subject matches a dosing day exclusion criterion, Visit 2 can be rescheduled to the earliest possibility after resolution but rescheduling should not exceed 2 weeks.

Subjects assessed as screening failures will not be randomized at Visit 2. For screening failures, only date of informed consent, demographic data, lesion counts, IGA/mIGA (investigator and independent evaluator (if applicable))/PAS/mPAS (if available), Fitzpatrick skin type and date/reason of screening failure have to be reported in the eCRF.

Re-screening of a subject that was a previous screening failure is possible and a complete screening, including the ICF process and assignment of a new subject ID, has to be performed.

7.6 Subjects of reproductive potential

Female subjects of reproductive potential (i.e. ovulating, pre-menopausal, or postmenopausal for less than 3 years, not surgically sterile) must use a medically accepted contraceptive regimen during the clinical study as outlined below. The contraceptive method(s) chosen should be medically, culturally, and geographically acceptable.

- 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).
If oral contraception is used, the same product and dose should be taken for at least 6 months before the first treatment and throughout the entire study.
 - Sexual intercourse with a vasectomized partner
 - True abstinence
- Combined use of 2 effective methods such as:
 - Latex condoms with spermicidal gel
 - Diaphragms with spermicidal gel
 - Cervical caps with spermicidal gel
 - Vaginal sponge with spermicidal gel

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

If a subject becomes pregnant during the study, she must inform the investigator immediately. The subject will not receive a further PDT treatment with the IMP but can remain in the study until Visit 4a, Visit 5a or Visit 6, as applicable. The further treatment of acne lesions should be addressed on a case-by-case basis with the treating physician and the investigator according to the investigator's discretion and not as part of the study.

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

8 STUDY TREATMENT

8.1 Details of investigational products

8.1.1 Investigational Medicinal Products

The drug component of the IMPs will be BF-200 ALA, a gel formulation of 7.8% ALA. The vehicle used as comparator is a formulation similar to the BF-200 ALA gel formulation but without the active ingredient ALA and indistinguishable in color, appearance, smell and texture from BF-200 ALA.

The compositions are as follows:

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.

The BF-200 nanoemulsion gel is an oil-in-water dispersion of 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 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 4.1](#).

The quantitative composition of the vehicle is 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, water and pH.

The IMP will be delivered in aluminum tubes containing 2 g gel (containing 156 mg ALA in case of verum). For each session, one tube of IMP will be provided. The whole face should be homogeneously covered with a thin layer of IMP, excluding the periocular area. Up to 3 tubes with identical content (either BF-200 ALA or vehicle) will be provided per subject, allowing a maximum of 3 sessions per subject. Each box is labeled with and can be identified and assigned to a specific subject by the unique random number.

8.1.2 Investigational Medical Device

The Class III device BF-RhodoLED[®] was granted US marketing approval as a combination product with Ameluz[®] for the lesion- or field-directed treatment of mild to moderate AK on the face and scalp in May 2016 (NDA 208081).

The PDT lamp is manufactured in compliance with ISO 13485: 2016 standard by:

Biofrontera Pharma GmbH
Hemmelrather Weg 201
51377 Leverkusen
Germany

The PDT lamp utilizes 128 LEDs and lenses (arranged in a rectangle) to emit a uniform, bundled, visible red light with a typical peak wavelength at approximately 635 nm and a half bandwidth of 20 nm. The total area illuminated by the lamp is 8 cm x 18 cm with an effective illumination area of 6 cm x 16 cm. The treatment distance is 5 – 8 cm, as the calibration of the lamp ensures that the skin area illuminated receives a total light dose of 37 J/cm² when maintaining a total illumination time of 10 min at a distance of 5 – 8 cm. Therefore, it must be confirmed and documented that the applied light dose (37 J/cm²) and distance between the lamp and the treatment field have been met. Otherwise, reasons for not meeting the requirements must be provided. The lamp is programmed to automatically provide a total illumination time of 10 min with a total light dose of approx. 37 J/cm². In case of necessary interruptions, e.g. due to unbearable pain or repositioning of the subject, the lamp will continue until the required illumination time is achieved.

For the purpose of this study, the study site will be equipped with 1 or 2 PDT lamp(s). All site personnel handling the lamp will be instructed properly on the handling and usage of the lamp, according to the user manual.

The recommended conditions for illumination with the PDT lamp are shown in [Table 3](#).

Table 3: Key parameters of PDT lamp used

	Recommendation
Peak Wavelength (λ_{em})	approx. 635 nm
Light dose (10 minutes)	approx. 37 J/cm ²
Max irradiance	77 mW/cm ²
Illumination time	10 min
Distance skin-lamp	5 – 8 cm

Detailed handling and operating instructions as well as a list of warnings and precautions when handling the PDT lamp are provided in the user manual.

8.2 Storage

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

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

The PDT lamps have to be stored inaccessible to unauthorized persons.

8.3 Application of investigational medicinal products

The treatment field is defined in [Section 3](#) and refers to the entire area to which IMP is applied to.

The treatment field will be vigorously cleansed with gauze soaked with ethanol or isopropanol for approximately 2 minutes to remove skin oils and is thereby lightly exfoliated. Care should be taken to avoid bleeding.

After this preparation, the study medication will be homogenously applied as a thin layer to the treatment field. The application will be performed using glove-protected fingertips or a spatula. Care should be taken to avoid that the study medication is applied to the periorcular area of 1 cm below the eyes or the area between the eyes and eyebrows including upper eyelid. The treatment field shall be such that it can be illuminated in two sessions. If two subsequent illuminations are required (e.g. site is equipped with only one PDT lamp, the IMP

should be applied to each illumination area with a 15 min time interval in order to ensure similar incubation times).

After drug application, the subject should stay inside for 1 h + 5 min or 3 h + 10 min, respectively.

The following information concerning this procedure should be documented:

- preparation of treatment field
- unique randomization number
- time of IMP application and removal

Acne lesions located outside the treatment field will not be considered for treatment in this study and will be treated separately whenever possible after the end of the clinical study with conventional local therapy according to the investigator's choice. Please refer to [Section 9.2](#).

8.4 Illumination with PDT lamp

After removal of any remaining gel, the entire treatment field will be illuminated using the PDT lamp, until a total light dose of approximately 37 J/cm² is achieved. During illumination, the lamp(s) will be positioned at a distance of 5 – 8 cm from the skin surface as indicated in the user manual. It should be ensured that half of the face is covered by 1 illumination area.

The lamp is programmed to automatically provide a total light energy of approximately 37 J/cm² over a total illumination time of 10 min. In case of necessary interruptions, e.g. due to unbearable pain or repositioning of the subject, the lamp will continue until the required illumination time is achieved. After each PDT, the following should be documented:

- Starting time and duration of illumination
- Distance of lamp to illumination area
- Potential interruptions (including reason for interruption) and/or pain-relieving measures

For the purpose of this study, each study site will be equipped with 1 or 2 PDT lamp(s). All site personnel handling the lamp will be instructed properly on the handling and usage of the lamp, according to the user manual.

During illumination, subjects and medical personnel must wear suitable protective eye goggles.

Detailed handling and operating instructions as well as a list of warnings and precautions when handling the PDT lamp can be derived from the user manual.

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

pain experienced during illumination will be evaluated by all subjects after the treatment, the PDT should be started without analgesic measures with the exceptions noted in [Section 9.2](#). In cases where the pain is regarded as unbearable by the subject, pain relieving measures as outlined in [Section 9.2](#) may be applied.

The subject should be informed about restrictions defined in [Table 4](#) and in [Section 9.2](#).

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

Although a nearly complete loss of PpIX by photobleaching is assumed to occur during illumination, subjects should avoid exposure to intensive sun light or prolonged and intense light (e.g. tannings beds or sun lamps) for about 48 h since new PpIX may accumulate from remaining ALA. Additional light exposure may enhance the typical side effects of PDT. Subjects should not expose themselves to intensive ultraviolet (UV)-radiation (solarium, sunbathing, etc.) during the course of the study (see also [Section 7.4](#)) to avoid UV-induced post-inflammatory hyperpigmentation of the healing tissue.

8.5 Dosage schedule

A maximum of 3 PDT sessions with 1 tube of IMP each will be applied according to the study design described in [Section 6.1](#), [Section 8.3](#) and [Figure 1](#).

8.6 Randomization and treatment assignment

The IMP will be administered exclusively to subjects matching the eligibility criteria and for whom the written informed consent is available (see [Section 15.3](#)).

Each subject will be assigned a subject number in the chronological order of enrollment (within each site). For this purpose, the next higher subject number is always assigned. This number will be documented and will be used to identify the subject until s/he is either found to be eligible for the study and is then assigned with a randomization number or is identified as a screening failure (i.e. the subject is not eligible for the study). The subject number will be automatically provided by the electronic case report form (eCRF) platform.

Treatment assignment at the study sites will be performed in the following way:

The IMPs will be labeled with the randomization numbers. Subjects eligible at Visit 2 will be assigned a unique randomization number. For this purpose, the investigator will use the box with the next higher randomization number. This randomization number will be documented in source and in the eCRF.

Subjects will be randomized for treatment with PDT with either vehicle (control group) or BF-200 ALA (Ameluz[®], test group) with respective incubation times of either 1 or 3 hours. A randomization ratio of 2:2:1:1 to BF-200 ALA (1 hour incubation), BF-200 ALA (3 hours incubation), vehicle (1 hour incubation), and vehicle (3 hours incubation) will be applied. Thus, the chance of receiving verum will be ~66%. 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 IMP is packed in tubes, each containing 2 g gel. A minimum of 12 to a maximum of 36 subjects should be randomized per study site but no site should randomize more than 24 subjects unless prior approval of the sponsor is obtained.

The randomization schedule and the allocation to treatment groups will not be known by the sponsor until completion of the clinical study, except in case of an emergency. In case of emergency the investigator can request unblinding of a specific randomization number via the eCRF system. The qualified person for pharmacovigilance (QPPV) and the responsible project manager at Biofrontera will receive immediate notice from the system about the request. The QPPV will provide any necessary information to the investigator at earliest possibility. 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 at maximum 3 times with a 1-month interval each which is considered single application(s) and as there is no substance-specific treatment for adverse reactions. Therefore, no immediate unblinding is foreseen during this study.

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 random numbers to the investigator, whenever required. All these individuals are separate from the study team.

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

8.7 Blinding, packaging, and labeling

8.7.1 Investigational Medicinal Product

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

Responsible for manufacturing and release of IMP (BF-200 ALA and vehicle):

Biofrontera Pharma GmbH
Hemmelrather Weg 201
D-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 cardboard box is provided containing 3 tubes with BF-200 ALA or vehicle. Each box is labeled with a tear-off label and can be identified and assigned to a specific subject by a unique random number.

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

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

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

8.7.2 Investigational Medical Device

The PDT lamp will be distributed and assembled/maintained at the sites by technicians or other properly trained delegates of:

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

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

For the purpose of this study, each site will be provided with 1 or 2 PDT lamps. It is exclusively intended to be used in conjunction with the study medication within a clinical study. As the lamp will be assembled on site by a technician or delegate of Biofrontera Inc., there will be no immediate packaging available. All labeling will be applied directly to the lamp.

8.8 Supplies and accountability

After the study protocol was approved or accepted by the Institutional Review Board(s) (IRB(s)) and by FDA, the sponsor will initiate the study sites which includes installation of 1 or 2 PDT lamps and thereafter supply the study site with study medication, together with all relevant documentation. The sponsor is responsible for delivery of the investigational products to the study site.

The investigator will inventory and acknowledge receipt of all shipments of IMP and IMD. The investigator is responsible for maintaining documentation listing all 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 site on an ongoing basis during the study. At the latest at the end of the study, all remaining study medication including used tubes should be returned to the drug supplier

acting on behalf of sponsor for disposal. The monitor will prepare a final report of accountability of the investigational products for filing in the Investigator Site File (ISF).

After the last subject completed the treatment, all lamps will be disassembled by a technician and returned to Biofrontera Inc unless they are still being used for another Biofrontera sponsored study. Receipt and return of the PDT lamp will be acknowledged and documented accordingly.

8.9 Compliance

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

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

PDT lamps will be exclusively operated by previously trained study personnel.

9 PRIOR AND CONCOMITANT MEDICAL CONDITIONS AND TREATMENTS

9.1 Prior and concomitant medical conditions

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

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

9.2 Prior and concomitant medications/treatments

Any medication/treatment taken by a subject at study or treatments the subject is undergoing at the time of study entry or throughout the study that are not related to any study-specific procedures (PDT with IMP), are considered concomitant medications or treatments. The use of required concomitant medications or treatments, which are known not to interfere with the IMP or to mask their effect, is unrestricted and may be continued during the study. Forbidden facial treatments throughout the treatment period include but are not limited to dermabrasion, chemical or laser peels as well as exposure to UV radiation (other than sunlight). Medical cleansers, defined here as prescription-only cleansers, are forbidden from one week before Visit 2/Baseline until the final visit. Over-the-counter face washes (not prescription-strength) are allowed and the product used must stay the same throughout the study.

The following treatments are permitted in the designated time periods to alleviate pain and discomfort (please consider the information provided in the respective PIs):

- Prior to illumination
 - No prophylactic analgesic treatment is allowed.
- During illumination
 - In cases where the pain is regarded as unbearable by the subject, the illumination may be interrupted and/or cooling with an air stream or nebulized water may be offered.
 - Severe cases of pain might require to briefly interrupt illumination, e.g. to inject a local, fast-acting anesthetic, such as xylocaine or to cool briefly with cooling packages.
- Treatment of pain and discomfort post illumination
 - Cooling the illuminated area(s) with wet or refrigerated compresses or a cold air stream
 - Analgesic treatment with acetaminophen (e.g. Tylenol®) or NSAIDs (ibuprofen up to 1200 mg per day; acetylsalicylic acid up to 3750 mg per day)

All concomitant medications/treatments underwent/taken during the study must be documented in the eCRF system along with the indication, single dose, route of

administration, frequency of administration as well as start and stop date of administration. The subject should confer with the investigator prior to the use of new medication during the course of the study.

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, 3, 4b)	8 weeks prior to Visit 1	Final Visit	12 weeks prior to Visit 1	Final Visit
Cytotoxic drugs/ Cytostatic drugs	8 weeks prior to Visit 1 inside or in close proximity to treatment field (<10 cm)	Final Visit inside or in close proximity to treatment field (<10 cm)	6 months prior to Visit 1	Final Visit
Immunosuppressive therapies	8 weeks prior to Visit 1 inside or in close proximity to treatment field (<10 cm)	Final Visit inside or in close proximity to treatment field (<10 cm)	12 weeks prior to Visit 1	Final Visit
Interferon	---	---	6 weeks prior to Visit 1	Final Visit
Glucocorticosteroids	7 days prior to Visit 2 inside or in close proximity to the treatment field (<10 cm)	Final Visit inside or in close proximity to treatment field (<10 cm)	6 weeks ^a prior to Visit 1	Final Visit ^a
Antibiotics^{b,d} (if taken for longer time period/ if used for acne-treatment; for short time use: the 5-fold half time should pass prior to performing PDT)	With Visit 1 inside or in close proximity to the treatment field (<10 cm)	Final Visit inside or in close proximity to treatment field (<10 cm)	8 weeks prior to Visit 2	Final Visit
Vitamin A derivatives (e.g. isotretinoin)	4 weeks prior to Visit 2	Final Visit	6 months prior to Visit 2	Final Visit
Hormonal therapy (other than hormonal birth control)	6 months prior to Visit 2	Final Visit	6 months prior to Visit 2	Final Visit
NSAIDs (others than	7 days prior to	7 days post	7 days prior to	7 days post PDT

listed below)	PDT	PDT	PDT	
Acetylsalicylic acid >3750 mg/day	---	---	7 days prior to PDT	7 days post PDT
Ibuprofen >1200 mg/day	---	---	7 days prior to PDT	7 days post PDT
Diclofenac	---	---	>100 mg/day; 7 days prior to PDT	>100 mg/day; 7 days post PDT
Hypericin or drugs with phototoxic/ photoallergic potential^{c,d}	4 weeks prior to Visit 1 inside or in close proximity to treatment field (<10 cm)	Final Visit inside or in close proximity to treatment field (<10 cm)	8 weeks prior to Visit 1	Final Visit
Investigational drugs	8 weeks prior to Visit 1	Final Visit	8 weeks prior to Visit 1	Final Visit
Drugs known to have major organ toxicity	---	---	8 weeks prior to Visit 1	Final Visit
EMLA[®] cream	On day of PDT inside the treatment field (Visit 2, 3 and 4a, if applicable)	On day of PDT inside the treatment field (Visit 2, 3 and 4a, if applicable)	---	---

^a Does not apply to inhaled glucocorticosteroids (inhalation = topical application).

^b Potential phototoxic abilities of antibiotics need to be taken into account when applied outside the treatment field (please refer to “Hypericin or drugs with phototoxic/photoallergic potential”), a washout period of the 5-fold half-life time applies prior to each PDT.

^c Start of therapy with any photosensitizer or systemically-acting drugs with phototoxic or photoallergic potential, such as psoralenes, tetracyclines, nalidixic acid, furosemide, amiodarone, phenothiacines, chinolones, fibrates, or phytotherapy with St. John’s wort, arnica, or valerian or topically applied phototoxic substances like tar, pitch, psoralenes or some dyes like thiazide, methylene blue, toluidine blue, eosin, rose bengal, or acridine. Subjects may, however, be eligible if such medication was taken longer than 4 to 8 weeks (topical vs. systemic) prior to screening without evidence of an actual phototoxic/photoallergic reaction.

^d Other timelines may apply for photo-active antibiotics which may have to be decided on a case-by-case scenario after consultation with sponsor

10 STUDY PROCEDURES AND SCHEDULE

All data obtained from subjects, e.g. assessments, questionnaires and examination results, should be sufficiently documented in source and all entries into the eCRF should be sufficiently reflected in the source accordingly.

10.1 Description of study days

[Table 1](#) summarizes the study schedule.

10.1.1 Visit 1/Screening (≤ 6 weeks prior to PDT-1)

Potential subject will be evaluated to determine if they fulfill the inclusion and exclusion criteria (see [Sections 7.3](#) and [7.4](#)). The following procedures will be performed at Visit 1 (Screening):

- Obtain informed consent and HIPAA form prior to any other study-related procedures
- Assign subject number
- Documentation of prior and concomitant medical conditions (diseases/illnesses; relevant medical history), and concomitant medications/treatments (see [Section 9.2](#))
- Documentation of facial care products use (facial cleansers and face cream) (see [Section 9.2](#))
- Obtain demographic data (age, sex, ethnicity, race)
- Document body measures (height and weight)
- Check inclusion and exclusion criteria
- Assess skin type according to Fitzpatrick, 1988 ([44](#))
- Clinical assessment of acne severity (IGA, mIGA, lesion count (numbers of inflammatory and non-inflammatory lesions, cysts, nodules)) and acne scars by investigator
- If site is equipped with the Canfield Visia-CR[®] system: generation of pictures of subject's facial lesions with Canfield Visia-CR and subsequent centralized assessment of the subjects' lesions, erythema, skin texture, Coproporphyrin III (CPIII) and PAS/mPAS. In case of a discrepancy to the assessment of the investigator, and Canfield, an independent evaluator may perform a third assessment (IGA/mIGA) based on the corresponding pictures (only upon sponsor's request; see [Section 10.2.3](#))
- General physical examination
- Measurement of vital signs (HR, BP)
- Clinical laboratory tests (including routine hematology, blood chemistry, serum pregnancy test, and urinalysis)
- Documentation of (S)AEs
- Instruct subject about forbidden concomitant treatments (see [Section 9.2](#))

10.1.2 Visit 2/Baseline (PDT-1)

The following procedures will be performed at Visit 2:

- Re-evaluation of inclusion and exclusion criteria for confirmation of subject's eligibility
- Evaluation of dosing day exclusion criteria
- Acne assessment by the investigator to make a final decision for randomization, IGA score should not improve by ≥ 1 score and should not improve to a level below IGA = 3, according to the clinical re-assessment performed at Visit 2; if it does the subject must not be randomized and has to be screen failed
- Clinical assessment of acne severity (mIGA, IGA and lesion count (numbers of inflammatory and non-inflammatory lesions, cysts, nodules)) and acne scars by investigator
- If site is equipped with the Canfield Visia-CR[®] system: generation of pictures with Canfield Visia-CR of subject's facial lesions and subsequent centralized assessment of the subject's lesions, erythema, skin texture, CPIII, mPAS, and PAS. In case of a discrepancy to the assessment of the investigator, an independent evaluator may perform a third assessment (IGA/mIGA) based on the corresponding pictures (only upon sponsor request; see [Section 10.2.3](#)).
- Assign randomization number
- Measurement of vital signs (HR, BP)
- Pregnancy test (urine) for females of reproductive potential prior to PDT (in case urine pregnancy test is positive, another blood draw is acceptable to verify subject's pregnancy)
- Preparation of treatment field and application of study medication according to treatment description in [Section 8.3](#)
- Date and time of study drug application and removal will be recorded. If a subsequent illumination is planned, a staggered application of IMP has to be performed (15 min time interval) in order to ensure similar incubation times.
- Illumination of treatment field with PDT lamp(s) until a total light dose of 37 J/cm² is achieved (according to treatment description in [Section 8.4](#))
- Duration of illumination and distance between PDT lamp(s) and the treatment field will be documented. Otherwise, reasons for not meeting the requirements must be given. The duration, reason, and frequency of any interruptions and any additional pain-relieving measures must be recorded if applicable.
- Documentation of concomitant medications/treatments (e.g. for pain management that might be required prior to, during or post illumination) (see [Section 9.2](#) and [Table 4](#))
- Documentation of facial care products use (facial cleansers and face cream) (see [Section 9.2](#))
- Assessment of application site pain during illumination via an 11-point numeric rating scale (NRS-11)
- Documentation of (S)AEs (including adverse device effects, ADEs), application site skin reactions and application site discomfort (e.g. after IMP application, prior to, during and post illumination)

- Instruct subject about forbidden concomitant medications/treatments (see [Section 9.2](#) and [Table 4](#))
- Inform subjects to avoid sunlight, prolonged or intense light (e.g., tanning beds, sun lamps) on treatment field(s) for approximately 48 hours following treatment whether exposed to illumination or not.

10.1.3 Phone call (1 week ($\pm$ 2 days) post PDT-1)

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

The following information will be collected during the phone contact:

- Documentation of (S)AEs including application site skin reactions and application site discomfort, and concomitant medications/treatments
- Instruct subject about forbidden concomitant medications/treatments (see [Section 9.2](#) and [Table 4](#))

10.1.4 Visit 3 (tolerability & safety assessment, 4 ($\pm$ 1) weeks post PDT-1)

- Clinical assessment of acne severity (IGA, mIGA, and lesion count (numbers of inflammatory and non-inflammatory lesions, cysts, nodules)) by investigator and decision if the subject will require a 2nd PDT
- If site is equipped with the Canfield Visia-CR[®] system: generation of pictures with Canfield Visia-CR of subject's facial lesions. A centralized assessment of the subject's lesions, erythema, skin texture, CPIII and PAS/mPAS will be only conducted in case the subject drops out as last observation carried forward.
- Measurement of vital signs (HR, BP)
- Documentation of (S)AEs, including application site skin reactions and application site discomfort and concomitant medications/treatments

For responders, please proceed for the next visit with Visit 4a.

For non-responders, please continue with the following treatment:

- Evaluation of dosing day exclusion criteria
- Pregnancy test (urine) for females of reproductive potential prior to PDT (in case urine pregnancy test is positive, another blood draw is acceptable to verify subject's pregnancy)
- Preparation of treatment field and application of study medication according to treatment description in [Section 8.3](#)

- Date and time of study drug application and removal will be recorded. If a subsequent illumination is planned, a staggered application of IMP has to be performed (15 min time interval) in order to ensure similar incubation times.
- Illumination of treatment field with PDT lamp(s) until a total light dose of 37 J/cm² is achieved (according to treatment description in [Section 8.4](#))
- Duration of illumination and distance between PDT lamp(s) and the treatment field will be documented. Otherwise, reasons for not meeting the requirements must be given. The duration, reason, and frequency of any interruptions and any additional pain-relieving measures must be recorded if applicable.
- Documentation of concomitant medications/treatments (e.g. for pain management that might be required prior to, during or post illumination) (see [Section 9.2](#) and [Table 4](#))
- Documentation of facial care products use (facial cleansers and face cream) (see [Section 9.2](#))
- Assessment of application site pain during illumination via NRS-11
- Documentation of (S)AEs (including ADEs), application site skin reactions and application site discomfort (e.g. after IMP application, prior to, during and post illumination)
- Instruct subject about forbidden concomitant medications/treatments (see [Section 9.2](#) and [Table 4](#))
- Inform subjects to avoid sunlight, prolonged or intense light (e.g., tanning beds, sun lamps) on treatment field(s) for approximately 48 hours following treatment whether exposed to illumination or not.

Please proceed for retreated subjects with the phone call 2 after 1 week and Visit 4b (see Sections [10.1.6](#) and [10.1.7](#)).

10.1.5 Visit 4a (tolerability & safety assessment, 8 (± 1) weeks post PDT-1), Final Visit

- Clinical assessment of acne severity (IGA and mIGA, lesion counts (inflammatory, non-inflammatory lesions, nodules, cysts)) and acne scars by investigator
- Assessment of esthetic appearance by investigator
- If site is equipped with the Canfield Visia-CR[®] system: generation of pictures of subject's facial lesions with Canfield Visia-CR and subsequent centralized assessment of the subjects' lesions, erythema, skin texture, Coproporphyrin III (CPIII) and PAS/mPAS. In case of a discrepancy to the assessment of the investigator, and Canfield, an independent evaluator may perform a third assessment (IGA/mIGA) based on the corresponding pictures (only upon sponsor's request; see [Section 10.2.3](#))
- General physical examination
- Measurement of vital signs (HR, BP)
- Clinical laboratory tests (including routine hematology, blood chemistry, serum pregnancy test, and urinalysis)

- Esthetic outcome and satisfaction with PDT by subject (by subject questionnaire)
- Documentation of (S)AEs, including application site skin reactions and application site discomfort
- Documentation of concomitant medications/treatments (see [Section 9.2](#) and [Table 4](#))
- Documentation of facial care products use (facial cleansers and face cream) (see [Section 9.2](#))

10.1.6 Phone call 2 (1 week ($\pm$ 2 days) post PDT-2)

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

The following information will be collected during the phone contact:

- Documentation of (S)AEs including application site skin reactions and application site discomfort, and concomitant medications/treatments
- Instruct subject about forbidden concomitant medications/treatments (see [Section 9.2](#) and [Table 4](#))

10.1.7 Visit 4b (tolerability & safety assessment, 4 ($\pm$ 1) weeks post PDT-2)

- Clinical assessment of acne severity (IGA and mIGA and lesions count (numbers of inflammatory, noninflammatory lesions, nodules, cysts)) by investigator and decision if the subject will require a 3rd PDT
- If site is equipped with the Canfield Visia-CR[®] system: generation of pictures with Canfield Visia-CR of subject's facial lesions. A centralized assessment of the subject's lesions, erythema, skin texture, CPIII and PAS/mPAS will be only conducted in case the subject drops out as last observation carried forward.
- Measurement of vital signs (HR, BP)
- Documentation of (S)AEs, including application site skin reactions and application site discomfort
- Documentation of concomitant medications/treatments (see [Section 9.2](#) and [Table 4](#))

For responders, please proceed for the next visit with Visit 5a.

For non-responders, please continue with the following treatment:

- Evaluation of dosing day exclusion criteria
- Pregnancy test (urine) for females of reproductive potential prior to PDT (in case urine pregnancy test is positive, another blood draw is acceptable to verify subject's pregnancy)
- Preparation of treatment field and application of study medication according to treatment description in [Section 8.3](#)

- Date and time of study drug application and removal will be recorded. If a subsequent illumination is planned, a staggered application of IMP has to be performed (15 min time interval) in order to ensure similar incubation times.
- Illumination of treatment field with PDT lamp(s) until a total light dose of 37 J/cm² is achieved (according to treatment description in [Section 8.4](#))
- Duration of illumination and distance between PDT lamp(s) and the treatment field will be documented. Otherwise, reasons for not meeting the requirements must be given. The duration, reason, and frequency of any interruptions and any additional pain-relieving measures must be recorded if applicable.
- Documentation of concomitant medications/treatments (e.g. for pain management that might be required prior to, during or post PDT) (see [Section 9.2](#) and [Table 4](#))
- Documentation of facial care products use (facial cleansers and face cream) (see [Section 9.2](#))
- Assessment of application site pain during illumination via NRS-11
- Documentation of (S)AEs (including ADEs), application site skin reactions, application site discomfort (e.g. after IMP application, prior to, during and post illumination)
- Instruct subject about forbidden concomitant medications/treatments (see [Section 9.2](#) and [Table 4](#))
- Inform subjects to avoid sunlight, prolonged or intense light (e.g., tanning beds, sun lamps) on treatment field(s) for approximately 48 hours following treatment whether exposed to illumination or not.

Please proceed for retreated subjects with phone call 3 after 1 week and Visit 5b (see [Sections 10.1.9](#) and [10.1.10](#)).

10.1.8 Visit 5a (tolerability & safety assessment, 8 (± 1) weeks post PDT-2), Final Visit

- Clinical assessment of acne severity (IGA, mIGA, lesion count (numbers of inflammatory and non-inflammatory lesions, nodules, cysts)) and acne scars by investigator
- Assessment of esthetic appearance by investigator
- If site is equipped with the Canfield Visia-CR[®] system: generation of pictures of subject's facial lesions with Canfield Visia-CR and subsequent centralized assessment of the subjects' lesions, erythema, skin texture, Coproporphyrin III (CPIII) and PAS/mPAS. In case of a discrepancy to the assessment of the investigator, and Canfield, an independent evaluator may perform a third assessment (IGA/mIGA) based on the corresponding pictures (only upon sponsor's request; see [Section 10.2.3](#))
- General physical examination
- Measurement of vital signs (HR, BP)

- Clinical laboratory tests (including routine hematology, blood chemistry, serum pregnancy test, and urinalysis)
- Esthetic outcome and satisfaction with PDT by subject (by subject questionnaire)
- Documentation of (S)AEs, including application site skin reactions and application site discomfort.
- Documentation of concomitant medications/treatments (see [Section 9.2](#) and [Table 4](#))
- Documentation of facial care products use (facial cleansers and face cream) (see [Section 9.2](#))

10.1.9 Phone call 3 (1 week ($\pm$ 2 days) post PDT-3)

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

The following information will be collected during the phone contact:

- Documentation of (S)AEs including application site skin reactions and application site discomfort, and concomitant medications/treatments

10.1.10 Visit 5b (tolerability & safety assessment, 4 ($\pm$ 1) weeks post PDT-3)

- Clinical assessment of acne severity (IGA, mIGA and lesion count (numbers of inflammatory and non-inflammatory lesions, cysts and nodules) by investigator
- If site is equipped with the Canfield Visia-CR[®] system: generation of pictures with Canfield Visia-CR of subject's facial lesions. A centralized assessment of the subject's lesions, erythema, skin texture, CPIII and PAS/mPAS will be only conducted in case the subject drops out as last observation carried forward.
- Measurement of vital signs (HR, BP)
- Documentation of (S)AEs, including application site skin reactions and application site discomfort, and of concomitant medications/treatments (see [Section 9.2](#) and [Table 4](#))
- Documentation of facial care products use (facial cleansers and face cream) (see [Section 9.2](#))

10.1.11 Visit 6 (tolerability & safety assessment, 8 ($\pm$ 1) weeks post-PDT-3), Final Visit

- Clinical assessment of acne severity (IGA, mIGA, lesion count (numbers of inflammatory and non-inflammatory lesions, nodules, cysts)) and acne scars by investigator
- Assessment of esthetic appearance by investigator

- If site is equipped with the Canfield Visia-CR[®] system: generation of pictures of subject's facial lesions with Canfield Visia-CR and subsequent centralized assessment of the subjects' lesions, erythema, skin texture, Coproporphyrin III (CPIII) and PAS/mPAS. In case of a discrepancy to the assessment of the investigator, and Canfield, an independent evaluator may perform a third assessment (IGA/mIGA) based on the corresponding pictures (only upon sponsor's request; see [Section 10.2.3](#))
- General physical examination
- Measurement of vital signs (HR, BP)
- Clinical laboratory tests (including routine hematology, blood chemistry, serum pregnancy test, and urinalysis)
- Esthetic outcome and satisfaction with PDT by subject (by subject questionnaire)
- Documentation of (S)AEs, including application site reactions and application site discomfort
- Documentation of concomitant medications/treatments (see [Section 9.2](#) and [Table 4](#))
- Documentation of facial care products use (facial cleansers and face cream) (see [Section 9.2](#))

10.2 Assessments

10.2.1 Evaluation of demographic data

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

- Sex
- Age
- Race
- Ethnicity

10.2.2 Body Measures

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

- Height
- Weight

10.2.3 Clinical criteria for diagnosis of acne vulgaris

IGA Scores

- At all visits, acne severity will be determined by the investigator using 2 methods: (i) grading according to the 5-point Investigator Global Assessment rating score (IGA) and modified IGA (mIGA) rating score, (ii) lesion counting.

- At screening (Visit 1) and baseline (Visit 2), each subject's disease status should be moderate or severe according to IGA score (see [Table 5](#)), and subjects should have at least 20 inflammatory and at least 20 non-inflammatory lesions on the face.
- The co-primary endpoints are calculated based on the assessments performed at 8 weeks after last PDT (Visit 4a, Visit 5a or Visit 6).
- At screening, baseline and the Final Visit, an additional evaluation by an independent evaluator may be performed upon sponsor request, in case of a discrepancy among the assessment by the investigator and the Canfield algorithm, if applicable.

Table 5: Investigator's Global Assessment (IGA) severity 5 scale of acne vulgaris severity

IGA of acne vulgaris severity		
0	'Clear'	No acne lesions present. Residual hyperpigmentation and erythema may be present
1	'Almost clear'	A few scattered comedones and a few small papules
2	'Mild'	Easily recognizable; less than half the face is involved. Some comedones and some papules and pustules
3	'Moderate'	More than half the face is involved. Many comedones, papules and pustules. One nodule may be present
4	'Severe'	Entire face is involved, covered with comedones, numerous papules and pustules, and few nodules and cysts

Modified Investigator's Global Assessment severity 5 scale of acne vulgaris severity – excluding comedones:

Table 6: Modified Investigator's Global Assessment (mIGA) severity 5 scale of acne vulgaris severity – excluding comedones

mIGA of acne vulgaris severity		
0	'Clear'	Residual hyperpigmentation and erythema may be present (comedones not considered)
1	'Almost clear'	A few small papules (comedones not considered)
2	'Mild'	Easily recognizable; less than half the face is involved. Some papules and pustules (comedones not considered)
3	'Moderate'	More than half the face is involved. Many papules and pustules. One nodule may be present (comedones not considered)
4	'Severe'	Entire face is involved, covered with numerous papules and pustules, and few nodules and cysts (comedones not considered)

Centralized assessment

IGA, mIGA and lesion counts are assessed/performed by investigators during all clinical visits. Although the investigator's assessment is the basis for eligibility and efficacy, this approach may lead to site-specific differences in the assessment of severity. To implement a common standard across multiple clinical sites (not all sites might be equipped with the Canfield Visia-CR[®] system at all times), an automated assessment of acne severity based on photos captured by the Canfield Visia-CR system can be performed. In case of a mismatch between the clinical assessment by the Investigator and the automated Canfield assessment, an independent evaluator may be asked to provide a 3rd severity assessment. Although assessment of acne severity, including the determination of subject's eligibility and calculation of the primary outcome of the study will be based on the investigators assessment only, the acne grading by the Canfield system will be analyzed as an exploratory endpoint. Any data provided by the independent evaluator will not directly impact the IGA score or the Parametric Acne Score (PAS). Instead, this data will be separately listed and will be further evaluated in additional supplementary analyses (if applicable). Details will be outlined in the statistical analysis plan.

The automated assessment by the Canfield algorithm includes an automated count of inflammatory and non-inflammatory lesions, measurement of erythema, skin texture and CPIII. Based on these parameters, a PAS (1) or modified PAS (mPAS) will be calculated. Whereas PAS takes into account all of these parameters and is analog to IGA, mPAS will not take into account the CPIII fluorescence measurements and will be analog to the mIGA. A PAS of 0 to <0.1 is classified as clear (IGA = 0), of 0.1 to <0.15 as almost clear (IGA = 1), of 0.15 <to 0.35 (0.3 in case of subjects with Fitzpatrick skin type I) as mild (IGA = 2), of 0.35 to <0.7 (0.3 in case of subjects with Fitzpatrick skin type I) as moderate (IGA = 3) and a PAS of 0.7 and higher is rated as severe (IGA = 4). The PAS and mPAS scores can be used as an investigator-independent evaluation to grade acne severity, without site-specific bias. A set of photos with different lighting and filters will be taken at every visit while the sites are equipped with the Canfield system. Only photos captured at Visit 1, Visit 2 and Final Visit will be systematically analyzed with the Canfield algorithm and reported in the eCRF.

All photos will be anonymized after upload to the Canfield database. The results will be reported to the site staff for data entry into the eCRF.

10.2.4 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 Appendix A (see Section 18.1).

10.2.5 Acne scar assessment

Acne scars will be assessed at screening (Visit 1), at baseline (Visit 2) and at the Final Visit (Visit 4a, Visit 5a, or Visit 6) according to the following criteria:

- Acne scar severity (clear- almost clear- mild- moderate- severe-very severe) – Physical Global Scale for Acne Scars (PGA) (45).

- 0 = clear, no visible scars from acne
- 1 = almost clear, hardly visible scars from about 100 cm away (personal distance)
- 2 = mild, easy recognizable, less than half of the face involved
- 3 = moderate, more than half of the face involved
- 4 = severe, entire face involved
- 5 = very severe, entire face with prominent atrophic or hypertrophic scars

- Acne scars by type (atrophic (ice pick, boxcar, rolling), hypertrophic, keloid)

The following question will be answered by the investigator at the Final Visit (Visit 4a, Visit 5a, or Visit 6):

- Did acne scarring improve (overall improvement) – yes/no?

10.2.6 Assessment of esthetic appearance and of subject satisfaction

Assessment of esthetic appearance by the investigator

Esthetic appearance will be assessed at the Final visit (Visit 4a, Visit 5a, or Visit 6). The study personnel will assess the esthetic appearance of the treatment field using a 4-point scale as follows:

0 = very good: The esthetic appearance is rated as very good if the appearance at a given visit has significantly improved compared to baseline.

1 = good: The esthetic appearance is rated as good if the appearance at a given visit has improved compared to baseline.

2 = satisfactory: The esthetic appearance is rated as satisfactory if the appearance at a given visit is comparable to baseline.

3 = unsatisfactory: The esthetic appearance is rated as unsatisfactory if the appearance at a given visit has worsened compared to baseline

Assessment of subject satisfaction and esthetic outcome

Subjects will be asked to rate their satisfaction regarding the overall esthetic outcome at the Final visit (Visit 4a, Visit 5a, or Visit 6) using a 4-point scale as follows:

0 = very good

1 = good

2 = satisfactory

3 = unsatisfactory

Additionally, subjects will be asked:

- if they are satisfied with the treatment (yes/no)
- if they would choose PDT treatment in the future again (yes/no)
- how they would rate the PDT treatment in comparison with other treatment modalities for Acne vulgaris (worse/similar/better)

Only the subjects' evaluation of overall esthetic outcome and whether the subject would choose PDT again in the future is reported in the eCRF.

10.2.7 Safety

Physical examination

The physical examination will involve head and neck, skin, lymph nodes, thorax including heart and lungs, abdomen, and musculoskeletal, peripheral vascular and nervous system status. In the eCRF, only abnormal physical examination findings are required to be reported. Abnormal findings that are considered clinically significant will be documented in the medical history (Visit 1) or afterwards as AEs. In case of a missing examination a reason should be provided.

Vital signs

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

Safety laboratory

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 at the Final Visit (Visit 4a, Visit 5a, or Visit 6). Pregnancy tests will be performed to ensure the safety of the female subjects with reproductive potential (see below). The total blood loss for safety laboratory examinations will be approximately 21 ml. The following parameters will be measured:

- *Clinical chemistry parameters*
glucose (non-fasting), 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.

The following central laboratory is responsible for safety laboratory assessments:

ACM Global Laboratories
160 Elmgrove Park
Rochester, NY 14624

Urine

An approx. 30 mL urine sample will be collected at screening (Visit 1) and at Final Visit (Visit 4a, Visit 5a, or Visit 6), respectively. The following parameters will be measured:

- *Urinalysis parameters*
Leukocytes, Nitrite, Urobilinogen, protein, pH, Blood, Specific Gravity, ketones, Bilirubin, Glucose and ascorbate.

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

Pregnancy test (if applicable)

A serum pregnancy test (β -human chorionic gonadotropin (β -hCG) test) will be performed at screening (Visit 1), and at the Final Visit (Visit 4a, Visit 5a, or Visit 6) for females of reproductive potential. At PDT-visits (Visit 2, Visit 3 and Visit 4b (if required)), a urine dipstick pregnancy test will be performed prior to each PDT. In case of a positive urine pregnancy test, the subject cannot receive PDT during the visit and a serum pregnancy test can be performed to confirm the pregnancy. If the positive pregnancy test occurred after PDT-1, the pregnancy must be reported as described in [Section 11.3.1.2](#).

Adverse events

During the study, all (S)AEs have to be recorded as outlined in [Section 11](#). Severity-assessment is outlined in more detail in [Section 11.1.1](#).

If possible, each subject should be assessed by the same investigator/staff personnel throughout the study.

Application site discomfort

At PDT visits (Visit 2, Visit 3 (if required) and Visit 4b (if required)), application site discomfort during illumination will be assessed. At the phone call(s), Visit 4a, Visit 5a, Visit 5b and Visit 6, respectively, application site discomfort since last illumination will be assessed asking non-leading questions (by subject questionnaire) like “Have you noticed anything in the treatment area since we last saw you?”.

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 and application site skin reactions. Application site reactions inside the treatment field will be evaluated by the investigator (or delegate) and documented on the AE eCRF page after PDT at baseline (Visit 2) and at each subsequent clinical visit. In addition, subjects will be asked about application

site reactions during the phone call(s) using non-leading questions like “How did you feel since your photodynamic treatment session?”.

During phone calls, AEs including application site skin reactions will be assessed by asking for AEs using non-leading questions as described above.

Assessment of pain at the application site during illumination

At Visit 2, and at Visit 3 and Visit 4b for retreated subjects, subjects will assess the pain experienced **during illumination** using an 11-point NRS ranging from 0 (no pain at all) to 10 (worst possible pain) (Appendix B, see [Section 18.2](#)).

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 and this rating is documented in the corresponding eCRF page, it will not be documented as an additional 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.

11 ADVERSE EVENTS

11.1 Definitions

11.1.1 Adverse events

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

For the purpose of the study, clinically relevant abnormal results of diagnostic procedures including abnormal laboratory findings (e.g. requiring unscheduled diagnostic procedures or treatment measures or resulting in withdrawal from the study) discovered at screening will be related to medical history or are considered to be AEs if they are detected post screening. Any AE with onset after IMP application and before the completion of the subject's last Visit is considered as treatment emergent adverse event (TEAE).

Maximum severity should be assigned to one of the following categories:

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

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

Examples of AEs include 1 of the following or a combination of 2 or more of these factors:

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

AEs can be categorized as "non-serious" and "serious" (see [Section 11.1.2](#)).

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

these measures are not AEs, if the condition(s) was (were) known before the study period (see [Section 9.1](#)) and do not worsen during the study. In the latter case, the condition should be reported as medical history.

11.1.2 Serious adverse events

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

- Results in death.
- Is life-threatening.
“Life-threatening” means that the subject was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
This means that hospital inpatient admission or prolongation of a hospital stay were required for the treatment of the AE, or that they occurred as a consequence of the event.
- Results in persistent or significant disability or incapacity.
“Persistent or significant disability or incapacity” means a permanent or significant and substantial disruption of a person’s ability to carry out normal life functions”.
- 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 and may require interventions to prevent 1 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.

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

11.1.3 Alert terms and other reasons for expedited reporting to Pharmacovigilance

Adverse Event of Special Interest (AESI): 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 subject 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. Immediate reporting is required even if the event is non-serious. For further details on reporting please refer to [Section 11.3.1.1](#). The subject should be referred to a neurologist for further evaluation and confirmation of the diagnosis.

For details on known adverse reactions see Ameluz® PI 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 11.3.1.2](#).

11.1.4 Investigational medicinal product complaints

Complaints associated with the IMP quality must be reported to the CRO via e-mail.

11.1.5 Investigational medical device complaints

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

Nevertheless, ADEs occurring in third persons as well as technical complaints associated with the IMDs must be reported to the CRO via e-mail.

ADEs reported by the treated subject must be reported via the eCRF and on the AE log.

11.2 Period of AE collection

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

- AEs developing between signing the ICF until Visit 2 with a suspected causal relationship to any study procedures will be considered and documented as an PTAE.
- TEAEs are AEs occurring between the first IMP application at Visit 2 (baseline) and the completion of the Final Visit (Visit 4a, Visit 5a or Visit 6).

- If an investigator detects an SAE in a subject after the Final Visit, and considers the event possibly related to prior study treatment or procedures, s/he should report this event to the pharmacovigilance department of the sponsor (see [Section 11.3.1](#)).

11.3 Documentation and reporting of adverse events by investigator

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

The following approach will be taken for documentation:

- **All AEs** (whether serious or non-serious) must be documented throughout the study.
- If the AE is serious (see [Section 11.1.2](#)) or an AESI, the investigator must complete, in addition to the “Adverse Event” page in the eCRF, an “SAE Report” form at the time the investigator became aware of the SAE or AESI. This form must be marked as “initial” and be sent immediately (within 24 h) to the sponsor’s Pharmacovigilance department by email or fax (according to Biofrontera’s Standard Operating Procedure (SOP)). SAEs or the AESI must be identified as such in eCRF by stating the applicable SAE criteria that were met.
- When a “significant overdose” of IMP occurs without an AE or in other situations where the sponsor requires an expedited report without an AE (see [Section 11.1.3](#)), this information should be provided by the investigator via the “Serious Adverse Event/Expedited Report from a Clinical Trial for Combination products form”. It should be clearly stated that no AE was observed. In this case, there is no need to complete the “Adverse Event” page in the eCRF.
- The following details regarding AEs are required:
 - confirmed medical diagnosis or symptoms (if applicable)
 - location (inside/outside treatment field)
 - time frame (by providing start/stop date and time)
 - severity (see [Section 11.1.1](#))
 - outcome (recovered/resolved, recovering/resolving; recovering with sequelae, not recovered/not resolved, fatal, unknown)
 - seriousness criteria (if applicable), and
 - AESI (yes/no), and
 - if the AE is related to IMP only, IMD only, or both (cannot be ambiguously assigned to one or the other).

- The causality/relatedness of AEs has to be assessed:
 - UNRELATED: AEs that are judged to be clearly and incontrovertibly due to a cause other than the IMP/IMD and study procedure (concurrent disease etc.).
 - UNLIKELY RELATED: the temporal sequence is atypical, and the AE does not follow a known pattern of response to IMP/IMD; another causative factor is present but causal role of the study drug cannot be excluded.
 - POSSIBLY RELATED: either an event that is temporally associated with the use of the IMP/IMD or a known pharmacological effect/associated reaction, which is also recognized with another concomitant therapy/disease or other external cause.
 - PROBABLY RELATED: appropriate temporal association, known pharmacological effect, recognized to be an associated IMP/IMD reaction and for which no other possible cause is evident.
 - DEFINITELY RELATED: the reaction has occurred with this IMP/IMD previously (i.e. positive re-challenge) and there is an appropriate temporal relationship between therapy and reaction; and the reaction follows a known or expected response pattern to the suspected drug.

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

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

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

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

11.3.1 Immediate Reporting

11.3.1.1 Reporting of SAEs and AESIs to CRO

SAEs or AESIs observed throughout the study must be documented on an “SAE Report” form in accordance with instructions for completing the “SAE Report” form. This form and the instructions will be provided in the investigator file and must be completed and supplied immediately to the CRO within 24 h after becoming aware of the SAE (21CFR§ 312.32, 21CFR§ 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 the following contact data:

Email: [REDACTED] PPD

Fax: [REDACTED] PPD

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

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

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

Note:

For regulatory reporting purposes, events which are assessed by the CRO 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 CRO 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 CRO and the Investigators will ensure that all legal reporting requirements to the competent authorities and the IRB(s) are met (see [Section 11.4.2](#)).

11.3.1.2 Reporting of pregnancies to CRO

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

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

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

11.3.1.3 Reporting of USADEs to the CRO and to IRBs by investigator

Events which can be clearly assigned to the IMD and which are assessed by the investigator as “possibly, probably or definitely related” to the IMD and which are both serious and unanticipated will be considered as unanticipated serious adverse device effect (USADE). A report of any USADE occurring during an investigation shall be submitted to the reviewing IRB and the CRO within 10 working days after the investigator first learns of the effect (21 CFR §812.150 (a)(1)).

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

Note: Reporting of USADEs to the sponsor is equal to SAE reporting described in [Section 11.3.1.1](#).

11.3.2 Unblinding

If the unblinding (throughout the study) is performed by the investigator due to a medical requirement, the subject will discontinue trial participation (see [Section 8.6](#) for additional information).

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

11.4 Documentation and reporting of adverse events by sponsor/ CRO

11.4.1 Determination of expectedness, Reference Safety Information

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

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

11.4.2 Reporting of SUSARs and USADEs to competent authorities and investigators by sponsor

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

The sponsor will also report USADEs to the FDA, central IRB and to all investigators.

In case of local IRBs, the sponsor will cooperate with the responsible site personnel to ensure submission of SUSARs and USADEs to the local IRB within the applicable timelines.

11.4.3 Periodic reporting of adverse events 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 (14th June, in agreement with authorities). The same report will also be submitted to the IRB(s) to ensure a continuing review of the project.

11.4.3.1 Development safety update report (DSUR)

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

11.5 Continuous risk assessment

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

12 WITHDRAWALS

12.1 Withdrawal of subjects

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

- At their own request (withdrawal of informed consent).
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being (e.g. due to AE(s)).
- If subject was unblinded (e.g. SUSAR)
- Upon request by sponsor

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 due to investigator's decision, e.g. due to an AE, the reason has to be documented as reason of withdrawal.

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

For subjects that may not be treated due to screening failures or who decide to terminate the study prior to treatment, at least the following parameters must be documented in the eCRF: date of informed consent, demographic data, lesion counts, IGA/mIGA, PAS/mPAS (if available), Fitzpatrick skin type and date/reason for screening failure/withdrawal.

Subjects must be withdrawn from the IMP under the following circumstance:

- Pregnancy. In case a pregnancy is identified at Visit 3/PDT-2 or Visit 4b/PDT-3, the subject must not receive additional PDT and only receive Final Visit assessments.

12.2 Replacement of subjects

Subjects who discontinue will not be replaced.

12.3 Withdrawal of samples

Not applicable.

12.4 Withdrawal of pictures

As centralized assessment is based on pictures taken from subjects, any pictures taken prior to withdrawal cannot be withdrawn and will be considered during analysis of study data.

13 EMERGENCY PROCEDURES

13.1 Emergency CRO contact

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

PPD (Biofrontera contact person in the USA)

13.2 Emergency identification of investigational medicinal products

There is no apparent reason to break the randomization code in the event of an adverse drug reaction. The subjects receive all treatments on a relatively small treatment area. In the case of an adverse reaction triggered by the respective treatment, no further treatment is scheduled. There is no substance-specific treatment for adverse reactions. Therefore, special emergency identification procedures are not applicable to this trial.

13.3 Emergency treatment

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

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

14 STATISTICAL PROCEDURES

14.1 General considerations

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

Statistical testing will be applied to compare both active treatment groups (1h or 3h incubation time) vs. vehicle (both incubation times combined). Confirmatory hypothesis tests will be performed for the 2 co-primary efficacy endpoints comparing 3 h incubation time BF-200 ALA vs. vehicle and 1 h incubation time BF-200 ALA vs. vehicle. Due to the Phase II type of this study, a one-sided significance level of 5% ($\alpha=0.05$) will be used. The primary analysis will be performed on the full analysis set (FAS) dataset. The analysis will be repeated as supplementary analysis for the per-protocol set (PPS) dataset. Additionally, a second supplementary analysis will only include subjects which did not switch any cleanser. As further supplementary analysis, the co-primary efficacy endpoints will be displayed separately for subjects treated with vehicle 1 hour incubation time vs. 3 hours incubation time. Further sensitivity analyses or supplementary analyses will be specified in the SAP, if required.

The pairwise comparison will always start with the 3 h BF-200 ALA vs. vehicle comparison followed by 1 h BF-200 ALA vs. vehicle comparison. A hierarchical testing procedure will be used to ensure the family wise error rate. If the comparison 3 h BF-200 ALA vs. vehicle for both co-primary endpoints is significant, the co-primary endpoint will be analyzed comparing 1 h BF-200 ALA vs. vehicle.

Further secondary efficacy variables will be analyzed in an exploratory manner.

Selected secondary endpoints will be analyzed with two-sided statistical testing procedures using a significance level of 10% ($\alpha=0.1$). Where appropriate, two-sided local 90% CIs of differences between BF-200 ALA (1 h and 3 h incubation time) and vehicle will be presented. As the secondary endpoint analysis, including the calculation of CIs, and the exploratory endpoints are not confirmatory, an adjustment for multiplicity is not considered 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.

Subjects who withdraw from study participation before randomization will be considered as screening failures. The demographic data from screening failures are entered into the clinical database and will not be passed through the data cleaning process. Their data are listed separately from data of treated subjects.

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

14.2 Analysis variables

If not otherwise stated, the following endpoint calculations will be conducted based on the assessments performed by the investigator.

The primary objective of the study is to compare the efficacy of BF-200 ALA PDT (containing 7.8% 5-aminolevulinic acid (ALA) as active ingredient) with vehicle PDT, utilizing BF-RhodoLED® illumination, in the treatment of moderate to severe Acne vulgaris on the face.

The co-primary efficacy variables are:

1. Relative change in the number of inflammatory lesions (percentage change from baseline) 8 weeks after the last PDT as assessed by investigator.
2. Treatment success defined by a minimum improvement of the mIGA score by at least 2 assessed 8 weeks after the last PDT and resulting in an mIGA score of 0 (clear) or 1 (almost clear).

The secondary objective of the study is to evaluate the safety and secondary efficacy parameters related to BF-200 ALA/BF-RhodoLED® PDT for the treatment of moderate to severe Acne vulgaris.

Secondary efficacy variables:

1. Absolute and/or percentage change from baseline in the number of lesions as assessed by investigator:
 - a. Inflammatory lesions – 4 weeks after the last PDT
 - b. Inflammatory lesions – 8 weeks after the last PDT
 - c. Non-inflammatory lesions – 4 weeks after the last PDT
 - d. Non-inflammatory lesions – 8 weeks after the last PDT
 - e. Inflammatory & non-inflammatory lesions – 4 weeks after the last PDT
 - f. Inflammatory & non-inflammatory lesions – 8 weeks after the last PDT
2. Absolute and percentage change from baseline in the number of lesions as assessed by investigator:
 - a. Inflammatory lesions – 4 weeks after PDT-1
 - b. Non-inflammatory lesions – 4 weeks after PDT-1
 - c. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-1
 - d. Inflammatory lesions – 4 weeks after PDT-2
 - e. Non-inflammatory lesions – 4 weeks after PDT-2
 - f. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-2
 - g. Inflammatory lesions – 4 weeks after PDT-3
 - h. Non-inflammatory lesions – 4 weeks after PDT-3
 - i. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-3
 - j. Inflammatory lesions – 8 weeks after PDT-3
 - k. Non-inflammatory lesions – 8 weeks after PDT-3
 - l. Inflammatory & non-inflammatory lesions – 8 weeks after PDT-3

3. Absolute and percentage change from baseline in the number of lesions as assessed by investigator, only for responders at Visit 3 /4 weeks after PDT-1:
 - a. Inflammatory lesions – 4 weeks after PDT-1
 - b. Inflammatory lesions – 8 weeks after PDT-1
 - c. Non-Inflammatory lesions – 4 weeks after PDT-1
 - d. Non-Inflammatory lesions – 8 weeks after PDT-1
 - e. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-1
 - f. Inflammatory & non-inflammatory lesions – 8 weeks after PDT-1
4. Absolute and percentage change from baseline in the number of lesions as assessed by investigator, only for responders at Visit 4b /4 weeks after PDT-2:
 - a. Inflammatory lesions – 4 weeks after PDT-2
 - b. Inflammatory lesions – 8 weeks after PDT-2
 - c. Non-Inflammatory lesions – 4 weeks after PDT-2
 - d. Non-Inflammatory lesions – 8 weeks after PDT-2
 - e. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-2
 - f. Inflammatory & non-inflammatory lesions – 8 weeks after PDT-2
5. Absolute and percentage change from baseline in the number of lesions as assessed by investigator, only for responders at Visit 5b /4 weeks after PDT-3:
 - a. Inflammatory lesions – 4 weeks after PDT-3
 - b. Inflammatory lesions – 8 weeks after PDT-3
 - c. Non-Inflammatory lesions – 4 weeks after PDT-3
 - d. Non-Inflammatory lesions – 8 weeks after PDT-3
 - e. Inflammatory & non-inflammatory lesions – 4 weeks after PDT-3
 - f. Inflammatory & non-inflammatory lesions – 8 weeks after PDT-3
6. Change in the number of nodules & cysts 8 weeks after the last PDT (absolute change and percentage change from baseline) as assessed by investigator.
7. Treatment success defined by a minimum improvement of the IGA by at least 2, 8 weeks after the last PDT.
8. Improvement of the IGA, 8 weeks after the last PDT.
9. Improvement of the mIGA, 8 weeks after the last PDT.
10. Improvement of scar severity and overall esthetic appearance 8 weeks after last PDT (assessed by investigator).
11. Subject satisfaction regarding esthetic outcome and treatment, 8 weeks after the last PDT.

Safety variables

Safety analysis variables include:

- Frequency and severity of adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESI), and treatment-emergent adverse events (TEAEs). TEAEs are defined as all AEs with onset after first treatment with IMP up to the last visit of the subject (approximately 8 weeks post last PDT).
- Application site skin reactions, assessed by the investigators.
- Application site discomfort reported by the subjects.
- Pain during illumination, reported by the subjects (pain will be assessed on an 11-point numeric rating scale).
- Vital signs data.
- Safety laboratory data.
- Physical examinations data.

Exploratory variables

1. Change in the number of inflammatory and/or non-inflammatory lesions (absolute change and/or percentage change from baseline) as assessed by the Canfield algorithm for:
 - a. Inflammatory lesions – 8 weeks after the last PDT
 - b. Non-inflammatory lesions – 8 weeks after the last PDT
 - c. Inflammatory & non-inflammatory lesions – 8 weeks after the last PDT
2. Treatment success defined by a minimum improvement of the PAS equivalent to an improvement of IGA by at least 2, assessed by the Canfield algorithm 8 weeks after the last PDT (see [Section 10.2.3](#)).
3. Treatment success defined by a minimum improvement of the mPAS equivalent to an improvement of mIGA by at least 2, assessed by the Canfield algorithm 8 weeks after the last PDT (see [Section 10.2.3](#)).

14.3 Analysis sets

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

- Consented set: All subjects who provided informed consent to participate in the study.

- 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 and secondary 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 endpoints and may also be used for selected analysis of secondary endpoints.

14.4 Estimands

The primary objective of the study is to compare the efficacy of BF-200 ALA PDT (containing 7.8% 5-aminolevulinic acid (ALA) as active ingredient) with vehicle PDT, utilizing BF-RhodoLED® illumination, in the treatment of moderate to severe Acne vulgaris on the face.

The efficacy endpoints will be analyzed focusing on the co-primary estimands I and II.

The following possible intercurrent events are considered:

- a) the use of medication with immunomodulating properties in a temporal relation to PDT which might influence the efficacy of the treatment,
- b) use or change of cleansers and soaps during the trial,
- c) pain during illumination as the main disadvantage of PDT treatment which may lead to refusal to undergo the 2nd or 3rd PDT treatment,
- d) treatment discontinuation,
- e) postponement of 2nd or 3rd PDT treatment.

The treatment performed aims to evaluate the study objective by randomizing the subjects to BF-200 ALA or vehicle. After administration of the IMP, subjects will remain inside for 1 h + 5 min or 3 h + 10 min, respectively. Incubation with IMP is followed by a 10 min illumination with BF-RhodoLED®. Each subject will receive up to 3 PDTs at a 4-week interval. The final assessment will be performed 8 weeks post last PDT.

Co-primary estimand I is defined by:

- **Population**: The population targeted by the clinical questions will be represented by the entire trial population defined through inclusion / exclusion criteria (Full analysis set). The target population of this trial are subjects suffering from moderate to severe acne. As severity increase among others with pubertal age and lasts until adulthood

subjects of 16 years of age will be included (46). A minimum of 20 inflammatory and 20 non-inflammatory lesions are required per subject to enable a profound assessment. No further demographic factors influencing acne development are considered.

- Variable: Continuous response variable defined as the percent change from baseline in number of inflammatory lesions 8 weeks after the last PDT.
- Intercurrent event (ICE): The occurrence of all intercurrent events will be handled using the treatment-policy strategy. All values will be used regardless of occurrence of the above mentioned intercurrent events prior 8 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 median of percent changes from baseline in number of inflammatory lesions 8 weeks after the last PDT will be calculated for the treatment groups. BF-200 ALA, 1h or 3h incubation, will be compared to vehicle (all subjects treated with vehicle independent from incubation time) using the difference in median values. Two one-sided Wilcoxon rank-sum tests will be applied to test on superiority of BF-200 ALA vs vehicle. An estimate of the location shift will additionally be used to quantify the treatment effect.

Co-primary estimand II is defined by:

- Population: See co-primary estimand I
- Variable: Treatment success [binary: yes/no], defined by a minimum improvement of the mIGA score by at least 2 assessed 8 weeks after the last PDT and resulting in an mIGA score of 0 (clear) or 1 (almost clear).
- Intercurrent event: See co-primary estimand I
- Population-level summary: The difference in response proportions between treatment conditions 8 weeks after the last PDT will be used to compare BF-200 ALA, 1h or 3h incubation, vs vehicle (all subjects treated with vehicle independent from incubation time). Two one-sided Fisher's exact tests will be applied to test on superiority of BF-200 ALA vs vehicle.

As supplementary analysis, the population of the co-primary estimands I and II will be restricted to the Per-protocol set. Additionally, a second supplementary analysis will only include subjects which did not switch any cleanser. As further supplementary analysis, the co-primary estimands I and II will be displayed separately for subjects treated with vehicle 1 hour incubation time vs. 3 hours incubation time.

The estimands target 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 co-primary estimands, regardless of the use of medications with immunomodulating properties, the use or change of cleansers and soaps, refusal of 2nd or 3rd PDT treatment due to pain, any other type of treatment discontinuation, or postponement of 2nd or 3rd PDT treatment.

The co-primary estimands are based on clinical assessments 8 weeks after the last PDT. If a subject dropped out before the planned visit 8 weeks after the last PDT, or the variable value on this is missing, the results based on the last available visit before the planned visit 8 weeks after last PDT with a non-missing variable value will be used for the primary analysis.

14.5 Handling of missing data

Co-primary efficacy endpoints are based on:

- a) Relative change from baseline in number of inflammatory lesions as assessed by investigator
- b) Treatment success defined by an improvement of the mIGA score (combined assessment)

The co-primary efficacy endpoints are based on clinical assessments 8 weeks after the last PDT. If a subject with at least one assessment after PDT dropped out before the planned visit 8 weeks after the last PDT, or the variable value on this is missing, the results based on the last available visit before the planned visit 8 weeks after last PDT with a non-missing variable value will be used for the primary analysis (last observation carried forward).

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

14.5.1 Handling of photos with insufficient quality/missing analysis by Canfield algorithm

In case the quality of pictures captured by the Canfield Visia-CR system is insufficient, it will be possible to re-capture these visits to generate new pictures and to use those for exploratory endpoint analysis. This will not be possible at PDT-visits.

14.6 Statistical methods

14.6.1 Disposition of subjects and exposure

The number and relative frequencies 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, by treatment (1 h incubation time BF-200 ALA, 3 h incubation time BF-200 ALA, vehicle) and study site.

Premature discontinuation from the study and completion of the study 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.

14.6.2 Demographic and background characteristics

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

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

14.6.3 Evaluation of the Co-Primary Efficacy Endpoints

14.6.3.1 Primary efficacy analysis

The co-primary efficacy variables will be tested for the following hypotheses:

Relative (percentage) change in the number of inflammatory lesions:

The first co-primary null hypothesis (H_{01} , one-sided) is that the relative change in the number of inflammatory lesions (percentage change from baseline taken at Visit 2) assessed 8 weeks after the last PDT in subjects treated with BF-200 ALA is not superior to subjects treated with vehicle. The first co-primary alternative hypothesis (H_{11} , one-sided) is that the relative change in the number of inflammatory lesions for subjects treated with BF-200 ALA is superior to subjects treated with vehicle. Two one-sided Wilcoxon rank-sum tests will be used to test the first co-primary hypothesis on a significance level of 5% ($\alpha=0.05$).

Improvement of mIGA:

The second co-primary null hypothesis (H_{02} , one-sided) is that BF-200 ALA is not superior to subjects treated with vehicle with respect to the success rate. Success is defined as at least a 2-grade improvement in the mIGA score, assessed 8 weeks after the last PDT, and resulting in an mIGA score of 0 (clear) or 1 (almost clear). The second co-primary alternative hypothesis (H_{12} , one-sided) is that success rates for subjects treated with BF-200 ALA are superior to subjects treated with vehicle. Two one-sided Fisher's exact tests will be used to test the secondary co-primary hypothesis on a significance level of 5% ($\alpha=0.05$).

The pairwise comparison will always start with the 3 h BF-200 ALA vs. vehicle comparison followed by 1 h BF-200 ALA vs. vehicle comparison. A hierarchical testing procedure will be used to ensure the family wise error rate. If the comparison 3 h BF-200 ALA vs. vehicle for both co-primary endpoints is significant, the co-primary endpoint will be analyzed comparing 1 h BF-200 ALA vs. vehicle.

As additional exploratory analyses, the co-primary efficacy variables will be analyzed descriptively by subject-based subgroups sex, age group (age categories 16-17, ≥ 18 years), and category of Fitzpatrick skin type at Baseline (I-III, IV-VI) and Acne severity at Baseline (IGA 3 or IGA 4). Subgroup analyses will be conducted both for the FAS and PPS.

14.6.3.2 Secondary efficacy analyses

Secondary efficacy endpoints and exploratory endpoints (see [Section 14.2](#)) will be analyzed in an exploratory way. The analyses on secondary efficacy endpoints will be performed on the FAS dataset. Exploratory endpoints will be analyzed on all subjects from the FAS for whom corresponding data was collected. Secondary efficacy endpoints 1 and 7 will be tested, but the results of these statistical tests will be considered exploratory. These secondary efficacy endpoints will additionally be analyzed for the PPS.

14.6.4 Safety analysis

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. Treatment emergent AESIs, TEAEs leading to death and TEAEs resulting in discontinuation of study will be tabulated using frequency tables if a reasonable number of AEs of this type are observed. In addition, treatment-emergent adverse events (TEAEs) will be summarized for the SAF stratified by age group (16 to 17; 18 or older), sex and Fitzpatrick skin type at Baseline (I-III and IV-VI).

All laboratory values will be classified as normal or abnormal according to the laboratory's normal ranges and indicated as clinically significant or not clinically significant by the investigator. Out of range laboratory values that are considered clinically significant (CS) will be documented in the medical history (Visit 1) or as AEs (Visit 4a, Visit 5a, or Visit 6) and listed as such. Details of further analyses will be specified in the SAP.

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

The physical examination will involve head and neck, skin, lymph nodes, thorax including heart and lungs, abdomen, and musculoskeletal, peripheral vascular and nervous system status. All clinically significant abnormal physical findings will be listed. Details of further analyses will be specified in the SAP.

14.7 Interim analysis

No formal interim analysis will be performed.

14.8 Sample size justification

A total sample size of 126 subjects was estimated. Subjects will be randomized with a ratio of 2:2:1:1 to BF-200 ALA (1 hour incubation), BF-200 ALA (3 hours incubation), vehicle (1 hour incubation), and vehicle (3 hours incubation). Thus, subjects will receive BF-200 ALA with a chance of ~66%. Statistical testing will be applied to compare both active treatment groups vs. vehicle (both incubation times combined).

This sample size will ensure a power of 80% with an alpha level set to 5% ($\alpha = 0.05$) using a one-sided Wilcoxon rank sum test to demonstrate statistically significant superiority in co-primary endpoint (1) "Relative change in the number of inflammatory lesions (percent change from baseline)", and Fisher's Exact Test to demonstrate statistically significant superiority in co-primary endpoint (2) "Treatment success defined by a minimum improvement of the mIGA score by 2 assessed 8 weeks after the last PDT and resulting in an mIGA score of 0 (clear) or 1 (almost clear)" in the FAS. The power calculation assumes a relative change in inflammatory lesions of 50 for BF-200 ALA, 20 for vehicle, and clearance rates of 75% for BF-200 ALA, and 40% for vehicle, respectively, 8 weeks after the last PDT.

The sample size includes about 12 % (15 subjects) additional subjects. These aims to ensure that a) a sufficient number of subjects in the per protocol analysis set and b) a sufficient number of subjects distributed to moderate and to severe acne grading.

This estimate was based on the following quantities and assumptions:

Absolute change:

- Absolute changes in active group in Pariser et al. (16) is reported with -15 (after 4 PDTs), in Wiegell et al. (11,16,30,39,40) with -24 (median values). The standard deviation in the active group is reported being 15 in Pariser et al. (16), and can be estimated using the parameters min, max, and N being 16 in Wiegell et al. (11,16,30,39,40).
- Absolute changes in vehicle group in Pariser et al. (16) is reported with -8 (after 4 PDTs), in Wiegell et al. (11,16,30,39,40) with 0 (median values). The standard deviation in the vehicle group is reported being 21 in Pariser et al. (16), and can be estimated using the parameters min, max, and N being 18 in Wiegell et al. (11,16,30,39,40).
- Overall a maximum placebo effect of -8 can be expected. The active effect is assumed being -20. An SD of 20 is assumed.

Percentage change:

- Percentage changes in active group in Pariser et al. (16) is reported with -37% (after 4 PDTs), in Wiegell et al. (11,16,30,39,40) with -68% (median values), in Hörfelt et al. (11,16,30,39,40) -54% (median values). The standard deviation in the active group is reported being 40 in Pariser et al. (16).
- Percentage changes in vehicle group in Pariser et al. (16) is reported with -16% (after 4 PDTs), in Wiegell et al. (11,16,30,39,40) with 0% (median values), in Hörfelt et al. (11) with -20% (median values). The standard deviation in the vehicle group is reported being 54 in Pariser et al. (16).
- Overall a maximum placebo effect of -20% can be expected. The active effect is assumed being -50%. An SD of 50 is assumed.

14.9 Major Protocol Deviations

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

- The treatment differs significantly from protocol (e.g. incubation period differs by more than 30 min from times indicated by the protocol; distance of the lamp differs by more than 1 cm from the range indicated by the manual; illumination time differs by more than 20% (2 min) from the pre-defined illumination time of 10 min.
- Forbidden anti-inflammatory medication (within ± 7 days of PDT visit)
- Other forbidden medication will be decided on a case-by-case basis.
- Meeting an exclusion criterion throughout the treatment period of the study

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

15 ETHICAL AND LEGAL ASPECTS

15.1 Good clinical practice

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

15.2 Delegation of investigator duties

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

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

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

15.3 Subject information, informed consent and HIPAA form

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

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

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

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

15.4 Confidentiality

To ensure confidentiality the subject's data will be collected for the clinical data base and analysis in a strictly pseudonymous form, i.e. using a subject number instead of the subject's name. The subject number will also be used for SAE reporting purposes. On supporting documents of an SAE report, such as hospital reports or laboratory reports, the subject's name and if required by regulations the physician's name has to be obliterated.

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

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

The sponsor adheres to data protection regulations.

15.5 Protocol deviations

Protocol deviations have to be documented and explained by the investigator and/or the sponsor. Major protocol deviations have to be escalated to the sponsor. The investigator needs to report major protocol deviations to the responsible ethics committee (EC)/IRB if required by law (federal or state laws) or regarding to the EC/IRB's guidelines.

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

15.6 Protocol amendments

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

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

15.7 Approval of the clinical study protocol and amendments

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

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

A protocol amendment has to be submitted to the IEC/IRB and, if required, to the regulatory authority(ies). In case of a non-substantial amendment these bodies only will be notified but they need to approve any substantial amendment to the protocol before it can be implemented.

Amendments must be evaluated to determine whether the subject information leaflet and ICF should also be revised.

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

15.8 Ongoing information for the institutional review board

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

15.9 Closure of the study

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

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

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

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

15.10 Record retention

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

Within the United 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 2 years, following the date a marketing application is approved for the drug and the indication for which it is being approved. In case no application is to be filed or if the application is not approved for such indication, records will be kept for 2 years after the investigation is discontinued and FDA is notified.

This regulation applies to:

- Adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered IMP (BF-200 ALA or vehicle) and PDT such as:
 - Case report forms and supporting data.
 - Signed and dated consent forms.
 - Medical records including e.g. progress notes of the physician and nurse.
 - The case history of each subject shall document that informed consent was obtained prior to participation in the study.

- Records documenting disposition of IMP and IMD (including dates, quantity, use and return to the sponsor) if the investigation is terminated, suspended, discontinued or completed.

15.11 Liability and insurance

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

15.12 Financial disclosure

Prior to the start of the study, the investigator will disclose to the sponsor any proprietary or financial interests he or she might hold in the IMP, the IMD or the sponsor company as outlined in the financial disclosure forms (i.e., 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 1 year after study completion/termination.

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

16 QUALITY CONTROL, QUALITY ASSURANCE, AND INSPECTIONS

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

16.1 Study monitoring and source data verification

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

The results of monitoring visits will be documented in monitoring reports. Issues arising will be escalated and dealt with in a timely manner. The escalation process is defined in the respective SOPs of the sponsor.

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

16.2 Site audits

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

16.3 Site Inspections

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

17 DOCUMENTATION AND USE OF STUDY FINDINGS

17.1 Documentation of study findings

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

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

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

A source data location list will be prepared and updated during the study. It will specify which types of source data are available and where they are stored (e. g. electronic or paper subject files etc.), and which data may be entered directly into the eCRF. This list will be filed in both the TMF and the ISF and updated as necessary. The sites should establish appropriate work sheets or record the source data directly in subjects' notes. Aid by sponsor can be provided. 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, 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 completed eCRFs will be provided to the concerned investigator.

17.2 Use of study findings

All information concerning the product as well as any matter concerning the operation of the sponsor, such as clinical indications for the IMP or IMD, 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 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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18 APPENDICES

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

Appendix B: NRS-11 for pain during illumination

18.1 APPENDIX A

Fitzpatrick's Skin Type Test

Fitzpatrick's 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 2 main factors that influence skin type are:

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

Skin type is determined genetically and is 1 of the many aspects of the 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 to following questionnaires to assess subject's skin type.

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

Fitzpatrick's Skin Type Test

(cont.)

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

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

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

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

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

18.2 APPENDIX B

Numeric rating pain scale for pain during photodynamic therapy

Pain sensation during illumination will be assessed after the PDT by the subject using the 11-point numeric rating pain scale, shown below:

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

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

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