COVER PAGE

CLINICAL STUDY PROTOCOL

Study ALA-BCC-CT013

NCT03573401

A randomized, double blind, vehicle-controlled multicenter phase III study to evaluate the safety and efficacy of BF-200 ALA (Ameluz®) and BF-RhodoLED® in the treatment of superficial basal cell carcinoma (sBCC) with photodynamic therapy (PDT)

Document date: 17 July 2018

Sponsor
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51377 Leverkusen, Germany

CLINICAL STUDY PROTOCOL

VERSION 3.0

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ALA-BCC-CT013 5-aminolevulinic acid hydrochloride

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SYNOPSIS

A randomized, double blind, vehicle-controlled multicenter phase III study to evaluate the safety and efficacy of BF-200 ALA (Ameluz®) and BF-RhodoLED® in the treatment of superficial basal cell carcinoma (sBCC) with photodynamic therapy (PDT).

Investigators, study sites

Approximately 12 sites in the United States of America (US) will participate in this study. Each site should randomize between 10 and 20 subjects. No site should randomize more than 20 subjects unless prior approval of the sponsor is obtained. The maximum number per site should not exceed 30 subjects.

Investigational medicinal product and medical device

BF-200 ALA or placebo to BF-200 ALA (vehicle) will be applied at a 4:1 ratio.

BF-200 ALA (marketed in the US as Ameluz® for the treatment of actinic keratosis (AK) in conjunction with BF-RhodoLED®), is a gel formulation of 7.8% 5-aminolevulinic acid (5-ALA) corresponding to 10% 5-ALA hydrochloride. The vehicle is indistinguishable by appearance or smell from BF-200 ALA, but does not contain the active ingredient 5-ALA. The IMP will be packed in tubes, containing 2 g each.

The study treatment requires illumination of treatment fields with BF-RhodoLED® (red light with emission at ~635 nm, ~37 J/cm²). Please refer to BF-RhodoLED® user manual for detailed lamp operating and safety instructions.

Subjects and lesions

Each subject should have one or several superficial BCC lesion(s) that will be included into the study. Since only one tube of study medication will be provided per PDT, the combined treatment field must not exceed 20 cm^2. All lesions included in the study will initially be confirmed by biopsy as superficial BCC. All lesions should have a minimal diameter of 0.6 cm.

Prior to PDT-1, a Main Target Lesion will be selected for surgical excision at the end of the clinical observation phase for histopathological assessment. All other lesions included in the study will be defined as Additional Target Lesions. Suitability of the Main Target Lesion for excision is decided by the investigator based on size and location.

Number of subjects

It is planned to randomize 186 subjects, with 149 subjects in the BF-200 ALA group and 37 subjects in the vehicle group. This sample size will ensure a power of at least 90% with an alpha level set to 0.1% (α = 0.001) using a one-sided Cochran-Mantel-Haenszel Test with stratification factors lesion baseline characteristics (lesion count 1 vs ≥2 lesion(s)) and center to demonstrate statistically significant superiority in responses in subjects treated with BF-200 ALA vs. vehicle treated subjects in the full analysis set (FAS). The FAS includes all subjects randomized and treated at least once with IMP and PDT (IMP application and illumination). The power calculation assumes combined clinical and histological clearance rates of 65% for BF-200 ALA, 25% for vehicle.

Objectives

Primary objective: To compare the efficacy of BF-200 ALA PDT (containing 7.8% 5-aminolevulinic acid (5-ALA) as active ingredient) with vehicle PDT, utilizing BF-RhodoLED® illumination, in the treatment of superficial BCC.

The primary efficacy variable is the composite clinical and histological complete clearance of the subject's Main Target Lesion, assessed 12 weeks after the start of the last PDT cycle that included treatment of the Main Target Lesion (Visit 5 or Visit 8).

Secondary objectives: To evaluate the safety and secondary efficacy parameters related to BF-200 ALA and BF-RhodoLED® for the treatment of superficial BCC with PDT, also including clinical clearance of Additional Target Lesions on the same subjects.

Study duration and dates

Duration of the study per subject: Double blind clinical observation period up to 7 months (up to 4 weeks screening and pre-randomization period, and up to 6 months clinical observation period) followed by a 5-year follow-up (FU) period after completion of the 1st PDT cycle (Visit 5).

The treatment will start with an initial cycle of 2 PDTs (at an interval of 1-2 weeks). 12 weeks after the start of PDT cycle 1 (PDT-1), a clinical assessment will be performed. For clinically completely cleared subjects (complete clinical responders after the 1st PDT cycle, i.e., subjects with complete remission of all target lesions according to clinical assessment), the clinical observation period of the study will end and these subjects will enter the FU part of the study. Subjects that still show clinically apparent target lesions after the 1st PDT cycle (partial or non-responders according to clinical assessment after the 1st PDT cycle) will enter a 2nd cycle of 2 PDTs with identical schedule starting the same day. During this 2nd cycle, only those lesions will be retreated that were not clinically cleared after the 1st cycle. 12 weeks after start of the 2nd PDT cycle (PDT-3), the clinical observation period of the study will end for those subjects, who will then enter the FU part of the study.

All Main Target Lesions that are assessed as clinically clear at Visit 5, 12 weeks after PDT-1, will be excised on this same day. All Main Target Lesions that show partial or non-response at Visit 5 will undergo a 2nd cycle of treatment and will be excised at Visit 8, 12 weeks after Visit 5 (irrespective of their clinical clearance). Any remaining Additional Target Lesions at Visit 5 will receive a 2nd cycle of PDT treatments, starting on the same day. To verify the exact position of the Main Target Lesion, the tumor will be surrounded by at least 3 ink marks prior to PDT-1. The ink marks should have a distance of ~3-4 mm from the visible tumor margin, and be excised along with the lesion. No ink marks shall be applied within the tumor as they may interfere with the PDT.

All subjects who completed the clinical observation period will be followed up for 5 years (i.e. 5 years after completing their 1st PDT cycle (Visit 5)). Results of FU visits will be analyzed and reported separately as they are not part of the clinical observation period of the study. The end of the study is defined as the date of final data base lock after follow-up.

- Recruitment period: ~9 months
- First subject in: approx. September 2018
- Last subject in: approx. May 2019
- Last subject out (clinical phase): approx. November 2019
- Last subject out (follow-up phase): approx. August 2024
- End of study (data base lock follow-up phase): approx. October 2024

Study design

This is a phase III, multicenter, randomized, vehicle controlled, double blind, parallel group study comparing BF-200 ALA with vehicle (4:1 ratio). The study is divided into 2 parts, a clinical observation part consisting of a screening period and a treatment period, as well as a FU part. The "illumination period" is defined as a component of the PDT treatment in which subjects are exposed to the red light source BF-RhodoLED® for 10 minutes.
To guarantee the blind status of the investigator assessing efficacy after each PDT cycle, a second investigator or delegated person will perform drug application and light treatment. The second investigator or delegated person will furthermore conduct all safety evaluations at visits where PDT is applied and during the phone call 1 week after each PDT cycle, respectively. Both investigators (delegated person(s)) are not entitled to exchange information about the study outcome and side effects.

Complete response of the Main Target Lesion is assessed 12 weeks after the start of the last PDT cycle that included treatment of the Main Target Lesion and is defined as a Main Target Lesion that is completely clinically and histologically cleared. For **clinically complete responders after the 1st PDT cycle**, i.e., subjects showing complete clinical remission of all target lesions 12 weeks after PDT cycle 1, the clinical observation period of the study consists of a screening visit at which a biopsy is taken of each eligible BCC for confirmation of diagnosis (Visit 1), a pre-randomization period lasting up to 4 weeks, a randomization and treatment visit (Visit 2, PDT-1) at which also the ink marks are applied, a first-cycle retreatment visit 1-2 weeks later (Visit 3, PDT-2), a phone call 1 week ± 2 days after PDT-2 and two visits for assessment of efficacy and safety (Visit 4: 5 weeks ± 1 week after PDT-1; and Visit 5: 12 weeks ± 1 week after PDT-1).

Non-responders or partial responders according to clinical assessment after the 1st PDT cycle, i.e., subjects with visible remaining target lesions at Visit 5 (Week 12 after PDT-1), will have the clinically remaining lesions retreated with a 2nd PDT cycle starting at Visit 5 (PDT-3). If the Main Target Lesion is clinically cleared at this time point, it will be excised at this Visit 5. PDT-4 will be applied 1-2 weeks later, at Visit 6. Subjects will then be contacted by phone 1 week ± 2 days after the 2nd PDT cycle ended, and attend two further visits for assessment of efficacy and safety (Visit 7: 5 weeks ± 1 week after PDT-3, and Visit 8: 12 weeks ± 1 week after PDT-3). At Visit 8, a final clinical assessment will be performed identifying complete clinical responders 12 weeks after the start of the 2nd PDT cycle and partial or non-responders, i.e., subjects still showing remaining target lesions after the 2nd PDT cycle. A retreated Main Target Lesion will be excised on this day, irrespective of the clinical outcome.

In general, clinically complete responders are categorized 12 weeks after the start of the last PDT cycle (PDT-1 or PDT-3) according to clinical assessment only and are defined as subjects with all Target Lesions (Main plus Additional Target Lesions) clinically cleared.

All subjects will receive excision of their Main Target Lesion, at the latest at Visit 8 for histopathological evaluation of lesion status. Along with the excision of the area of the Main Target BCC Lesion, the ink marks applied at Visit 2 will be removed. Any remaining Additional Target Lesions at Visit 8 will be treated at the discretion of the investigator following completion of final assessments of the clinical observation period.

For all subjects who completed the clinical observation period, four FU visits are scheduled (12 ± 1 months, 24 ± 2 months, 36 ± 2 months and 60 ± 2 months after completion of PDT cycle 1 (Visit 5)). All subject data listed in Section 7.1 and results of assessments have to be recorded in the subject electronic case report form (eCRF). Data reported during the FU part of the study will be analyzed and reported separately and are not part of the clinical observation period of the study.

Inclusion and exclusion criteria

Main inclusion criteria:

- Willingness and ability to sign the informed consent form and Health Insurance Portability and Accountability Act (HIPAA) form. A study-specific informed consent form and a HIPAA form must be obtained in writing for all subjects prior to starting any study procedures.
- Men or women ≥18 years of age.
- Presence of ≥1 naïve sBCC lesion in the treatment areas face/forehead, bald scalp, extremities and/or neck/trunk, all of which are, according to the clinical judgement of the investigator, likely to be histologically confirmed as sBCCs. Lesions should not be within the embryonic fusion planes (H-zone), especially within 2 cm of the hair zone or on the ears. In case of multiple lesions, one lesion is defined as Main Target Lesion which will be excised at the end of the clinical observation period. Only eligible naïve sBCCs, confirmed by histology taken at screening, are allowed to be included in the study as Main or Additional Target Lesions. Thus, eligible sBCCs must lack any histological evidence of aggressive growth patterns (e.g. severe squamous metaplasia, infiltrative/desmoplastic features or basosquamous features). BCCs assessed as non-naïve (e.g. previously treated or recurrent) or non-eligible by biopsy taken at screening (and in a distance >5 cm from the next lesion included in the study) should be excised by surgery or removed by cryotherapy in a timely manner. Other treatments for these lesions are not allowed during the study.
- The diameter of each eligible lesion should be ≥ 0.6 cm, and the entire treatment field must not exceed ~20 cm². The treatment field is defined as the field to which IMP is applied, usually including the target lesions and margins surrounding the lesions of up to 1 cm. For the Main Target Lesion, the maximal lesion size should be such that surgical excision without a skin transplant is feasible according to the investigator's judgement.
- Target BCC lesions must be discrete and located within 1–2 illumination areas (the illumination area is defined by the effective illumination area of the BF-RhodoLED® device with approximately 6 x 16 cm).
- Willingness to receive up to 4 PDTs within 3.5 months and excision of the Main Target Lesion either at Visit 5, if clinically cleared, or at the end of the clinical observation period 12 weeks after the start of the last PDT cycle (Visit 8), irrespective of whether the treated Main Target Lesion was clinically cleared or not.
- Free of significant physical abnormalities (e.g. tattoos, dermatoses) within the potential treatment field plus a 5 cm radius surrounding the target lesion(s) as they may interfere with examination or final evaluation.
- Willingness to stop the use of moisturizers and any other cosmetics within the treatment field plus a 5 cm radius surrounding the target lesion(s) 48 hours prior to an office visit and 48 hours after each PDT session. Sunscreen will be allowed, but should not be applied to the treatment field plus the 5 cm radius surrounding the target lesion(s) within approximately 24 h prior to a clinical visit.
- Acceptance to abstain from extensive sunbathing and the use of a solarium during the clinical observation period. Subjects with sunburn within treatment areas cannot be included until fully recovered.
- Healthy subjects and subjects with clinically stable medical conditions, including, but not limited to controlled hypertension, diabetes mellitus type II, hypercholesterolemia, and osteoarthritis, will be permitted to be included in the study if their medication is not prohibited by this protocol.
- Women of childbearing potential are permitted to participate in this study only if they have a negative serum pregnancy test at screening and are willing to use a highly effective method of contraception during the clinical observation period of the study.

Main exclusion criteria:

- History of hypersensitivity to 5-ALA or any ingredient of BF-200 ALA which includes soybean phosphatidylcholine.
- Hypersensitivity to porphyrins.
- Current treatment with immunosuppression therapy.
- Presence of photodermatoses.
- Presence of porphyria.
- Presence of clinically significant inherited or acquired coagulation defect.
- Evidence of clinically significant (CS) unstable medical conditions, such as:
    - Metastatic tumor or tumor with high probability of metastasis.
    - Cardiovascular disease class III, IV (New York Heart Association [NYHA]).
    - Immunosuppressive condition.
    - Hematologic, hepatic, renal, neurologic, or endocrine condition.
    - Collagen-vascular condition.
    - Gastrointestinal condition.
- Clinically relevant cardiovascular, hepatic, renal, neurologic, endocrine, or other major systemic diseases that complicate implementation of the protocol or interpretation of the study results.
- Gorlin Syndrome or Xeroderma pigmentosum.
- Presence and/or physical treatment of skin tumors other than (naïve) sBCC (e.g. malignant melanoma, squamous cell carcinoma (SCC), Bowen's disease, aggressive BCC or nBCC diagnosed at the screening visit by clinical assessment) within a distance of ≤ 5 cm from the nearest target lesion within 4 weeks prior to PDT (Visit 2) until the end of the clinical observation period. However, biopsied lesion(s) that were not confirmed eligible at screening and which are located at a distance of > 5 cm from any lesion(s) that will be included in the study can be surgically removed. Treatment by PDT or topical medication during the course of the clinical observation period of the study triggers exclusion of the subject.
- If lesion(s) are assessed as non-eligible by biopsy during initial screening and these lesions are localized within a distance of 5 cm from an otherwise suitable lesion, this suitable lesion must be excluded from the study.
- Any AK lesions within the treatment field (lesion area including margin of 0.5 to 1.0 cm).
- Any topical medical treatment of AK, other non-melanoma skin cancers (NMSC), or melanoma (except for IMP treatment of the target lesion(s)) starting 12 weeks prior to Visit 2 (PDT-1) and lasting until the end of the clinical observation period.
- Any other topical medical treatment of the skin 12 weeks prior to Visit 2 (PDT-1) until the end of the clinical observation period, with the exception of:
    - Topical treatments with corticosteroids (allowed throughout the clinical observation period of the study).
    - Topical non-steroidal anti-inflammatory drugs (NSAIDs such as diclofenac) (allowed throughout the clinical observation period of the study with the restriction of 7 days prior to and 7 days after PDTs).
- Start of intake of medication with hypericin or systemically acting drugs with phototoxic or photoallergic potential within 8 weeks prior to screening.
- Any of the **systemic treatments** listed below, within the designated period prior to PDT and during the clinical observation period.

Treatment	Period
Interferon	6 weeks
Immunomodulators or immunosuppressive therapies	12 weeks
Cytotoxic drugs	6 months
Investigational drugs	8 weeks
Drugs known to have major organ toxicity	8 weeks
Corticosteroids (oral or injectable)	6 weeks
MAL or ALA	12 weeks

- **Systemic** treatment with NSAIDs is not to be used 7 days prior to and 7 days after PDT. ASA (e.g. Aspirin®) up to 100 mg/ day, ibuprofen up to 200 mg/ day, and acetaminophen (e.g. Tylenol®) is allowed during this period.
- Presence of tattoos, skin inflammation, wounds, etc. in the treatment field(s) plus a 5 cm radius surrounding the target lesion(s).

Treatment

Subjects will be randomized, stratified by the number of eligible lesions (1 and ≥2 lesions) and center, into one out of two groups to be treated with PDT by applying either BF-200 ALA (Ameluz®, the test group) or vehicle (the control group) at a 4:1 ratio. The investigational medicinal products (IMPs) are packed in tubes, each containing 2 g gel. A pack of four tubes will be assigned to each subject to allow a maximum of 2 PDT cycles comprising of a total of 4 PDTs. The quantity of 2 g gel per tube is sufficient to cover up to ~20 cm² with a 1 mm layer (i.e., 1 tube of IMP is sufficient to cover the entire permitted lesion area during each PDT session).

Target lesions should be prepared prior to drug application by degreasing (using ethanol or isopropanol), removal of all scabs and crusts, and roughening of the surface, if appropriate (e.g. by mild debridement for the removal of crusts). Bleeding should be avoided. The formulations will then be applied to the lesions (maximal combined lesion area incl. margin is 20 cm^2) located in 1 to 2 illumination areas. The medication should be applied to the entire lesion(s) plus a 0.5 – 1.0 cm margin surrounding each lesion at a thickness of 1 mm, allowed to dry (for approximately 10 minutes), covered with light-tight dressing, and incubated for approximately 3 h. Thereafter, any remnants of the IMP will be removed carefully and the PDT illumination will be administered using the light emitting diode (LED) red light device BF-RhodoLED®. One to two weeks after PDT-1, the same procedure will be repeated (PDT-2).

Subjects diagnosed as clinically completely cleared 12 weeks after the start of the 1st PDT cycle will have completed the clinical observation period and will enter FU.

Subjects clinically diagnosed as only partial responders or non-responders at this time point, will receive a 2nd treatment cycle during which all Target Lesions not yet clinically cleared will receive two more PDTs, PDT-3 and PDT-4, again one or two weeks apart. If the Main Target Lesion of partial responders is clinically cleared 12 weeks after PDT-1, it will be surgically excised on the same day, prior to the PDT-3 treatment. 12 weeks after start of the 2nd PDT cycle, subjects will be reexamined and enter FU at this time point, either as full responders or as partial or non-responders. If the Main Target Lesion was not excised at Visit 5, it will be excised at this last visit of the clinical observation period (Visit 8) irrespective of the outcome of the clinical assessment.

Thus, all subjects will undergo excision surgery of their Main Target Lesion for histopathological assessment of clinical outcome at the end of the 1st or 2nd treatment cycle, depending on the clinical assessment after the 1st treatment cycle. If any Additional Target Lesions remain 12 weeks after the start of the 2nd PDT cycle (at Visit 8), they have to be treated at the discretion of the investigator after completion of Visit 8.

Efficacy data

The primary efficacy variable is the composite clinical and histological response of the subject's Main Target Lesion as assessed 12 weeks after the start of the last PDT cycle that included treatment of the Main Target Lesion (Visit 5 or Visit 8).

A confirmatory hypothesis test will be performed for the primary efficacy endpoint using the FAS dataset. Additional key secondary efficacy variables will be analyzed with confirmatory statistics, using a hierarchical testing procedure, whereas further secondary efficacy variables will be tested descriptively and in an exploratory manner.

The key secondary efficacy variables include:

1. Main Target Lesion clinical response (according to clinical assessment only) assessed 12 weeks after the start of the last PDT cycle.
2. Main Target Lesion histological response (according to histological assessment only) assessed 12 weeks after the start of the last PDT cycle.
3. Subject complete clinical response (complete clearance of all target lesions according to clinical assessment only) assessed 12 weeks after the start of the last PDT cycle.
4. Subject complete response (clinically and histologically cleared Main Target Lesion (see above) and complete clinical remission of all Additional Target Lesions) assessed 12 weeks after the start of the last PDT cycle.

Confirmatory hypothesis testing of key secondary variables measured during the double-blind treatment period will be done only after the test of the primary efficacy variable is passed, and will be done strictly in the given order to ensure the Family Wise Error Rate (FWER). Confirmatory hypothesis testing in the pre-defined order will stop once the first non-significant test result is obtained.

Analysis of key secondary endpoints will be performed using the FAS.

Further secondary efficacy variables include:

- Lesion complete clinical response rate per treatment arm (complete clearance of individual lesions (Main and Additional Target Lesions)) according to clinical assessment only, assessed 12 weeks after the start of the last PDT cycle.
- Main Target Lesion complete response (clinically and histologically cleared) assessed 12 weeks after PDT-1.
- Main Target Lesion clinical response (according to clinical assessment only) assessed 12 weeks after PDT-1.
- Main Target Lesion histological response (according to histological assessment only) assessed 12 weeks after PDT-1.
- Lesion complete clinical response rate per treatment arm (complete clearance of individual lesions (Main and Additional Target Lesions)) according to clinical assessment only, assessed 12 weeks after PDT-1.
- Subject complete clinical response (complete clearance of all target lesions according to clinical assessment only) assessed 12 weeks after PDT-1.
- Subject complete response (clinically and histologically cleared Main Target Lesion (see above) and complete clinical remission of all Additional Target Lesions) assessed 12 weeks after PDT-1.
- For all Target Lesions, assessment of esthetic appearance by the investigator 12 weeks after the start of the last PDT cycle, but prior to surgical excision of the Main Target Lesion and any alternative treatment of Additional Target Lesions.

- Subjects' satisfaction regarding esthetic outcome and treatment 12 weeks after the start of the last PDT cycle, but prior to surgical excision of the Main Target Lesion or alternative treatment of Additional Target Lesions at the end of the clinical observation period.

Further secondary endpoints will be analyzed descriptively and in an exploratory manner. Where appropriate, two-sided local 95% confidence intervals (CIs) of differences between BF-200 ALA and vehicle will additionally be presented.

<u>For the FU period of the study, the following analysis variables will be collected and analyzed descriptively and in an exploratory manner:</u>

- Recurrence of the subject's Main Target Lesion after surgical excision (defined as in composite endpoint).
- Subject recurrence rate defined as the percentage of subjects with all Additional Target Lesions completely clinically cleared 12 weeks after the start of the last PDT cycle with at least one recurrent lesion during FU.
- Subject recurrence rate defined as the percentage of subjects with all Additional Target Lesions completely clinically cleared 12 weeks after the start of PDT-1 with at least one recurrent lesion during FU.
- Lesion recurrence rate per treatment arm defined as the percentage of completely cleared individual Additional Target Lesions 12 weeks after the start of the last PDT cycle showing recurrence during FU.
- Lesion recurrence rate per treatment arm defined as the percentage of completely cleared individual Additional Target Lesions 12 weeks after the start of PDT-1 showing recurrence during FU.
- Esthetic appearance for all Main Target Lesions following surgical excision, and for all Additional Target Lesions that were clinically cleared 12 weeks after the last PDT cycle and did not receive additional treatments.
- Subject satisfaction regarding treatment and esthetic outcome for all Target Lesions that did not receive additional treatment after the last PDT cycle.

The results from the FU period of the study will be analyzed and reported separately and are not part of the clinical observation period of the study.

Safety data

The safety analysis variables during the clinical observation period include:

- Frequency and extent of adverse events (AEs), serious AEs (SAEs), and treatment-emergent adverse events (TEAEs). TEAEs are defined as all AEs with onset or worsening after treatment with randomized IMP within 4 weeks after each PDT cycle (until Visit 4 or Visit 7, respectively).
- New AK, NMSC and melanoma, including location of lesion(s).
- Local skin reactions at the treatment field(s), assessed by the investigators.
- Local discomfort or pain during illumination, reported by the subjects.
- Vital signs.
- Safety laboratory.
- Physical examinations.

The safety analysis variables during the FU period include:

- Any local AEs or conditions within the treatment field(s) that may be relevant for proper assessment of the recurrence of the treated lesions. Any relevant SAE or serious adverse reaction (SAR).
- New NMSC and melanoma, including location of lesion(s).

- New AK lesions within the treatment field(s) and treated subarea(s).

Statistical Procedures

No interim analysis is planned for this study. The main statistical analysis will be performed after database lock and subsequent unblinding of all data after the end of the clinical observation period. Additional data from the FU period of the study (12, 24, 36 and 60 months after completion of the 1st PDT cycle (Visit 5)) will be analyzed and reported separate from the clinical observation period of the study.

The primary analysis variable for the assessment of efficacy is the overall subject's combined clinical and histological clearance of the Main Target Lesion, i.e., the percentage of subjects in which the Main Target Lesion is completely cleared according to clinical as well as histological assessment at 12 weeks after the start of the last PDT cycle (PDT-1 or PDT-3, respectively) that included treatment of the Main Target Lesion. A Main Target Lesion with a complete clinical and histological response is defined as a completely cleared Main Target Lesion.
The primary hypothesis will be tested on the full analysis set (FAS) as follows: The primary null hypothesis (H_{01}, one-sided) is that the overall subjects combined clinical and histological complete response of the Main Target Lesion assessed 12 weeks after the start of the last PDT cycle that included treatment of the Main Target Lesion for subjects treated with BF-200 ALA is equal to or lower than that of subjects treated with vehicle. The primary alternative hypothesis (H_{11}, one-sided) is that the overall subjects combined clinical and histological complete response of the Main Target Lesion assessed 12 weeks after the start of the last PDT cycle that included treatment of the Main Target Lesion for subjects treated with BF-200 ALA is higher than the response for subjects treated with vehicle. A Cochran-Mantel-Haenszel Test with stratification factors lesion baseline characteristics (lesion count 1 vs ≥2 lesion(s)) and center will be used to test the primary hypothesis at a significance level of 0.1% ($\alpha = 0.001$) (one-sided). The primary analysis will be performed on the FAS and will be repeated for the PPS as sensitivity analysis.

For subjects, who should have received a 2nd PDT cycle but were erroneously classified as complete responders at Visit 5, the results from the 1st PDT cycle will be used for the primary analysis.

Exploratory subgroup analyses will be performed for the primary efficacy variable. Subgroups will be specified by categorical or categorized variables e.g. sex, age, number of lesions at baseline, location of lesions, baseline size of lesions.

Confirmatory hypothesis testing of key secondary variables measured during the double-blind clinical observation period will be done only after the test of the primary efficacy variable was passed at a significance level of 0.1% (alpha = 0.001). Testing will be done strictly in the given order to ensure the family wise error rate (FWER). Confirmatory hypothesis testing in the pre-defined order will stop once the first non-significant test result is obtained. Any remaining key secondary variables will be tested in the same way as the further secondary endpoints.

For further secondary endpoints, performed on the full analysis set (FAS), two-sided statistical testing procedures will be conducted using an alpha level of 5% ($\alpha = 0.05$). Two-sided local 95% confidence intervals (CIs) of differences between BF-200 ALA and vehicle will additionally be calculated wherever appropriate.

Technical details of the statistical analyses will be specified in a separate statistical analysis plan (SAP).

Analysis sets

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 analyses.

Full analysis set (FAS): all subjects randomized and treated at least once with IMP and 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 the primary, key secondary and further secondary endpoints.

Per-protocol set (PPS): all subjects of the FAS without any major protocol deviations. The assignment of subjects to the treatment groups will be as actually treated. The PPS will be used for sensitivity analyses of the primary and key secondary endpoints and may also be used for selected analyses of further secondary endpoints.

Table 1: Study schedule

	All subjects	All subjects (1st PDT cycle)				Complete responder	Partial or non-responder	Retreated subjects only (2nd PDT cycle)				All subjects			
Assessment or activity	**Screening**	**PDT-1**	**PDT-2**	**Phone call 1**	**Clinic visit**	**Clinic visit [i]**	**PDT-3 [h]**	**PDT-4 [h]**	**Phone call 2 [h]**	**Clinic visits [h]**		**Follow-up**			
	Visit 1 (≤ 4 weeks prior to PDT-1)[l]	**Visit 2 (Base-line)**	**Visit 3 (1 -2 weeks post-PDT-1)**	**(1 week ± 2 days post-PDT-2)**	**Visit 4 (5 weeks ± 1 week post-PDT-1)**	**Visit 5 (12 weeks ± 1 week post-PDT-1)**	**Visit 5 (12 weeks ± 1 week post-PDT-1)**	**Visit 6 (1-2 weeks post-PDT-3)**	**(1 week ± 2 days post-PDT 4)**	**Visit 7 (5 weeks ± 1 week post-PDT 3)**	**Visit 8 (12 weeks ± 1 week post-PDT 3)**	**FU1 (12 months ± 1 month post-PDT) [d]**	**FU2 (24 months ± 2 month post-PDT) [d]**	**FU3 (36 months ± 2 months post-PDT) [d]**	**FU4 (60 months ± 2 months post-PDT) [d]**
Clinical visit	X	X	X		X	X	X	X		X	X	X	X	X	X
Informed Consent/ HIPAA form	X														
Assign subject number	X														
Demographics	X														
Skin type assessment [a]	X														
Skin disease history, including NMSC and melanoma history / NMSC and melanoma status	X														
Relevant medical history	X														
Inclusion / exclusion criteria	X	X													
Assign randomization number		X													
Randomization		X													
sBCC baseline assessment and ink marks (definition of borders for later		X													

Assessment or activity	All subjects	All subjects (1st PDT cycle)				Complete responder	Partial or non-responder	Retreated subjects only (2nd PDT cycle)				All subjects			
	Screening	PDT-1	PDT-2	Phone call 1	Clinic visit	Clinic visit [i]	PDT-3 [h]	PDT-4 [h]	Phone call 2 [h]	Clinic visits [h]		Follow-up			
	Visit 1 (≤ 4 weeks prior to PDT-1)[l]	Visit 2 (Base-line)	Visit 3 (1 -2 weeks post-PDT-1)	(1 week ± 2 days post-PDT-2)	Visit 4 (5 weeks ± 1 week post-PDT-1)	Visit 5 (12 weeks ± 1 week post-PDT-1)	Visit 5 (12 weeks ± 1 week post-PDT-1)	Visit 6 (1-2 weeks post-PDT-3)	(1 week ± 2 days post-PDT 4)	Visit 7 (5 weeks ± 1 week post-PDT 3)	Visit 8 (12 weeks ± 1 week post-PDT 3)	FU1 (12 months ± 1 month post-PDT) [d]	FU2 (24 months ± 2 month post-PDT) [d]	FU3 (36 months ± 2 months post-PDT) [d]	FU4 (60 months ± 2 months post-PDT) [d]
excision of the Main Target Lesion)															
Clinical assessment of target lesion(s)	X				X	X	X			X	X	X	X	X	X
Generation of a template (grid foil)	X														
Biopsy of target lesion(s) for confirmation of diagnosis [g]	X														
Mandatory excision of the Main Target Lesion and histopathological examination [g]						X	X[n]				X				
Treatment of non-responding Additional Target Lesions (Investigators decision)[h]											X[o]				
Assessment of esthetic appearance by investigator or esthetic outcome by						X	X[p]				X	X	X	X	X

	All subjects	All subjects (1st PDT cycle)				Complete responder	Partial or non-responder	Retreated subjects only (2nd PDT cycle)				All subjects			
Assessment or activity	**Screening**	**PDT-1**	**PDT-2**	**Phone call 1**	**Clinic visit**	**Clinic visit [i]**	**PDT-3 [h]**	**PDT-4 [h]**	**Phone call 2 [h]**	**Clinic visits [h]**		**Follow-up**			
	Visit 1 (≤ 4 weeks prior to PDT-1)[l]	**Visit 2 (Baseline)**	**Visit 3 (1 -2 weeks post-PDT-1)**	**(1 week ± 2 days post-PDT-2)**	**Visit 4 (5 weeks ± 1 week post-PDT-1)**	**Visit 5 (12 weeks ± 1 week post-PDT-1)**	**Visit 5 (12 weeks ± 1 week post-PDT-1)**	**Visit 6 (1-2 weeks post-PDT-3)**	**(1 week ± 2 days post-PDT 4)**	**Visit 7 (5 weeks ± 1 week post-PDT 3)**	**Visit 8 (12 weeks ± 1 week post-PDT 3)**	**FU1 (12 months ± 1 month post-PDT) [d]**	**FU2 (24 months ± 2 month post-PDT) [d]**	**FU3 (36 months ± 2 months post-PDT) [d]**	**FU4 (60 months ± 2 months post-PDT) [d]**
subject (by subject questionnaire)															
Application of BF-200 ALA or vehicle and PDT		X	X				X	X							
Record date and time of study drug application and removal and illumination		X	X				X	X							
Confirm time of exposure, maximal light intensity, and distance between illumination source and treated lesions		X	X				X	X							
Assessment of subject's satisfaction with PDT (by subject questionnaire)						X					X	X	X	X	X
Local skin reaction during PDT		X	X				X	X							
Assessment of pain and discomfort during		X	X				X	X							

	All subjects	All subjects (1st PDT cycle)				Complete responder	Partial or non-responder	Retreated subjects only (2nd PDT cycle)				All subjects			
Assessment or activity	**Screening**	**PDT-1**	**PDT-2**	**Phone call 1**	**Clinic visit**	**Clinic visit [i]**	**PDT-3 [h]**	**PDT-4 [h]**	**Phone call 2 [h]**	**Clinic visits [h]**		**Follow-up**			
	Visit 1 (≤ 4 weeks prior to PDT-1)[l]	**Visit 2 (Base-line)**	**Visit 3 (1 -2 weeks post-PDT-1)**	**(1 week ± 2 days post-PDT-2)**	**Visit 4 (5 weeks ± 1 week post-PDT-1)**	**Visit 5 (12 weeks ± 1 week post-PDT-1)**	**Visit 5 (12 weeks ± 1 week post-PDT-1)**	**Visit 6 (1-2 weeks post-PDT-3)**	**(1 week ± 2 days post-PDT 4)**	**Visit 7 (5 weeks ± 1 week post-PDT 3)**	**Visit 8 (12 weeks ± 1 week post-PDT 3)**	**FU1 (12 months ± 1 month post-PDT) [d]**	**FU2 (24 months ± 2 month post-PDT) [d]**	**FU3 (36 months ± 2 months post-PDT) [d]**	**FU4 (60 months ± 2 months post-PDT) [d]**
PDT (by subject questionnaire)															
General physical examination	X					X					X				
Vital signs (HR, BP)	X	X	X		X	X	X	X		X	X				
Clinical laboratory tests [b]	X					X					X				
Serum pregnancy test [m]	X														
Urine pregnancy test [m]		X	X			X	X	X			X				
Concomitant medications/ treatments	X	X	X	X [c]	X	X	X	X	X [c]	X	X				
(S)AEs and local skin reactions		X	X	X [c]	X	X	X	X	X [c]	X	X				
New lesions (NMSC, melanoma, AK)		X	X		X	X	X	X		X	X	X	X	X	X
Relevant concomitant medications/ treatments [e]												X	X	X	X
Relevant (S)AEs or SARs[k] and local skin reactions [f]												X	X	X	X

	All subjects	All subjects (1st PDT cycle)				Complete responder	Partial or non-responder	Retreated subjects only (2nd PDT cycle)				All subjects			
Assessment or activity	**Screening**	**PDT-1**	**PDT-2**	**Phone call 1**	**Clinic visit**	**Clinic visit [i]**	**PDT-3 [h]**	**PDT-4 [h]**	**Phone call 2 [h]**	**Clinic visits [h]**		**Follow-up**			
	Visit 1 (≤ 4 weeks prior to PDT-1)[l]	**Visit 2 (Base-line)**	**Visit 3 (1 -2 weeks post-PDT-1)**	**(1 week ± 2 days post-PDT-2)**	**Visit 4 (5 weeks ± 1 week post-PDT-1)**	**Visit 5 (12 weeks ± 1 week post-PDT-1)**	**Visit 5 (12 weeks ± 1 week post-PDT-1)**	**Visit 6 (1-2 weeks post-PDT-3)**	**(1 week ± 2 days post-PDT 4)**	**Visit 7 (5 weeks ± 1 week post-PDT 3)**	**Visit 8 (12 weeks ± 1 week post-PDT 3)**	**FU1 (12 months ± 1 month post-PDT) [d]**	**FU2 (24 months ± 2 month post-PDT) [d]**	**FU3 (36 months ± 2 months post-PDT) [d]**	**FU4 (60 months ± 2 months post-PDT) [d]**
Treatment of recurrent lesions with conventional therapy												X	X	X	X
Investigator will advise subject about restrictions of medications prior and after PDT	X	X	X		X		X	X							
Investigator will send a subject status confirmation by FAX or email	X	X				X					X				X

	All subjects	All subjects (1st PDT cycle)				Complete responder	Partial or non-responder	Retreated subjects only (2nd PDT cycle)				All subjects			
Assessment or activity	**Screening**	**PDT-1**	**PDT-2**	**Phone call 1**	**Clinic visit**	**Clinic visit [i]**	**PDT-3 [h]**	**PDT-4 [h]**	**Phone call 2 [h]**	**Clinic visits [h]**		**Follow-up**			
	Visit 1 (≤ 4 weeks prior to PDT-1)[l]	**Visit 2 (Base-line)**	**Visit 3 (1 -2 weeks post-PDT-1)**	**(1 week ± 2 days post-PDT-2)**	**Visit 4 (5 weeks ± 1 week post-PDT-1)**	**Visit 5 (12 weeks ± 1 week post-PDT-1)**	**Visit 5 (12 weeks ± 1 week post-PDT-1)**	**Visit 6 (1-2 weeks post-PDT-3)**	**(1 week ± 2 days post-PDT 4)**	**Visit 7 (5 weeks ± 1 week post-PDT 3)**	**Visit 8 (12 weeks ± 1 week post-PDT 3)**	**FU1 (12 months ± 1 month post-PDT) [d]**	**FU2 (24 months ± 2 month post-PDT) [d]**	**FU3 (36 months ± 2 months post-PDT) [d]**	**FU4 (60 months ± 2 months post-PDT) [d]**

AE: adverse event; BCC: basal cell carcinoma; BP: blood pressure; eCRF: electronic case report form; FU: follow-up; HIPAA: Health Insurance Portability and Accountability Act; HR: heart rate; NMSC: non-melanoma skin cancer; NRPS: numeric rating pain scale; PDT: photodynamic therapy; SAE: serious adverse event; SAR: serious adverse reaction; WHO: World Health Organization

a: Skin type will be assessed according to the Fitzpatrick rating criteria (see Appendix A)[(1)].
b: Clinical laboratory tests will include routine hematology, blood chemistry, and urinalysis.
c: AEs and concomitant medications will be assessed via phone call.
d: After completion of PDT cycle 1 (visit 5) .
e: Topical treatments within the treatment field plus a 5 cm radius surrounding the target lesion).
f: Local AEs in the treatment field.
g: Histopathological assessment to be performed according to WHO criteria[(2)] in a central dermatopathological laboratory.

h: Only for partial or non–responders (according to clinical assessment).
i: Only for complete responders (according to clinical assessment).
k: relevant SAEs or SARs should be reported up to FU4 (60 months after start of last PDT cycle).
l: The time interval may be expanded after approval of the sponsor.
m: All female participants of childbearing potential will undergo a pregnancy test.
n: Only, for partial responders whose Main Target Lesion was assessed as clinically clear.
o: Treatment of any remaining Additional Target Lesion(s) should be carried out after final assessments and after completion of visit 8.
p: Only, for partial responders whose Main Target Lesion was assessed as clinically clear, esthetic appearance/outcome assessment of the Main Target Lesion should be conducted prior to its excision.

Unscheduled visits may be performed for safety reasons.

ABBREVIATIONS AND DEFINITIONS

λ_{em}	Emitted wavelength
ADE	Adverse device event
AE	Adverse event
AK	Actinic keratosis
5-ALA	5-aminolevulinic acid
ALT (SGPT)	Alanine aminotransferase
AP	Alkaline phosphatase
AST (SGOT)	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
BCC	Basal cell carcinoma
BD	Bowen's disease/ squamous cell carcinoma (SCC) *in situ*
BF-200 ALA	Nanoemulsion gel formulation containing 7.8% ALA (development name for Ameluz®)
BMI	Body mass index
BP	Blood pressure
cm	centimeter(s)
CFR	Code of Federal Regulations
CI	Confidence interval
CRO	Contract Research Organization
CS	Clinically significant
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EU	European Union
FWER	Family Wise Error Rate
FAS	Full analysis set
FDA	Food and Drug Administration
FU	Follow-up
G	Gram(s)
GCP	Good clinical practice
GmbH	Gesellschaft mit beschraenkter Haftung, Ltd, limited liability company
GMP	Good manufacturing practice
H	Hour(s)
β-HCG	β human chorionic gonadotropin
HIV	Human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational medicinal product(s)

IRB	Institutional Review Board
J	Joule
IUD	Intrauterine device
LED	Light emitting diode
Ltd	Limited
Main Target Lesion	The Main Target Lesion is the lesion preselected at Visit 2 for excision 12 weeks after the last PDT for this lesion. For the Main Target Lesion, the maximal lesion size should be such that surgical excision without a skin transplant is feasible according to the investigator's judgement. The Main Target Lesion should be representative for the eligible lesions of the subject. In addition, the burden for the subject should be considered during selection of the Main Target Lesion. If two or more lesions would qualify as Main Target Lesion, the lesion whose excision would cause the least burden for the subject should be selected.
MAL	Methyl-aminolevulinic acid
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram(s)
min	Minutes
Ml	Milliliter(s)
mm	Millimeter(s)
mW	Milliwatt
nBCC	Nodular basal cell carcinoma
NCS	Not clinically significant
NDA	New Drug Application
Nm	Nanometer
NMSC	Non-melanoma skin cancer
NRPS	Numeric rating pain scale
NYHA	New York Heart Association
pH	pH-value (grade of acidity)
PDT	Photodynamic therapy
PI	Prescribing Information
PP	Per-protocol
PpIX	Protoporphyrin IX
QPPV	Qualified person for pharmacovigilance
RBC	Red blood cell count
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAR	Serious adverse reaction
sBCC	Superficial basal cell carcinoma
SCC	Squamous cell carcinoma

SD	Standard deviation
SOP	Standard Operating Procedure
SPC	Summary of product characteristics
SUSAR	Suspected unexpected serious adverse reaction
Target lesion	Eligible sBCC lesion confirmed by biopsy. In case of several target lesions one lesion has to be selected as Main Target Lesion which will be excised 12 weeks after the start of the last PDT cycle for this lesion for histological examination. Further lesions will be defined as Additional Target Lesions.
TEAE	Treatment-emergent adverse event
Treatment area	Body areas in which the target lesions are located: face/forehead, bald scalp, neck/trunk, and extremities
Treatment field	Area of a target lesion including 0.5-1.0 cm margin of surrounding skin
UK	United Kingdom
US, USA	United States (of America)
USADE	Unanticipated serious adverse device effect
UV	Ultraviolet
WBC	White blood cell count
WHO	World Health Organization
WMA	World Medical Association

1 INTRODUCTION AND STUDY RATIONALE

1.1 INTRODUCTION

Biofrontera Bioscience GmbH has developed a nanoemulsion-based gel formulation for the treatment of actinic keratosis (AK) and non-aggressive superficial and nodular basal cell carcinoma (BCC) with photodynamic therapy (PDT). The development name for this formulation is BF-200 ALA, and it is marketed in the EU, Switzerland, Israel and the USA under the brand name of Ameluz®. BF-200 ALA contains 10% 5-aminolevulinic acid (5-ALA) hydrochloride, equivalent to 7.8% 5-ALA in a nanoemulsion formulation which enhances stability and skin penetration (3, 4).
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 BF-RhodoLED® medical device was CE-marked and subsequently launched in the European market. In September 2016 the approval was extended to the indication of field cancerization, and in January 2017 to the treatment of superficial and nodular BCC. In March 2018, the posology was extended to the treatment of AK with daylight PDT. Ameluz® furthermore received marketing approval in Switzerland for the treatment of mild to moderate AK on the face and scalp in November 2015 (Swissmedic number: 65693). In Israel, Ameluz® was granted marketing authorization for the treatment of mild to moderate actinic keratosis on the face and scalp with PDT in May 2016. Biofrontera's illumination device BF-RhodoLED® was registered in Israel in May 2017.

In the US, approval for the treatment of lesion-directed and field-directed treatment of mild to moderate AK on the face and scalp, using Ameluz® in combination with BF-RhodoLED® lamp for illumination, was granted in May 2016 (NDA 208081).

The approvals for AK were based on 3 phase III trials (a multicenter vehicle-controlled study randomizing 122 subjects at 8 clinical sites in Germany, a multinational phase III study comparing efficacy and safety of BF-200 ALA and Metvix(ia)® on 571 subjects at 26 clinical sites in Germany, Austria and Switzerland, and a study with 87 subjects in 7 German centers in which BF-200 ALA was used in field-directed AK treatment together with the PDT lamp BF-RhodoLED®). Efficacy and safety of the combination of BF-200 ALA and BF-RhodoLED® in superficial and/or nodular BCC was demonstrated in a pivotal study with 281 subjects at 24 sites in Germany and the UK. The efficacy of daylight PDT in the treatment of AK was established in an intraindividual, active-controlled phase III study with 52 subjects at 4 sites in Germany and 3 sites in Spain.

The Marketing Authorization Holder (Biofrontera Bioscience GmbH) now intends to perform a vehicle-controlled phase III study in the US to demonstrate safety and efficacy of Ameluz® in the treatment of superficial BCC (sBCC) with PDT when utilizing BF-RhodoLED® for illumination, aiming at approval of a label extension for the indication sBCC.

BCC, first described by Jacob in 1827 (5), represents the most common non-melanoma skin cancer (NMSC) worldwide affecting mainly adult (age ≥40), fair-skinned individuals (2, 6). BCCs develop predominately in sun-damaged skin and occur with an incidence rate of 1,406/100,000 in the United States (US) (1998/99), 3,252/100,000 in Queensland/Australia (1997) and 143/100,000 in Germany (2004) (7). Incidence rates are dramatically increasing, e.g. in the US an increase by 50% in males and 20% in females is observed between 1977/78 and 1998/99 (7). Other authors describe an annual increase of 3 to 10% (8). The life risk of developing BCC is 30% and increases to 44% in subjects with a BCC in the 3 previous years (6).

Skin damage caused by accumulative ultraviolet (UV) exposure and the tendency to sunburn are the main etiological factors for developing BCC (6, 9). BCCs are locally invasive tumors and metastases occur in less than 1 out of 10,000 tumors (2). Though 70% of BCC cases occur on the skin of the head or neck; 85% of metastatic cases and 90% of recurrent cases occur at these sites (6).

BCCs are composed of proliferating basaloid cells of the epidermis that usually show a relatively innocuous course, with slow growth and only minimal local extension. Accordingly, this disease typically has a favorable prognosis. BCCs occasionally demonstrate an aggressive phenotype with deep local invasion and resistance to standard treatment (6, 10).

A histological classification of keratinocytic skin tumors and BCC in particular is described in detail in the World Health Organization (WHO) classification of tumors including superficial, nodular (solid), micronodular, infiltrating, and fibroepithelial BCCs, BCC with adnexal differentiation, and basosquamous and keratotic BCCs (2). Taking these histological variations into consideration, BCCs are divided based on their prognosis into non-aggressive, low-risk BCCs and aggressive, high-risk forms with fundamentally different biological characteristics (2, 6, 11, 12).

In these 2 groups, nodular (nBCC) and superficial BCC (sBCC) or mixed superficial and nodular BCCs tend to be less aggressive in general (good to intermediate prognosis) (6, 13). sBCCs are characterized by proliferation of atypical basaloid cells that grow within an axis parallel to the epidermal surface, while nBCCs show a translucent papule or nodule characterized by discrete nests of basaloid cells in either the papillary or reticular dermis (14).

Aggressive BCCs with a poor prognosis are usually histologic variants such as morpheiform, infiltrating, and basosquamous/mixed phenotypes, or demonstrate perineural or perivascular invasion. Tumor nests of aggressive BCCs generally extend to dermal and subcutical layers and thus deeper than sBCCs or nBCCs. Furthermore, aggressive BCCs are often located in facial regions, particularly mid face, nose, temporal area and ears (H-zone; see Appendix B) (10, 13). Aggressive BCCs may present neglected or longstanding tumors or may result from an incomplete excision (6, 10). Multiple recurrences with deep residual tumors on the head may be associated with particular morbidity as they can eventually penetrate the cranium. Increased recurrences are associated with infiltrative, morpheiform and micronodular BCCs where surgical margins may be underestimated (2). Tumors recurring after radiotherapy are usually aggressive and infiltrative. Metastasizing lesions are usually large, ulcerated, deeply infiltrating, and recurrent (2).

Surgical procedures remain the gold standard for the treatment of both high- and low-risk non-melanoma skin cancers, including BCC. However, other treatment alternative are required for subjects where treatment related morbidity and/or cosmetic outcome render surgery difficult (11, 13, 15). Particularly with multifocal sBCCs it may be difficult even with Mohs surgery to precisely determine tumor boundaries (2, 11), therefore requiring more widespread treatment of the tumor margins. Such alternatives include topical medications and photodynamic therapy (PDT).

Dermatological guidelines for the treatment of BCC consider PDT appropriate for the treatment of low-risk tumors, particularly for subjects with large or multiple lesions (11, 13, 15). Several studies provided good evidence for the efficacy of PDT with 5-ALA (e.g. BF-200 ALA) or its derivative methyl-aminolevulinic acid (MAL) in the treatment of superficial and nodular BCCs (8, 16-22). In the US, FDA approval for PDT drugs (Ameluz® or Levulan® Kerastick) is currently limited to the treatment of AK. In the EU, Ameluz® is also approved for the treatment of superficial and nodular BCC if surgical treatment is not suitable due to treatment-related morbidity and/or poor cosmetic outcome.

5-ALA, the active ingredient in BF-200 ALA, acts as precursor in porphyrin synthesis and is enzymatically converted to protoporphyrin IX (PpIX) after cellular uptake, which is the actual photosensitizer. Upon exposure to an appropriate wavelength e.g. blue or red light (absorption maximum of PpIX is at approximately 410 nm and 635 nm, respectively), PpIX becomes activated and induces the formation of cytotoxic singlet oxygen. In neoplastic cells, uptake of 5-ALA as well as their enzymatic conversion to PpIX is enhanced, whereas PpIX degradation is decreased. Thus, after exposure to 5-ALA, PpIX accumulates selectively in neoplastic cells, permitting selective destruction of such cells upon illumination. With increasing thickness of neoplastic lesions, long wavelength light becomes advantageous due to its better tissue penetration. Thus, it is generally agreed in the literature that BCC treatment with PDT should be done with red light of 635 nm, rather than using the blue absorption peak of PpIX that can also be used for AK (23). In the US, Ameluz® (BF-200 ALA) is approved for use in combination with BF-RhodoLED®, an LED lamp emitting light of 635 nm.

A phase III study performed in Germany and the United Kingdom with 281 subjects compared BF-200 ALA (Ameluz®) with MAL (Metvix(ia)®) in the treatment of non-aggressive BCC, including both superficial and nodular BCC with a thickness of <2 mm as confirmed by biopsy. Each subject had up to 3 BCCs, which were treated with 1 or 2 cycles of PDT. Each cycle consisted of 2 PDTs 1 week apart. Subjects were monitored 3 months after the 1st PDT cycle, and received the 2nd treatment cycle if clinically visible BCC of at least 1 lesion remained. 12 weeks later they were assessed again, and the outcome after 1 or 2 cycles was then used to determine efficacy in the primary and secondary study endpoints. All subjects entered a 5-year follow-up 12 weeks after their last PDT, which is still ongoing. Currently, 24-month follow-up data are available. Complete subject clearance from all BCCs 12 weeks after the last PDT cycle was 93.4% for BF-200 ALA and 91.8% for MAL (for the per protocol population). For sBCCs only, the lesion response rates increased to 95.8% versus 96.9%, respectively. At 1-year follow-up 7.0% and 7.2% of lesions relapsed in the BF-200 ALA and MAL groups for all BCCs, respectively which increased to 11% for both treatment arms after 2 years (FAS). For sBCCs only the accumulated lesion recurrence rates after 1-year follow-up were 5.8% and 6.8% for BF-200 ALA and MAL groups, respectively, and 7.7% and 11.2% after 2-year follow-up (FAS).

Safety data reported in this study demonstrated that adverse reactions (AEs) mainly include application site reactions such as erythema, pain, edema and irritation, arising from the underlying mode of action and are similar to those observed in AK studies applying PDT. In general, most side effects are of a transient and self-limiting nature and usually disappear 1-2 weeks after the treatment. A common side effect of PDT treatment is pain during the illumination. In the EU study, pain scores [11-point visual analogue score ranging from 0 (no pain) to 10 (worst pain)] ranged between 2.2 and 5.5 for BF-200 ALA for BCC (data on file) compared to mean pain scores in AK studies ranging from 3.0 to 5.8 (24, 25).

The efficacy of BF-200 ALA together with different sources of illumination was compared in 2 phase III studies for the treatment of AK (25, 26). LED devices providing a red narrow light spectrum achieved higher efficacy rates paralleled by an increase in AE rates (25, 26). Based on these results BF-RhodoLED® was designed as a high-power LED lamp emitting light of 635 nm. A phase III study for field treatment of AK confirmed the high efficacy of the combination of BF-200 ALA with BF-RhodoLED® and led to FDA approval of this combination (24).

Overall, PDT with 5-ALA is well tolerated in humans. Over the past 20 years, the use of PDT with 5-ALA was extended from the treatment of dermal lesions to the identification and eradication of neoplastic or preneoplastic cells in internal tissues/organs such as the vagina, bladder, gastrointestinal

tract, respiratory tract, and the brain. For non-dermal indications, systemic applications of 5-ALA are commonly used.

1.2 STUDY RATIONALE

It is Biofrontera's intention to expand the US marketing authorization of Ameluz® in combination with BF-RhodoLED® to the treatment of sBCC on the face/forehead, bald scalp, extremities, and neck/trunk. This goal is supported by the existing European phase III trial data and favorable post-approval experience with Ameluz® for low-risk BCC in the EU (8, 27, 28). As discussed with FDA during the telephone conference on July 19, 2017 (PIND 115412), the study design foresees one obligatory PDT cycle with 2 PDT sessions 1-2 weeks apart. In case of partial or no response, a 2nd PDT cycle will be administered 3 months later. All subjects will receive surgical excision treatment of the Main Target Lesion at the end of the 1st or 2nd PDT cycle (12 weeks after PDT-1 or PDT-3). This Main Target Lesion will be pre-selected for surgical excision prior to PDT. The Main Target Lesion should be representative for the eligible lesions of the subject and its maximal lesion size should be such that surgical excision without a skin transplant is feasible according to the investigator's judgement. The burden for the subject should also be considered during selection of the Main Target Lesion. If two or more lesions would qualify as Main Target Lesion, the lesion whose excision would cause the least burden for the subject should be selected. The primary clinical endpoint will be the composite endpoint consisting of the full clinical and histological clearance of the Main Target Lesions. Additional sBCCs (so-called Additional Target Lesions) may also be treated as part of the study, but they will only be included into the secondary efficacy and safety analysis. All subjects will be monitored in a 60-months follow up (FU) period which starts after completion of the 1st PDT cycle (Visit 5). The proposed treatment regime is expected to provide a highly effective therapy with an excellent clinical outcome.

Subjects will be randomized to a verum and a vehicle group at a ratio of 4:1, respectively. During randomization, a stratification into subjects with 1 or ≥2 lesion(s) and center will be considered to avoid imbalance in subjects with >1 lesions across treatment arms. The vehicle does not contain the active ingredient 5-ALA but is indistinguishable from BF-200 ALA with respect to color, appearance, and texture. The planned sample size will ensure at least 90% power on a significance level of 0.1% (α=0.001). BF-200 ALA or vehicle will be administered by study personnel who have been intensively trained in performing PDT with the study medication. No other illumination devices besides BF-RhodoLED® may be utilized throughout the study.

Since visible application site effects are expected to occur in the BF-200 ALA group, an investigator will be responsible for all clinical assessments before and after treatments, but PDTs and all assessments within the 1st week following PDT will be applied by a second investigator or delegated person. Both investigators (or delegated person) are not entitled to exchange information in order to maintain the blinded status.

Risk-benefit analysis

All subjects participating in this study will receive surgical excision of the Main Target Lesion after the 1st or 2nd treatment cycle (12 weeks after PDT-1 or PDT-3) which represents the current standard in the treatment of sBCC. If additional lesions are included in the study (Additional Target Lesions) and these lesions are assessed as clinically cleared 12 weeks after the last PDT cycle, the lesions will not be excised in order to minimize the burden of the subject. However, they will be observed during

follow-up. The Additional Target Lesions will not be included in the calculation of the primary endpoint since no histological data are available. They will, however, contribute to the hierarchical testing of key secondary endpoints, further secondary endpoints and safety. Additional Target Lesions that remain clinically apparent 12 weeks after the 2nd PDT cycle will be treated at the discretion of the investigator. Irrespective of the treatment outcome all subjects will be regularly monitored during the follow-up period.

Due to the chosen ratio of study medications, 80% of the subjects will benefit from PDT with the IMP – BF-200 ALA (Ameluz®), and only one-fifth of subjects will receive vehicle. Based on >5.5 years of post-marketing experience and the experience from 4 phase III trials, Ameluz® is considered well tolerated. We do not expect any AEs in this study that differ from those observed previously. The most frequent side effects that are also expected in this trial are transient application site effects such as erythema, pruritus. edema, paresthesia, scab, induration, discharge, exfoliation, and erosion, as well as pain during the illumination, as described in the Ameluz® prescribing information and in the Investigator's Brochure.

Pain management may, if required, be performed according to established guidelines but restrictions for co-medication described in this protocol must be considered (10, 29).

All subjects treated with placebo/vehicle will receive treatment (e.g. surgical excision) at the end of the clinical phase (which is estimated to be about 6 months after the first treatment). In general, BCC demonstrates a relatively innocuous course and with slow growth and minimal local extension (6); metastases are very rare for BCC, they occur in less than 1 in 10,000 tumors (2). Moreover, sBCC is considered as the least aggressive form of BCC (13). Thus, the risk for placebo-treated subjects is deemed acceptable. Furthermore, all subjects will be closely monitored for the duration of the trial. Any change of the BCCs during the study that worsens the clinical characteristics of the BCC will trigger their immediate surgical removal. However, due to the availability of endogenous 5-ALA PDT-related effects cannot be ruled out for this subject group.

In this study, inclusion and exclusion criteria have been chosen to minimize possible risks due to the administration of BF-200 ALA (Ameluz®) and BF-RhodoLED® and to enable a uniform study population. BF-200 ALA or placebo/vehicle will be administered by study personnel who have been intensively trained in performing PDT with the study medication. The sponsor will provide training to the study personnel if appropriate. No other illumination devices besides BF-RhodoLED® may be utilized throughout the study to ensure an effective and continuous light treatment.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

Primary objective: To compare the efficacy of BF-200 ALA PDT (containing 7.8% 5-aminolevulinic acid (5-ALA) as active ingredient) with vehicle PDT, utilizing BF-RhodoLED® illumination in the treatment of superficial BCC.

The primary efficacy variable is the composite clinical and histological response of the subject's Main Target Lesion as assessed 12 weeks after the start of the last PDT cycle that included treatment of the Main Target Lesion (Visit 5 or Visit 8). A Main Target Lesion with a complete clinical and histological response is defined as a completely cleared Main Target Lesion. A confirmatory hypothesis test will be performed for the primary efficacy endpoint using the FAS dataset.

2.2 SECONDARY OBJECTIVES

Secondary objectives: To evaluate the safety and secondary efficacy parameters related to BF-200 ALA and BF-RhodoLED® for the treatment of sBCC with PDT, we also include clinical clearance of Additional Target Lesions on the same subjects. Key secondary efficacy variables will be tested in a confirmatory manner using a hierarchical testing procedure, whereas further secondary efficacy variables will be tested descriptively and in an exploratory manner.

Confirmatory hypothesis testing of key secondary variables measured during the double-blind clinical observation period will be done only after the test of the primary efficacy variable is passed, and will be done strictly in the given order to ensure the Family Wise Error Rate (FWER). Confirmatory hypothesis testing in the pre-defined order will stop once the first non-significant test result is obtained.

Analysis of key secondary endpoints will be performed using the FAS.

The key secondary efficacy variables include:

1. Main Target Lesion clinical response (according to clinical assessment only) assessed 12 weeks after the start of the last PDT cycle.
2. Main Target Lesion histological response (according to histological assessment only) assessed 12 weeks after the start of the last PDT cycle.
3. Subject complete clinical response (complete clearance of all target lesions according to clinical assessment only) assessed 12 weeks after the start of the last PDT cycle.
4. Subject complete response (clinically and histologically cleared Main Target Lesion (see above) and complete clinical remission of all Additional Target Lesions) assessed 12 weeks after the start of the last PDT cycle.

Further secondary efficacy variables include:

- Lesion complete clinical response rate per treatment arm (complete clearance of individual lesions (Main and Additional Target Lesions)) according to clinical assessment only, assessed 12 weeks after the start of the last PDT cycle.
- Main Target Lesion complete response (clinically and histologically cleared) assessed 12 weeks after PDT-1.
- Main Target Lesion clinical response (according to clinical assessment only) assessed 12 weeks after PDT-1.
- Main Target Lesion histological response (according to histological assessment only) assessed 12 weeks after PDT-1.
- Lesion complete clinical response rate per treatment arm (complete clearance of individual lesions (Main and Additional Target Lesions)) according to clinical assessment only, assessed 12 weeks after PDT-1.
- Subject complete clinical response (complete clearance of all target lesions according to clinical assessment only) assessed 12 weeks after PDT-1.
- Subject complete response (clinically and histologically cleared Main Target Lesion (see above) and complete clinical remission of all Additional Target Lesions) assessed 12 weeks after PDT-1.
- For all Target Lesions, assessment of esthetic appearance by the investigator 12 weeks after the start of the last PDT cycle, but prior to surgical excision of the Main Target Lesion and any alternative treatment of Additional Target Lesions.
- Subjects' satisfaction regarding esthetic outcome and treatment 12 weeks after the start of the last PDT cycle, but prior to surgical excision of the Main Target Lesion or alternative treatment of Additional Target Lesions at the end of the clinical observation period.

For the follow-up (FU) period of the study, the following analysis variables will be collected and analyzed descriptively and in an exploratory manner:

- Recurrence of the subject's Main Target Lesion after surgical excision (defined as in composite endpoint).
- Subject recurrence rate defined as the percentage of subjects with all Additional Target Lesions completely clinically cleared 12 weeks after the start of the last PDT cycle with at least one recurrent lesion during FU.
- Subject recurrence rate defined as the percentage of subjects with all Additional Target Lesions completely clinically cleared 12 weeks after the start of PDT-1 with at least one recurrent lesion during FU.
- Lesion recurrence rate per treatment arm defined as the percentage of completely cleared individual Additional Target Lesions 12 weeks after the start of the last PDT cycle showing recurrence during FU.

- Lesion recurrence rate per treatment arm defined as the percentage of completely cleared individual Additional Target Lesions 12 weeks after the start of PDT-1 showing recurrence during FU.
- Esthetic appearance for all Main Target Lesions following surgical excision, and for all Additional Target Lesions that were clinically cleared 12 weeks after the last PDT cycle and did not receive additional treatments.
- Subject satisfaction regarding treatment and esthetic outcome for all Target Lesions that did not receive additional treatment after the last PDT cycle.

The results from the FU period of the study will be analyzed and reported separately and will not be included into the CSR describing the clinical observation period of the study.

Subject recurrence rate is generally defined as the percentage of subjects with at least one recurrent lesion during FU, who were previously (i.e., 12 weeks after the last PDT cycle) assessed as completely cleared as defined in the primary endpoint for Main Target lesions and clinically cleared for Additional Target Lesions during assessment 12 weeks after the last PDT cycle.

The safety analysis variables during the clinical observation period include:

- Frequency and extent of adverse events (AEs), serious AEs (SAEs), and treatment-emergent adverse events (TEAEs). TEAEs are defined as all AEs with onset or worsening after treatment with randomized IMP within 4 weeks after each PDT cycle (until Visit 4 or Visit 7, respectively).
- New AK, NMSC and melanoma, including location of lesion(s).
- Local skin reactions at the treatment field(s), assessed by the investigators.
- Local discomfort or pain during illumination, reported by the subjects.
- Vital signs.
- Safety laboratory.
- Physical examinations.

The safety analysis variables during the FU period include:

- Any local AEs or conditions within the treatment field(s) that may be relevant for proper assessment of the recurrence of the treated lesions. Any relevant SAE or serious adverse reaction (SAR).
- New NMSC and melanoma, including location of lesion(s).
- New AK lesions within the treatment field(s) and treated subarea(s).

3 STUDY DESIGN, DURATION AND DATES

3.1 STUDY DESIGN

This protocol describes a randomized, double blind, vehicle-controlled (4:1 ratio) multicenter phase III study aiming to evaluate the safety and efficacy of BF-200 ALA (Ameluz®) utilizing BF-RhodoLED® in the treatment of sBCC with PDT. The study will be conducted at approximately 12 sites in the United States of America (US). The study is divided into two parts: a clinical observation part lasting up to 7 months per subject and consisting of a screening and pre-randomization period (up to 4 weeks) and a clinical observation period (up to 6 months). Subjects will be followed-up for 60 months after completion of the 1st PDT cycle (Visit 5)) (see Figure 1). The "illumination period" is defined as a component of the PDT treatment in which subjects are exposed to the red light source BF-RhodoLED® for 10 minutes (see Section 5.1.3).
To guarantee the blind status of the investigator assessing efficacy after each PDT cycle, a second investigator or delegated person will perform drug application and light treatment. The second investigator or delegated person(s) will furthermore conduct all safety evaluations at visits where PDT is applied and during the phone call 1 week after each PDT-cycle, respectively. Both investigators (and delegated person(s)) are not entitled to exchange information about the study outcome and side effects.

Complete response of the Main Target Lesion is assessed 12 weeks after the start the last PDT cycle that included treatment of the Main Target Lesion and is defined as a Main Target Lesion that is clinically and histologically cleared. **Clinically complete responders** are categorized 12 weeks after start of the last PDT cycle (PDT-1 or PDT-3) and are defined as subjects whose lesions (Main Target and Additional Target Lesions) are completely cleared clinically.

For **clinically complete responders after the 1st PDT cycle**, i.e., subjects showing complete clinical remission of all target lesions after the 1st PDT cycle, the clinical observation period of the study consists of a screening visit at which a biopsy is taken of each eligible BCC for confirmation of diagnosis (Visit 1), a pre-randomization period lasting up to 4 weeks, a randomization and treatment visit (Visit 2, PDT-1) at which also the ink marks are applied, a first-cycle retreatment visit 1-2 weeks later (Visit 3, PDT-2), a phone call 1 week ± 2 days after PDT-2 and two visits for assessment of efficacy and safety (Visit 4: 5 weeks ± 1 week after PDT-1; and Visit 5: 12 weeks ± 1 week after PDT-1).

Non-responders or partial responders according to clinical assessment after the 1st PDT cycle, i.e., subjects with visible remaining target lesions at Visit 5 (Week 12 after PDT-1), will have all remaining target lesions retreated with a 2nd PDT cycle starting at Visit 5 (PDT-3). If the Main Target Lesion should be clinically cleared at this time point, it will be excised prior to retreatment of the remaining lesions with a 2nd treatment cycle starting the same day. PDT-4 will be applied 1-2 weeks later, at Visit 6. Subjects will then be contacted by phone 1 week ± 2 days after the 2nd PDT cycle ended, and attend two further visits for assessment of efficacy and safety (Visit 7: 5 weeks ± 1 week after PDT-3, and Visit 8: 12 weeks ± 1 week after PDT-3). At Visit 8, a final clinical assessment will be performed identifying complete clinical responders 12 weeks after the start of the last PDT cycle and partial or non-responders, i.e., subjects still showing remaining target lesions after the 2nd PDT cycle. A retreated Main Target Lesion will be excised on this day, irrespective of the clinical outcome.

All subjects will receive excision of their Main Target Lesion at latest at the end of the clinical observation period (Visit 8) for histopathological evaluation of lesion status irrespective of the outcome of the clinical assessment. Along with the excision of the BCC, the ink marks applied at Visit 2 will be removed. All remaining Additional Target Lesions at Visit 8 will be treated at the discretion of the investigator.

For all subjects, four FU visits are scheduled (12 ± 1, 24 ± 2, 36 ± 2, and 60 ± 2 months after completion of PDT cycle 1 (Visit 5)). All subject data listed in Section 7.1 and results of assessments have to be recorded in the subject electronic case report form (eCRF).

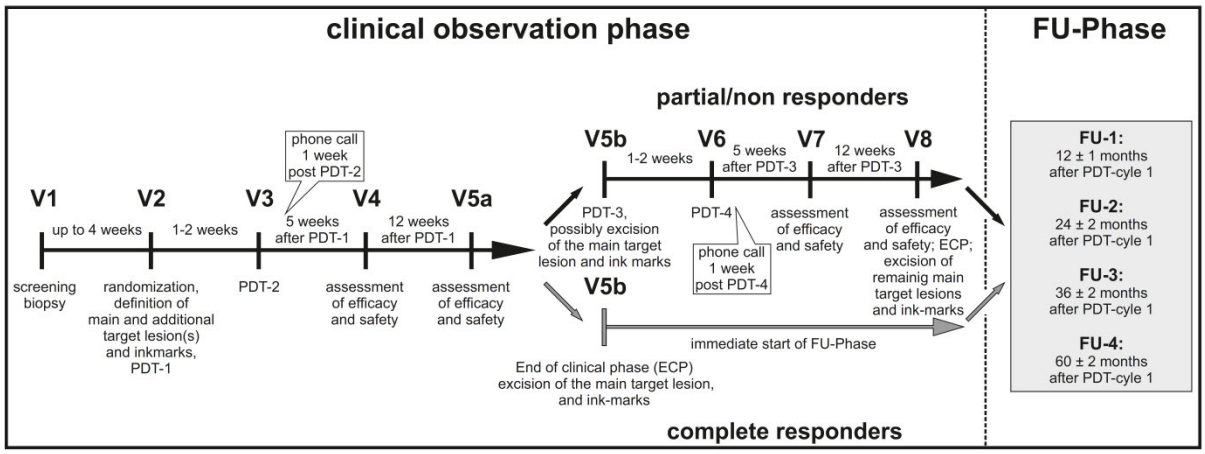

Figure 1: Summary of study visits for complete and partial/non responders

The procedures to be performed at each study visit are listed in the study schedule (Table 1).

Data reported during the FU part of the study will be analyzed and reported separately and are not part of the clinical observation period of the study.

3.2 STUDY DURATION, DATES, AND END-OF-STUDY DEFINITION

The last subject last visit of the study is expected to be approximately in August 2024.

A recruitment period of approximately 9 months will be followed by a clinical observation period of either 12 or 24 weeks. This is determined by the response status of the subject at Visit 5, 12 weeks after PDT-1. After this period, i.e. 12 weeks after the start of the last PDT cycle, the clinical observation part of the study will be completed (last subject out of the clinical phase approximately in November 2019). The clinical observation part is followed by a FU part that includes 4 additional visits (i.e., 12, 24, 36 as well as 60 months after completion of the 1st PDT cycle (Visit 5)) and will be completed for the last subject approximately in August 2024. The actual duration of the subject recruitment period and consequently the whole study may vary.

The end of the study is defined as the date of database lock, approx. 2 month after the last follow-up visit of the last subject (approx. in October 2024).

4 SELECTION OF SUBJECTS

4.1 NUMBER OF SUBJECTS

Approximately 186 subjects should be randomized (4:1) in this study with approximately 149 subjects in the BF-200 ALA group and 37 subjects in the vehicle group (see Section 11.6 for details). This sample size will ensure a power of at least 90% with a significance level set to 0.1% (α=0.001) using a one-sided Cochran-Mantel-Haenszel Test with stratification factors lesion baseline characteristics (lesion count 1 vs ≥2 lesion(s)) and center to demonstrate statistically significant superiority in response rates in subjects treated with BF-200 ALA in comparison to subjects treated with vehicle in the full analysis set (FAS). Subjects will be recruited at approximately 12 study sites in the US. Each site should randomize between 10 and an absolute maximum of 30 subjects. Randomization will be stratified by the number of lesions (1 vs ≥2 Lesion(s)) and center. No site should randomize more than 20 subjects unless prior approval of the sponsor is given. Sponsor approval will be based on

i) consideration of the potential impact for the statistical analysis and
ii) the quality of work performed to date by the site, as assessed through monitoring or auditing. Enrollment will be stopped once the anticipated subject number has been achieved across all study sites.

4.2 RECRUITMENT ARRANGEMENTS

Investigators may enroll their existing or incoming subjects. Recruitment will be competitive within the limits described above.

4.3 MAIN INCLUSION CRITERIA

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

- Willingness and ability to sign the informed consent form and Health Insurance Portability and Accountability Act (HIPAA) form. A study-specific informed consent form and a HIPAA form must be obtained in writing for all subjects prior to starting any study procedures.
- Men or women ≥18 years of age.
- Presence of ≥1 naïve sBCC lesion in the treatment areas face/forehead, bald scalp, extremities and/or neck/trunk, all of which are, according to the clinical judgement of the investigator, likely to be histologically confirmed as sBCCs. Lesions should not be within the embryonic fusion planes (H-zone), especially within 2 cm of the hair zone or on the ears. In case of multiple lesions, one lesion is defined as Main Target Lesion which will be excised at the end of the clinical observation period. Only eligible naïve sBCCs, confirmed by histology taken at screening, are allowed to be included in the study as Main or Additional Target Lesions. Thus, eligible sBCCs must lack any histological evidence of aggressive growth patterns (e.g. severe squamous metaplasia, infiltrative/desmoplastic features or basosquamous features). BCCs assessed as non-naïve (e.g. previously treated or recurrent) or non-eligible by biopsy taken at screening (and in a distance >5 cm from the next lesion included in the study) should be excised by surgery or removed by cryotherapy in a timely manner. Other treatments for these lesions are not allowed during the study.

- The diameter of each eligible lesion should be ≥ 0.6 cm, and the total treatment field must not exceed ~20 cm². The treatment field is defined as the field to which IMP is applied, usually including the target lesions and margins surrounding the lesions of up to 1 cm. For the Main Target Lesion, the maximal lesion size should be such that surgical excision without a skin transplant is feasible according to the investigator's judgement.
- Target BCC lesions must be discrete and located within 1–2 illumination areas (the illumination area is defined by the effective illumination area of the BF-RhodoLED® device with approximately 6 x 16 cm).
- Willingness to receive up to 4 PDTs within 3.5 months and excision of the Main Target Lesion either at Visit 5, if clinically cleared, or at the end of the clinical observation period 12 weeks after the start of the last PDT cycle (Visit 8), irrespective of whether the Main Target Lesion was clinically cleared or not.
- Free of significant physical abnormalities (e.g. tattoos, dermatoses) within the potential treatment field plus a 5 cm radius surrounding the target lesion(s) as they may interfere with examination or final evaluation.
- Willingness to stop the use of moisturizers and any other cosmetics within the treatment field plus a 5 cm radius surrounding the target lesion(s) 48 hours prior to an office visit and 48 hours after each PDT session. Sunscreen will be allowed, but should not be applied to the treatment field plus the 5 cm radius surrounding the target lesion(s) within approximately 24 h prior to a clinical visit.
- Acceptance to abstain from extensive sunbathing and the use of a solarium during the clinical observation period. Subjects with sunburn within treatment areas cannot be included until fully recovered.
- Healthy subjects and subjects with clinically stable medical conditions, including, but not limited to controlled hypertension, diabetes mellitus type II, hypercholesterolemia, and osteoarthritis, will be permitted to be included in the study if their medication is not prohibited by this protocol.
- Women of childbearing potential are permitted to participate in this study only if they have a negative serum pregnancy test at screening and are willing to use a highly effective method of contraception during the clinical observation period of the study.

4.4 EXCLUSION CRITERIA

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

- History of hypersensitivity to 5-ALA or any ingredient of BF-200 ALA which includes soybean phosphatidylcholine.
- Hypersensitivity to porphyrins.
- Current treatment with immunosuppression therapy.
- Presence of photodermatoses.
- Presence of porphyria.
- Presence of clinically significant inherited or acquired coagulation defect.
- Evidence of clinically significant (CS) unstable medical conditions, such as:

  - Metastatic tumor or tumor with high probability of metastasis.
  - Cardiovascular disease class III, IV (New York Heart Association [NYHA]).
  - Immunosuppressive condition.
  - Hematologic, hepatic, renal, neurologic, or endocrine condition.
  - Collagen-vascular condition.
  - Gastrointestinal condition.

- Clinically relevant cardiovascular, hepatic, renal, neurologic, endocrine, or other major systemic diseases that complicate implementation of the protocol or interpretation of the study results.
- Gorlin Syndrome or Xeroderma pigmentosum.
- Presence and/or physical treatment of skin tumors other than (naïve) sBCC (e.g. malignant melanoma, squamous cell carcinoma (SCC), Bowen's disease, aggressive BCC or nBCC diagnosed at the screening visit by clinical assessment) within a distance of ≤ 5 cm from the nearest target lesion within 4 weeks prior to PDT (Visit 2) until the end of the clinical observation period. However, biopsied lesion(s) that were not confirmed eligible at screening and which are located at a distance of > 5 cm from any lesion(s) that will be included in the study can be surgically removed. Treatment by PDT or topical medication during the course of the clinical observation period of the study triggers exclusion of the subject.
- If lesion(s) are assessed as non-eligible by biopsy during initial screening and these lesions are localized within a distance of 5 cm from an otherwise suitable lesion, this suitable lesion must be excluded from the study.
- Any AK lesions within the treatment field (lesion area including margin of 0.5 to 1.0 cm).
- Any topical medical treatment of AK, other non-melanoma skin cancers (NMSC), or melanoma (except for IMP treatment of target lesion(s)) starting 12 weeks prior to Visit 2 (PDT-1) and lasting until the end of the clinical observation period.
- Any other topical medical treatment of the skin 12 weeks prior to Visit 2 (PDT-1) until the end of the clinical observation period, with the exception of:
  - Topical treatments with corticosteroids (allowed throughout the clinical observation period of the study).
  - Topical non-steroidal anti-inflammatory drugs (NSAIDs such as diclofenac) (allowed throughout the clinical observation period of the study with the restriction of 7 days prior to and 7 days after PDTs).
- Start of intake of medication with hypericin or systemically acting drugs with phototoxic or photoallergic potential within 8 weeks prior to screening.
- Any of the **systemic treatments** listed below, within the designated period prior to PDT and during the clinical observation period.

Treatment	Period
Interferon	6 weeks
Immunomodulators or immunosuppressive therapies	12 weeks
Cytotoxic drugs	6 months
Investigational drugs	8 weeks

Drugs known to have major organ toxicity	8 weeks
Corticosteroids (oral or injectable)	6 weeks
MAL or ALA	12 weeks

- **Systemic** treatment with NSAIDs is not to be used 7 days prior to and 7 days after PDT. ASA (e.g. Aspirin®) up to 100 mg/ day, ibuprofen up to 200 mg/ day, and acetaminophen (e.g. Tylenol®) is allowed during this period.
- Presence of tattoos, skin inflammation, wounds, etc. in the treatment field(s) plus a 5 cm radius surrounding the target lesion(s).

Further exclusion criteria include the following:

- Pregnancy.
- Breast feeding.
- Participation in a clinical study within 2 months prior to screening.
- Drug or alcohol abuse in the preceding 2 years.
- Subject is the investigator or any subinvestigator, research assistant, pharmacist, study coordinator, other staff, or relative thereof directly involved in the conduct of the protocol.
- Mental condition rendering the subject unable to understand the nature, scope, and possible consequences of the study.
- Subject is unlikely to comply with protocol, e.g. due to an uncooperative attitude, inability to return for FU visits, and unlikelihood of completing the study.
- Known confirmed diagnosis of human immunodeficiency virus (HIV) based on clinical history.

A subject may not be enrolled in this study more than once.

4.5 SCREENING FAILURES

All subjects that match one or both of the following criteria prior to IMP application will be considered as screening failures:

- They do not meet one or more inclusion criteria.
- They meet one or more exclusion criteria.

Subjects assessed as screening failures will not be randomized at Visit 2. Hence, they will be considered as dropouts that do not contribute to the Randomized set.

4.6 SUBJECTS OF REPRODUCTIVE POTENTIAL

Female subjects of childbearing 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 observation period. The contraceptive method(s) chosen should be medically, culturally, and geographically acceptable as well as proven to have an acceptably low failure rate (Pearl Index below

1, failure rate less than 1% per year). If properly used, this applies to implants, injectables, combined oral contraceptives, some IUDs, sexual intercourse with a vasectomized partner, or true abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

If a randomized subject becomes pregnant during the clinical observation period, she must inform the investigator immediately. If possible, the clinical visits as well as the FU visits should be completed, but no further PDT should be applied. The further treatment should be addressed on a case-by-case basis with the treating physician and the investigator.

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

If a female subject becomes pregnant during the clinical observation period, she must be followed up until the outcome of the pregnancy is known.

5 STUDY TREATMENTS

5.1 DETAILS OF INVESTIGATIONAL PRODUCTS

The IMP will be BF-200 ALA, a gel formulation of 7.8% 5-ALA (Ameluz®). The vehicle used as comparator is a formulation similar to the BF-200 ALA gel formulation but without the active ingredient 5-ALA and indistinguishable in color, appearance and texture from the verum medication.

The compositions of the IMPs are as follows:

Table 2: Composition and manufacturer of study medication

Drug:	BF-200 ALA (Ameluz®)	Vehicle
Brand name:	Ameluz®	not applicable
Chemical name:	5-amino-4-oxopentanoat hydrochloride	not applicable
International non-proprietary name:	5-ALA hydrochloride	not applicable
Formulation:	BF-200 ALA containing 7.8% 5-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 the 5-ALA
Manufacturer:	Biofrontera Pharma GmbH Hemmelrather Weg 201 51377 Leverkusen, Germany	Biofrontera Pharma GmbH Hemmelrather Weg 201 51377 Leverkusen, Germany

5-ALA: 5-aminolevulinic acid;

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

The BF-200 nanoemulsion gel is an oil-in-water dispersion of very small and homogenous vesicles, composed of a lipid core surrounded by a lecithin/co-surfactant monolayer. BF-200 nanoemulsion has a mean vesicle size of less than 30 nm with a very narrow size distribution. BF-200 ALA contains ingredients that are well established and approved worldwide in medicinal and cosmetic products. The formulation of BF-200 ALA, as applied in this study, is identical to the currently marketed formulation as well as the formulation that was used in the confirmatory clinical trials summarized in Section 1.2.

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

Vehicle and BF-200 ALA are indistinguishable in appearance, color and texture.

The IMP will be delivered in aluminum tubes containing 2 g gel (BF-200 ALA for the test group or vehicle for the control group). Four tubes will be provided per subject, one for each PDT. The quantity provided for each PDT is sufficient to cover a 20 cm^2 area with a 1 mm thick layer. Thus, 1 tube of IMP is sufficient to cover the entire permitted total lesion area during each PDT session.

For each subject, a card box is provided containing four tubes with the same content (either BF-200 ALA or vehicle). Each box is labeled with and can be identified and assigned to a specific subject by the unique random number.

5.1.1 Storage

At the study sites, IMP has to be stored at 2°C to 8°C (36°F – 46°F) (rounded) in a locked and temperature-controlled cabinet, inaccessible by unauthorized persons. Temperature records (minimal-actual-maximal) 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 IMP appropriately after delivery at study site) have to be immediately announced to the monitor and the sponsor, and IMP cannot be used unless sponsor's release for this specific event was given.

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

Used IMP must be stored for drug accountability purposes and will be returned to the drug supplier for destruction.

5.1.2 Application of investigational products

The specifications for appearance, color, viscosity, and pH of vehicle and BF-200 ALA are identical, except for the absence of the active ingredient, slightly increased contents of xanthan gum, water, and pH-adjustment. Thus, BF-200 ALA and vehicle are indistinguishable during treatment.

To guarantee the blind status of the investigator assessing efficacy after each PDT cycle, a second investigator or delegated person will perform drug application and light treatment. The second investigator or delegated person(s) will furthermore conduct all safety evaluations at visits where PDT is applied and during the phone call 1 week after each PDT-cycle, respectively. Both investigators (and delegated person(s)) are not entitled to exchange information about the study outcome and side effects.

After determination of the number, location and size of all target sBCC lesions within the face, bald scalp, extremities and neck/trunk, clinical and histological assessment of their subtypes (biopsies are taken at Visit 1), and graphical documentation of the lesions (Visit 1), the unique subject randomization number will be assigned at Visit 2. One lesion is, furthermore, defined as Main Target Lesion that will undergo surgical excision at the end of the clinical observation phase (12 weeks after start of the last PDT cycle). Therefore this lesion will be marked by at least 3 ink marks prior to PDT at Visit 2 to enable precise excision. Ink marks should be applied about ~3-4 mm from the sBCC margin.

All target lesions should be prepared for drug application by degreasing (using ethanol or isopropanol), removal of all scabs and crusts, and roughening of the surface, if appropriate (e.g. by mild debridement for the removal of crusts). Care should be taken to avoid bleedings. The formulations will be applied to target lesions (maximal combined lesion area incl. margin is 20 cm^2) located in 1 to 2 illumination areas (6 x 16 cm). The medication should be applied to the entire target lesion(s) (including a 0.5 – 1.0 cm margin surrounding each target lesion) at a thickness of 1 mm, allowed to dry (for ~10 minutes), covered with a light-tight dressing (e.g. Tegaderm™ dressing plus aluminum foil), and incubated for 3 h + 0.5 h. Care should be taken to avoid that the IMP is applied to the upper and lower eyelids, the lip area (not past the vermilion border), or in the nostrils. Thereafter, any remnants of the IMP will be removed carefully and the PDT illumination will be administered using the light emitting diode (LED) red light device BF-RhodoLED® (see Section 5.1.3). One to two weeks after PDT-1, the same procedure will be repeated at Visit 3 (PDT-2).

Subjects diagnosed as clinically completely cleared 12 weeks after start of the 1st PDT-cycle (i.e., the Main Target and all Additional Target Lesions are clinically cleared) will complete the clinical observation period and will enter FU. Subjects that still show at least one clinically apparent target lesion after the 1st PDT cycle at Visit 5 (partial or non-responders according to clinical assessment after the 1st PDT cycle) will enter a 2nd PDT cycle of two PDTs with identical schedule starting the same day. For these subjects, all remaining target lesions included in the study will be retreated. The clinical observation period of the study will end for those subjects at Visit 8, 12 weeks after the start of the 2nd PDT-cycle, and they will enter the FU part of the study after completion of Visit 8. If the Main Target Lesion of partial responders is clinically cleared 12 weeks after PDT-1, it will be surgically excised prior to PDT-3 treatment at the same day.

All subjects will undergo surgical excision of their Main Target Lesion for histopathological assessment either at Visit 5, if clinically cleared, or at the end of the clinical observation period, irrespective of their clinical assessment. The excision will be performed after the clinical assessment of all Main and Additional Target Lesions, the evaluation of esthetic outcome and prior to entering FU, if applicable. All Main Target Lesions will be surgically excised. Any remaining Additional Target Lesions at Visit 8 (12 weeks after start of the 2nd PDT cycle) will have to be treated at the discretion of the investigator after completion of Visit 8. Any treatment of remaining target lesions that were not clinically cleared at the end of the clinical observation phase should be documented accordingly.

The time of IMP application and removal must be documented.

5.1.3 Illumination with BF-RhodoLED®

Following the incubation for 3 + 0.5 h, the light-tight dressing is removed and the entire treatment field(s) (including healthy skin between or around lesions) will be illuminated using red light at approximately 635 nm with the narrow spectrum LED lamp BF-RhodoLED®, until a total light dose of approximately 37 J/cm^2 is achieved. During illumination, the lamp will be positioned at a distance of 5-8 cm from the skin surface as indicated in the user manual.

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 current study aims at demonstrating the effectiveness and safety of Ameluz® in conjunction with BF-RhodoLED® in the treatment of sBCC, and the handling of BF-RhodoLED® will be identical to

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

BF-RhodoLED® utilizes 128 LEDs and lenses (arranged in a rectangle) to emit a uniform, bundled, visible red light with a typical peak wavelength at approximately 635 nm and a half bandwidth of 20 nm. The illumination area of the lamp is 8 x 18 cm with an effective treatment area of 6 x 16 cm and an optimum treatment distance of 5-8 cm. The calibration of the lamp ensures that the skin area illuminated receives a total light dose of 37/cm^2 when maintaining a total illumination time of 10 min at a distance of 5-8 cm. Therefore, it must be confirmed and documented that the applied light dose (37 J/cm²) and distance between the lamp and the lesion have been met. Otherwise, reasons for not meeting the requirements must be provided. The lamp is programmed to automatically provide a total illumination time of 10 min. In case of necessary interruptions, e.g. due to unbearable pain, the lamp will continue until the required illumination time is achieved. For the purpose of this study, each site will be equipped with at least one BF-RhodoLED® lamp. All site personnel handling the lamp will be instructed properly on the handling and usage of the lamp, according to the latest version of the user manual.
The recommended conditions for illumination with the LED lamp are shown in Table 3.

Table 3: Key parameters of LED lamp used

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

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

Discomfort and pain during PDT are caused by the intended phototoxic reaction, but their perception is also related to a strong psychological component. The extremely bright red light may be perceived as threatening by some subjects and may psychologically be associated with "heat". Although the light is completely cold, subjects may have the feeling of being burned. The latter is caused by a generally harmless, but in some subjects very unpleasant, biochemical reaction during PDT.

As pain experienced during PDT will be evaluated by all subjects after the treatment, the PDT should be started without measures to relieve pain. In cases where the pain is regarded as unbearable by the subject, cooling with an air stream or nebulized water may be offered. Severe cases might require to shortly interrupt illumination, e.g. to inject a local, fast-acting anesthetic, such as xylocaine. Both, the pain level experienced by the subject and, if applicable, any physical or therapeutic intervention shall be documented. If it becomes necessary to interrupt illumination, the reason and the duration of the interruption must be documented.

After PDT, further analgesic treatment with acetaminophen (e.g. Tylenol®) may be indicated and is allowed. Topical corticosteroids are also permitted.

The following therapies should not be used to treat pain and discomfort **during and up to 7 days after the PDT**:

- Systemic
    - Acetylsalicylic acid >100 mg/day
    - NSAIDs such as diclofenac or ibuprofen (>200 mg/day)
    - Corticosteroids
- Topical
    - EMLA® cream
    - NSAIDs such as diclofenac

The subject should be informed about these restrictions.

During the hours following PDT, it may be useful to cool the illuminated area(s) with wet or refrigerated compresses. A further analgesic treatment with acetaminophen (e.g. Tylenol®) or ibuprofen (up to a maximal dose of 200 mg/day) may be indicated and is allowed. Please, consider restrictions as outlined in the exclusion criteria and in Section 6 and 7.2.1, respectively.

A surgical dressing of the treated area is normally not required.

Although a nearly complete loss of PpIX is assumed to occur during PDT, subjects should avoid exposure to intensive sun light for about 48 hours since new PpIX may accumulate from remaining 5-ALA. Additional light exposure may increase the typical side effects of PDT. In general, subjects should not expose themselves to intensive UV-radiation (solarium, sun bathing, etc.) during the course of the study. These instructions are not given for reasons related to PDT but due to the possible risk of developing UV-induced post-inflammatory hyperpigmentation of the healing tissue.

5.2 DOSAGE SCHEDULE

Up to 2 g of BF-200 ALA gel or vehicle will be administered prior to each PDT session. The IMP should be allowed to dry for approximately 10 min before the lesions are covered with a light-tight dressing. After an incubation time of 3 h + 0.5 h, the dressing and any remnant gel are removed and illumination as part of the PDT is applied. Up to three additional PDT sessions will be applied according to the study design described in Section 3.1 and Figure 1.

5.3 RANDOMIZATION AND TREATMENT ASSIGNMENT

The IMP will be administered exclusively to subjects matching the eligibility criteria and for whom the written informed consent and HIPAA form is available (see Section 12.3).

Each subject for whom informed consent and HIPAA is obtained will be assigned a subject number in the chronological order of enrollment (within each center). This subject number will be documented and will be used to identify the subject until he/she 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 randomization will be stratified according to the number of eligible lesions (1 vs ≥2). Additionally the randomization procedure will ensure a stratification by center. The randomization number will be assigned accordingly and will be provided by the eCRF platform upon entering the total number of eligible lesions to be included in the study.

Subjects will be randomized at a 4:1 allocation ratio of active treatment (BF-200 ALA) to control (vehicle). Randomization numbers will be blocked. 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). A minimum of 10 to a maximum of 30 subjects should be randomized per study site but no site should randomize more than 20 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 observation period of the study, except in case of an emergency. The randomization schedule and the allocation to treatment groups will remain unknown to the investigator until completion of follow-up. In case of emergency the investigator can request unblinding of a specific randomization number via an interactive web response system (IWRS). The qualified person for pharmacovigilance (QPPV) as well as the responsible project manager at Biofrontera Bioscience GmbH will receive immediate notice from the system about the code breaking . There is no apparent reason to break the randomization code in the event of an adverse drug reaction. This is because the subjects receive all treatments on only small treatment fields two or four times within 3 months and there is no substance-specific treatment for adverse reactions.

The randomization schedule(s) will be generated using Rancode Professional by medicomp, a subcontractor of [redacted]. Rancode Professional is a validated program that automates the random assignment of treatments to randomization numbers. The randomization schedule will link sequential numbers to treatment codes. A sealed randomization schedule will be kept at [redacted] in a locked environment accessible by the management board of [redacted] only, which is separate from the study team. Copies of the randomization schedule will furthermore be delivered to the provider of the electronic data capture system, the drug supplier responsible for packaging and labeling of the IMP, and a Biofrontera representative responsible for the release of study medication. On specific request, the latter will provide information about specific random numbers to the QPPV, whenever required. All these individuals are separate from the study team.

The IMP will be labeled with the randomization number and the assigned PDT session.

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

5.4 BLINDING, PACKAGING, AND LABELING

5.4.1 IMP

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

Responsible for manufacturing and release of IMP (BF-200 ALA) and vehicle:
Biofrontera Pharma GmbH
Hemmelrather Weg 201
D-51377 Leverkusen
Germany

The appropriate number of tubes and card board boxes will be labeled in English according to the pre-defined distribution of treatment numbers. The labels will include all information required by 21 CFR

312.6 (including the statement: “Caution: New Drug—Limited by United States law to investigational use”).

In addition to the labels affixed to the tubes and card board boxes, a separate tear-off label with the same labeling information will be found on the outside of each individual card board box, and this label must be affixed to 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 as well as the labels of the IMP in the Trial Master File.

5.4.2 MEDICAL DEVICE (BF-RHODOLED®)

BF-RhodoLED® is manufactured in compliance with ISO 13485 standards by:
Biofrontera Pharma GmbH
Hemmelrather Weg 201
D-51377 Leverkusen
Germany

and will be distributed and assembled/maintained at the sites by technicians of:

Biofrontera Inc.
201 Edgewater Drive
Wakefield, MA 01880
USA

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

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

For the purpose of this study, each site will be provided with at least one BF-RhodoLED®. It is exclusively intended to be used in conjunction with the IMP for the study-related treatment of sBCC. As the lamp will be assembled on site by a technician of Biofrontera Inc., there will be no immediate packaging available. All labelling will be applied directly to the lamp.

5.5 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 and thereafter supply the investigators and the study centers with IMP and at least one BF-RhodoLED® lamp per site, together with all relevant documentation including a description of the storage conditions. The sponsor is responsible for IMP delivery to the sites.

The investigator will inventory and acknowledge receipt of all shipments of the IMP. The IMP must be stored in a locked and temperature-controlled area with restricted access and must be handled in accordance with the instruction provided by Biofrontera Pharma GmbH. The investigator is responsible for maintaining documentation showing the amount of IMP provided to the investigational site, and dispensed to and collected from each study subject. Discrepancies in IMP accountability must be explained and documented. The monitor is responsible for verifying the investigator's documentation on receipt, use, and return of IMP. The monitor will check drug accountability at the site on an ongoing basis during the study. At the end of the study, all IMP and vehicle must be returned to the drug supplier acting on behalf of Biofrontera Pharma GmbH for disposal. The monitor will prepare a final report of IMP accountability for filing in the investigator file.

After the last subject completed the clinical observation phase, all lamps will be disassembled by a technician and returned to Biofrontera Inc. Receipt and return of BF-RhodoLED® will be acknowledged and documented accordingly.

5.6 COMPLIANCE

The application of IMP will be administered/supervised by the investigator or subinvestigator. Any delegation of this responsibility should follow the guidelines stated in Section 12.2.

The IMP will not be handed over to the subjects but applied by study personnel, rendering individual compliance assessments unnecessary.

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

6 PRIOR AND CONCOMITANT DISEASES AND TREATMENTS

6.1 PRIOR AND CONCOMITANT DISEASES

Additional diseases present at the time of signing of the informed consent and HIPAA are regarded as concomitant diseases and must be documented, along with any relevant prior diseases. See Section 4.4 for forbidden concomitant diseases.

Diseases first occurring or detected during the study, and worsening of a concomitant disease during the study, are to be regarded as AEs and must be documented (see Section 8).

6.2 CONCOMITANT TREATMENTS

All treatments taken by the subject at study entry or at any time during the study, in addition to the IMP, are regarded as concomitant treatments. The use of required concomitant treatments, which are known not to interfere with the IMP or to mask their effect, is unrestricted and may be continued throughout the study. All concomitant treatments taken during the study must be documented along with the indication, daily dose, route of administration, and dates of administration. The subject should confer with the investigator prior to the use of a new medication during the course of the study. Any complimentary nutrition are not required to be documented.

The following concomitant treatments / procedures are not permitted during this clinical observation period of the study:

- Any systemic or topical AK, NMSC, and melanoma therapy (including treatment of lesions other than the target lesions; see also below), any photodynamic or radiation therapy, or any topical treatment within the treatment region.
- Any invasive therapy such as cryosurgery, electrodessication, surgical removal of lesions, curettage, or treatment with chemical peels such as trichloroacetic acid within the treatment region, or within a radius less than 5 cm away from the nearest target lesion. Lesions other than the target lesions may be treated with these methods if the distance to the target lesions is more than 5 cm. Lesion(s) that could not be confirmed to be eligible by biopsy at screening and which are located at a distance of ≥ 5 cm from any target lesion(s) can be excised surgically. Treatment by PDT or topical medication during the course of the clinical observation period of the study is not allowed.
- Concomitant therapy with any experimental drug or drugs known to have major organ toxicity, immunomodulators, immunosuppressive therapies, 5-fluorouracil preparations, or interferon preparations **throughout the clinical observation period** (from Visit 1 to Visit 5 or Visit 8).
- Concomitant therapy with drugs containing corticosteroids, ibuprofen, diclofenac, or acetylsalicylic acid preparations **within 7 days prior and after each PDT treatment**. (Details see exclusion criteria, Section 4.4) with the following exceptions:
    - topical treatments with corticosteroids, which is allowed
    - Ibuprofen ≤ 200 mg/day, oral and topical, which is allowed
    - acetylsalicylic acid ≤ 100 mg/day, oral and topical, which is allowed.

- With the exception of the IMP applied in the treatment field(s) at the treatment visit(s) and the exceptions described above as well as the allowed treatments for intercurrent conditions described in Section 4.3, all medications, preparations, and treatments listed in the exclusion criteria (Section 4.4), will not be allowed for treatment at any time during the blinded clinical observation period of the study. Sunscreens will be allowed, but should not be applied in the treatment fields within approximately 24 hours of a clinic visit that includes a lesion count.
- 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, eosine, Bengal rose, or Acridine within 8 weeks prior to screening. Subjects may, however, be enrolled if such medication was taken for more than 8 weeks prior to screening without evidence for an actual phototoxic/photoallergic reaction. Within 8 weeks prior to screening, such medication must not be newly prescribed. Should such a prescription become unavoidable for medical reasons during the clinical observation period of the trial, the investigator has to consult with the sponsor, who may discontinue the subject's study participation, if deemed necessary. For some beta-blockers, it is mentioned that "allergic skin reactions (redness, itching, exanthema, photosensitivity)" may occur after use. Subjects who have been taking such beta-blockers for a long time, but have had no skin reactions can be included in the clinical trial. Subjects who have taken such beta-blockers only for a short time should not be included since the risk for the occurrence of skin irritation cannot be foreseen.
- Acetylsalicylic acid (>100 mg/day) and EMLA® cream should not be used to treat PDT-induced pain and discomfort.

These restrictions apply for the clinical observation part of the study only (until 12 weeks after the start of last PDT cycle). They are not valid during the FU part of the study.

If the investigator, at any time during the study, suspects or diagnoses a lesion within or outside the treatment field(s) to have progressed into a manifest malignancy, the investigator should treat this lesion according to standard medical practice, irrespective of whether or not this treatment leads to the exclusion of the subject from the study.

The investigator will record any medications given for the treatment of AEs. Any medication taken by the subject during the course of the study including over-the-counter medicinal products (such as herbal medications) should also be recorded. Data recorded will include the name of the medication, total daily dose, route of intake, indication, and start and termination dates of its application.

In follow-up, only relevant (S)AEs and related SAEs (SARs) have to be documented (see Section 8.2). Therefore, only the applicable concomitant medication to treat the relevant AEs/S AEs must be documented. Relevant AEs are those (including local AEs or any conditions affecting skin health inside the treatment field(s)) that might impair proper assessment of the recurrence of the treated BCC target lesions, or other clinically relevant events at the investigator's discretion. In consequence, relevant concomitant medication is defined as any medication used for the treatment of relevant (S)AEs or SARs.

7 STUDY PROCEDURES AND SCHEDULE

7.1 OVERVIEW OF DATA COLLECTION

The following main types of data will be collected in this study:

Efficacy data

- Data concerning the sBCC target lesions and the treated area(s) (number, size, location).
- Data concerning the esthetic outcome/appearance of the treatment field(s).
- Data concerning subject's satisfaction.

Safety data

- Frequency and duration of adverse events (AEs), serious AEs (SAEs), and treatment-emergent adverse events (TEAEs). TEAEs are defined as all AEs with onset or worsening after treatment with randomized IMP within 4 weeks after each PDT cycle (until Visit 4 or Visit 7, respectively).
- New NMSC and melanoma, including location of lesion(s).
- New AK lesions including location of lesion(s).
- Local skin reactions at the treatment field(s), assessed by the investigators.
- Local discomfort and pain during or after illumination, reported by the subjects.
- Vital signs (blood pressure (BP), heart rate (HR)).
- Standard laboratory safety data (hematology, biochemistry and urinalysis).
- Data from physical examinations.

Other data

- Demographic data.
- Skin type assessment.
- Biopsy data of BCC lesions and histological examination for confirmation of diagnosis
- Excision of Main Target BCC Lesion and results of histopathological examination.
- Treatment of remaining or recurrent Additional Target Lesions
- Medical history.
- Concomitant medications/treatments.

7.2 DESCRIPTION OF STUDY DAYS

The study schedule is provided in Table 1 and is furthermore depicted in Figure 1.

7.2.1 Clinical observation phase

Visit 1, Screening (≤ 4 weeks prior to PDT-1)

Potential subjects will be evaluated to determine whether they fulfill the inclusion and exclusion criteria (see Sections 4.3 and 4.4). The following additional evaluations and procedures will be performed at Visit 1 (Screening):

- Subject will be informed about the study and signs the informed consent agreement and the HIPAA form for study participation. The signed consent must be available prior to any other study-related procedures.
- Assignment of subject number (randomization number will be assigned at Visit 2).
- Evaluation and documentation of demographic data.
- Evaluation of inclusion and exclusion criteria.
- Documentation of relevant medical history and concomitant medication (see Section 6).
- Assessment of the skin type according to Fitzpatrick (see Appendix A)[(1)].
- Documentation of skin disease history, including NMSC and melanoma history.
- Documentation of current AK, NMSC and melanoma status, including location of lesion(s).
- Clinical assessment of sBCC lesions (location(s), size (minimal diameter 0.6 cm, for the Main Target Lesion the maximal diameter should be limited by the suitability for surgical excision at the end of the clinical observation period, please refer also to *Definition of Target Lesions, illumination and treatment region*, Section 7.3.1). The combined treatment field(s) should not exceed 20 cm² (including 0.5 – 1.0 cm margins surrounding the target lesion(s)) (see Section 4.3).
- Generation of a template (on provided grid foil) to locate and mark the target lesions to be treated relative to specific body marks. Additional recording of target lesions shall be indicated on the body map cartoon provided together with the grid foil (to be kept in subject file).
- Biopsies (3 mm punch biopsies) of selected clinically diagnosed sBCC to histologically confirm the diagnosis. Biopsy must be unambiguously assigned to the specific target lesion and sent to the central dermatopathological laboratory for evaluation. Containers and fixation solution will be provided to the centers by the central dermatopathological laboratory. In order to minimize the burden of the subject, 3 mm punch biopsies taken within a period up to 2 months prior to screening can be considered. In this case, slides and/or blocks, or digitalized images of slides/blocks, of the specified lesion(s) should be sent to the central dermatopathological laboratory for re-evaluation taking an accurate pseudomysation of the subject's data into account. The samples/images will be assessed according to the WHO criteria for the histological typing of skin tumors[(2)].
- Withdrawal of blood and collection of urine samples for clinical laboratory tests and urinalysis.
- Serum pregnancy tests for female subjects of reproductive potential.
- General physical examination.

- Measurement of vital signs (HR and BP).
- Subject should be reminded about allowed and forbidden medications (see below)
- Investigator will send a subject status confirmation by FAX or email.

The inflammation induced by the PDT is an important part of the therapeutic mode of action and is intended. Therefore, the investigator should advise the subject about the following restrictions prior and after each PDT:

Up to 7 days prior to PDT, intake and/or any other systemic treatment with NSAIDs is not to be used. ASA up to 100 mg/day, ibuprofen up to 200 mg/day is allowed in this period. Topical NSAIDs such as diclofenac are not to be used 7 days prior to each PDT in- and outside the treatment fields. Topical treatments with corticosteroids are allowed throughout the clinical phase of the study.

After PDT, analgesic treatment with acetaminophen (e.g. Tylenol®) may be indicated and is allowed.

The following therapies should not be used to treat pain and discomfort **during and up to 7 days after the PDT**:

- Systemic
    - Acetylsalicylic acid >100 mg/day
    - NSAIDs such as diclofenac or ibuprofen (>200 mg/day)
    - Corticosteroids
- Topical
    - EMLA® cream
    - NSAIDs such as diclofenac

The subject should be informed about these restrictions accordingly.

The following evaluations and procedures will be performed at either the study visits or through the phone contact:

Visit 2, PDT-1 (Baseline)

- Double check all inclusion and exclusion criteria, in particular the confirmation of diagnosis of sBCC for at least one lesion based on the result of the histopathological evaluation. The subject must not be randomized if no lesion fulfills the criteria or if all eligible lesions are located closer than 5 cm to one of the non-suitable BCC lesions.
- Randomization and assignment of randomization number.
- Assessment of the sBCC lesion(s) (lesion count, location, and size).
- Measurement of vital signs (HR and BP).
- Pregnancy test (urine) for females of reproductive potential.

- Definition of the Main Target Lesion and application of at least 3 ink marks to establish its exact position. Further lesions included in the study will be regarded as Additional Target Lesions. The Main Target Lesion should be representative for the eligible lesions of the subject and should take the burden for the subject into account. However, for the Main Target Lesion, the maximal lesion size should be such that surgical excision without a skin transplant is feasible according to the investigator's judgement. In cases where two or more lesions would qualify as Main Target Lesion, the lesion whose excision will cause the least burden for the subject shall be selected. (Please refer also to *Definition of Target Lesions, illumination and treatment region*, Section 7.3.1)
- Thorough preparation of eligible lesions and application of IMP (see Section 5.1.2).
- Documentation of time of IMP application and removal.
- All target lesion(s) will be illuminated with BF-RhodoLED® until a total light dose of 37 J/cm^2 per treatment field is achieved. In cases of severe pain, illumination may be shortly interrupted, e.g. to inject a fast acting local anesthetic, such as xylocaine (see Section 5.1.3).
- Documentation of illumination procedures, including time of illumination (10 min) and distance of the LED lamp to the treated lesion(s) (5-8 cm). Additional documentation of possible pain induced interruptions (duration, frequency) and pain relieving measures during illumination. Deviations from the standard illumination procedure have to be justified.
- Pain reported by the subject during the illumination will be recorded using the numeric rating pain scale (NRPS) by the provided subject's pain questionnaire (see Section 7.3.2).
- Discomfort reported by the subject during the illumination will be recorded by the provided subject's discomfort questionnaire (see Section 7.3.2).
- Documentation of AEs, including local skin reactions, local discomfort, and pain during and/or after PDT at the treatment field(s).
- Documentation of new AK, NMSC and melanoma, including location of lesion(s).
- Documentation of concomitant medications/treatments including those, which might be taken for pain management during and/or after PDT.
- Subject should be reminded about allowed and forbidden medications (see Visit 1).
- Investigator will send a subject status confirmation by FAX or email.

Visit 3, PDT-2 (1-2 weeks post PDT-1 (Visit 2))

- Assessment of how the subject is feeling since last PDT. Using non-leading questions such as "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 documented.
- Measurement of vital signs (HR and BP).
- Pregnancy test (urine) for females of reproductive potential.
- Thorough preparation of the treated BCC target lesion(s) and application of IMP (see Section 5.1.2).
- Documentation of time of IMP application and removal.

- The target lesion(s) will be illuminated with an LED lamp (BF-RhodoLED®) until a total light dose of 37 J/cm^2 (per treatment field) is achieved. In cases of severe pain, illumination may be shortly interrupted, e.g. to inject a fast acting local-anesthetic, such as xylocaine (see Section 5.1.3).
- Documentation of illumination procedures, including time of illumination (10 min) and distance of the LED lamp to the treated lesion(s) (5-8 cm). Additional documentation of possible pain induced interruptions (duration, frequency) and pain relieving measures during illumination. Deviations from the standard illumination procedure have to be justified.
- Pain reported by the subject during the illumination will be recorded using the NRPS by the provided subject's pain questionnaire (see Section 7.3.2).
- Discomfort reported by the subject during the illumination will be recorded by the provided subject's discomfort questionnaire (see Section 7.3.2).
- Documentation of AEs, including local skin reactions, local discomfort, and pain during and/or after PDT at the treatment field(s).
- Documentation of new AK, NMSC and melanoma, including location of lesion(s).
- Documentation of concomitant medications/treatments including those, which might be taken for pain management during and/or after PDT.
- Subject should be reminded about allowed and forbidden medications (see Visit 1).

Phone call 1 (1 week ± 2 days post-PDT-2 (Visit 3))

The aim of this safety telephone contact is to achieve an overall impression on the tolerability of the PDT with the study drug and to evaluate how the subject is feeling since the last PDT session. Using non-leading questions such as "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 documented.

The following information will be collected during each phone contact:

- Concomitant medications/treatments.
- (S)AEs, including local skin reactions, local discomfort, and pain at the treatment field(s).

Visit 4 (5 weeks ± 1 week post-PDT-1 (Visit 2))

- Assessment of Main Target Lesion and Additional Target BCC Lesion(s) (count, size, and location).
- Measurement of vital signs (HR and BP).
- Documentation of AEs, including local skin reactions, local discomfort, and pain at the treatment field(s).
- Documentation of new AK, NMSC and melanoma, including location of lesion(s).
- Documentation of concomitant medications/treatments.

- Subject should be once again informed about the possibility of a 2nd PDT cycle at visit 5 and thus about restrictions concerning intake of certain medications 7 days prior to/after PDT (see Visit 1).

Visit 5, PDT-3 (12 weeks ± 1 week post-PDT-1 (Visit 2))

- **For complete responders (i.e., subjects with all treated target lesions [Main and Additional Target Lesions] clinically cleared):** End of clinical observation period of the study for these subjects.
- Assessment of treated BCC target lesion(s) (count, size, and location).
- Assessment of esthetic appearance of the treated lesions (treatment field(s)) by investigator prior to excision.
- Assessment of subject's satisfaction regarding PDT treatment and esthetic outcome prior to excision.
- Measurement of vital signs (HR and BP).
- Documentation of AEs, including local skin reactions, local discomfort, and pain at the treatment field(s).
- Documentation of new AK, NMSC and melanoma, including location of lesion(s).
- Documentation of concomitant medications/treatments.
- General physical examination.
- Withdrawal of blood and collection of urine samples for safety laboratory tests and urinalysis.
- Pregnancy test (urine) for females of reproductive potential.
- Excision of the Main Target Lesion including ink-marks and histological assessment.
- Subjects will be asked to return for the 1st FU visit in approx. 12 months (12 ± 1 months post completion of 1st PDT cycle).
- Investigator will send a subject status confirmation by FAX or email.

For partial- or non-responders (not all target lesions are clinically cleared): Start of 2nd PDT cycle.

- Assessment of the treated BCC target lesion(s) (lesion count, size and location).
- Measurement of vital signs (HR and BP).
- Pregnancy test (urine) for females of reproductive potential.
- If the Main Target Lesion is assessed as clinically cleared:
    - Assessment of esthetic appearance of the Main Target Lesion by investigator prior to excision.
    - Assessment of subject's satisfaction of esthetic outcome of the Main Target Lesion prior to excision.
    - Excision of the Main Target Lesion including ink-marks and histological assessment.

- Thorough preparation of all remaining target lesion(s) included in the study and application of IMP (see Section 5.1.2).
- Documentation of time of IMP application and removal.
- All lesion(s) that are not yet clinically cleared will be illuminated with an LED lamp (BF-RhodoLED®) until a total light dose of 37 J/cm^2 (per treatment field) is achieved. In cases of severe pain, illumination may be shortly interrupted, e.g. to inject a fast acting local-anesthetic, such as xylocaine (see Section 5.1.3).
- Documentation of illumination procedures, including time of illumination (10 min) and distance of the LED lamp to the treated lesion(s) (5-8 cm). Additional documentation of possible pain induced interruptions (duration, frequency) and pain relieving measures during illumination. Deviations from the standard illumination procedure have to be justified.
- Pain reported by the subject during the illumination will be recorded using the NRPS by the provided subject's pain questionnaire (see Section 7.3.2).
- Discomfort reported by the subject during the illumination will be recorded by the provided subject's discomfort questionnaire (see Section 7.3.2).
- Documentation of AEs, including local skin reactions, local discomfort, and pain during and/or after PDT at the treatment field(s).
- Documentation of new AK, NMSC and melanoma, including location of lesion(s).
- Documentation of concomitant medications/treatments including those, which might be taken for pain management during and/or after PDT.
- Subject should be reminded about allowed and forbidden medications (see Visit 1).

Visit 6, PDT-4 (1-2 weeks –post PDT-3 (Visit 5))

- Assessment of how the subject is feeling since last PDT. Using non-leading questions such as "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 documented.
- Measurement of vital signs (HR and BP).
- Pregnancy test (urine) for females of reproductive potential.
- Thorough preparation of all remaining target lesion(s) included in the study and application of IMP (see Section 5.1.2).
- Documentation of time of IMP application.
- All lesion(s) that are not yet clinically cleared will be illuminated with an LED lamp (BF-RhodoLED®) until a total light dose of 37 J/cm^2 (per treatment field) is achieved. In cases of severe pain, illumination may be shortly interrupted, e.g. to inject a fast acting local-anesthetic, such as xylocaine (see Section 5.1.3).
- Documentation of illumination procedures, including time of illumination (10 min) and distance of the LED lamp to the treated lesion(s) (5-8 cm). Additional documentation of possible pain induced interruptions (duration, frequency) and pain relieving measures during illumination. Deviations from the standard illumination procedure have to be justified.

- Pain reported by the subject during the illumination will be recorded using the NRPS by the provided subject's pain questionnaire (see Section 7.3.2).
- Discomfort reported by the subject during the illumination will be recorded by the provided subject's discomfort questionnaire (see Section 7.3.2).
- Documentation of AEs, including local skin reactions, local discomfort, and pain during and/or after PDT at the treatment field(s).
- Documentation of new AK, NMSC and melanoma, including location of lesion(s).
- Documentation of concomitant medications/treatments including those, which might be taken for pain management during and/or after PDT.
- Subject should be reminded about allowed and forbidden medications (see Visit 1).

Phone call 2 (1-week ± 2 days post-PDT-4 (Visit 6))

The aim of this safety telephone contact is to achieve an overall impression on the tolerability of the PDT with the study drug and to evaluate how the subject is feeling since the PDT session. Using non-leading questions such as "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 documented.

The following information will be collected during each phone contact:

- Concomitant medications/treatments.
- (S)AEs and local skin reactions, local discomfort, and pain at the treatment field(s).

Visit 7 (5 weeks ± 1 week post-PDT-3 (Visit 5))

- Assessment of treated BCC target lesion(s) (count, size and location).
- Measurement of vital signs (HR and BP).
- Documentation of AEs, including local skin reactions, local discomfort, and pain at the treatment field(s).
- Documentation of new AK, NMSC and melanoma, including location of lesion(s).
- Documentation of concomitant medications/treatments.

Visit 8 (12 weeks ± 1 week post-PDT-3 (Visit 5))

End of clinical observation period of the study for all subjects that entered a 2nd PDT cycle.

- Assessment of BCC target lesion(s) (count, size, and location).
- Assessment of esthetic appearance of the treated lesions (treatment field(s)) prior to excision of the Main Target Lesion.

- Assessment of subject's satisfaction regarding PDT treatment and esthetic outcome prior to excision of the Main Target Lesion.
- Measurement of vital signs (HR and BP).
- Documentation of AEs, including local skin reactions, local discomfort, and pain at the treatment field(s).
- Documentation of new AK, NMSC and melanoma, including location of lesion(s).
- Documentation of concomitant medications/treatments.
- General physical examination.
- Withdrawal of blood and collection of urine samples for safety laboratory tests and urinalysis.
- Pregnancy test (urine) for females of reproductive potential.
- Excision of the Main Target Lesion (regardless of whether they are clinically cleared or not and only if not already excised at Visit 5) including ink-marks and histological assessment.
- Subjects will be asked to return for the 1st FU visit in approx. 9 months (12 ± 1 months post completion of 1st PDT cycle).
- Treatment of not or partially cleared Additional Target Lesions with conventional therapy at the discretion of the investigator.
- Investigator will send a subject status confirmation by FAX or email.

7.2.2 End of treatment

The end of treatment is defined as Visit 5 for subjects who were clinically classified as complete responders following the 1st PDT-cycle. For subjects entering a 2nd PDT-cycle (clinically classified as partial- or non-responders at Visit 5), the end of treatment is defined as Visit 8. Depending on the success of the treatment, Main Target Lesions, including the ink marks, will be surgically excised at the respective time point (Visit 5 or Visit 8, respectively). Remaining Additional Target Lesions at Visit 8 will be treated by conventional therapy at the end of this visit. Other reasons for an advanced end of treatment could occur at any time throughout the study due to an AE, withdrawal of consent, or at the discretion of the investigator. After the end of the clinical observation (treatment) part, subjects will enter the FU part of the study. Unscheduled visit(s) may be necessary for aftercare of the excised lesion.

7.2.3 Follow-up visits

All subjects who completed the clinical observation period in this clinical trial should be followed up for 5 years post-treatment in order to assess the long-term treatment effect with respect to recurrences of the sBCC target lesions and subject's safety. Follow-up (FU) visits will be scheduled 12 ± 1 months, 24 ± 2 months, 36 ± 2 months and 60 ± 2 months after completion of the 1st PDT cycle (Visit 5). Subjects who are drop outs should be encouraged to a final visit for safety documentation.

The following procedures will be performed at FU visits:

- Visual inspection of the treatment fields for any recurrent sBCC target lesion, and determination of size and location in case of recurrence.
- Assessment of esthetic appearance of the treated lesion(s) (treatment field(s)).
- Assessment of subject's satisfaction regarding PDT treatment and esthetic outcome.
- Documentation of relevant (S)AEs (any local AE or conditions within the treatment field(s) that may be relevant for proper assessment of the recurrence of the treated lesions or SAE that impairs the conduct of the study) and related SAEs (SARs) as well as the applicable concomitant medication to treat the relevant AEs/S AEs. Furthermore, any AEs that are considered relevant by the investigator will be documented.
- Documentation of new NMSC and melanoma, including location of lesion(s).
- Documentation of new AK lesions within the treatment field(s) and the treated subarea(s).
- Treatment of recurrent lesions with conventional therapy at the discretion of the investigator.
- The subject will be asked to return for the next follow-up visit, if applicable.
- Investigator will send a subject status confirmation by FAX or email (only for the last regular follow-up visit (FU4).

The results from the FU period of the study will be analyzed and reported separately, and are not part of the clinical observation period of the study.

7.3 METHODS

7.3.1 Efficacy data

The primary efficacy variable is the composite clinical and histological response of the subject's Main Target Lesion as assessed 12 weeks after the start of the last PDT cycle that included treatment of the Main Target Lesion (Visit 5 or Visit 8). A Main Target Lesion with a complete clinical and histological response is defined as a completely cleared Main Target Lesion.

A confirmatory hypothesis test will be performed for the primary efficacy endpoint using the FAS dataset.

Additional key secondary efficacy variables will be tested in a confirmatory manner using a hierarchical testing procedure, whereas further secondary efficacy variables will be tested descriptively and in an exploratory manner. Confirmatory hypothesis testing of key secondary variables measured during the double-blind treatment period will be done only after the test of the primary efficacy variable is passed, and will be done strictly in the given order to ensure the Family Wise Error Rate (FWER). Confirmatory hypothesis testing in the pre-defined order will stop once the first non-significant test result is obtained.

Analysis of key secondary endpoints will be performed using the FAS.

The key secondary efficacy variables include:

1. Main Target Lesion clinical response (according to clinical assessment only) assessed 12 weeks after the start of the last PDT cycle.
2. Main Target Lesion histological response (according to histological assessment only) assessed 12 weeks after the start of the last PDT cycle.
3. Subject complete clinical response (complete clearance of all target lesions according to clinical assessment only) assessed 12 weeks after the start of the last PDT cycle.
4. Subject complete response (clinically and histologically cleared Main Target Lesion (see above) and complete clinical remission of all Additional Target Lesions) assessed 12 weeks after the start of the last PDT cycle.

Further secondary efficacy variables include:

- Lesion complete clinical response rate per treatment arm (complete clearance of individual lesions (Main and Additional Target Lesions)) according to clinical assessment only, assessed 12 weeks after the start of the last PDT cycle.
- Main Target Lesion complete response (clinically and histologically cleared) assessed 12 weeks after PDT-1.
- Main Target Lesion clinical response (according to clinical assessment only) assessed 12 weeks after PDT-1.
- Main Target Lesion histological response (according to histological assessment only) assessed 12 weeks after PDT-1.

- Lesion complete clinical response rate per treatment arm (complete clearance of individual lesions (Main and Additional Target Lesions)) according to clinical assessment only, assessed 12 weeks after PDT-1.
- Subject complete clinical response (complete clearance of all target lesions according to clinical assessment only) assessed 12 weeks after PDT-1.
- Subject complete response (clinically and histologically cleared Main Target Lesion (see above) and complete clinical remission of all Additional Target Lesions) assessed 12 weeks after PDT-1.
- For all Target Lesions, assessment of esthetic appearance by the investigator 12 weeks after the start of the last PDT cycle, but prior to surgical excision of the Main Target Lesion and any alternative treatment of Additional Target Lesions.
- Subjects' satisfaction regarding esthetic outcome and treatment 12 weeks after the start of the last PDT cycle, but prior to surgical excision of the Main Target Lesion or alternative treatment of Additional Target Lesions at the end of the clinical observation period.

<u>For the FU period of the study, the following analysis variables will be collected and analyzed descriptively and in an exploratory manner:</u>

- Recurrence of the subject's Main Target Lesion after surgical excision (defined as composite endpoint).
- Subject recurrence rate defined as the percentage of subjects with all Additional Target Lesions completely cleared clinically 12 weeks after the start of the last PDT cycle with at least one recurrent lesion during FU.
- Subject recurrence rate defined as the percentage of subjects with all Additional Target Lesions completely cleared clinically 12 weeks after the start of PDT-1 with at least one recurrent lesion during FU.
- Lesion recurrence rate per treatment arm defined as the percentage of completely cleared individual Additional Target Lesions 12 weeks after the start of the last PDT cycle showing recurrence during FU.
- Lesion recurrence rate per treatment arm defined as the percentage of completely cleared individual Additional Target Lesions 12 weeks after the start of PDT-1 showing recurrence during FU.
- Esthetic appearance for all Main Target Lesions following surgical excision, and for all Additional Target Lesions that were clinically cleared 12 weeks after the last PDT cycle and did not receive additional treatments.
- Subject satisfaction regarding treatment and esthetic outcome for all Target Lesions that did not receive additional treatment after the last PDT cycle.

The results from the FU period of the study will be analyzed and reported separately and are not part of the clinical observation period of the study.

Definitions and criteria to be used to evaluate the efficacy variables are defined below.

Definition of target lesions, illumination and treatment region

In this study, we discriminate the treatment areas, the treatment field(s), and the illumination area of BF-RhodoLED®.

The **treatment area(s) are the area(s) in which the target lesion(s) are located and** are defined as treatment area A (Face) with the subareas whole face (but excluding H-zones i.e. eyes, ears, temporal area, nose and mouth, and with a distance of >2 cm from the hair zone; see Appendix B) and forehead; treatment area B (Bald scalp) with the subarea bald scalp; treatment area C (Neck/trunk) with the subareas neck, back, belly, décolleté, throat, other; and treatment area D (Extremities) with the subareas hand, lower arm, lower leg, upper arm, upper leg, foot, other. Only sBCC lesions located within one of these treatment areas will be treated and analyzed.

The **treatment field** is defined by the sBCC lesion(s) treated with IMP. It should contain ≥ 1 eligible sBCC lesion but should not exceed ~20 cm^2 in total (including lesion area and 0.5 – 1.0 cm of surrounding tissue per lesion). In this study, sBCC lesions may be located in up to 2 separate illumination areas within one treatment area comprising not more than 20 cm^2 in total (including 0.5 – 1.0 cm of surrounding tissue per lesion).

The **illumination area** is defined as the area that is effectively illuminated by BF-RhodoLED®, spanning approximately 6 x 16 cm.

Target Lesions are BCC lesions which are histologically confirmed as sBCC (by biopsy) at screening (Visit 1) and are eligible according to the inclusion and exclusion criteria. Target lesions will be treated with PDT.

Main Target Lesion is defined as the one sBCC lesion per subject that is pre-selected at baseline (Visit 2) for excision after completion of the clinical observation phase (Visit 5 or Visit 8, respectively). Only Main Target Lesions will be included into the primary efficacy endpoint. Criteria for selection are: (i) the maximal lesion size should be such that surgical excision without a skin transplant is feasible according to the investigator's judgement; (ii) the lesion should be representative for the eligible lesions of the subject; (iii) the burden for the subject should be considered during selection of the Main Target Lesion. If two or more lesions would qualify as Main Target Lesion, the lesion whose excision would cause the least burden for the subject should be selected.

Additional Target Lesions are defined as all other target lesions that are treated by PDT without excision at the end of the clinical observation period and will only be included into secondary efficacy and safety endpoints.

Clinical criteria for diagnosis of superficial BCC

Subjects must have ≥ 1 clinically typical, visible, naïve, sBCC lesion in the respective treatment areas to be eligible in the study (see Section 4.3). These lesion(s) should furthermore lie within 1-2 illumination area(s) that should not exceed an area of 6 x 16 cm each. The accumulated area of treatment fields should not exceed ~20 cm^2 in total.

sBCC lesions generally have a good or intermediate prognosis and are characterized as follows:

The **sBCC** subtype is a flat, red, well-circumscribed plaque, with very slow centrifugal spread, sometimes covered with small scales or crusts. The characteristic keratin pearls are usually invisible to the naked eye. It may present immediately as multiple lesions and develops mainly in areas where the skin is covered. Histologically, it is characterized by a proliferation of atypical basaloid cells growing in parallel to the epidermal surface. Tumor nests are usually attached to the epidermis and/or hair follicles, with peripheral palisading of the nuclei. Retraction features are usually present and separate the tumor cells from the stroma. Usually, there appear to be multiple tumor foci, separated by areas of normal skin (2, 14).

sBCC is considered as the least aggressive form of BCC (13).

In some cases, melanin pigmentation of the epithelium and in the histiocytes in the subjacent stroma is observed. Pigmented subtypes should not be considered due to a possible impairment of efficacious illumination during PDT.

The sBCC lesion(s) must be discrete and quantifiable; the diameter of each eligible BCC lesion must not be smaller than 0.6 cm. To describe irregular lesions (ellipsoidal), investigators will measure the major and minor axes, which both must lie within the acceptable limits defined above.

Naïve lesions are defined as lesions which were not previously treated and are not recurrent.

BCC lesion assessments

Only sBCC of a minimal diameter of 0.6 mm will be treated with PDT and analyzed in the current study. The lesions can be located in one of the following treatment areas: the face and forehead (treatment area A), on the bald scalp (treatment area B), at the neck/trunk (treatment area C) or on the extremities (treatment area D). Excluded are on the H-zone (e.g. eyes, ears, temporal area, nose, or mouth; Appendix B) or within a distance of ≤2 cm from the hair zone.

The total sBCC lesion size per subject results from the sum of all single lesions including a 0.5-1 cm margin surrounding each lesion at Visit 2 and must not exceed ~20 cm^2 in total. Measurements of the lesions will be performed at each clinical visit and will be measured by comparing the BCC count of eligible lesions at baseline with the count at Visit 4, Visit 5, Visit 7, and Visit 8 and during FU visits. A BCC lesion is considered as "clinically cleared" after all complete visual disappearance of any typical indicators for BCC.

The overall subject complete response (primary efficacy variable) for the Main Target Lesion is evaluated 12 weeks after the start of the last PDT cycle (PDT-1 or PDT-3) by clinical and histopathological assessment. At the same time, all secondary efficacy variables are evaluated as well.

Subjects or lesions will be assessed as recurrent if they were clinically and histologically cleared for the Main Target Lesion or clinically cleared for Additional Target Lesion(s) at the **end of the clinical observation period** (at Visit 5 or Visit 8, respectively), and reoccur during follow-up as defined by clinical assessment.

Biopsy and excised tissue

A 3 mm punch biopsy will be taken from the thickest (according to clinical assessment) area of every lesion at the screening visit (Visit 1). The localization and size of the biopsies should be marked on the graphic template and on the cartoon.

In order to minimize the burden of the subject, 3 mm punch biopsies taken within a period up to 2 months prior to screening can be considered. In this case, slides and/or blocks of the specified lesion(s), or digitalized images of slides and/or blocks, should be sent to the central dermatopathological laboratory for re-evaluation taking an accurate pseudomysation of the subject's data into account. Digital slides will be acceptable for re-assessment to simplify the process and handling of the dermatological samples.

The biopsies will be evaluated histopathologically by a central dermatopathological laboratory to confirm the diagnosis of sBCC. The evaluation of the biopsy will be based on the histopathological classification of subtypes according to WHO histological typing of skin tumors (2). Thus, eligible sBCCs must lack any histological evidence of aggressive growth patterns (e.g. severe squamous metaplasia, infiltrative/desmoplastic features or basosquamous features).

The result of the histopathological evaluation must confirm the clinical diagnosis sBCC and the result of the histopathological assessment must be available at the study center before the investigator is allowed to start treatment of this subject. In case no clear histopathological assessment can be performed, the lesion cannot be included into the study.

If the biopsy does not confirm the clinical diagnosis sBCC for at least one lesion, the subject must not be randomized. If lesion(s) are assessed as non-eligible by biopsy and these lesions are localized within a distance of 5 cm from an otherwise suitable lesion, this suitable lesion must also be excluded from the study.

At Visit 5 for subjects with at least a clinically cleared Main Target Lesion or Visit 8 for partial and non-responders after PDT cycle 1, whose Main Target Lesion was not cleared at Visit 5, each subject's Main Target Lesion including the ink marks will be surgically excised and will be histopathologically evaluated at the same laboratory that already analyzed the biopsies taken at Visit 1.

The following central dermatopathological laboratory is responsible for evaluating the biopsies and excised tissue:

[redacted]

Containers with fixation solution and shipping material will be provided by the central dermatopathological laboratory.

Histopathological assessment of biopsies and excised tissue

Each biopsy and excised tissue will be assessed histopathologically according to WHO – histological typing of skin tumors[(2)].

The lesion(s) will be histopathologically diagnosed and the results will be reported to the respective investigator. Based on the outcome of the assessment, the lesion(s) will be classified as either eligible or non-eligible. The subject is only eligible for the study if at least one lesion is classified as naïve, non-pigmented, superficial BCC lesion. Only lesions matching these criteria are allowed to be included in the study.

Each Main Target Lesion will be histopathologically diagnosed and the results will be reported to the respective investigator. Based on the outcome of the assessment, the Main Target Lesion(s) will be classified as either histologically cleared or not-cleared with respect to sBCC. The report will include further details underlying the diagnosis.

The investigator has to review the results and document its acknowledgement by signing and dating the report after receipt.

Assessment of skin type

Subjects' skin will be assessed at screening according to the Fitzpatrick Skin Type Test[1] as follows:

Table 4: Correlation of skin types score to Fitzpatrick skin type

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

A detailed description of the Fitzpatrick Skin Type Test is available in Appendix A.

Assessment of esthetic appearance

Esthetic appearance for the Main Target Lesion will be assessed **prior to surgical excision of this lesion.** Esthetic appearance of **Additional Target Lesion(s)** will be assessed at the end of the clinical observation period (12 weeks after PDT-1 (Visit 5) or PDT-3 (Visit 8), respectively, and, furthermore, for all Target Lesions at the follow-up visits. The study personnel will assess the esthetic appearance of the treatment field(s) using a 4-point scale as follows:

0 = very good
1 = good
2 = satisfactory
3 = unsatisfactory

Assessment of subject satisfaction

Esthetic outcome of the Main Target Lesion will be assessed **prior to surgical excision of this target lesion.** Esthetic outcome of Additional Target lesion(ns) as well as subjects' overall satisfaction with the treatment will be assessed at the end of the clinical observation period of the study (12 weeks after PDT-1 (Visit 5) or 12 weeks after PDT-3 if re-treated (Visit 8)) and, furthermore, for all Target Lesions at the follow-up visits. Both parameters will be assessed using the 4-point scale as follows:

0 = very good
1 = good
2 = satisfactory
3 = unsatisfactory

In this context, subjects will also be asked if they would choose the PDT treatment again in the future.

7.3.2 Safety data

Adverse events

At each visit and during the phone contact(s), subjects will be asked indirectly regarding (S)AEs. Subjects will also be questioned indirectly to determine whether they had any pain, burning, itching, urticaria-like symptoms, or any other adverse events. For further information see Section 8.

Local skin reactions, local discomfort, and pain

Local skin reactions in the treatment field(s) (also referred to as application site skin reactions) will be evaluated separately by the investigator (or equally qualified person) at each clinical visit during and after PDT. The observations will be documented in the source data and in the eCRF, including date and the time frame of the treatment (starting and ending point, as well as duration of the treatment).

The below mentioned AE intensity grading should be used.

The **local skin reaction** categories listed below will be checked by visual inspection of the treatment field(s) by a designated member of the study team during the visits (and documented in source and in the eCRF).

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

For the investigator (or delegated person's) assessment the following 4-point scale should be used to assess the severity of local skin reaction in the treatment areas:

- 0 = no reaction
- 1 = mild reaction
- 2 = moderate reaction
- 3 = severe reaction.

In addition to the investigator (or delegated person's) assessments of local skin reactions, subject-reported local discomfort and pain during PDT for each subject will be recorded as reported by the subject (on subject questionnaire) and as assessed by the investigator (or delegated person) (as AE) and documented.

The **local discomfort** (also referred to as application site discomforts) categories listed below will be recorded according to the subject's complaint by a designated member of the study team during the PDT visits:

- Burning
- Itching
- Others

Subjects will be asked to assess local discomfort events as none, mild, moderate, severe (4-point scale see above) on the subject questionnaire. The severity result indicated by the subject should be confirmed/ assessed by an investigator or delegated person for documentation of the local discomfort.

Pain reported during/following PDT will be assessed using an 11-point numeric rating pain scale (NRPS) assessment by the subject (see Appendix C). The assessed pain should be additionally documented in the eCRF. Further, the NRPS result indicated by the subject should be transformed for documentation in the AE eCRF page as follows: pain 1-3 = mild, 4-7 = moderate, 8-10 = severe.

If possible, each subject should be assessed by the same investigator(s)/staff personnel at each visit.

At each visit or during the phone contact(s) after the PDT sessions, subjects will also be asked if they have experienced any adverse reaction since their previous clinic visit using questions like "Have you noticed anything in the study surrounding areas since we last saw you?" Any signs or symptoms reported by the subject that correspond to one of the 10 local skin reaction categories and/or 3 local discomfort categories listed above should be scored for severity according to the subject's response to the following question: "How much, if any, difficulty or disruption has this (sign) caused you?"

Using the information provided by the subject, the clinical staff should record the most severe reaction reported by the subject in each category with start and stop date (if applicable) using the descriptors listed below:

- 0 = none (no reaction recalled by the subject)
- 1 = mild (the subject is aware of the signs and symptoms, but the signs and symptoms are well tolerated and do not interfere with daily activities)
- 2 = moderate (the signs and symptoms are sufficient to restrict, but not to prevent, usual daily activities for the subject)
- 3 = severe (the subject is unable to perform usual daily activities).

New lesions

Assessment of new lesions during the clinical observation period and the FU part of the study will include new NMSC and melanoma, as well as new AK lesions.

New lesions with indication of localization(s) and reference to the treatment field(s) should be reported as (S)AE. These new lesions may be treated during the clinical observation period with

physical measures at the discretion of the investigator and without restriction during the follow-up period. Please refer to Section 6.2 *Concomitant treatments* for restrictions.

Physical examination

General physical examinations will be performed at screening (Visit 1), and 12 weeks after the start of the 1st PDT cycle (Visit 5 for complete responder after the 1st PDT cycle) or 2nd PDT cycle (Visit 8 for partial or non-responder after the 1st PDT cycle), respectively.

The conduct and outcome of the physical examination will be documented. In the eCRF, only abnormal physical examination findings are required to be documented by parameter and reason.

Physical examination of the skin and medical history of the skin will be requested in more detail and will be documented accordingly.

Vital signs

BP (systolic and diastolic blood pressure) and pulse rate will be measured at each clinical visit after resting for 5 minutes in a sitting position.

Safety laboratory assessments

Clinical laboratory safety tests will be performed at screening (Visit 1) and at the end of the clinical observation period (12 weeks after start of the 1st PDT cycle (Visit 5) or, if applicable, 12 weeks after the start of the 2nd PDT cycle (Visit 8)).

The tests will be conducted by a central laboratory that will send the results to the investigators. The investigator has to review the results and document the review process (e.g. clinically significant (CS) or not) by signing and dating the print-out. Values indicated as CS have to be documented as AEs.

The following central laboratory is responsible for safety laboratory assessments:

[redacted]

Blood

A 2 ml EDTA (ethylenediaminetetraacetic acid) blood sample and a 5 ml serum sample will be collected at screening (Visit 1) at the end of the clinical observation period (12 weeks after start of the 1st PDT cycle (Visit 5) or, if applicable 12 weeks after the start of the 2nd PDT cycle (Visit 8)). The following parameters will be measured:

Hematology: hemoglobin, hematocrit, red blood cell count (RBC), and leukocyte count (WBC) with differential and platelet count.

Serum chemistry: glucose (non-fasting), creatinine, total bilirubin, aspartate aminotransferase (AST [SGOT]), alanine aminotransferase (ALT [SGPT]), lactate dehydrogenase (LDH), alkaline phosphatase (AP), gamma glutamyltransferase, potassium, sodium, calcium, total protein, albumin,

and - at screening only - a serum pregnancy test (β-human chorionic gonadotropin [β-HCG]) for females of child-bearing potential.

The outcome of the laboratory investigations should be documented in source. Parameters outside the normal range must be evaluated as clinically significant (CS) or not clinically significant (NCS) by the investigator and the reports must be signed and dated by the evaluating investigator, accordingly. The outcome of parameters assessed as clinically significant (CS) as well as missing parameters have to be documented.

A female is considered to be of childbearing potential if she has an uterus and at least one ovary, has not had a tubal ligation, or is postmenopausal for less than 3 years. The pregnancy test must be negative to allow inclusion.

In total, approximately 14 ml of blood will be collected from each subject during the course of the study.

Urine

A 30 ml urine sample will be collected at screening (Visit 1) and at the end of the clinical observation period (12 weeks after start of the 1st PDT cycle (Visit 5) or, if applicable, 12 weeks after the start of the 2nd PDT cycle (Visit 8)). The following parameters will be measured:

Urinalysis: color and appearance, pH, protein, glucose, ketones, and specific gravity.

The outcome of the urinalysis should be comprehensibly documented in source. Parameters must be evaluated as clinically significant (CS) or not clinically significant (NCS) by the investigator. Reports must be signed and dated by the evaluating investigator, accordingly. Only abnormal findings or missing parameters in urinalysis have to be documented in the eCRF.

Urine sticks for the measurement of the requested parameters will be provided. Evaluation will be performed directly at the site.

Urine pregnancy tests will be performed in females of child-bearing potential prior to each PDT (i.e., Visit 2, Visit 3 and if applicable, also at Visit 5 and Visit 6) and 12 weeks after start of the last PDT cycle (Visit 5 or Visit 8, if applicable).

In general, the pregnancy tests at Visit 1, Visit 2, Visit 3, and Visit 5, and if applicable Visit 8 must be negative to allow further participation. In case of a positive pregnancy test, no further PDT should be applied and the subject should continue with at least FU visits, if applicable.

Urine pregnancy tests will be provided for direct assessment at the site.

7.4 GENERAL AND DIETARY RESTRICTIONS

Exposure of the BCC lesions to sunlight should be avoided or minimized throughout the whole study course. Subjects with sunburn within the treatment areas cannot be included until fully recovered. The consumption of alcoholic beverages should be moderate. The use of certain concomitant medications is restricted (for further information, see Sections 4.3, 4.4 and 6).

8 ADVERSE EVENTS

8.1 DEFINITIONS

8.1.1 Adverse events

The term **AE** covers any unfavorable and unintended sign, symptom, syndrome, or illness that develops or worsens during the period of observation in the clinical study. No causal relationship with the IMP or the medical device or with the clinical study procedure is implied by the use of the term "adverse event". 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) are considered to be AEs.

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

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

The routine evolution of the condition under treatment may be measured by efficacy parameters. However, if there is a worsening of a sign or symptom of the condition under treatment and the outcome fulfills the definition of an "SAE", it must be recorded as such (see Section 8.1.2).

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

- A new sign, symptom, illness, or syndrome.
- Worsening of a concomitant illness.
- An effect of the IMP, including comparator or concomitant medication.
- An effect of the medical device, if applicable
- An effect of an invasive procedure required by the protocol.
- An accident or injury.

AEs can be categorized as "non-serious" and "serious" (see Section 8.1.2).

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 period of observation (see Section 8.2) and did not worsen during the study. In the latter case, the condition should be documented as medical history.

8.1.2 Serious adverse event

Any adverse event should be assigned to be unrelated or related to either the study medication, the medical device (BF-RhodoLED®, or both, as this will be important for evaluation of the safety of BF-200 ALA or the lamp.

In general, an **SAE** is one that occurs at any dose (including overdose) and

- Results in death.
- Is life-threatening.

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

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

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

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

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

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

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

8.1.3 Alert terms and other reasons for expedited reporting to Pharmacovigilance

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

In the pivotal AK and BCC clinical trials conducted in the EU (ALA-AK-CT002 and ALA-AK-CT003 with BF-200 ALA and various light sources, or ALA-AK-CT007 and ALA-BCC-CT008 utilizing BF-200 ALA in combination with BF-RhodoLED®) almost all subjects developed local, treatment-related phototoxicity reactions. However, most of these phototoxic reactions were mild to moderate, and occurred only temporarily in most cases.

The most common signs and symptoms at the application site are irritation, erythema, pain, and edema. The intensity of these effects is dependent on the lesion site and the type of illumination used for PDT. The increased effects correlate with the higher clearance rate of narrow spectrum lamps such as BF-RhodoLED®. Most adverse reactions occur during illumination or shortly afterwards. The symptoms are usually of mild or moderate intensity (investigator's assessment on a 4-point scale), and last for 1 to 4 days in most cases. However in some cases, they may persist for 1 to 2 weeks or even longer. In rare cases, the adverse reactions may require interruption or discontinuation of the illumination.

As most AEs observed were of mild to moderate severity and as we have no reason to expect any other side effect than stated above, no alert terms and other reasons for expedited reporting to Pharmacovigilance are defined.

For details on known adverse reactions see Ameluz® PI (30) and current Investigator's Brochure.

Furthermore, all adverse events reported in the past were not directly related to BF-RhodoLED® but either to the medication or PDT. Therefore, we do not expect any adverse events that relate directly to BF-RhodoLED®, provided that it is properly used as described in the user manual.

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

8.1.4 Investigational product complaints

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

8.1.5 Investigational medical device complaints

Complaints associated with the medical device BF-RhodoLED® (Adverse Device Effect - ADE) must be reported to the sponsor/CRO.

8.2 PERIOD OF OBSERVATION

For the purposes of this study, the period of observation for collection of AEs extends from the time the subject gives informed consent until the end of the clinical observation period of the study at Visit 5 or Visit 8 (in case of re-treatment with a 2nd PDT cycle).

At the FU visits, any local AEs (i.e., AEs affecting skin health in the treatment fields), which might impair proper assessment of the recurrence of the treated sBCC lesions, or other clinically relevant

events at the investigator's discretion, or conditions that may be relevant for proper assessment of the recurrence of the treated BCC lesions) should be documented including any recurrent BCC lesions and any new lesions (AK, other NMSC, and melanoma) (see Section 7.2.3).

Relevant SAEs or related SAEs (SARs) should be documented until the end of the FU period (60 months after completion of the 1st PDT cycle (Visit 5)).

If the investigators detect an SAE in a subject after the end of the FU period, and considers the event possibly related to prior study treatment or procedures, they should report this event to the pharmacovigilance department of the sponsor.

8.3 DOCUMENTATION AND REPORTING OF ADVERSE EVENTS

8.3.1 Documentation and reporting of adverse events by investigator

All AEs as well as any SAE that occur during the observation period (see Section 8.2) must be documented in accordance with the instructions for the completion of AE reports in clinical studies. During the follow-up phase only local AEs or conditions affecting skin health in the treatment fields and the surrounding treatment area have to be documented which might thus impair a proper assessment of the recurrence of the treated AK lesions, or other clinically relevant events at the investigator's discretion as well as any relevant SAE or SAR during the follow-up phase, respectively. If possible, AEs should be assigned to be either unrelated or related to the study medication or the medical device (BF-RhodoLED®), or both.

These instructions will be provided to the investigator.

The following approach will be taken for documentation:

- **All AEs** (whether serious or non-serious, or considered as an alert term) must be documented during the clinical observation period.
- If the AE is serious (see Section 8.1.2), the investigator must complete, in addition to the "Adverse Event" page in the eCRF, a "Serious Adverse Event/Expedited Report for Combination Products from a Clinical Trial" form at the time the SAE is detected. This form must be marked as "initial" and be sent immediately (within 24 hours) to the sponsor's Pharmacovigilance department by email or fax (according to Biofrontera's Standard Operating Procedure (SOP)). SAEs must be identified as such in eCRF by stating the applicable SAE criteria that were met. During the follow-up phase only relevant SAEs or SARs according to the investigators decision have to be reported.
- 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 8.1.3), the investigator should only complete a "Serious Adverse Event/Expedited Report from a Clinical Trial for Combination products" form. It should be clearly stated that no adverse event was observed. Instructions on where to send this form will be provided. In this case, there is no need to complete the "Adverse Event" page in the eCRF.
- The following details regarding AEs are required: diagnosis, location (inside/ outside treatment field(s)/ treatment area), source (study medication/device/both), time frame (by providing start/stop date and time), intensity (see Section 8.1.1), outcome, seriousness criteria

(if applicable), and if the AE is related to IMP only, medical device only, or cannot be ambiguously assigned to one of both. Detailed instructions on AE documentation will be handed out by the sponsor.

- 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/BF-RhodoLED® and study procedure (concurrent illness etc.).
  - UNLIKELY RELATED: the temporal sequence is atypical and the AE does not follow a known pattern of response to IMP/BF-RhodoLED®; 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/BF-RhodoLED® or a known pharmacological effect/associated reaction, which is also recognized with another concomitant therapy/illness or other external cause.
  - PROBABLY RELATED: appropriate temporal association, known pharmacological effect, recognized to be an associated IMP/BF-RhodoLED® reaction and for which no other possible cause is evident.
  - DEFINITELY RELATED: the reaction has occurred with this IMP/BF-RhodoLED® 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 de-challenge or 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 medical device or not, should be monitored to determine the outcome. The clinical course of the AE will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate FU. Should the AE result in death, a full pathologist's report should be supplied, if possible.

See Section 8.2 for details on the observation period of AEs and SAEs or SARs, respectively.

8.3.2 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 annual anniversary of the date, the IND went into effect. The same report will also be submitted to the IRB(s) to ensure a continuing review of the project.

8.4 IMMEDIATE REPORTING BY INVESTIGATOR TO SPONSOR

8.4.1 Reporting of SAEs

SAEs during the clinical observation period as well as relevant SAEs or SARs during the follow-up phase must be documented on a 'Serious Adverse Event/Expedited Report for Combination Products from a Clinical Trial form' in accordance with instructions for completing the 'Serious Adverse Event/Expedited Report for Combination Products from a Clinical Trial form'. This form and the instructions will be provided in the investigator file and must be completed and supplied immediately to the sponsor (21CFR§ 312.32, 21CFR§ 312.64).

Any SAE that occurs during the clinical observation period of the study, whether or not related to the IMP or the medical device, and any relevant SAE or SAR during the follow-up phase must be reported by the investigator within 24 h by fax, or by e-mail, to the following persons:

Email: [redacted]
Fax: [redacted]

The initial report must be as complete as possible, including details of the current illness and (serious) AE, and an assessment of the causal relationship between the event and the IMP(s) or medical device 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 a 'Serious Adverse Event/Expedited Report for Combination Products from a Clinical Trial form', with the box "Follow-up" checked under "Report type".

The instructions for completing the 'Serious Adverse Event/Expedited Report for Combination Products from a Clinical Trial form' give more detailed guidance on the reporting of SAEs, AEs that comply with alert terms, 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 to the sponsor on a "Serious Adverse Event/Expedited Report for Combination Products from a Clinical Trial" form.

Pregnancies occurring during a subject's participation in the study, although not typically considered SAEs, must be notified to the sponsor within the same timelines as an SAE (within 24 h after becoming aware of the pregnancy) on a pregnancy notification form. If possible, the clinical visits as well as the FU visits should be completed, but no further PDT must be applied. Further treatment will be addressed on a case-by-case basis with the treating physician and the investigator.

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

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

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

Note:

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

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

8.4.2. Reporting of USADEs to the IRB

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

In case a serious and unexpected event which cannot clearly assigned to the medical device BF-RhodoLED®, it should be treated as an SAE (see Section 8.4.1).

Note: Reporting of USADEs to the sponsor is equal to SAE reporting described in section 8.4.1.

8.5 UNBLINDING DUE TO REGULATORY REPORTING OR INVESTIGATOR

If the unblinding (during the clinical observation period) is performed by the investigator due to a medical requirement, the subject will discontinue trial participation.

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

Reporting obligations to the local IRBs of the investigator will be fulfilled by the investigator, unless otherwise specified.

8.6 CONTINUOUS RISK ASSESSMENT

The sponsor’s safety department will apply appropriate monitoring measures to continuously survey the benefit risk ratio of the investigational medicinal product, the medical device and study procedures.

9 WITHDRAWALS

9.1 WITHDRAWAL OF SUBJECTS

Subjects must be withdrawn from the 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.

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

- Pregnancy (applies only during the clinical observation period of the study).
- If new lesions that develop in close proximity to a treated lesion after the 1st PDT require immediate treatment in the opinion of the investigator (during clinical observation period of the study).
- In case of a SUSAR or USADE.

In all cases, the reason for and date of withdrawal must be documented. Subjects are not obliged to specify a reason for their withdrawal. If they refuse to do so, the withdrawal should be documented as "withdrawal of consent". The subject must be followed up to establish whether the reason was an AE, and, if so, this must be documented in accordance with the procedures in Section 8.

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.

The investigator must make every effort to contact subjects lost to FU. Attempts to contact such subjects must be documented in the subject's records (e.g. at least 3 times and dates of attempted telephone contact, receipt for sending a registered letter).

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

9.2 REPLACEMENT OF SUBJECTS

Randomized subjects will not be replaced after they have discontinued the study.

9.3 WITHDRAWEL OF SAMPLES

Not applicable.

10 EMERGENCY PROCEDURES

10.1 EMERGENCY SPONSOR CONTACT

In emergency situations, the investigator should contact the sponsor by telephone at the number given on the title page of the protocol or in Section 8.4, if that is regarded as necessary.

10.2 EMERGENCY IDENTIFICATION OF INVESTIGATIONAL 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 only small treatment areas. 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.

In case the investigator still needs to unblind for a specific randomization number, this can be done via an interactive web response system (IWRS). The qualified person for pharmacovigilance (QPPV) as well as the responsible project manager at Biofrontera Bioscience GmbH will immediately be informed about the code braking by the system. In case a subject needs to be unblinded, the affected subject is not allowed to receive retreatment, e.g. at Visit 3 or in case that the subject presents non-responding lesions at Visit 5 or Visit 6 (partial or non-responder after the 1st PDT cycle). The subject must be withdrawn from the study.

10.3 EMERGENCY TREATMENT

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 CS laboratory values, related to the trial. The investigator or institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

11 STATISTICAL PROCEDURES

The statistical planning of the study, and the statistical analyses will be conducted following the principles as specified in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Topic E9 (ICH, 1998), and will be carried out by a qualified statistician in accordance with the ICH guidelines and adequate biostatistical SOPs. The statistical analyses will be performed separately for the clinical observation part of the study, which includes the clinical observation period (1st and 2nd PDT cycle), and for the FU part of the study. The statistical analysis of the clinical observation period of the study (up to Visit 8) will be performed after database lock and subsequent unblinding of all data to the statistician, data manager, and sponsor. The statistical analysis of the FU part of the study will be performed after database locks for the 12, 24, 36 and 60 months data, respectively.

Technical details of the statistical analyses will be specified in separate statistical analysis plans (SAPs). The SAP for the clinical observation period of the study will be generated in parallel to the clinical study protocol. The SAP for the FU part of the study will be finalized prior to the database lock for the 12-month data time point.

A confirmatory hypothesis test will be performed for the primary and the key secondary efficacy endpoint only. A Cochran-Mantel-Haenszel Test with stratification factors lesion baseline characteristics (lesion count 1 vs ≥2 lesion(s)) and center will be used to test the primary hypothesis on a significance level of 0.1% (α=0.001; one-sided) on the full analysis set (FAS). The primary analysis will be repeated for the PPS as sensitivity analysis. Additional key secondary efficacy variables will be tested confirmatory using a hierarchical testing procedure using the FAS, whereas further secondary efficacy variables will be tested descriptively and in an exploratory manner.

Confirmatory hypothesis testing of key secondary variables measured during the double-blind clinical observation period will be done only after the test of the primary efficacy variable is passed, and will be done strictly in the given order to ensure the FWER. Hypothesis testing in the pre-defined order will stop once the first non-significant test result is obtained.

For further secondary endpoints, two-sided statistical testing procedures will be conducted using a significance level of 5% (α=0.05). Additionally and where appropriate, two sided local 95% CIs of differences between BF-200 ALA and vehicle will be presented. As the secondary endpoint analysis, including the calculation of CIs 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.

Statistical analyses will be conducted using SAS version 9.3 or higher (SAS Institute, 2010).

11.1 ANALYSIS VARIABLES

11.1.1 Primary efficacy analysis variable

The primary efficacy variable is the composite clinical and histological response of the subject's Main Target Lesion as assessed 12 weeks after the start of the last PDT cycle that included treatment

of the Main Target Lesion (Visit 5 or Visit 8). A Main Target Lesion with a complete clinical and histological response is defined as a completely cleared Main Target Lesion.

11.1.2 Secondary efficacy analysis variables

The key secondary efficacy variables include the following variables and will be hierarchically tested in the given order:

1. Main Target Lesion clinical response (according to clinical assessment only) assessed 12 weeks after the start of the last PDT cycle.
2. Main Target Lesion histological response (according to histological assessment only) assessed 12 weeks after the start of the last PDT cycle.
3. Subject complete clinical response (complete clearance of all target lesions according to clinical assessment only) assessed 12 weeks after the start of the last PDT cycle.
4. Subject complete response (clinically and histologically cleared Main Target Lesion (see above) and complete clinical remission of all Additional Target Lesions) assessed 12 weeks after the start of the last PDT cycle.

Further secondary efficacy variables include:

- Lesion complete clinical response rate per treatment arm (complete clearance of individual lesions (Main and Additional Target Lesions)) according to clinical assessment only, assessed 12 weeks after the start of the last PDT cycle.
- Main Target Lesion complete response (clinically and histologically cleared) assessed 12 weeks after PDT-1.
- Main Target Lesion clinical response (according to clinical assessment only) assessed 12 weeks after PDT-1.
- Main Target Lesion histological response (according to histological assessment only) assessed 12 weeks after PDT-1.
- Lesion complete clinical response rate per treatment arm (complete clearance of individual lesions (Main and Additional Target Lesions)) according to clinical assessment only, assessed 12 weeks after PDT-1.
- Subject complete clinical response (complete clearance of all Target Lesions according to clinical assessment only) assessed 12 weeks after PDT-1.
- Subject complete response (clinically and histologically cleared Main Target Lesion (see above) and complete clinical remission of all Additional Target Lesions) assessed 12 weeks after PDT-1.
- For all Target Lesions, assessment of esthetic appearance by the investigator 12 weeks after the start of the last PDT cycle, but prior to surgical excision of the Main Target Lesion and any alternative treatment of Additional Target Lesions.
- Subjects' satisfaction regarding esthetic outcome and treatment 12 weeks after the start of the last PDT cycle, but prior to surgical excision of the Main Target Lesion or alternative treatment of Additional Target Lesions at the end of the clinical observation period.

11.1.3 Efficacy variables of the FU period of the study

For the FU period of the study, the following analysis variables will be collected and analyzed descriptively and in an exploratory manner:

- Recurrence of the subject's Main Target Lesion after surgical excision (defined as in composite endpoint).
- Subject recurrence rate defined as the percentage of subjects with all Additional Target Lesions completely cleared clinically 12 weeks after the start of the last PDT cycle with at least one recurrent lesion during FU.
- Subject recurrence rate defined as the percentage of subjects with all Additional Target Lesions completely cleared clinically 12 weeks after the start of PDT-1 with at least one recurrent lesion during FU.
- Lesion recurrence rate per treatment arm defined as the percentage of completely cleared individual Additional Target Lesions 12 weeks after the start of the last PDT cycle showing recurrence during FU.
- Lesion recurrence rate per treatment arm defined as the percentage of completely cleared individual Additional Target Lesions 12 weeks after the start of PDT-1 showing recurrence during FU.
- Esthetic appearance for all Main Target Lesions following surgical excision, and for all Additional Target Lesions that were clinically cleared 12 weeks after the last PDT cycle and did not receive additional treatments.
- Subject satisfaction regarding treatment and esthetic outcome for all Target Lesions that did not receive additional treatment after the last PDT cycle.

The results from the FU period of the study will be analyzed and reported separately and are not part of the clinical observation period of the study.

11.1.4 Demographic and background characteristics

- Age
- Sex
- Study site
- Race
- Ethnicity
- Weight
- Height
- Skin type
- BCC lesion count, subtype, size, and location
- Medical history, including NMSC and melanoma history
- Concomitant medications

11.1.5 Subject disposition and exposure

- Subject discontinuation and reason for discontinuation
- Number of PDT sessions
- PDT details (e.g. incubation time of IMP, duration of illumination, distance between illumination source and treatment area, interruptions/pauses, interferences/ relief measures).

11.1.6 Safety analysis variables

The safety analysis variables during the clinical observation period include:

- Frequency and extent of adverse events (AEs), serious AEs (SAEs), and treatment-emergent adverse events (TEAEs). TEAEs are defined as all AEs with onset or worsening after treatment with randomized IMP within 4 weeks after each PDT cycle (until Visit 4 or Visit 7, respectively).
- New AK, NMSC and melanoma, including location of lesion(s).
- Local skin reactions at the treatment field(s) assessed by the investigators.
- Local discomfort or pain during illumination, reported by the subjects.
- Vital signs.
- Safety laboratory.
- Physical examinations.

The safety analysis variable during the FU period include:

- Any local (S)AEs or conditions within the treatment field(s) that may be relevant for proper assessment of the recurrence of the treated lesions. Any relevant SAE or serious adverse reaction (SARs).
- New NMSC and melanoma, including location of lesion(s).
- New AK lesions within the treatment field(s) and treated subarea(s).

11.2 ANALYSIS POPULATIONS

Treatment/clinical observation part of study

- Enrolled set: All subjects enrolled in this study i.e. that 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 analyses.

- Full analysis set (FAS): all subjects randomized and treated at least once with IMP and 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, key secondary and further secondary endpoints.
- Per-protocol set (PPS): All subjects of the FAS without any major protocol deviations. The assignment of subjects to the treatment groups will be as actually treated. The PPS will be used for sensitivity analysis of the primary and key secondary endpoints and may also be used for selected analyses of secondary endpoints.

Follow-up part of the study

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

Further details will be specified within a separate SAP for the follow-up part of the study.

11.3 STATISTICAL METHODS

Complete details of the statistical analyses and methods, including data conventions, will be contained in a separate SAP, which will be finalized in parallel to the study protocol. The SAP for the FU part of the study will be finalized prior to the database lock for the 12-month data time point.

11.3.1 Disposition of subjects and exposure

The number and relative frequencies of subjects in each analysis set such as the enrolled set, the randomized set, the SAF set, the FAS, and the PPS will be presented overall, and by treatment, site, and study part (clinical observation period or FU).

The number and relative frequency of subjects who prematurely discontinued the study and the number of subjects completing the study parts will be presented. Reasons for discontinuation will be tabulated by treatment group.

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

11.3.2 Demographics and background characteristics

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

Previous and 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 by treatment group.

The data will be presented for all subjects in the FAS. Selected data may be presented for the PPS as well. Safety data will refer to the SAF set.

11.3.3 Efficacy analyses

Primary efficacy analysis

The primary efficacy variable is the composite clinical and histological response of the subject's primary lesion as assessed 12 weeks after the start of the last PDT cycle that included treatment of the Main Target Lesion (Visit 5 or Visit 8). A primary lesion with a complete clinical and histological clearance is defined as a completely cleared Main Target Lesion.

The primary null hypothesis (H_{01}, one-sided) is that the complete clinical and histological response of the subject's Main Target Lesion assessed 12 weeks after the start of the last PDT cycle for subjects treated with BF-200 ALA is equal or lower to that of subjects treated with vehicle:

$$H_{01}: r_{ALA} \leq r_{vehicle}$$

where r_{ALA} denotes the complete clinical and histological response rate of the subject's Main Target Lesion in the BF-200 ALA group and $r_{vehicle}$ denotes the complete clinical and histological response rate of the subject's Main Target Lesion in the vehicle group.

The primary alternative hypothesis (H_{11}, one-sided) is that the complete clinical and histological response rate of the subject's Main Target Lesion assessed 12 weeks after the start of the last PDT cycle for subjects treated with BF-200 ALA is superior to the complete clinical and histological response rate of the subject's Main Target Lesion for subjects treated with vehicle:

$$H_{11}: r_{ALA} > r_{vehicle}$$

Superiority of BF-200 ALA in comparison to vehicle is established if the primary null hypothesis can be rejected. A Cochran-Mantel-Haenszel Test will be used to test the primary hypothesis on a significance level of 0.1% (α=0.001; one-sided). Baseline number of lesion (1 vs. ≥2 lesion) and center will be used as stratification factors. The primary analysis will be performed on the FAS and will be repeated, in sense of sensitivity analyses, for the PPS.

A missing clinical and/or histological lesion assessment will be considered as non-response. Exploratory subgroup analyses will be performed for the primary efficacy variable. Subgroups will be specified by categorical or categorized variables e.g. sex, age, number of lesions at baseline, location of lesions, baseline size of lesions.

Key secondary efficacy analyses

After the test of the primary efficacy variable is passed, the key secondary efficacy endpoints will be tested for differences between BF-200 ALA and vehicle. The corresponding null and alternative hypotheses to be tested are

$H_{0i}: \theta_{ALA} \leq \theta_{vehicle}$ vs. $H_{1i}: \theta_{ALA} > \theta_{vehicle}$ $(i = 2, \ldots)$

where θ denotes the population parameters associated with the respective key secondary endpoint.

1. Main Target Lesion clinical response (according to clinical assessment only) assessed 12 weeks after the start of the last PDT cycle.

   The same analyses that was previously described for the primary endpoint variable will be conducted.

   A missing 12-week assessment will be imputed by the preceding 5-week assessment using a last observation carried forward (LOCF) approach. If no assessment is available, the lesion will be regarded as non-responding.

2. Main Target Lesion histological response (according to histological assessment only) assessed 12 weeks after the start of the last PDT cycle.

   The same analyses that was previously described for the primary endpoint variable will be conducted. A missing histological lesion assessment will be regarded as non-response.

3. Subject complete clinical response (complete clearance of all target lesions according to clinical assessment only) assessed 12 weeks after the start of the last PDT cycle.

   The same analyses that was previously described for the primary endpoint variable will be conducted.

   A missing 12-week assessment will be imputed by the preceding 5-week assessment using a last observation carried forward (LOCF) approach. If no assessment is available, the lesion will be regarded as non-responding.

4. Subject complete response (clinically and histologically cleared Main Target Lesion (see above) and complete clinical remission of all Additional Target Lesions) assessed 12 weeks after the start of the last PDT cycle.

   The same analyses that was previously described for the primary endpoint variable will be conducted.

   A missing clinical and/or histological lesion assessment of the Main Target Lesion will be considered as non-response. A missing 12-week assessment for all Additional Target Lesions will be imputed by the preceding 5-week assessment using a last observation carried forward (LOCF) approach. If no assessment is available, the lesion will be regarded as non-responding.

   A missing 12-week assessment will be imputed by the preceding 5-week assessment using a last observation carried forward (LOCF) approach. If no assessment is available, the lesion will be regarded as non-responding.

Confirmatory hypothesis testing of key secondary variables measured during the double-blind clinical observation period will be done only after the test of the primary efficacy variable is passed, and will be done strictly in the given order to ensure the FWER. Confirmatory hypothesis testing in the pre-defined order will stop once the first non-significant test result is obtained.

The key secondary efficacy analysis will be performed on the FAS. All analyses will be repeated as sensitivity analysis for the PPS.

Further secondary efficacy analyses

For further secondary endpoints, two-sided statistical testing procedures will be conducted in a descriptive and exploratory manner using a significance level of 5% (α=0.05). Two-sided local 95% confidence intervals (CIs) of differences between BF-200 ALA and vehicle will additionally be calculated whenever appropriate. For more details on secondary efficacy variables see Section 11.1.2. Secondary efficacy analysis will be performed for the FAS. Selected data may be provided for the PPS as well.

11.3.4 Safety analyses

All secondary safety endpoints (see Section 7.3.2 and Section 11.1.6) will be analyzed descriptively and in an exploratory way. These safety analyses will be performed for the SAF set.

AEs will be coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA) version available at the day of database closure. The analysis will focus on the TEAEs. TEAEs will be summarized and tabulated according to primary system organ class and preferred term. TEAEs leading to death and TEAEs resulting in discontinuation of study will be tabulated using frequency tables if a reasonable number of AEs of this type are observed. The occurrence of any new lesions by type (AK, NMSC, and melanoma) will be tabulated using frequency tables.

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

The frequency of local skin reactions at the treatment field and of local discomfort will be presented together with the respective CIs for each treatment group. The mean and the maximal pain score and the respective CIs will be presented for each assessment time point and treatment group.

All laboratory values will be classified as normal or abnormal according to the laboratory's normal ranges and indicated as CS or NCS by the investigator. Out of range laboratory values that are considered CS will be documented in the medical history (Visit 1) or as AEs (Visit 5 or Visit 8) 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.

General physical examinations will include the following body systems: heart, lung, abdomen, nervous system, skin, musculoskeletal system, lymph nodes, limbs, head, ears, eyes, nose, throat, and others. All clinically significant abnormal physical findings will be listed. Details of further analyses will be specified in the SAP.

11.3.5 Analyses of follow-up data

The follow-up period is performed as a separate part of the study. Data from the follow-up visits will be analyzed and reported separately. In case any data assigned to the observation part of the study should be documented during the follow-up period (e.g. an adverse event will be reported during follow-up phase with start of onset during observation period), those data will be separately listed but not used for descriptive analysis of follow-up data. The analysis variables of the follow-up period are presented in Section 11.1.3.

11.4 HANDLING OF MISSING DATA

A missing lesion assessment (in the FAS data set) will be handled as follows:

- For the analysis of the primary endpoint a missing clinical and/or histological lesion assessment of the Main Target Lesion will be considered as non-response.
- For the analysis of clinical assessment only a missing 12-week clinical assessment for all Main Target Lesions and Additional Target Lesions will be imputed by the preceding 5-week assessment using a last observation carried forward (LOCF) approach. If no assessment is available, the lesion will be regarded as a non-responding.
- For subjects, who should have had a second cycle but were misleadingly classified as complete responders at Visit 5, the results from cycle 1 will be used for the primary analysis.

For complete responders after cycle 1 who by mistake received a second treatment cycle, evaluations of the 1st cycle will also be considered for all efficacy analyses, including the primary analysis. Further details are also described in Section 11.3.3.

Subjects that missed Visit 4 or Visit 7 but attended at Visit 5 or Visit 8, will not be excluded from the Per-Protocol Set (PPS) (see Section 11.2), as these visits are safety visits and are considered not relevant for the outcome of the study.

Subjects with missing post-baseline data of the primary variable (i.e., a missing clinical and histological assessment 12 weeks after the start of the last PDT cycle) will be regarded as non-responders.

Missing data of safety variables will not be replaced.

Details on the handling of missing data will be specified in the SAP.

11.5 INTERIM ANALYSIS

No interim analysis is planned for this study.

11.6 SAMPLE SIZE JUSTIFICATION

A sample size of 186 subjects in total (BF-200 ALA: 149 subjects and vehicle: 37 subjects) in the FAS at a randomization of 4:1 was estimated to ensure at least 90% power to demonstrate superiority of BF-200 ALA compared to vehicle by means of a Cochran-Mantel-Haenszel Test with baseline number of lesion (1 vs. ≥2 lesion) and center as stratification factors on a significance level of 0.1% (α=0.001; one-sided).

This estimate was based on the following quantities and assumptions:

- The estimated response rate for sBCCs is based on data previously established during ALA-BCC-CT008 that was conducted in the EU comparing safety and efficacy of BF-200 ALA with Metvix®. This study revealed a complete clinical patient response rate of 91% (FAS) for subjects with sBCC only, treated with BF-200 ALA and a 1-year cumulated recurrence rate of 11% and a 2-year recurrence rate of 18% (FAS) setting identified recurrent patients as well as patient lost to follow-up as recurrent (data on file and (31)).

- With respect to individual sBCC lesions, this study revealed a total lesion response rate for BF-200 ALA of 93% (FAS). The respective lesion recurrence rates after 1 year and 2 years were 8.8% and 16% taking recurrent as well as lost to follow up lesions into account.
- Taking into account a maximum of 18% of patients showing a recurrence (worst case, also lost to follow-up patients are regarded as recurrent) at 2 years follow-up. These may have shown a potentially histologically positive result at the last clinical visit which leads to the estimate of 72.9% of patients who are assumed to be clinically and histologically cleared 12 weeks after the last PDT. We expect a proportion of 10% of patients with a missing histological assessment 12 weeks after the last PDT.
- As no further data on vehicle/placebo treatment in sBCC in combination with PDT are available, historic data were used as a basis for the sample size calculation with respect to vehicle treatment:
  i) Published data from the FDA Clinical and Statistical Review presentation (NDA 21-576) on nBCC studies with Metvix® PDT. These revealed a complete clinical and histological subject response to verum ranging from 64% and 73% and to vehicle ranging from 15% to 25% according to Agency Analysis.
  ii) Data derived from a double-blind, vehicle-controlled phase II trial for the treatment of sBCC with 5% imiquimod cream. Patients treated with vehicle displayed a complete clinical and histological clearance rate of 19% which is within the range observed with vehicle treatment in the studies under point i), (32).
- The clinical and histological response proportion for BF-200 ALA will be estimated as follows: assuming a response rate of 73% and a proportion of 10% of patients with missing assessment 12 weeks after the last PDT, i.e. 15 out of the 149 BF-200 ALA patients will be non-responders due to missing assessments, the number of responders can be estimated as: 149-15=134*0.73=98 responders, which equals a response rate of 98/149=65.8%.

Based on this information, the parameters were set as follows:

- (Clinical and histological) response proportion for BF-200 ALA: 65%
- Response proportion for vehicle: 25%
- Difference between BF-200 ALA and vehicle: 40%
- Odds Ratio: 5.6
- One-sided superiority test, alpha: 0.001
- Targeted power: 90%
- Randomization: 4:1

Power and sample size were calculated with NCSS PASS 2017 (version: 15.0.4).

11.7 MAJOR PROTOCOL DEVIATIONS

The following protocol deviations will results 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)

by the pre-defined illumination time of 10 min.

- Forbidden anti-inflammatory medication (within ± 7 days of PDT)
- Other forbidden medication will be decided on a case-by-case basis.
- Missing visits (with exception of the safety interim Visit 4 or Visit 7)
- The interval between 2 PDT treatments of the same cycle exceeded the interval indicated by the protocol by more than 4 days.
- Treatment with a 2nd treatment cycle, although the lesion(s) has/have been clinically cleared already after the 1st treatment cycle.
- Meeting an exclusion criteria throughout the treatment period of the study

All other protocol deviations (including violation of timelines) will be handled in a case by case manner.

12 ETHICAL AND LEGAL ASPECTS

12.1 GOOD CLINICAL PRACTICE

This study is to be conducted according to globally accepted standards of good clinical practice (GCP) (as defined in the ICH E6 Guideline for GCP), in agreement with the Declaration of Helsinki from 2013 and in keeping with local regulations (see Appendix D).

12.2 DELEGATION OF INVESTIGATOR DUTIES

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

As all investigators and subinvestigators are required to be listed in the protocol, the investigator should immediately report any changes in study personnel to the sponsor who will then initiate a protocol amendment, if applicable. Besides that, the investigator should maintain a list of subinvestigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

The investigator should designate a deputy investigator with appropriate qualifications being able to fully replace the investigator in cases of absence.

12.3 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, a physician will carry out an oral information session during which the subjects will be given sufficient time and opportunity to clarify remaining questions.

Afterwards, the subject and the investigator will sign the informed consent and the HIPAA form. The original initialed and dated subject information as well as the signed informed consent and HIPAA forms will be archived in the investigator's file. The subject will receive a copy of these documents. The investigator will acknowledge instruction of every subject in accordance with the clinical trial protocol and the existence of a signed consent and HIPAA form.

The investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained. The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

12.4 CONFIDENTIALITY

A limited dataset will be used by the sponsor for final evaluation and data analysis. Thus, subject names will not be supplied to the sponsor or representatives of the sponsor. Instead, a subject number will be recorded in the eCRF, and if the subject name appears on any other document (e.g. laboratory report), it must be obliterated on the copy of the document to be supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws.

The subjects will be informed and must agree with that representatives of the sponsor, the Contract Research Organization (CRO), IRB(s), or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

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. 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.

12.5 PROTOCOL AMENDMENTS

Neither the investigator nor the sponsor will alter this clinical study protocol without obtaining the written agreement of the other. Once the study has started, amendments should be made only upon changes in study personnel or in exceptional cases. The changes then become part of the clinical study protocol.

12.6 APPROVAL OF THE CLINICAL STUDY PROTOCOL AND AMENDMENTS

Prior to the start of the study, the clinical study protocol, subject information leaflet and informed consent form, 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. As required by local regulation or by the IRB(s), the sponsor or investigator will also submit the financial arrangements for the study or other financial interests of the investigator in the IMP, the medical device or sponsor company to the IRB(s).

Until enrollment of the first subject in the study, all ethical and legal requirements must be met.

The IRB(s) and authorities (FDA) must be notified of all subsequent amendments and administrative changes, in accordance with local legal requirements. Amendments must be evaluated and approved by the IRB(s) and FDA, if applicable, prior to any implementation of the respective changes. Amendments must be evaluated to determine whether the subject information leaflet and informed consent form should also be revised.

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

12.7 ONGOING INFORMATION FOR THE INSTITUTIONAL REVIEW BOARD

Unless otherwise instructed by the IRB(s) or local law, the following information will be annually submitted for consideration by the IRB(s) in continuing review:

- The number of subjected accrued (at the local site and at the total number of sites).

- A brief summary of any amendments to the research approved by the IRB(s) since the IRB's review or the last continuing review.
- Any new and relevant information (published or unpublished) since the last IRB review, especially information about risks associated with the research.
- A summary of any unanticipated problems.
- A summary of any subject withdrawals from the research since the last IRB review, and the reasons for withdrawal, if known.
- A summary of any complaints about the research from subjects enrolled at the local site since the last IRB review.
- The latest version of the protocol and sample informed consent document or protocol.
- The current Investigator's Brochure, including any modifications.
- Any other significant information related to subject risks, such as the most recent report, if any, from data monitoring committees.
- Information about relevant regulatory actions occurring since the last review that could affect safety and risk assessment (e.g., withdrawal or suspension from marketing in any country on the basis of safety, reports of recalls, and device disposition required by 21 CFR 812.150(b)(6)).

12.8 CLOSURE OF THE STUDY

The study must be closed at each investigational site upon completion.

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

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

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

12.9 RECORD RETENTION

The investigator must obtain approval in writing from the sponsor prior to destruction of any records, and must document any change of ownership.

The investigator must 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 the IMP and medical device (including dates, quantity, use and return to the sponsor) if the investigation is terminated, suspended, discontinued or completed.

12.10 LIABILITY AND INSURANCE

Liability and insurance provisions for subjects will be arranged according to legal requirements. Liability and insurance provisions for investigators participating in this study will be defined in a separate agreement, if applicable.

12.11 FINANCIAL DISCLOSURE

Prior to the start of the study, the investigator will disclose to the sponsor and, if appropriate, CRO any proprietary or financial interests he or she might hold in the IMP, the medical device or the sponsor company as outlined in the financial disclosure forms (i.e., Form FDA 3454 or FDA 3455). Under 21 CFR §54.4(b), all clinical investigators that are not full- or part-time employees of the sponsor are required to provide this information with sufficient accuracy to allow for complete disclosure or certification. This information needs to be updated as soon as possible in case of any relevant changes occurring throughout the study and for an additional year following its completion. The investigator also agrees that, where required by law or regulation, the sponsor may submit this financial information to domestic or foreign regulatory authorities in applications for marketing authorizations.

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.

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

13 QUALITY CONTROL AND QUALITY ASSURANCE AUDIT

Quality control mechanisms are implemented on a functional level and quality assurance audits will be done according to GCP (ICH Topic E6, 1996) and the applicable regulatory requirements. Monitoring and auditing procedures will be conducted as implemented in the Clinical Monitoring and the Quality Assurance SOPs of the CRO or the sponsor in accordance with GCP guidelines. Direct access to the on-site study documentation and medical records must be ensured.

13.1 STUDY MONITORING AND SOURCE DATA VERIFICATION

According to the Clinical Monitoring SOPs, the frequency of monitoring and co-monitoring visits, and the degree of source data verification are defined in the monitoring plan. Monitoring will be done by personal visits from a representative of the CRO or sponsor (clinical monitor), who will check the eCRFs for completeness and clarity, and crosscheck them with source documents. 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 CRO or sponsor.

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

13.2 ON-SITE AUDITS

Domestic and foreign regulatory authorities, the IRB(s), and an auditor authorized by the sponsor may request access to all source documents, eCRFs, and other study documentation for on-site audit or inspection. Audits can be conducted at any time during or after the trial to assure the validity and integrity of the study data. On-site audits will be conducted by an independent auditor from the respective quality assurance unit of the CRO or the sponsor or by a contracted auditor. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities. Medical records and other study documents may be copied during audit or inspection provided that subject names are obliterated on the copies to ensure confidentiality.

14 DOCUMENTATION AND USE OF STUDY FINDINGS

14.1 DOCUMENTATION OF STUDY FINDINGS

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

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

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

A source data location list will be prepared and updated during the study. It will specify which types of source data are available and where they are stored (e. g. electronic or paper subject files etc.), and which data may be entered directly into the eCRF. This list will be filed in both the trial master file and the investigator study file 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 have to be made visible and signed and dated by the respective study team member.

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

14.2 USE OF STUDY FINDINGS

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

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

By signing the clinical study protocol, 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.

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

15 DECLARATIONS OF SPONSOR AND INVESTIGATORS

15.1 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 IMP.
- The current risk-benefit evaluation of the medical device.
- The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki from 2013 and the principles of GCP for the conduct of clinical trials.

The investigator will be supplied with details of any significant or new findings, including AEs, relating to treatment with the IMP.

Sponsor

Date: _____ Signature: _____

Name (block letters): _____

Coordinating Investigator

Date: _____ Signature: _____

_____ Name (block letters): _____

15.2 DECLARATION OF INVESTIGATOR

The sub/investigator confirms that s/he have read the above protocol. S/he understand it, and s/he will work according to the principles of GCP and according to applicable national and local requirements.

The sub/investigator has been adequately informed about the IMP and the medical device BF-RhodoLED® to date, and confirms the receipt of the current PI for Ameluz® and the current manual for the BF-RhodoLED®. S/he has read this clinical study protocol and agrees that it contains all the information required to conduct the study. S/he agrees to conduct the study as set out in this protocol. If s/he becomes aware of any protocol deviation, s/he will communicate details to a representative of the sponsor.

The sub/investigator will not enroll the first subject in the study until s/he have received approval from the appropriate IRB and until all legal requirements in the country s/he works in have been fulfilled.

The study will be conducted in accordance with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki from 2013 and ICH-GCP principles.

The sub/investigators agrees to obtain, in the manner described in this clinical study protocol, written informed consent to participate for all subjects enrolled in this study.

S/he agrees to make all trial-related records, including source documents and medical records, available for direct access to the monitor, auditor, IRB, or regulatory authority upon request.

S/he agrees to disclose any proprietary or financial interests s/he may hold in the IMP, the medical device or sponsor company as specified in Section12.11**.**

S/he is aware of the requirements for the correct reporting of SAEs, and s/he undertakes to document and to report such events as requested.

S/he agrees to supply the sponsor with evidence of current laboratory accreditation, the name and address of the laboratory, and a list of normal values and ranges, if applicable.

S/he agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals.

S/he agrees to keep all source documents as specified in Section 12.9 of this protocol.

S/he will provide curriculum vitae before the study starts, which will be submitted to regulatory authorities.

Confirmation and acceptance of the above mentioned items will be recorded on the "CSP Confirmation and Receipt Form".

15.3 DECLARATION OF BIOSTATISTICIAN

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

Date: _____ Signature: _____

Name (block letters): _____

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APPENDICES

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

Appendix B: H-zone according to Baxter et al. (2012)

Appendix C: NRPS for pain during PDT

Appendix D: Declaration of Helsinki (2013)

Appendix E: Clinical sites with principle investigator and responsible IRB

Appendix F: List of the reviewing IRB(s)

APPENDIX A

Fitzpatrick's Skin Type Test

Fitzpatrick's Skin Type Test according to Fitzpatrick, 1988[1]

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

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

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

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

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

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

Fitzpatrick's Skin Type Test
(cont.)

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

Fitzpatrick's Skin Type Test
(cont.)

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: _____					

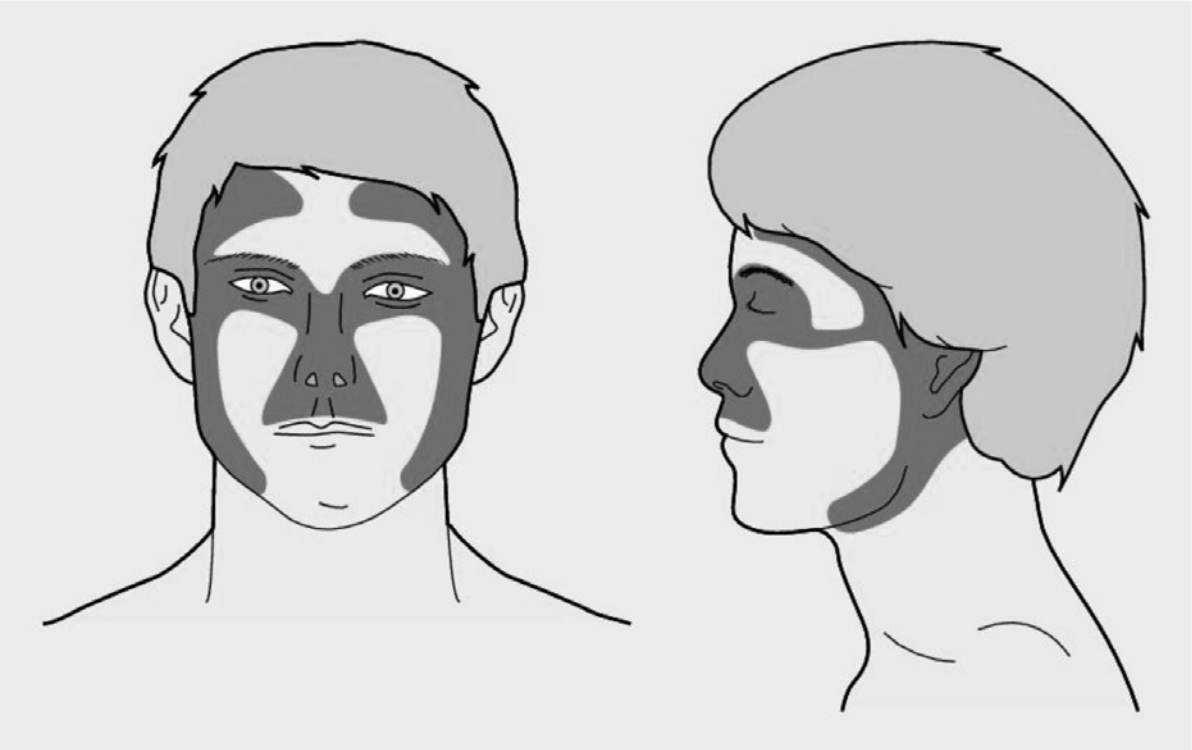
Add up the total scores for each of the three sections for your Skin Type Score.

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

APPENDIX B

Definition of the H-zone on the face

The H-zone on the face is defined according to Baxter et al. (2012)[33]



The H-zone of the face indicated as a dark grey area

APPENDIX C

Numeric rating pain scale for pain during photodynamic therapy

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

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

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.

APPENDIX D

World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

World Medical Association
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington, DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimizes possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made

the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX E

Clinical sites with principle investigator and responsible IRB

Name of PI	Name of Site	Name of responsible IRB
Dr. David Pariser, MD	Pariser Dermatology Specialists	Quorum IRB

APPENDIX F

List of responsible Institutional Review Boards

Institutional Review Boards	Addresses
Quorum IRB	1501 Fourth Avenue Suite 800 Seattle, WA 98101