COVER PAGE

STATISTICAL ANALYSIS PLAN

Study ALA-AK-CT019

NCT05662202

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

Document date: 17 Dec 2025

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

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Date (ddmmmyyyy)	Signature CRO acting on behalf of sponsor (PPD , Biofrontera Discovery GmbH)

Revision history

Version	Author	Date	Change description
1.0	PPD	02Jun2025	First final version
2.0	PPD	17Dec2025	Second final version due to: - Incorporating of inconsistences detected during programming - Derivation of TEAE flag specified more precisely - TEAE definition adapted - Presentation of worst severity of ASRs added - Smal changes, e.g. typos, breaks, etc.

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List of abbreviations

In the following abbreviations are listed as used within this statistical analysis plan or which might occur within the table, listing, and graph outputs:

AE	Adverse event
AESI	Adverse event of special interest
ADaM	Analysis data model
AK	Actinic keratosis
ATC	Anatomical therapeutic chemical
BCC	Basal cell carcinoma
BD	Bowen's disease
BDRM	Blind data review meeting
CI	Confidence interval
CM	Concomitant medication
CMH	Cochran-Mantel-Haenszel
CONS	Consented set
CP	Concomitant procedure
eCRF	Electronic case report form
EoS	End of study
FAS	Full analysis set
FAS-FUP	Full analysis set follow-up phase
FU	Follow-up
FUP	Follow-up phase
H0, H_0	Null hypothesis
H1, H_1	Alternative hypothesis
ICE	Intercurrent event
IMP	Investigational medicinal product
LOCF	Last observation carried forward
LSLV	Last subject last visit
LSLV-TP	Last subject last visit of the treatment phase
LSLV-FU	Last subject last visit of the follow-up phase
MA	Main analysis
N	Number of subjects
NMSC	Non-melanoma skin cancer
NRS	Numeric rating scale
OR	Odds ratio
PD	Protocol deviation
PDT	Photodynamic therapy
PPS	Per-protocol set
PPS-FUP	Per-protocol set follow-up phase
PT	Preferred term
RAND	Randomized set
SAE	Serious adverse event
SAF	Safety analysis set
SAF-FUP	Safety analysis set follow-up phase
SAP	Statistical analysis plan
SCC	Squamous cell carcinoma
SD	Standard deviation
SDTM	Study data tabulation model
SF	Screening failures set
SOC	System organ class
TEAE	Treatment-emergent adverse event
TLGs	Tables, listings, and graphs
US	United States of America

USV	Unscheduled visit

1 Introduction

This statistical analysis plan (SAP) was defined by the CRO acting on behalf of sponsor and the responsible statistician without knowledge of the randomization code. It is based on the study protocol (Version 3.0 of 31-May-2023) and the current electronic case report forms (eCRF) version 3.0 and contains detailed description of the statistical methods described therein.

The statistical analyses will be performed separately for the treatment phase (Visit 1 to Visit 6) and the follow-up phase (FU1 and FU2). This SAP prospectively describes the main analyses for the treatment phase, which will be performed after database lock and subsequent unblinding of all data after the end of the treatment phase, as well as analyses for the for the follow-up phase, which will be performed after database lock after completion of the follow-up phase.

The SAP was finalized before database lock and unblinding of the treatment phase.

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

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

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

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

Within 4 weeks after the screening visit (Visit 1) and following confirmation of eligibility, subjects will be randomized and PDT-1 will be performed (baseline, Visit 2). A phone call 1 week after PDT-1 to assess transient side effects will be performed and an onsite assessment 4 weeks after PDT-1 (Visit 3) to assess safety and preliminary efficacy parameters. At Visit 4, 12 weeks after PDT-1, a final evaluation of safety and efficacy will be performed for complete responders, i.e., subjects with all AK target lesions clinically cleared. Subjects with at least one remaining AK target lesion (non- or partial responders) at Visit 4 will receive a second PDT (PDT-2) on the same day, followed by a phone call and visits (Visit 5 and Visit 6) at the same intervals as after PDT-1. All subjects who are clinically not completely cleared 12 weeks after PDT-2 will receive further non-study treatment at the discretion of the investigator. All subjects will enter a follow-up phase starting approx. 12 weeks after the last PDT, entailing follow-up visits at 6 months (FU1) and 12 months (FU2) after the last PDT.

Results of the treatment phase (Visit 1 to Visit 4 or Visit 6) will be reported after last subject last visit of the treatment phase (LSLV-TP). The results of the two follow-up visits will be analyzed and reported separately from the treatment phase. End of study (EoS) is defined as Last Subject Last Visit of the follow-up phase (LSLV-FU).

1.1 Study objectives

Primary objective

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

Secondary objectives

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

Tertiary objectives

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

1.2 Study design

Two separate analyses will be performed within this study: the main statistical analysis will be performed as soon as the 12-week post last PDT data are available for analysis. Additional data from the follow-up phase (6 months and 12 months after the last PDT) will be analyzed and reported separately from the report of the treatment phase of the study. Statistical testing will be applied to compare active treatment vs vehicle. Within this SAP, both analyses are described.

1.3 Sample size justification

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

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

  Extremities:
  - BF-200 ALA: N=39, cleared: N=24 (61.5 %)
  - Vehicle: N=39, cleared: N= 3 (7.7 %)

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

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

A stratified randomization by treatment area (extremities vs neck/trunk) will be used. As the distribution of subjects with AK lesions for those two treatment areas cannot be exactly determined, and the effect especially in the treatment area neck/trunk is not robust due to low numbers of subjects with lesions in

this treatment area in study CT010, an overall difference in response rates of 38 % is assumed for the sample size calculation.

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

This estimate is based on the following assumptions:

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

1.4 Randomization and blinding

Randomization

Subjects will be randomized for treatment with PDT with either BF-200 ALA (Ameluz®, test group) or vehicle (control group). The ratio of BF-200 ALA to vehicle will be 4:1. Eligible subjects will be assigned a unique 4-digit randomization number in the applicable stratum (either extremities or neck/trunk). For this purpose, the investigator will use the patient pack with the next higher randomization number of the applicable stratum.

Blinding

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

2 Statistical analysis sets

Set	Definition	Treatment used for analysis
Consented set (CONS)	All subjects who provided informed consent to participate in the study.	Actual treatment
Randomized set (RAND)	All subjects randomized to IMP irrespective of whether they received IMP or not.	Planned treatment
Safety analysis set (SAF)	All subjects treated at least once with IMP (IMP application).	Actual treatment
Full analysis set (FAS)	All subjects randomized and treated at least once with PDT (IMP application and illumination).	Planned treatment
Per-protocol set (PPS)	All subjects of the FAS without any major protocol deviations (PDs). Protocol deviations will be identified and classified for each subject during a data review (see Section 5.14).	Actual treatment
SAF-FUP	All subjects treated at least once with the IMP entering the FU period.	Actual treatment
FAS-FUP	All subjects from the FAS of the clinical observation period entering the FU period.	Planned treatment
PPS-FUP	All subjects from the PPS (without any major protocol deviations) of the clinical observation period entering the FU period.	Actual treatment

Actual treatment means that all subjects will be analyzed by the treatment they received.
Planned treatment means that all subjects will be analyzed by the treatment to which they were randomized ('intention-to-treat').

The randomized set is the analysis set for the summary of subject discontinuation.

The SAF is the analysis set for all safety analysis.

The FAS will be the analysis set applied to the evaluation of primary efficacy endpoint, key secondary efficacy endpoints and further secondary efficacy endpoints.

The PPS will be used for supplementary analysis of the primary and key secondary efficacy endpoints and for selected analysis of further secondary efficacy endpoints.

SAF-FUP will be used for safety analysis of follow-up data.

FAS-FUP will be used for the efficacy analysis of follow-up data. PPS-FUP will be used for selected efficacy analysis of follow-up data.

3 Subgroup analysis

The following subgroups will be analyzed:

- Treatment area (extremities, neck/trunk)
- Skin type class (grouped) (type I – III, type IV – VI)
- Size of the treatment field (80 cm², 160 cm², 240 cm²)
- AK target lesion size at baseline (i.e. AK target lesion size (grouped) (Size of AK target lesions at baseline divided into three groups according to the corresponding tertiles: first, second, and third of the ordered data))
- AK target lesion number per subject at baseline (i.e. Number of AK target lesions (grouped) (4-7, 8-11, 12-15))
- AK target lesion severity at baseline (according to Olsen)
- Sex (Male, Female)
- Age (grouped) (from 18-64 years / from 65-74 years / 75 years and older)
- Site (grouped) as determined during blind data review meeting (BDRM) (Section 5.14): sites with less than 5 subjects in the FAS will be combined

The number of subjects/lesions per subgroup will be reviewed during the BDRM. If there will be fewer than 5 subjects/lesions within a subgroup, it will be decided in the BDRM whether to combine groups or not to conduct the subgroup analyses.

4 Efficacy and safety variables

4.1 Primary efficacy variable

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

4.2 Key secondary efficacy variables

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

4.3 Further secondary efficacy variables

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

4.4 Tertiary efficacy variables

- Subject recurrence rate defined as the percentage of subjects with all AK target lesions clinically cleared 12 weeks after the last PDT presenting with at least one recurrent lesion during follow-up, stratified by demographics, study sites, AK baseline parameters (e.g., AK target lesion number per subject at baseline, maximal AK target lesion severity at baseline, size of the treatment field, and treatment area).
- Percentage of AK target lesions showing recurrence in follow-up in relation to total number of clinically cleared AK target lesions 12 weeks after last PDT, overall and stratified by treatment area and AK severity at baseline (according to Olsen et al., 1991 (1)).

- Percentage of severe AK lesions showing recurrence in follow-up in relation to total number of clinically cleared severe AK lesions 12 weeks after last PDT, overall and stratified by treatment area.
- The esthetic appearance at follow-up visits as assessed by the investigator, overall and stratified by treatment area.
- The esthetic outcome at follow-up visits as assessed by the subject, overall and stratified by treatment area.
- Satisfaction with PDT treatment at follow-up visits as assessed by the subject, overall and stratified by treatment area.

4.5 Safety variables

- Adverse events (AEs)
- Adverse events of special interest (AESIs)
- Serious adverse events (SAEs)
- Treatment-emergent adverse events (TEAEs)
- Assessment of new lesions (AK, non-melanoma skin cancer [NMSC, including Basal cell carcinoma (BCC), Squamous cell carcinoma (SCC), or Bowen's disease (BD)] or melanoma) inside the treatment field
- Assessment of application site reactions according to a 4-point scale
- Application site pain during illumination, reported by the subjects assessed on an 11-point numeric rating scale, overall and stratified by size of the treatment field and treatment area
- Safety laboratory data
- Vital signs data
- Physical examination data

4.6 Tertiary safety variables

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

4.7 Other variables

- Lesion directed treatment after final assessment
- Optional biopsy of suspicious lesions
- Confirmation of contact dermatitis
- Emergency unblinding

5 Statistical evaluation

5.1 General analysis considerations

SDTM datasets will be used to create ADaM datasets using ADaM Implementation Guide (Version 1.3) and Analysis Data Model (Version 2.1). An ADaM specification document will be set-up as a MS Excel spreadsheet, describing the ADaM datasets. Based on the ADaM datasets and the specification document a define.xml (Version 2.1) will be created.

All subject data that are not mapped to SDTM will not be listed.

Listings will always be sorted by treatment group and subject. If a different sorting order should be used for some listings, this will be noted separately. The treatment group will be displayed as 'by-variable' within a subtitle. All listings will be presented for analysis sets as indicated in Appendix A. Indicator variables for further analysis sets, e.g., FAS, will be added for the subject disposition listing, for other selected listings only where informative. Dates and times will be displayed in data listings using the format yyyy-mm-dd and yyyy-mm-ddThh:mm:ss or yyyy-mm-ddThh:mm, respectively.

Data will be summarized by treatment group and overall.

For qualitative variables, the number and percentage in each category will be calculated. Percentages will be presented to one decimal. The calculation of percentages will be based on the number of non-missing values, if not stated otherwise. Missing values will not be presented and not be included in the calculation of percentages.

For quantitative variables, unless otherwise stated, the number of subjects (N), mean, standard deviation (SD), minimum, first quartile, median, third quartile, and maximum will be provided. In the description of the tables this will be denoted by 'summary statistics'. CRF records will be displayed with the same precision as they were recorded, derived or standardized values will be rounded to a reasonable number of digits. Mean, median, SD, and quartiles will be presented with one decimal more than the precision of the data. Minimum and maximum will be presented with the same precision as the raw data. P-values will be reported with four decimals (i.e., 0.xxxx). In summary statistics tables the overall number of missing values will not be given.

If randomization in the incorrect stratum occurred, i.e., the (planned) stratum information used for randomization deviates from the (actual) stratum information collected after randomization for the primary efficacy analysis, the subjects will be analyzed using the planned stratum information ('as randomized'). If the actual stratification information deviates for a considerable number of cases, it will be discussed during the blind data review meeting (BDRM) before database lock and unblinding if additional sensitivity analyses will be performed.

5.2 Specifications and definitions

- The duration of AE is calculated for complete dates only as stop date of AE - start date of AE + 1 day.
- For number of AK target lesions, number of severe AK lesions and total number of AK lesions in treatment field as well as all individual lesion information, eCRF data from PDT-1 visit will be used as baseline. Otherwise, baseline is defined as the last non-missing value before PDT-1 (including unscheduled visits (USVs)), i.e. non-missing observation on Visit 2 (PDT-1) or non-missing observation on Visit 1 (Screening) visit will be used as baseline value. Non-missing observation on PDT-1 visit will be used as baseline value if assessment was performed before treatment (before drug application and light treatment). Non-missing observation on Screening visit will be used as baseline value in following cases:
  - if no assessment on PDT-1 visit was performed,
  - if assessment on PDT-1 visit was performed after treatment (after drug application and illumination),
  - if assessment on PDT-1 visit was performed before treatment (before drug application and illumination) and assessment observation is missing.

- Change from baseline is calculated as follows: post-baseline value – baseline value.
- Baseline will be flagged in listings.
- Lesion size is calculated as largest diameter multiplied with perpendicular diameter.
- Maximal pain score during illumination will be derived as maximum of pain score of all illuminations over all PDTs.
- Sites with a small number of subjects are combined for using in efficacy analysis as stratification factor. Combination will be determined during BDRM (Section 5.14).
- Day relative to start of treatment (relative study day) is defined as follows:
  - if date (of event) is earlier than date of treatment start, then relative study day is calculated as study or event date – treatment start date;
  - if date (of event) is equal to or later than date of treatment start, then relative study day is calculated as study or event date – treatment start date + 1 day. Relative study day will only be derived for complete dates.
- Day relative to PDT-1 is defined as follows:
  - if date (of event) is earlier than date of PDT-1, then the day relative to PDT-1 is calculated as event date – PDT-1 date;
  - if date (of event) is equal to or later than PDT-1 date, then the day relative to PDT-1 is calculated as event date – PDT-1 date + 1 day. Day relative to PDT-1 will only be derived for complete dates.
- Day relative to PDT-2 is defined as follows:
  - if date (of event) is earlier than date of PDT-2, then the day relative to PDT-2 is calculated as event date – PDT-2 date;
  - if date (of event) is equal to or later than PDT-2 date, then the day relative to PDT-2 is calculated as event date – PDT-2 date + 1 day. Day relative to PDT-2 will only be derived for complete dates of non-responders or partial responders at Visit 4.
- For complete responders at Visit 4, Visit 4 result will be used as 12 weeks after the last PDT visit, for non-responders or partial responders at Visit 4, Visit 6 result will be used. For analysis reasons, these visits will be combined to the artificial visit “12 weeks after the last PDT” and will be displayed in the corresponding tables and used value will be indicated in corresponding listings, if applicable.
- USVs will only be listed and not included in any tables except for table ‘Subjects per visit’.
- Visit terminology:

Notation used in the protocol	Notation used for TLGs
Visit1, Screening (≤ 4 weeks prior to PDT-1)	Screening
Visit 2, PDT-1 (Baseline/treatment)	PDT-1
Not applicable	Baseline
Phone call 1 (1 week (± 2 days) post PDT-1)	1 week post PDT-1 (phonecall)
Visit 3 (4 weeks (± 1 week) post PDT-1)	4 weeks post PDT-1
Visit 4, PDT-2 (12 weeks (± 1 week) post PDT-1)	PDT-2 / 12 weeks post PDT-1
Phone call 2 (1 week (± 2 days) post PDT-2)	1 week post PDT-2 (phonecall)
Visit 5 (4 weeks (± 1 week) post PDT-2)	4 weeks post PDT-2
Visit 6 (12 weeks (± 1 week) post PDT-2)	12 weeks post PDT-2
Not applicable	FSA
Not applicable	12 weeks after the last PDT
FU1 (6 months (± 0.5 month) post last PDT)	6 months follow-up
FU2 (12 months (± 1 month) post last PDT)	12 months follow-up
Not applicable	USV*

FSA = Final safety assessment (according to eCRF), USV = Unscheduled visit
** USVs will be assigned to the corresponding visits and numbered in ascending order per visit.*

- Terminology for treatment groups:

Notation used in the protocol	Notation used for TLGs
BF-200 ALA	BF-200 ALA
vehicle	Vehicle

5.3 Disposition of subjects and analysis sets

The disposition of subjects and analysis sets, subjects per center, per visit and inclusion and exclusion criteria will be shown for the CONS and RAND for main and follow-up analyses. Additionally, subjects per visit will be presented for SAF, FAS, PPS, SAF-FUP, FAS-FUP and PPS-FUP. Furthermore, inclusion and exclusion criteria will be presented for SAF, FAS and PPS. Premature discontinuation from the study during the treatment phase and completion of the treatment phase will be summarized using CONS and RAND. Reasons for discontinuation and withdrawal from second treatment will be tabulated using CONS and RAND.

Randomization as well as actual and planned treatment information will be listed for the CONS. Premature discontinuation from the study during the follow-up phase and completion of the follow-up phase will be summarized using FAS.

No inferential assessments will be performed on disposition data.

5.4 Demographics and other covariates

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

No inferential assessments will be performed on demographics and other covariates.

5.4.1 Demographic data

Demographic data (age at inclusion and age (grouped), sex, ethnicity, race, body weight, body height) will be summarized descriptively for SAF, FAS, PPS, SAF-FUP, FAS-FUP and PPS-FUP.

5.4.2 Pregnancy test

The result of the urine and serum pregnancy test, if applicable, will be listed for female subjects for the SAF.

5.4.3 Medical history

The proportion of subjects with any relevant medical history, any medical skin history, any NMSC or melanoma history, any BCC, any SCC, any Bowen's disease, any melanoma, and any other skin diseases will be tabulated.

Further details regarding medical history, medical skin history, NMSC or melanoma history, and other skin diseases will be listed. The medical history will be presented for the SAF and FAS-FUP.

5.4.4 Prior and concomitant medications and procedures

Any medication taken by a subject or treatments the subject is undergoing that are not related to any study-specific procedures (PDT with IMP), starting with the time of signing the informed consent until the end-of-treatment phase are considered concomitant medications or treatments. If the start and/or end date of the medication/procedure is unknown or incomplete, so that no clear assignment can be made, medications/procedures will be assumed to be concomitant for the treatment phase as long as no corresponding AE exists with a start date after the end of the treatment phase.

Medications will be coded by the WHODrug Global.

Concomitant medication (CM) reported during the treatment period will be summarized descriptively by anatomical therapeutic chemical (ATC) level 2, ATC level 3, and preferred name.

If no preferred name can be found in the WHODrug Global for a documented medication, an umbrella term from the WHODrug Global will be used instead. A corresponding footnote will be added to the tables and listings concerned.

Concomitant procedures will be coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA) version available at the day of database closure. Concomitant procedures reported during the treatment period will be tabulated according to primary system organ class (SOC) and preferred term (PT). The number of events, as well as the number and percentage of affected subjects will be reported.

Medications and procedures will be presented for the SAF.

All medications/procedures started after the treatment phase will be regarded as medications/procedures during follow-up.

Medications and procedures concerning the follow-up phase will be presented for the SAF.

All Medications and procedures concerning the treatment phase, which are updated or retrospectively documented during follow-up phase, will be listed as well.

5.5 Other variables as measured at baseline

No inferential assessments will be performed on other variables as measured at baseline data.

Skin type assessment according to Fitzpatrick

Skin type class and skin type class (grouped) will be tabulated for the SAF, FAS, PPS, SAF-FUP, FAS-FUP and PPS-FUP.

Treatment field and target lesions characteristics at baseline

Treatment area, Size of the treatment field, Number of AK target lesions, Number of AK target lesions (grouped), No. severe AK lesions in treatment field, Total No. AK lesions in treatment field, AK target lesion severity (according to Olsen), AK target lesion size, AK target lesion size (grouped), Severe AK lesion size will be tabulated.

Treatment field and target lesions characteristics at baseline will be presented for the SAF, FAS, PPS, FAS-FUP and PPS-FUP.

5.6 Study drug administrations

Study drug administration

The absolute and relative frequency of subjects treated (PDT-1 only) and re-treated (PDT-1 and PDT-2) will be presented.

Study drug administration data will be presented for SAF, FAS, and PPS.

IMP and PDT details

Each subject will receive PDT using a RhodoLED lamp (BF-RhodoLED® XL or BF-RhodoLED®) with either BF-200 ALA or vehicle (IMP application). The treatment field may be continuous or in several patches and must be located within one effective illumination area of the BF-RhodoLED® XL or within up to three effective illumination areas of the BF-RhodoLED®.

The illumination time is CCI for BF-RhodoLED® XL in curved shape and CCI in flat shape. For BF-RhodoLED® the illumination time is CCI (up to three consecutive illuminations may be necessary).

For BF-RhodoLED® XL the planned duration of illumination will be recorded in the eCRF as preset length of illumination profile. For BF-RhodoLED® the planned duration of illumination for each illumination area will be set to CCI. The actual duration of illumination is calculated as follows:

Duration of illumination = planned duration of illumination – remaining illumination time.

The remaining illumination time will be set to 0 if the illumination was not prematurely terminated for calculations only.

The IMP and PDT details will be presented separately for both lamp models.

For BF-RhodoLED® XL the duration of incubation will be presented by visit. Additionally, the preset length of illumination profile, the duration of illumination, and the number of illumination interruptions will be presented by shape and visit.

For BF-RhodoLED® the duration of incubation, the duration of illumination, and the number of illumination interruptions will be tabulated by illumination field and visit.

Additionally, absolute and relative frequency of subjects treated with BF-RhodoLED® XL and BF-RhodoLED® as well as number of interruptions per subject will be presented per visit. Furthermore, absolute and relative frequency for premature termination of illumination will be presented per visit for BF-RhodoLED® XL and per visit and illumination field for BF-RhodoLED®.

IMP and PDT details will be presented for SAF, FAS, and PPS.

No inferential assessments will be performed on study drug administration data.

5.7 Efficacy analysis

All primary, key secondary, and further secondary efficacy variables will be analyzed descriptively. For tests of primary and key secondary variables, a one-sided significance level of 0.25 % will be applied. For tests of further key secondary variables, a two-sided significance level of 5 % will be applied. The analyses of the primary and key secondary efficacy variables using the FAS are considered confirmatory. The analyses of the primary and key secondary efficacy variables using the PPS as well as the further secondary efficacy analyses are considered exploratory. Therefore, no adjustment of the significance level will be done.

The main efficacy endpoints are based on the overall subject complete response rate assessed clinically 12 weeks after the last PDT. If a subject dropped out before the planned visit 12 weeks after the last PDT, or the variable value on this is missing and results cannot be obtained, the results based on the last available visit with a non-missing variable value will be used for the analyses on the overall complete subject response, i.e. last observation carried forward approach will be used to impute clinical assessments for the primary and key secondary endpoints.

If the outcome of a subject cannot be assessed, and the efficacy variable is completely missing, the subject will be counted as a non-responder. For subjects, who should have had a second PDT but were misleadingly classified as complete responders at Visit 4, the results from the first PDT will be used. For complete responders after the first PDT who by mistake received a second PDT, evaluations of the first PDT will also be considered.

5.7.1 Primary estimand

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

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

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

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

Primary estimand is defined by:

- Treatment: The treatment intended for the evaluation to address the study objective is the randomized treatment (BF-200 ALA or vehicle) administered to subjects at Visit 2 (PDT-1) and at Visit 4 (PDT-2), in case of remaining lesions at Visit 4. Treatment includes approx. 3 h incubation period of the IMP and a subsequent illumination with IMD until application of approx. 37 J/cm².
- Population: The population targeted by the clinical questions will be represented by the entire trial population defined through inclusion / exclusion criteria (Full analysis set, i.e., subjects randomized and treated at least once with PDT (IMP application and illumination)). A minimum of 4 to a maximum of 15 mild to moderate AK lesions with a diameter of ≥ 4 mm are required per subject to enable a profound assessment. No further demographic factors influencing AK development are considered.
- Variable: Treatment success [binary: yes/no], defined as subject being clinically completely cleared 12 weeks after the last PDT.
- Intercurrent event (ICE): The occurrence of all intercurrent events will be handled using the treatment-policy strategy according to ICH E9 (R1). All values will be used regardless of occurrence of the above mentioned intercurrent events up to 12 weeks after the last PDT. Before data base lock the occurrence of any other, not pre-defined ICE will be reviewed.
- Population-level summary: The difference in percentage of clinically completely cleared subjects 12 weeks after last PDT with BF-200 ALA vs vehicle.

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

The primary estimand is based on clinical assessments 12 weeks after the last PDT. For description of how to handle data missing on clinical visits 12 weeks after the last PDT please refer to Section 5.13.

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

5.7.2 Analysis of the primary efficacy variable

The primary efficacy variable is overall subject complete response rate 12 weeks after the last PDT [binary: yes/no], defined as the percentage of subjects with all AK target lesions clinically cleared 12 weeks after the last PDT.

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

The primary null hypothesis (H0, one-sided) is that the overall complete subject response rate assessed 12 weeks after the last PDT for subjects treated with BF-200 ALA is lower or equal to that of subjects treated with vehicle:

$$H_0: p_{BF\text{-}200\ ALA} \leq p_{Vehicle}$$

where $p_{BF\text{-}200\ ALA}$ is the overall complete subject response rate assessed 12 weeks after the last PDT for subjects treated with BF-200 ALA and $p_{Vehicle}$ is the overall complete subject response rate assessed 12 weeks after the last PDT for subjects treated with vehicle.

The primary alternative hypothesis (H1, one-sided) is that the overall complete subject response rate assessed 12 weeks after the last PDT for subjects treated with BF-200 ALA is greater than the response rate for subjects treated with vehicle:

$$H_1: p_{BF\text{-}200\ ALA} > p_{Vehicle}$$

A one-sided Cochran-Mantel-Haenszel test with stratification factor treatment area (extremities vs neck/trunk) will be used to test the primary hypothesis on a significance level of 0.0025 (one-sided, 0.25 %). A common odds ratio (OR) will be calculated (odds for response in BF-200 ALA group/ odds

for response in vehicle group). A common odds ratio > 1 indicates that the chance of overall complete subject response is higher for subjects treated with BF-200 ALA than for subjects treated with vehicle after adjusting for treatment area. As the Cochran-Mantel-Haenszel (CMH) test produces a two-sided p-value, the p-value for the one-sided test has to be derived; if the direction of the observed common odds ratio supports the superiority outcome (e.g. common odds ratio > 1), the two-sided p-value will be converted to a one-sided p-value by dividing by two. Otherwise, the one-sided p-value will be calculated as 1 - (the two-sided p-value divided by two). A two-sided 99.5 % confidence interval (CI) for the Mantel-Haenszel common odds ratio will additionally be presented. Frequency tables of overall subject complete response will be presented by treatment group and visit.

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

The primary endpoint will additionally be analyzed descriptively and in an exploratory way stratified by demographics (i.e. sex and age (grouped)), skin type class (grouped), study sites (grouped), and AK baseline parameters (AK target lesion number per subject at baseline (i.e. number of AK target lesions (grouped)), size of the treatment field, treatment area as well as combination of size of the treatment field and treatment area) for the FAS and PPS. Frequencies by treatment group and visit for each subgroup category and two-sided exact 95 % CI for the difference in response rates will be calculated.

Additionally, the response rate, i.e. the percentage of clinically cleared lesions (>=90%, >=75% - <90%, < 75%) of partial and non-responders 12 weeks after the last PDT will be presented by treatment area.

Additionally, summary statistics for percentage of clinical clearance of individual AK target lesions assessed 12 weeks after the last PDT in relation to total number of AK target lesions at baseline per treatment group will be presented by treatment area.

5.7.3 Analysis of key secondary efficacy variables

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

The primary null hypothesis (H0, one-sided) is that the overall complete subject response rate assessed 12 weeks after the last PDT for subjects treated with BF-200 ALA is lower or equal to that of subjects treated with vehicle on extremities or on neck/trunk, respectively:

$$H_{0i}: \; p_{BF\text{-}200\ ALA} \leq p_{Vehicle} \; (i = 1, 2)$$

where $p_{BF\text{-}200\ ALA}$ is the overall complete subject response rate assessed 12 weeks after the last PDT for subjects treated with BF-200 ALA and $p_{Vehicle}$ is the overall complete subject response rate assessed 12 weeks after the last PDT for subjects treated with vehicle and i the treatment area extremities or neck/trunk.

The primary alternative hypothesis (H1, one-sided) is that the overall complete subject response rate assessed 12 weeks after the last PDT for subjects treated with BF-200 ALA is greater than the response rate for subjects treated with vehicle on extremities or on neck/trunk, respectively:

$$H_{1i}: \; p_{BF\text{-}200\ ALA} > p_{Vehicle} \; (i = 1, 2)$$

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

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

Key secondary endpoints will additionally be analyzed descriptively and in an exploratory way stratified by AK baseline parameters (AK target lesion number per subject at baseline (i.e. Number of AK target

lesions (grouped)) and size of the treatment field) as well as by demographics (i.e. sex and age (grouped)) for the FAS and PPS. Frequencies by treatment group and visit for each subgroup category and two-sided exact 95 % CI for the difference in response rates will be calculated.

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

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

A one-sided chi-square test or if the number of expected cells counts is lower than five for any outcome the Fisher's exact test will be performed to test first key secondary hypothesis. The Odds ratio together with the corresponding one-sided p-value and a two-sided 99.5 % confidence interval (CI) will be presented.

Frequency tables of overall subject complete response will be presented by treatment group and visit.

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

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

A one-sided chi-square test or if the number of expected cells counts is lower than five for any outcome the Fisher's exact test will be performed to test first key secondary hypothesis. The Odds ratio together with the corresponding one-sided p-value and a two-sided 99.5 % confidence interval (CI) will be presented.

Frequency tables of overall subject complete response will be presented by treatment group and visit.

5.7.4 Analysis of further secondary efficacy variables

Further secondary efficacy endpoints will be analyzed descriptively and in an exploratory way. A two-sided significance level of 0.05 (5 %) will be applied for any statistical testing procedures for all further secondary efficacy variables. Where appropriate, two-sided local 95 % confidence intervals (CIs) of differences between BF-200 ALA and vehicle will be presented. As the secondary endpoint analyses, including the calculation of CIs, are not confirmatory, an adjustment for multiplicity will not be performed.

The analyses on secondary efficacy endpoints will be performed on the FAS.

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

Percentage of clinically cleared individual AK target lesions in relation to total number of AK target lesions at baseline (Visit 2) assessed 12 weeks after the last PDT, overall and stratified by treatment area and AK severity at baseline (according to Olsen et al., 1991 (1)).

Clinically cleared individual AK target lesions in relation to total number of AK target lesions at baseline will be analyzed descriptively. The absolute number of individual AK target lesions at baseline and the absolute and relative frequency of clinically cleared individual AK target lesions 12 weeks after the last PDT will be tabulated per treatment group.

Furthermore, clinically cleared individual AK target lesions in relation to total number of AK target lesions at baseline per treatment group will be analyzed descriptively by treatment area, AK severity at baseline and AK target lesion size at baseline (i.e. AK target lesion size (grouped)). The absolute number of individual AK target lesions at baseline and the absolute and relative frequency of clinically cleared individual AK target lesions 12 weeks after the last PDT will be presented.

These analyses will be performed on the FAS and PPS.

Percentage of clinically cleared individual severe AK lesions in relation to total number of severe AK lesions at baseline (according to Olsen et al., 1991 (1); Visit 2) assessed 12 weeks after the last PDT, overall and stratified by treatment area.

Clinically cleared individual severe AK lesions in relation to total number of severe AK lesions at baseline will be analyzed descriptively. The absolute number of individual severe AK lesions at baseline and the absolute and relative frequency of clinically cleared individual severe AK lesions 12 weeks after the last PDT will be tabulated per treatment group.

Furthermore, clinically cleared individual severe AK lesions in relation to total number of severe AK lesions at baseline per treatment group will be analyzed descriptively by treatment area. The absolute number of individual severe AK lesions at baseline and the absolute and relative frequency of clinically cleared individual severe AK lesions 12 weeks after the last PDT will be presented.

Subject complete response rate, 12 weeks after PDT-1, defined as the percentage of subjects with all AK target lesions clinically cleared, overall and stratified by AK baseline parameters (e.g., AK target lesion number per subject at baseline, size of the treatment field, and treatment area).

Subject complete response rate is defined as the percentage of subjects with all AK target lesions clinically cleared.

Subject complete response rate 12 weeks after PDT-1 will be analyzed using a Cochran-Mantel-Haenszel Test (incl. confidence interval) with treatment area as stratification factor.

As additional analyses, the subject complete response rate 12 weeks after PDT-1 will be analyzed descriptively by Number of AK target lesions (grouped), size of the treatment field and treatment area. Two-sided exact 95% CI for the difference in response rates will be calculated.

This analysis will be performed on the FAS and PPS.

Percentage of clinically cleared individual AK target lesions in relation to total number of AK target lesions at baseline (Visit 2) assessed 12 weeks after PDT-1, overall and stratified by treatment area and AK severity at baseline (according to Olsen et al., 1991 (1)).

Clinically cleared individual AK target lesions in relation to total number of AK target lesions at baseline will be analyzed descriptively. The absolute number of individual AK target lesions at baseline and the absolute and relative frequency of clinically cleared individual AK target lesions 12 weeks after PDT-1 will be tabulated per treatment group.

Furthermore, clinically cleared individual AK target lesions in relation to total number of AK target lesions at baseline per treatment group will be analyzed descriptively by treatment area and AK severity at baseline. The absolute number of individual AK target lesions at baseline and the absolute and relative frequency of clinically cleared individual AK target lesions 12 weeks after PDT-1 will be presented.

This analysis will be performed on the FAS and PPS.

Percentage of clinically cleared individual severe AK lesions in relation to total number of severe AK lesions at baseline (according to Olsen et al., 1991 (1); Visit 2) assessed 12 weeks after PDT-1, overall and stratified by treatment area.

Clinically cleared individual severe AK lesions in relation to total number of severe AK lesions at baseline will be analyzed descriptively. The absolute number of individual severe AK lesions at baseline and the absolute and relative frequency of clinically cleared individual severe AK lesions 12 weeks after the PDT-1 will be tabulated per treatment group.

Furthermore, clinically cleared individual severe AK lesions in relation to total number of severe AK lesions at baseline per treatment group will be analyzed descriptively by treatment area. The absolute number of individual severe AK lesions at baseline and the absolute and relative frequency of clinically cleared individual severe AK lesions 12 weeks after the PDT-1 will be presented.

The esthetic appearance 12 weeks after the last PDT as assessed by the investigator, overall and stratified by treatment area.

Esthetic appearance of all target lesions will be assessed 12 weeks after the last PDT and in the FUP. The esthetic appearance is assessed using the 4-point scale ranging from very good (0) to unsatisfactory (3).

The absolute and relative number of very good / good / satisfactory / unsatisfactory assessments 12 weeks after the last PDT will be tabulated per treatment group in overall and by treatment area.

The esthetic outcome 12 weeks after the last PDT as assessed by the subject, overall and stratified by treatment area.

Esthetic outcome of all target lesions will be assessed 12 weeks after the last PDT and in the FUP. The esthetic outcome is assessed using the 4-point scale ranging from very good (0) to unsatisfactory (3).

The absolute and relative number of very good / good / satisfactory / unsatisfactory assessments 12 weeks after the last PDT will be tabulated per treatment group in overall and by treatment area.

Satisfaction with PDT treatment 12 weeks after the last PDT as assessed by the subject, overall and stratified by treatment area.

Subjects' satisfaction with PDT treatment will be assessed 12 weeks after the last PDT and in the FUP. Subjects' satisfaction with PDT treatment is assessed by the question if the subject would choose the treatment again. Answers to the question if the subject would choose the treatment again 12 weeks after the last PDT will be tabulated per treatment group in overall and by treatment area.

5.7.5 Analysis of tertiary efficacy variables

All tertiary efficacy endpoints will be performed for the FAS-FUP, unless otherwise specified.

For calculation of cumulative recurrence rates, a subject/lesion that is recurrent at any FU visit is regarded as recurrent at all subsequent FU visits irrespective of whether the lesion was treated in the meantime or whether the subject is lost to follow-up. This implies that a recurrent subject/lesion will not be counted as still cleared or lost to follow-up at any visit after assessment of recurrence.

Subject recurrence rate defined as the percentage of subjects with all AK target lesions clinically cleared 12 weeks after the last PDT presenting with at least one recurrent lesion during follow-up, stratified by demographics, study sites, AK baseline parameters (e.g., AK target lesion number per subject at baseline, size of the treatment field, and treatment area).

For the analysis of subject recurrence rates, a subject with the overall subject complete response 12 weeks after the last PDT according to the primary efficacy endpoint (i.e. all lesions were clinically cleared 12 weeks after last PDT) is regarded as recurrent if any baseline AK target lesion recurs during FU.

For all follow-up visits (FU1 and FU2) the cumulative subject recurrence rates will be displayed:

- The cumulated number and percentage of subjects lost to follow-up since the beginning of the FUP
- The number and percentage of subjects with missing lesion assessments at the current visit and not yet considered as lost to follow-up
- The cumulated number and percentage of subjects with recurrent lesions since the beginning of the follow-up period
- The number and percentage of subjects still completely cleared

The denominator for all cumulative rates (= 100 %) is the number of subjects with overall subject complete response 12 weeks after the last PDT entering the follow-up phase.

This analysis will be performed on the FAS-FUP and PPS-FUP and will be repeated by demographics (i.e. sex and age (grouped)), site (grouped), AK baseline parameters (AK target lesion number per subject at baseline, size of the treatment field, and treatment area).

Percentage of AK target lesions showing recurrence in follow-up in relation to total number of clinically cleared AK target lesions 12 weeks after last PDT, overall and stratified by treatment area and AK severity at baseline (according to Olsen et al., 1991).

For the analysis of AK target lesions recurrence rates AK target lesion which was clinically cleared 12 weeks after last PDT is regarded as recurrent if it recurs during FU.

For all follow-up visits (FU1 and FU2) the cumulative lesion recurrence rates will be displayed:

- The cumulated number and percentage of recurrent lesions since the beginning of the follow-up period.
- The number and percentage of still completely cleared lesions

The denominator for all cumulative rates (= 100 %) is the number of clinically cleared AK target lesion 12 weeks after last PDT entering the follow-up part.

This analysis will be performed on the FAS-FUP and PPS-FUP and will be repeated by treatment area and AK target lesion severity at baseline (i.e. AK target lesion severity (according to Olsen)) as well as by AK target lesion size at baseline (i.e. AK target lesion size (grouped)).

Percentage of severe AK lesions showing recurrence in follow-up in relation to total number of clinically cleared severe AK lesions 12 weeks after last PDT, overall and stratified by treatment area.

For the analysis of severe AK lesions recurrence rates, severe AK lesion which was clinically cleared 12 weeks after last PDT is regarded as recurrent if it recurs during FU.

The same recurrence analysis as for the AK target lesions will be done for severe AK lesions.

This analysis will be performed on the FAS-FUP and PPS-FUP and will be repeated by treatment area.

The esthetic appearance at follow-up visits as assessed by the investigator, overall and stratified by treatment area.

Esthetic appearance of all target lesions will be assessed 12 weeks after the last PDT and in the FUP. The esthetic appearance is assessed using the 4-point scale ranging from very good (0) to unsatisfactory (3).

The absolute and relative number of very good / good / satisfactory / unsatisfactory assessments for all follow-up visits (FU1 and FU2) will be tabulated per treatment group in overall and by treatment area.

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

Esthetic outcome of all target lesions will be assessed 12 weeks after the last PDT and in the FUP. The esthetic outcome is assessed using the 4-point scale ranging from very good (0) to unsatisfactory (3).

The absolute and relative number of very good / good / satisfactory / unsatisfactory assessments for all follow-up visits (FU1 and FU2) will be tabulated per treatment group in overall and by treatment area.

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

Subjects' satisfaction with PDT treatment will be assessed 12 weeks after the last PDT and in the FUP. Subjects' satisfaction with PDT treatment is assessed by the question if the subject would choose the treatment again. Answers to the question if the subject would choose the treatment again for all follow-up visits (FU1 and FU2) will be tabulated per treatment group in overall and by treatment area.

5.8 Safety analysis

All safety endpoints will be analyzed descriptively and in an exploratory way. These safety analyses will be performed for the SAF, unless otherwise specified. Selected safety analyses will be conducted overall and stratified by age groups, sex, skin type class group and treatment area, as well as by size of the treatment field, as specified below.

5.8.1 Adverse events

AEs will be coded according to the latest MedDRA version available at the day of database closure. The analysis will focus on the TEAEs.

TEAEs (including application site skin reactions and discomfort) are defined as all AEs starting with or after IMP application and within 12 weeks + 7 days (91 days) after the last PDT. If the onset of an AE is more than 12 weeks + 7 days (91 days) after the last PDT but the AE is at least possibly related or with missing relationship to IMP or medical device, AEs will be assumed to be TEAEs. If the relationship is unclear due to unknown or incomplete start time/date, AEs will be assumed to be TEAEs, as far as the end time/date of the AE is not before the first treatment. The reference date will be calculated as date of last PDT + 91 days, i.e. date of PDT-1 or PDT-2, respectively. These reference dates will be used for assignment of TEAEs. The allocation of AEs as treatment-emergent will be derived for all AEs within the treatment phase.

Related TEAEs are defined as possibly, probably, or definitely related, or with missing relationship.

An AE overview table will be created displaying the number of events as well as the number and percentage of subjects with:

- Any AE
- Any SAE
- Any TEAE
- Any serious TEAE
- Any AESI
- Any TEAE related to IMP
- Any TEAE related to medical device
- Any TEAE related to IMP or medical device
- Any TEAE related to IMP and medical device
- Any TEAE resulting in discontinuation of study
- Any TEAE leading to death.

TEAEs will be summarized and tabulated according to primary SOC and PT. The number of events, as well as the number and percentage of affected subjects will be reported. AEs, AESIs, SAEs, TEAEs leading to death and TEAEs resulting in discontinuation of study will be tabulated using frequency tables presented by SOC and PT.

Additionally, serious TEAEs, TEAEs related to IMP, TEAEs related to medical device, TEAEs related to IMP or medical device, TEAEs related to IMP and medical device, will be presented separately by SOC and PT.

Furthermore, TEAEs will be presented by SOC, PT and

- relationship (unrelated / unlikely related / possibly related / probably related / definitely related) to IMP and/or medical device
- severity (mild / moderate / severe)
- subgroups age (grouped), sex, skin type class (grouped), size of the treatment field and treatment area

The extend of TEAEs will be presented by summarizing the duration of events descriptively by PT. Only PTs, where at least two events have occurred and events with complete start and end dates will be presented.

A listing of subjects with AEs will be provided for all AEs reported and all subjects randomized (separate presentation for subjects in SAF and not in SAF). In listings, the start day of the AE relative to start of treatment (relative study day), to start of PDT-1 (relative PDT-1 day) and to start of PDT-2 (relative PDT-2 day) will be displayed for complete start dates only.

5.8.2 Assessment of new lesions inside the treatment field

Assessment of new lesions inside the treatment field is documented on the AE page of the eCRF. New lesions (AK, non-melanoma skin cancer [NMSC, including BCC, SCC, or BD], melanoma, other) will be tabulated using frequency table presented by SOC and PT. The number of events, as well as the number and percentage of affected subjects will be reported.

5.8.3 Application site reactions

Application site reactions will be analyzed according to 4-point scale from none (grade 0) to severe (grade 3). The number and percentage of subjects experiencing application site discomfort (Burning, Hyperalgesia, Irritation, Paraesthesia, Pruritus) and of application site skin reactions (Bleeding, Discharge, Edema, Erosion, Erythema, Exfoliation, Induration, Pustules, Scabbing, Vesicles) will be presented by treatment area, illumination area and severity for each assessment time point.

In a separate table, the number and percentage of subjects experiencing application site reactions according to 4-point scale will be presented by treatment area only. For this table, the worst severity per subject across all assessment timepoints after IMP application overall illumination areas will be considered.

A separate listing will be provided for all application site reactions reported and all subjects randomized by SAF.

Additionally, application site discomfort (Burning, Irritation, Paraesthesia, Pruritus, Hyperalgesia, Other) and application site skin reactions (Bleeding, Discharge, Edema, Erosion, Erythema, Exfoliation, Induration, Pustules, Scabbing, Vesicles, Other) from eCRF AE-page will be presented by SOC, PT and severity (mild / moderate / severe).

5.8.4 Pain

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

Summary statistics together with 95% CIs for the mean for pain intensity during PDT will be presented by visit. Additionally, summary statistics together with 95% CIs for the mean for the worst pain intensity (maximal pain score) over all visits will be presented.

All analyses will be presented overall, by treatment area and by size of the treatment field.

5.8.5 Laboratory parameters

All laboratory values will be classified as normal or abnormal according to the laboratory's normal ranges and package insert of the urinalysis dipstick test. Only values considered clinically significant by the investigator will be documented in the eCRF and listed as such.

5.8.6 Vital signs

Blood pressure (systolic and diastolic) and pulse rate will be analyzed descriptively together with absolute changes from baseline to post-baseline visits.

5.8.7 Physical examination

The physical examination includes the following body systems: head, neck, skin, lymph nodes, thorax including heart and lung, abdomen, and musculoskeletal, peripheral vascular and nervous system. Physical examination data will be listed.

5.9 Tertiary safety analysis

All tertiary safety endpoints will be performed for the SAF-FUP, unless otherwise specified.

5.9.1 Adverse events during follow-up

All AEs started after completion date of treatment phase will be regarded as AEs during follow-up. If unclear due to unknown or incomplete start time/date of AE or completion date of treatment phase, AEs documented during follow-up phase will be assumed as AEs during follow-up, as far as end time/date of AE is not before completion date of treatment phase. All AEs concerning the treatment phase, which are updated or retrospectively documented during follow-up phase, are not a part of this endpoint and will be presented separately.

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

At the FU visits, any relevant AE (including AEs or conditions affecting skin health in the treatment field which may impair proper assessment of the recurrence rate of the treated AK lesions, or other clinically relevant events at the investigator's discretion) as well as SAEs that has occurred since the end-of-treatment visit (Visit 4 or Visit 6) should be documented.

An FU AE overview table will be created displaying the number of events as well as the number and percentage of subjects with:

- Any AE during follow-up
- Any SAE during follow-up
- Any AE during follow-up resulting in discontinuation of study
- Any AE during follow-up leading to death.

AEs during follow-up will be summarized and tabulated according to primary SOC and PT. The number of events, as well as the number and percentage of affected subjects will be reported. AEs during follow-up leading to death and AEs during follow-up resulting in discontinuation of study will be tabulated using frequency tables presented by SOC and PT. Additionally, SAEs, will be presented separately by SOC and PT. Furthermore, AEs during follow-up by SOC, PT and severity (mild / moderate / severe) will be presented. AEs during follow-up, SAEs during follow-up will be presented by SOC, PT and by following subgroups: age (grouped), sex and treatment area.

A listing of subjects with AEs will be provided for all AEs during follow-up. Additionally, all AEs concerning the treatment phase, which are updated or retrospectively documented during follow-up phase, will be listed as well of all subjects in RAND.

5.9.2 Assessment of new lesions inside the treatment field during follow-up

Assessment of new lesions (AK, NMSC or melanoma) inside the treatment field

Assessment of new lesions inside the treatment field is documented on the AE page of the eCRF. New lesions (AK, non-melanoma skin cancer [NMSC, including BCC, SCC, or BD], melanoma, other) will be tabulated using a frequency table presented by SOC and PT. The number of events, as well as the number and percentage of affected subjects will be reported.

5.10 Analysis of other variables

Lesion directed treatment after final assessment

Lesion directed treatment after final assessment details will be listed for FAS.

Optional biopsy of suspicious lesions

Optional biopsy of suspicious lesions details will be listed for FAS.

Confirmation of contact dermatitis

Confirmation of contact dermatitis details will be listed for SAF.

Emergency unblinding

Emergency unblinding details will be listed for RAND.

5.11 Protocol deviations

Protocol deviations (PDs) as classified during the (B)DRMs (Section 5.14) will be tabulated and listed.

The following PDs are a priori defined as leading to exclusion from PPS:

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

5.12 Interim analysis

No formal interim analysis will be performed.

5.13 Missing values

The main efficacy endpoints are based on the overall subject complete response rate assessed clinically 12 weeks after the last PDT. If a subject dropped out before the planned visit 12 weeks after the last PDT, or the variable value on this is missing and results cannot be obtained, the results based on the last available visit with a non-missing variable value will be used for the analyses on the overall complete subject response, i.e. last observation carried forward approach will be used to impute clinical assessments for the primary and key secondary endpoints.

If the outcome of a subject cannot be assessed, and the efficacy variable is completely missing, the subject will be counted as a non-responder. For subjects, who should have had a second PDT but were misleadingly classified as complete responders at Visit 4, the results from the first PDT will be used. For complete responders after the first PDT who by mistake received a second PDT, evaluations of the first PDT will also be considered.

Missing data of further secondary or tertiary efficacy variables or safety variables will not be replaced except for subgroup analysis of the primary endpoint. These subgroup analyses will be done using the same imputed data as for the primary endpoint.

5.14 Database closure and blind data review meeting

The database will be closed before the main analysis for treatment phase and before follow-up analysis for follow-up phase. All parameters will be checked, as specified in the data validation plan, and all queries resolved before respective database closure and analysis.

Two data review meetings will be conducted before respective analysis.

A data review for main analysis will be conducted before unblinding based on all data of treatment phase to check for protocol deviations and to allocate the subjects to the analysis sets for main analysis. At least the following items will be discussed:

- Violation of inclusion or exclusion criteria [BDRM listing 1.1.1]
- Incorrect allocation to treatment group
- The treatment differs significantly from protocol (e.g., incubation time differs by more than 30 min from times indicated by the protocol; applied light dose differs by more than 20 %). [BDRM listing 4.1 and BDRM listing 4.2]
- No final assessment visit (Visit 4 or Visit 6) [BDRM listing 1.1.4.1]
- Missing AK lesion clearance status at final assessment visits (Visit 4 or Visit 6) [BDRM listing 5.1.1]
- Forbidden medication will be decided on a case-by-case basis [BDRM listing 2.7.1 and BDRM table 2.3]
- Significant deviation from visit time window at Visit 4 or Visit 6 [BDRM listing 1.1.4.1]
- Wrong or expired IMP applied
- Any other deviation with impact on the primary efficacy variable(s)
- Unblinding within the conduct of the study [BDRM listing 8.4]
- Premature discontinuation during the study [BDRM listing 1.2.1.1]
- Missing data for derivation of primary efficacy variable at baseline and/or post-baseline [BDRM listing 5.1.1]
- Randomization in wrong stratum
- Number of subjects in different subgroups

A data review for follow-up analysis will be conducted based on data of follow-up phase to check for protocol deviations and to allocate the subjects to the follow-up analysis sets.

These assessments will be done together and in agreement with the sponsor, but FGK will provide the sponsor with the appropriate subject listings and tables (as defined in appendix A). The data review for both analyses will be done via a web conference.

The assignment of subjects to the SAF, FAS, and PPS will be done before unblinding. The assignment of subjects to the SAF-FUP, FAS-FUP, and PPS-FUP will be done after unblinding.

Data unblinding on the basis of the randomization listing and the analysis will be done after database closure / data review for main analysis has been conducted and data review minutes have been signed by both the CRO acting on behalf of sponsor and FGK.

5.15 Miscellaneous

A detailed description of the planned TLGs is given in Appendix A.

If no further note is given in the table description, the following format will be used for all tables with qualitative (frequency tables) and/or quantitative (summary statistics) variables (except for shift tables):

		<Actual/Planned> Treatment		
		BF-200 ALA (N=x)	**Vehicle (N=x)**	**Total (N=x)**
Qualitative Variable	n	x	x	x
Value x	n (%)	x (x.x)	x (x.x)	x (x.x)
Value y	n (%)	x (x.x)	x (x.x)	x (x.x)
Quantitative Variable [unit]	n	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x	x.x
	Q_1, Q_3	x.x, x.x	x.x, x.x	x.x, x.x
	Min, Max	x, x	x, x	x, x

For this standard format the description of the tables in Appendix A determines only the variables. If another format of table is described in the details to the tables, the real design will be determined by the technical possibilities within SAS and may not look identical to the example provided. All information as displayed will be included.

The following title will be used for all generated TLGs:

ALA-AK-CT019 Page # of #
Main/FUP analysis
Table/Listing/Graph <x.x>
<Title of table/listing/graph>
<Analysis set>

The numbering x.x of the TLGs will be stated in the detailed description (Appendix A).

The following footnote will be used for all generated TLGs:

Program: <Name of program> Run date/time: <Actual date (yyyy-mm-ddThh:mm)>

All TLGs will be generated in DIN A4 paper format.

The statistical evaluation will be performed using SAS Version 9.4 or higher.

6 Changes to the analyses planned in the protocol

The following statistical aspects as described in the protocol were changed:

- The protocol (version 3.0 of 31-May-2023) states: 'As the secondary endpoint analyses, including the calculation of CIs, are not confirmatory, an **adjustment** for multiplicity **is necessary**'. Not confirmatory analyses don't need adjustment for multiplicity. No adjustment for multiplicity will be performed for further efficacy analyses.
- The protocol (version 3.0 of 31-May-2023) states: 'For subjects, who should have had a second PDT but were misleadingly classified as complete responders at **Visit 5**, the results from the first PDT will be used. For complete responders after the first PDT who by mistake received a second PDT, evaluations of the first PDT will also be considered.' Determination of subject status takes place at Visit 4 and Visit6 (12 weeks post corresponding PDT). Wording in SAP adapted.

  The protocol (version 3.0 of 31-May-2023) defines "Frequency and extent of AEs, AESIs, SAEs, and treatment-emergent adverse events (TEAEs), overall and stratified by demographics, skin type class (I – III and IV – VI), size of the treatment field, and treatment area. TEAEs (including application site skin reactions and discomfort) are defined as all AEs with onset or worsening after treatment with IMP up to 12 weeks after the last PDT" as safety endpoint. This endpoint was worded misleadingly, as the stratification factors concern solely the TEAEs. Subgroup analyses for AEs, AESIs and SAEs may not be useful, as:- AEs usually do not differ substantially from the TEAEs, so the analysis would be doubled

  - AESIs are per definition seldom, so a subgroup analysis will be inconclusive

  - SAEs are usually also infrequent.

  Thus, subgroup analyses for stratified by demographics, skin type class (I – III and IV – VI), size of the treatment field, and treatment area will only be performed for TEAEs. This is in line with the description of the safety analyses in the protocol: "The analysis will focus on the TEAEs." (see Section 11.4.4 Evaluation of safety endpoints).
- The protocol (version 3.0 of 31-May-2023) states: 'TEAEs (including application site skin reactions and discomfort) are defined as all AEs with onset or worsening after treatment with IMP up to 12 weeks after the last PDT.' This definition is adapted in SAP to consider the start time of AEs and treatment and to avoid confusion between worsening of the illness, which is to be documented as AE, and worsening of AEs (change of severity).The adapted TEAE definition is: 'TEAEs (including application site skin reactions and discomfort) are defined as all AEs starting with or after IMP application and within 12 weeks + 7 days (91 days) after the last PDT. If the onset of an AE is more than 12 weeks + 7 days (91 days) after the last PDT but the AE is at least possibly related or with missing relationship to IMP or medical device, AEs will be assumed to be TEAEs.
- The protocol (version 3.0 of 31-May-2023) defines "[...] extent of AEs, AESIs, SAEs, and treatment-emergent adverse events (TEAEs) [...]" as part of a safety endpoint. Here, "extent" refers to the duration of the individual preferred terms of events. With regard to the available data, it was already clear before unblinding that such an analysis via summary statistics would not provide any conclusive results for AESIs and SAEs. Furthermore, AEs usually do not differ substantially from the TEAEs, so an analysis of the durations of TEAEs and AEs would be doubled. Hence, it was decided to focus on durations of TEAEs.
- The protocol (version 3.0 of 31-May-2023) defines efficacy analyses stratified by AK baseline parameters. As one example for these, the maximal AK target lesion severity at baseline was listed. However, efficacy analyses will be performed using other AK baseline parameters as stratification factors, as the maximal AK target lesion severity may not be clinically meaningful for the analysis of subject-based clearances.

7 Literature

1. Olsen EA, Abernethy ML, Kulp-Shorten C, Callen JP, Glazer SD, Huntley A, et al. A double-blind, vehicle-controlled study evaluating masoprocol cream in the treatment of actinic keratoses on the head and neck. J Am Acad Dermatol 1991;24(5 Pt 1):738–43. PubMed PMID: 1869646.