COVER PAGE

STATISTICAL ANALYSIS PLAN

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)

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Statistical Analysis Plan
for
final analysis

Version 3.0

Study:	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).
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Version	Author	Date	Reason for Revision
1.0	[redacted]	08May2018	1st final version
2.0	[redacted]	23Oct2023	2nd final version, update of 1st final version due to: • protocol amendment version 3.0 of 17 July 2018 • minor corrections in Appendix after finalization of CRF • detected findings during programming • consideration of COVID-19 pandemic
3.0	[redacted]	29Jul2024	3rd final version, update of 2nd final version due to: • clarification of TEAE definition • detected findings during programming

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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 tables, listings and graphs outputs:

AE	Adverse event
ATC	Anatomical therapeutic chemical classification
BCC	Basal cell carcinoma
BDRM	Blind data review meeting
BMI	Body mass index
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
eCRF	Electronic case report form
FAS	Full analysis set
FWER	Family-wise error rate
H0, H_0	Null hypothesis
H1, H_1	Alternative hypothesis
IMP	Investigational medicinal product(s)
LOCF	Last observation carried forward
MedDRA	Medical dictionary for regulatory activities
N	Number of subjects
NRPS	Numeric rating pain scale
PDT	Photodynamic therapy
PPS	Per-protocol set
PT	Preferred term
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
TEAE	Treatment emergent adverse event
TLG	Tables, listings, graphs
WHO-DD	World health organization drug dictionary

1 General

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 upon the Study Protocol (version 3.0 of 17 July 2018) and contains a detailed description of the statistical methods described therein.

The statistical analyses will be performed separately for the clinical observation phase and the follow-up phase. This SAP describes prospectively the main analyses for the clinical observation phase, which will be performed after database lock and subsequent unblinding of all data after the end of the clinical observation period. The SAP version 1.0 was finalized in parallel to the study protocol version 2.0, before the first study subject received study medication. Additional data from the follow-up period (12, 24, 36 as well as 60 months after completion of the 1st PDT cycle (Visit 5)) will be analyzed and reported separately from the report of the clinical observation phase of the study. All details of the statistical analyses and methods for the follow-up period will be specified in a separate SAP.

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, part 1 is the clinical observation part, consisting of a screening period and a treatment period, part 2 covers the FU.

To guarantee the blind status of the investigator assessing the 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 (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 of the last PDT cycle that included treatment of the Main Target Lesion, and is defined as complete clinical and histological clearance of the Main Target Lesion. 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 is comprised of a screening visit at which a biopsy of each eligible BCC is taken 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 the 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.

All subjects will receive complete excision of their Main Target Lesion for histopathological evaluation of lesion status, at the latest at Visit 8. 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.

Approximately 12 sites in the United States of America (US) will participate in this study.

The primary objective of this study is 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). A Main Target Lesion with 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 lesions (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.

1.1 Sample Size Calculation

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 lesions (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 superficial BCCs 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 subject response rate of 91% (FAS) for subjects with superficial BCC 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 subjects as well as subject lost to follow-up as recurrent (data on file and (1)).
- With respect to individual superficial BCC 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.
- We took a maximum of 18% of subjects showing a recurrence (worst case, also lost to follow up subjects are regarded as recurrent) at 2 years follow-up into account. These subjects may have shown a potentially histologically positive result at the last clinical visit which leads to the estimate of 72.9% of subjects who are assumed to be clinically and histologically cleared 12 weeks after the last PDT. Furthermore, we expect a proportion of 10% of subjects with a missing histological assessment 12 weeks after the last PDT.
- As no further data on vehicle/placebo treatment in superficial BCC 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 nodular BCC 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 superficial BCC with 5% imiquimod cream. Subjects 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) (2).
- The clinical and histological response proportion for BF-200 ALA will be estimated as follows: assuming a response rate of 73% and in addition a proportion of 10% of subjects with missing assessment 12 weeks after the last PDT, i.e. 15 out of the 149 BF-200 ALA subjects will be non-responders due to missing assessments, the number of responders can be estimated as: (149-15)*0.73=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).

1.2 Visit Terminology

The notation displayed in Table 1 will be used for table, listing, and graph presentation of visits.

Table 1: Visit terminology

Notation in protocol	Notation used for TLG presentation
Visit 1, Screening (≤ 4 weeks prior to PDT-1)	Screening
Randomization at Visit 2, PDT-1 (Baseline)	Randomization
Visit 2, PDT-1 (Baseline)	PDT-1
Not applicable	Baseline[1]
Visit 3, PDT-2 (1-2 weeks post-PDT-1)	PDT-2
Phone call 1 (1 week ± 2 days post-PDT-2)	1 week post-PDT-2
Visit 4 (5 weeks ± 1 week post-PDT-1)	5 weeks post-PDT-1
Visit 5, PDT-3 (12 weeks ± 1 week post-PDT-1)	PDT-3 / 12 weeks post-PDT-1
Visit 6, PDT-4 (1-2 weeks post-PDT-3)	PDT-4
Phone call 2 (1-week ± 2 days post-PDT-4)	1 week post-PDT-4
Visit 7 (5 weeks ± 1 week post-PDT-3)	5 weeks post-PDT-3
Visit 8 (12 weeks ± 1 week post-PDT-3)	12 weeks post-PDT-3
Not applicable	12 weeks after start of the last PDT cycle[2]

[1] Baseline is defined as last non-missing value until PDT-1, i.e. non-missing observation on PDT-1 visit or non-missing observation on 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 and non-missing observation on Screening visit is available,
- if assessment on PDT-1 visit was performed after treatment (after drug application and light treatment) and non-missing observation on Screening visit is available,
- if assessment on PDT-1 visit was performed before treatment (before drug application and light treatment) and assessment observation is missing and non-missing observation on Screening visit is available.

If the absolute change from Baseline is calculated for a parameter or Baseline characteristics are presented, this artificial visit will be displayed in the corresponding tables and Baseline value will be indicated in corresponding listings.

[2] For complete responders, Visit 5 will be used as 12 weeks after the start of the last PDT cycle visit, for non-responders or partial responders, Visit 8 will be used. For analysis reasons, these visits will be combined to the artificial visit "12 weeks after start of the last PDT cycle" and will be displayed in the corresponding tables and used value will be indicated in corresponding listings.

2 Efficacy and Safety Variables

2.1 Primary Efficacy 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.

2.2 Key Secondary Efficacy Variables

The following key secondary efficacy parameters will be analyzed:

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.

2.3 Further Secondary Efficacy Variables

The following further secondary efficacy parameters will be analyzed:

- 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.

2.4 Safety 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).
- 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.

3 Statistical Analysis Sets

3.1 Enrolled Set

The enrolled set consists of all subjects enrolled in this study, i.e. who provided informed consent to participate in the study.

3.2 Randomized Set

The randomized set consists of all subjects randomized to IMP irrespective of whether they received IMP or not.

3.3 Safety Analysis Set

The safety analysis set (SAF) consists of all subjects treated at least once with IMP (IMP application). The assignment of subjects to the treatment groups will be as actually treated. If the application of any study medication is not certain, the subject will be included in the SAF.

3.4 Full Analysis Set

The full analysis set (FAS) consists of 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.

3.5 Per-Protocol Set

The per-protocol set (PPS) consists of all subjects of the FAS without any major protocol deviations. The assignment of subjects to the treatment groups will be as actually treated.

Protocol deviations will be identified and classified for each subject during a blind data review (see section 4.8).

The following protocol deviations are a priori defined in the protocol to have a “major” grade and will lead to an exclusion from the PPS:

- The treatment differs significantly from protocol (e.g. incubation period differs by more than 30 min from times indicated by the protocol; distance of the lamp differs by more than 1 cm from the range indicated by the manual; illumination time differs by more than 20% (2 min) from the pre-defined illumination time of 10 min.
- Forbidden anti-inflammatory medication (within ± 7 days of PDT)
- Other forbidden medication will be decided on a case-by-case basis.
- Missing visits (with exception of Visit 4 or Visit 7 and Phone call 1 and Phone call 2)
- 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 any exclusion criteria throughout the treatment period of the study.

3.6 Additional Subgroup Analyses

Where appropriate, subgroup analyses will be performed for the main, key secondary and further secondary efficacy parameters if there are at least 5 subjects within the subgroups. The following subgroups are subject to further interest:

Subject based subgroups

- Sex (Males, Female)
- Age group (age group I (≥18 to <65, ≥65), age group II (≥18 to <65, ≥65 to <85, ≥85)
- Fitzpatrick skin type (grouped) (type I-III, IV-VI)
- Number of target lesions (grouped) (1, ≥2 lesion(s))
- Location of target lesions (grouped) (Face (treatment area A) [with the subareas whole face and forehead] , Bald Scalp (treatment area B) [if less than 5 subjects belong to treatment area A or B, treatment areas will be combined], Neck/Trunk (treatment area C) [with subareas neck, back, belly, décolleté, throat], Extremities (treatment area D) [with subareas hand, foot, lower arm, lower leg, upper arm, upper leg], multiple locations (combination of various treatment areas))
- Total area of Baseline target lesions (Total areas of all Baseline Target Lesions per subject divided into three groups according to the corresponding tertiles: first, second, and third of the ordered data)
- Baseline size of Main Target Lesion (Baseline size of all Main Target Lesions divided into three groups according to the corresponding tertiles: first, second, and third of the ordered data)
- Center (centers with less than 5 subjects will be combined)

Lesion based subgroups

- Location of lesion (Face (treatment area A) [with the subareas whole face and forehead] , Bald Scalp (treatment area B) [if less than 5 subjects belong to treatment area A or B, treatment areas will be combined], Neck/Trunk (treatment area C) [with subareas neck, back, belly, décolleté, throat, other], Extremities (treatment area D) [with subareas hand, foot, lower arm, lower leg, upper arm, upper leg, other])
- Baseline size of Target Lesion (Baseline size of all Target Lesions divided into three groups according to the corresponding tertiles: first, second, and third of the ordered data)

Subgroup variables used for specific analyses are described within the respective sections.

3.7 Assignment of Analysis Sets to Analysis

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

The PPS will be used for sensitivity analysis of the primary, key secondary and further secondary endpoints.

The enrolled set and the randomized set are the analysis sets for the summary of subject disposition and discontinuation.

The SAF is the analysis set for all safety analyses.

All analyses based on FAS, PPS, enrolled and randomized set will be performed for planned treatment, i.e. by the treatment group to which they were randomized (“intention-to-treat”). All analyses based on SAF will be performed for actual treatment, i.e.by the treatment they received.

4 Statistical Evaluation

Missing values of the primary endpoint will be regarded as non-responders. Missing values of clinical lesion assessments only will be imputed using a last observation carried forward (LOCF) approach. If no preceding assessment is available, the lesion will be regarded as non-responding. Further details of handling of missing data are described in section 4.6.

Unless otherwise stated, continuous data will be summarized by means of descriptive statistics, i.e. mean value, standard deviation (SD), first quartile, median, third quartile, range (minimum and maximum), and number of non-missing values. Categorical variables will be summarized by absolute and relative frequencies (percentages on non-missing values) of subjects by category.

Only data belonging to the clinical observation phase will be used for the analysis described in this SAP. For this, data of follow-up visits will be excluded from SDTM data sets used for analysis of clinical observation phase. For visit-scheduled datasets (incl. medical history), all records prior to or at Visit 8 (12 weeks post-PDT-3) - end of clinical study phase - will be included. Subjects with premature termination after Visit 8 will be removed from dataset “Study Termination” (i.e. they will not be identified as drop-outs). Furthermore, adverse events (AEs) and concomitant medications (CMs) starting after date of last visit/assessment of clinical phase (maximum date of all visit/assessment dates within non-log forms prior to or at Visit 8) on subject level will be excluded. If the month and/or day of the start date of AE or CM is not available, a worst-case-approach will be applied, and the first of the month and/or the first month of the year will be assumed, and the record will be included when that assumed date is prior or at the maximum date of all visits and assessments prior to or at Visit 8. If the complete start date is not known, a worst-case-approach will be applied, and a date of 2000-01-01 will be assumed, to ensure that it will be prior to the maximum date of all visits and assessments prior to or at Visit 8.

4.1 Dispositions of Subjects and Analysis Sets

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 presented. Premature discontinuation from the study and completion of the clinical observation period will be summarized. Reasons for discontinuation will be tabulated. No inferential assessments will be performed on disposition data.

Tables will be created using enrolled set, randomized set, SAF, FAS, and PPS.

4.2 Demographics and Other Covariates

Demographic data

Demographic data (Age at inclusion, Sex, Center, Race, Ethnicity, Weight [lb and kg], Height [inch and cm], Fitzpatrick skin type group (type I-III, IV-VI) will be tabulated by treatment. Additionally age subgroups will be tabulated by treatment.

Demographic tables will be created using SAF, FAS, and PPS.

The abuse of any alcohol or drug at Screening will be tabulated using SAF.

BCC lesion characteristics

Baseline assessments of BCC lesion characteristics will be analyzed as follows:

Basic statistics for number of target BCC lesions, Baseline size of Main Target Lesion, and total area of target lesions at Baseline (summary of size of all target BCC lesions) will be presented on a subject basis by treatment. Additionally, the subgroups according to the total lesion area at

Baseline and to the size of the Main Target Lesion at Baseline will be tabulated by treatment. BCC lesion size of all Target Lesions will be additionally presented on a lesion basis.

The number of target Lesions at Baseline (1 vs. ≥2 lesion(s)), the location of the Main Target Lesion, and location of all target BCC lesions (including combination of multiple locations) will be tabulated on a subject basis by treatment. Additionally, the location of target BCC lesions and the subgroup according to the size of target lesions at Baseline will be tabulated on a lesion basis by treatment.

The number of all lesions (target and non-target separately and in total) per treatment arm at Baseline will be tabulated.

Tables of BCC lesion characteristics will be created using SAF, FAS, and PPS.

Medical history

The proportion of subjects with any relevant medical and surgical history, any history of skin disease except for skin cancer, any history of skin cancer/actinic keratosis except for basal cell carcinoma, and any history of basal cell carcinoma will be tabulated.

Further details regarding medical history will be listed.

The medical history will be presented for the SAF.

Concomitant medication

Medications will be coded by the world health organization drug dictionary (WHO-DD).

Concomitant medication will be tabulated by Anatomical therapeutic chemical classification (ATC) level 1, ATC level 4, and WHO-DD preferred term using the SAF.

Fertility status and pregnancy test

Child-bearing potential, method of contraception and results of all pregnancy tests will be listed in detail for the SAF.

No inferential assessments will be performed on demographic and background characteristics.

4.3 Study Drug Administration

PDT details (duration of incubation, duration of illumination, duration of illumination excluding interruptions, number of illumination interruptions) will be tabulated by treatment, visit and illumination field using basic statistics.

Duration of illumination is calculated as follows:

Duration of illumination = Duration of illumination excluding interruptions + Total duration of interruptions.

Duration of illumination excluding interruptions will be set to 10 if illumination was done according to protocol.

The number of interruptions and total duration of interruptions will be set to 0 if the illumination was not interrupted for calculations only.

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

Further PDT details will be listed.

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

4.4 Efficacy Analysis

Confirmatory hypothesis tests will be performed for the primary and the key secondary efficacy endpoints using a one-sided alpha level of 0.001. A one-sided 99.9%-confidence intervals (CI) will be additionally presented for the primary and key secondary endpoints. Hierarchically ordered hypothesis testing for the primary and the key secondary hypotheses will be used to ensure control of the family-wise error rate (FWER) (multiple type I-error level) of 0.1% (one-sided). Two-sided local (in terms of the subgroups) 95% confidence intervals (CIs) of differences between BF-200 ALA and vehicle will additionally be calculated for the primary and the key secondary endpoints.
Further secondary endpoints will be analyzed descriptively and in an exploratory way. For further secondary endpoints, two-sided statistical testing procedures will be conducted using a significance level of 5% (α=0.05). Two-sided 95% confidence intervals (CIs) for the Mantel-Haenszel common odds ratio will be applied. Two-sided local (in terms of the subgroups) 95% confidence intervals (CIs) of differences between BF-200 ALA and vehicle will additionally be calculated for further secondary endpoints.

4.4.1 Analysis of Primary Efficacy 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, i.e. if both lesion status is documented as 'Cleared' and question 'Is the main target lesion histologically cleared?' is answered with 'Yes' at corresponding visit. Not cleared clinical or histological lesion (status not 'Cleared' or question answered with 'No'), Unknown or missing data will be considered as not completely cleared Main Target Lesion (non-response).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). As the CMH Test produces a two-sided p-value, 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). Baseline number of lesions (1 vs. ≥2 lesion(s)) and center will be used as stratification factors. A one-sided 99.9% confidence interval (CI) for the Mantel-Haenszel common odds ratio will additionally be applied. The primary analysis will be performed on the FAS and will be repeated, in sense of sensitivity analyses, for the PPS. Additionally, a sensitivity analysis using only subjects without missing values (complete-case analysis) will be performed.

Frequency tables of clinical and histological response of the Main Target Lesion will be presented by treatment group and visit.

As additional analyses, the primary efficacy variable will be analyzed descriptively by sex, age group I, Fitzpatrick skin type group, number of target lesions at baseline, location of Main Target Lesion, baseline size of Main Target Lesion, and center. Subgroup analyses will be conducted both for the PPS and FAS. 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.

4.4.2 Analysis of Key Secondary Efficacy Variables

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

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

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

Following the hierarchical testing strategy, the key secondary null hypotheses will only be tested if the first primary null hypothesis has been rejected and will be done strictly in the given order to ensure the family-wise error rate (FWER). Each subsequent test of a key secondary endpoint is conducted only if the preceding test was statistically significant on the planned one-sided alpha level of 0.001. 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 and will be repeated, in the sense of sensitivity analyses, for the PPS.

<u>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.</u>

Main Target Lesion clinical response is defined as response of the Main Target Lesion according to clinical assessment only.

The Main Target Lesion clinical response 12 weeks after the start of the last PDT cycle will be analyzed using a Cochran-Mantel-Haenszel Test (incl. confidence interval) with baseline number of lesions (1 vs. ≥2 lesion(s)) and center as stratification factors.

Frequency tables of clinical response of the Main Target Lesion will be presented by treatment group and visit.

As additional analyses, the Main Target Lesion clinical response 12 weeks after the last PDT cycle will be analyzed descriptively by baseline size of Main Target Lesion and location of Main Target Lesion. 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.

<u>Key secondary endpoint 2: Main Target Lesion histological response (according to histological assessment only) assessed 12 weeks after the start of the last PDT cycle.</u>

Main Target Lesion histological response is defined as response of the Main Target Lesion according to histological assessment only.

The Main Target Lesion histological response 12 weeks after the start of the last PDT cycle will be analyzed using a Cochran-Mantel-Haenszel Test (incl. confidence interval) with baseline number of lesions (1 vs. ≥2 lesion(s)) and center as stratification factors.

Frequency tables of histological response of the Main Target Lesion will be presented by treatment group and visit.

As sensitivity analysis additionally a complete case analysis will be performed.

As additional analyses, the Main Target Lesion histological response 12 weeks after the last PDT cycle will be analyzed descriptively by baseline size of Main Target Lesion and location of Main Target Lesion. 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 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 subject complete clinical response is defined as complete clearance of all target lesions according to clinical assessment only.

The subject complete clinical response 12 weeks after the start of the last PDT cycle will be analyzed using a Cochran-Mantel-Haenszel Test (incl. confidence interval) with baseline number of lesions (1 vs. ≥2 lesion(s)) and center as stratification factors.

Frequency tables of complete clinical responders will be presented by treatment group and visit.

As additional analyses, the subject complete clinical response 12 weeks after the last PDT cycle will be analyzed descriptively by location of lesions and number of lesions at baseline (1, ≥2 lesion(s)). 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 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 subject complete response is defined as clinically and histologically cleared Main Target Lesion and complete response of all Additional Target lesions according to clinical assessment only. Only Main Target Lesion will be considered if no Additional Target lesions available.

The subject complete response 12 weeks after the start of the last PDT cycle will be analyzed using a Cochran-Mantel-Haenszel Test (incl. confidence interval) with baseline number of lesions (1 vs. ≥2 lesion(s)) and center as stratification factors.

As sensitivity analysis additionally a complete case analysis will be performed.

Frequency tables of complete responders will be presented by treatment group and visit.

As additional analyses, the subject complete response 12 weeks after the last PDT_cycle will be analyzed descriptively by location of lesions and number of lesions at baseline (1, ≥2 lesion(s)). 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.

4.4.3 Analysis of Further Efficacy Variables

All further secondary efficacy variables will be analyzed descriptively and in an exploratory way. All analyses will be performed on the FAS and PPS. All statistical testing procedures will be done exploratory using a significance level of 5% (α=0.05, two-sided).

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.

The lesion complete clinical response rate is defined as the percentage of completely cleared individual lesions, in relation to the number of lesions at baseline (Visit 2).

The lesion complete clinical response rate per treatment arm 12 weeks after the start of the last PDT cycle will be analyzed descriptively. The absolute number of target lesions at baseline and the absolute and relative frequency of clinically cleared lesions 12 weeks after the start of the last PDT cycle will be tabulated per treatment arm.

As additional analyses, the lesion complete clinical response rate per treatment arm 12 weeks after the last PDT cycle will be analyzed descriptively by location of lesions and baseline size of lesions. Frequencies per subgroup category will be presented.

Main Target Lesion complete response (clinically and histologically cleared) assessed 12 weeks after PDT-1.

Main Target Lesion complete response is defined as response according to clinical and histological assessment.

The Main Target Lesion complete response 12 weeks after PDT-1 will be analyzed using a Cochran-Mantel-Haenszel Test (incl. confidence interval) with baseline number of lesions (1 vs. ≥2 lesion(s)) and center as stratification factors.

As additional analyses, the Main Target Lesion complete response 12 weeks after PDT-1 will be analyzed descriptively by location of Main Target Lesion and baseline size of Main Target Lesion. Two-sided exact 95% CI for the difference in response rates will be calculated.

Main Target Lesion clinical response (according to clinical assessment only) assessed 12 weeks after PDT-1.

Main Target Lesion clinical response is defined as response according to clinical assessment only.

The Main Target Lesion clinical response 12 weeks after PDT-1 will be analyzed using a Cochran-Mantel-Haenszel Test (incl. confidence interval) with baseline number of lesions (1 vs. ≥2 lesion(s)) and center as stratification factors.

As additional analyses, the Main Target Lesion clinical response 12 weeks after PDT-1 will be analyzed descriptively by location of lesions and baseline size of Main Target Lesion. Two-sided exact 95% CI for the difference in response rates will be calculated.

Main Target Lesion histological response (according to histological assessment only) assessed 12 weeks after PDT-1.

Main Target Lesion histological response is defined as response according to histological assessment only.

The Main Target Lesion histological response 12 weeks after PDT-1 will be analyzed using a Cochran-Mantel-Haenszel Test (incl. confidence interval) with baseline number of lesions (1 vs. ≥2 lesion(s)) and center as stratification factors.

As additional analyses, the Main Target Lesion histological response 12 weeks after PDT-1 will be analyzed descriptively by location of lesions and baseline size of Main Target Lesion. Two-sided exact 95% CI for the difference in response rates will be calculated.

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.

The lesion complete clinical response rate per treatment arm is defined as the percentage of individual lesions in the respective treatment arm with complete clearance.

The lesion complete clinical response rate per treatment arm 12 weeks after PDT-1 will be analyzed descriptively. The absolute number of target lesions at baseline and the absolute and relative frequency of clinically cleared lesions 12 weeks after the start of the last PDT cycle will be tabulated per treatment arm.

Subject complete clinical response (complete clearance of all Target Lesions according to clinical assessment only) assessed 12 weeks after PDT-1.

The subject complete clinical response is defined as complete clearance of all target lesions according to clinical assessment only.

The subject complete clinical response 12 weeks after PDT-1 will be analyzed using a Cochran-Mantel-Haenszel Test (incl. confidence interval) with baseline number of lesions (1 vs. ≥2 lesion(s)) and center as stratification factors.

Subject complete response (clinically and histologically cleared Main Target Lesion and complete clinical remission of all Additional Target Lesions) assessed 12 weeks after PDT-1.

The subject complete response is defined as clinically and histologically cleared Main Target Lesion and complete response of all Additional Target lesions according to clinical assessment only.

The subject complete response 12 weeks after PDT-1 will be analyzed using a Cochran-Mantel-Haenszel Test (incl. confidence interval) with baseline number of lesions (1 vs. ≥2 lesion(s)) and center as stratification factors.

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.

Esthetic appearance of the Main Target Lesion by the investigator will be assessed prior to surgical excision of this target lesion. Esthetic appearance of additional Target lesion(s) 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)). The esthetic appearance is assessed using the 4-point scale ranging from very good (0) to unsatisfactory (3).

The assessment of esthetic appearance by the investigator will be analyzed descriptively on a lesion basis. The absolute and relative number of very good / good / satisfactory / unsatisfactory / no answer assessments will be tabulated per treatment arm and visit.

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.

Esthetic outcome of the Main Target Lesion will be assessed prior to surgical excision of this target lesion. Esthetic outcome of additional Target Lesion(s) as well as subjects' overall satisfaction with PDT 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)). Satisfaction with esthetic outcome is assessed using the 4-point scale ranging from very good (0) to unsatisfactory (3). Subjects' overall satisfaction with PDT treatment is assessed by the question if the subject would choose the treatment again.

The subjects' satisfaction regarding esthetic outcome will be analyzed descriptively on a lesion basis. The absolute and relative number of very good / good / satisfactory / unsatisfactory / no answer assessments will be tabulated per treatment arm and visit.

The subjects' satisfaction regarding esthetic outcome and subjects' satisfaction with PDT treatment will be analyzed descriptively on a subject basis. If the subject has documented different satisfaction regarding esthetic outcome for different lesions, worst satisfaction will be considered for tabulation. The absolute and relative number of very good / good / satisfactory / unsatisfactory / no answer subject assessments of esthetic outcome as well as the answers to the question if the subject would choose the treatment again will be tabulated per treatment arm and visit.

4.5 Safety Analysis

All safety endpoints will be analyzed descriptively and in an exploratory way. The safety analyses will be performed for the SAF.

AEs will be presented with maximum intensity.

AEs will be coded according to the latest Medical Dictionary for Regulatory Activities (MedDRA) version available at the day of database closure, system organ class (SOC) and preferred term (PT) will be presented. The AE analysis will focus on the TEAEs.

Frequency and extent of TEAEs, including SAEs

TEAEs are defined as all AEs with time of onset on or after the time of treatment with randomized IMP within 4 weeks (28 days) after each PDT cycle. If time of onset of AEs is not within 4 weeks (28 days) after each PDT cycle, but is identified to be at least possibly related to IMP or medical device, AEs will be assumed as TEAEs. The reference dates will be calculated as date of last PDT within each PDT cycle + 28, i.e. date of PDT-2 and/or PDT-4, respectively. If PDT-2 and/or PDT-4 are not available, the dates of PDT-1 and/or PDT-3 will be used for calculation of reference dates. These reference dates will be used for assignment of TEAEs. If unclear due to incomplete start time/date of AE or PDT, AEs will be assumed as TEAEs, as far as end time/date of AE is not before first treatment in first PDT cycle. AEs and TEAEs will be summarized and tabulated according to primary system organ class and preferred term displaying the number of events as well as counts and percentages on a subject basis per treatment arm.

Additionally, TEAEs by sex, TEAEs by age group I, serious TEAEs and TEAEs by intensity (mild/moderate/severe/unknown) will be tabulated. Related TEAEs (defined as possibly, probably, or definitely related, or with missing relationship) will be presented by intensity overall (related to IMP or related to medical device), related to IMP only, related to IMP and medical device and related to medical device only. Additionally, TEAEs by relationship (unrelated / unlikely related / possibly related / probably related / definitely related) will be presented related to IMP and related to medical device separately.

TEAEs leading to death and TEAEs resulting in discontinuation of study will be tabulated if more than 5 events are observed. Specification of any action taken documented on AE page as 'Withdrawal from study' will be used for detection of TEAEs resulting in discontinuation of study.

A listing of subjects with TEAEs will be provided for all TEAEs reported. Non-TEAEs, i.e. AEs with onset before treatment or later than 4 weeks after each PDT cycle, will be listed separately for all subjects enrolled. In listings, the start day of the AE relative to start of treatment will be calculated for complete start dates only. Duration of events is only calculated for complete start and end dates.

Local reactions in the treatment field(s)

Local reactions, i.e. local skin reactions and local discomfort as assessed by investigator, are documented on AE page and can be identified as AEs with CRF question 'Is this (S)AE within a treatment field?' answered with 'yes' and are related (defined as possibly, probably, or definitely related, or with missing relationship) to IMP or medical device. Variable will be 'yes' if local reaction is documented at least once. Otherwise, variable will be 'no'. TEAEs identified as local reaction will be tabulated separately by intensity (mild/moderate/severe/unknown) separately for each PDT cycle. Therefore, local reactions with time of onset on or after the time of PDT-1 and before the time of PDT-3 will be categorized to PDT cycle 1. Local reactions with time of onset on or after the time of PDT-3 will be categorized to PDT cycle 2. If PDT-1 and/or PDT-3 are not available, the dates of PDT-2 and/or PDT-4 will be used for calculation respectively. If unclear due to incomplete start time/date of local reactions or PDT, local reactions will be categorized to PDT cycle unknown. Furthermore, the worst intensity (none/mild/moderate/severe) of at least one occurred PTs will be presented for local reactions. Thereby not available local reaction will be presented as intensity none. Missing or unknown intensity will not be considered for worst intensity analysis. Additionally, the frequency of any TEAEs identified as local reaction will be presented together with the respective CIs for each treatment group.

New lesions (AK, NMSC, melanoma)

The occurrence of any new lesions (AK, NMSC, melanoma, according to AE CRF page) since screening will be summarized and tabulated according to primary system organ class and preferred term displaying the number of events as well as counts and percentages on a subject basis. Additionally, the occurrence of any new lesions will be tabulated stratified by location in relation to the treatment field (outside/inside treatment field).

Local discomfort

The frequency and exact 95% CIs for each proportion of local discomfort during PDT (illumination) (using a 4-point scale ranging from none (0) to severe (3) for each category: burning, itching, other) will be presented by category and for each assessment time point. Local discomfort per illumination field, i.e. per lesion location (body system) as well, is available. Worst intensity over all timepoints for each lesion location and category will be considered for tabulation. In case of both illumination fields have same location, worst intensity of both illumination fields will be considered for tabulation. Missing or unknown intensity will not be considered for worst intensity analysis. Additionally, binary variables for each lesion location and category will be created for presentation of 95% CIs. Variable will be 'yes' if corresponding discomfort is documented at least once over all timepoints for corresponding lesion location. Otherwise, variable will be 'no'. In case of both illumination fields have same location, variable will be 'yes' if corresponding discomfort is documented at least once over all timepoints of both illumination fields for corresponding location. Otherwise, variable will be 'no'.

Pain

Pain reported during PDT (illumination) will be assessed using an 11-point numeric rating pain scale (NRPS) assessment by the subject. Pain assessment per illumination field, i.e. per lesion location (body system) as well, is available. The mean pain score with exact 95% CIs will be presented for each assessment time point and lesion location. In case of both illumination fields have same location, pain of both illumination fields will be considered for tabulation. Additionally, mean of the maximum pain score (worst intensity) over all timepoints with exact 95% CIs for each lesion location will be presented. In case of both illumination fields have same location, maximum pain score (worst intensity) of both illumination fields will be considered for tabulation.

Vital signs (blood pressure, heart rate)

Blood pressure (systolic and diastolic) and pulse rate will be analyzed using descriptive statistics by time point. In addition, absolute changes from baseline will be displayed by time point.

The absolute change from baseline to a visit will be calculated by the observed value at the respective visit minus the baseline value for non-missing observations.

Safety laboratory assessments

All details regarding laboratory assessments will be listed. In addition, a listing of clinically significant values will be provided.

Physical examinations

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.

4.6 Missing Values

Missing values for the primary and secondary endpoints will be imputed as follows:

For all subjects missing values for the primary and secondary endpoints for the first PDT cycle will be imputed as follows:

- For the analysis of the composite endpoint clinical and histological response of the Main Target Lesion a missing clinical and/or histological lesion assessment of the Main Target Lesion on Visit 5 will be considered as non-response.
- For the analysis of histological response only a missing histological lesion assessment of the Main Target Lesion on Visit 5 will be considered as non-response.
- For the analysis of clinical response only of the Main Target Lesion as well as for the clinical response of Additional Target Lesions a last observation carried forward (LOCF) approach will be used to impute clinical assessments on Visit 5: If the clinical assessment of lesion clearance (yes/no) on week 12 after PDT-1 (i.e. Visit 5) is missing but week 5 after PDT-1 (i.e. Visit 4) assessment is available, missing week 12 after PDT-1 data will be imputed by week 5 after PDT-1 data. If a lesion clearance is not assessed on week 5 after PDT-1 and on week 12 after PDT-1, the lesion will be regarded as non-responder on Visit 5. Lesions with missing clinical assessments on Visit 4 will be regarded as non-responders.

For partial/non-responders at Visit 5 or subjects imputed as partial/non-responders at Visit 5 missing values for the primary and secondary endpoints for the second PDT cycle will be imputed as follows:

- For the analysis of the composite endpoint clinical and histological response of the Main Target Lesion a missing clinical and/or histological lesion assessment of the Main Target Lesion on Visit 8 will be considered as non-response.
- For the analysis of histological response only a missing histological lesion assessment of the Main Target Lesion on Visit 8 will be considered as non-response, if the Main Target Lesion was not already clinically cleared and excised at Visit 5. If the Main Target Lesion was already clinically cleared and excised at Visit 5, the histological lesion assessment of the Main Target Lesion at Visit 5 will be carried forward to Visit 8 following a last observation carried forward (LOCF) approach.
- For the analysis of clinical response only of the Main Target Lesion as well as for the clinical response of Additional Target Lesions a last observation carried forward (LOCF) approach will be used to impute missing clinical assessments: If the clinical assessment of lesion clearance (yes/no) on week 12 after PDT-3 (i.e. visit 8) is missing but week 5 after PDT-3 (i.e. visit 7) assessment is available, missing week 12 after PDT-3 data will be imputed by week 5 after PDT-3 data. If a lesion clearance is not assessed on week 5 after PDT-3 and on week 12 after PDT-3, the lesion will be regarded as non-responder on Visit 7 and Visit 8.
- For complete responders after cycle 1 who by mistake received a second treatment cycle, evaluations of the 1st cycle will be considered for all efficacy analyses, including the primary analysis.
- No replacement of missing values will be done for the secondary endpoints assessment of esthetic appearance by the investigator and subjects' satisfaction regarding esthetic outcome.

No additional methods on replacement of missing values of efficacy variables will be applied.

As sensitivity analysis for the primary and selected secondary efficacy variables additionally a complete cases analysis will be done.

Missing values of safety variables will not be replaced.

4.7 COVID-19

Potential issues arising due to the COVID-19 pandemic will be monitored regularly regarding their impact on the statistical analysis and if there is need for action.

COVID-19 diseases will be entered as adverse events. COVID-19 vaccinations will be entered as concomitant medications.

In case of an increased number of missing values in the primary endpoint, the need for a sample size re-estimation will be discussed.

No additional analyses concerning COVID-19 and no subgroup analyses to compare pandemic/non-pandemic are planned. The need for additional analysis or for an adaptation of missing value imputation will be discussed during blind data review meeting.

4.8 Data Base Closure and Data Review

A data base closure will be performed prior to the analysis. All parameters of the clinical observation period (all data up to visit 8) will be checked, as specified in the data validation plan, and all queries resolved before data base closure and analysis.

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

- Any violation of inclusion/exclusion criteria (BDRM Listing 1.1)
- The treatment differs significantly from protocol (e.g. incubation period differs by more than 30 min from times indicated by the protocol; distance of the lamp differs by more than 1 cm from the range indicated by the manual; illumination time differs by more than 20% (2 min) from the pre-defined illumination time of 10 min. (BDRM Listing 3.1)
- Use of forbidden medication (anti-inflammatory medication and other forbidden medication) (BDRM Listing 2.9)
- Missing visits (with exception of the safety interim Visit 4 or Visit 7) (BDRM Listing 6.1)
- The interval between 2 PDT treatments of the same cycle exceeded the interval indicated by the protocol by more than 4 days. (BDRM Listing 6.1)
- Treatment with a 2nd treatment cycle although the lesion(s) has/have been clinically cleared already after the 1st treatment cycle. (BDRM Listing 4.3.1, BDRM Listing 3.1)
- Meeting any exclusion criteria throughout the treatment period of the study (determined by monitoring and medical review, BDRM Listing 1.1).
- Need to combine strata used for analysis of primary endpoint (center, baseline number of lesions).
- Impact of COVID-19 pandemic on analysis.

These evaluations and assessments will be done together and in agreement with the CRO acting on behalf of sponsor, however FGK will provide the CRO acting on behalf of sponsor with the appropriate subject listings (as defined in appendix A). Data review will be done via a web conference.

The affiliation of subjects to the SAF, the FAS, and the PPS set will be done prior to unblinding.

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

The affiliation of subjects to the treatment groups will be done after unblinding.

4.9 Miscellaneous

For qualitative variables the frequencies (absolute and relative) are calculated. If no further remark is given in the description of the tables the following format will be used for all tables with qualitative variables (total will only be calculated if appropriate):

	Y-variable(s) (e.g., treatment group)					
	Category 1		Category 2		Total	
X-variable(s)	N	%	N	%	N	%
category 1	xx	xx.x	xx	xx.x	xx	xx.x
category 2	xx	xx.x	xx	xx.x	xx	xx.x
Total	xx	100.0	xx	100.0	xx	100.0

For this standard format the description of the tables in Appendix A determines only the X- and Y-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/STAT® software and may not look identical to the provided example. However, all information as displayed will be included.

Quantitative parameters will be described by declaring the mean value, standard deviation, minimum, first quartile, median, third quartile, maximum, and number of non-missing observations. In the description of the tables this will be denoted by „basic statistics“.

The listings are always sorted by treatment group, center, and subject. If a different sorting order should be used for some listings this will be remarked separately. The variables for the special listings are explicitly given in the description of listings.

Enrolled but not treated subjects (e.g. withdrawal before treatment) will be considered in tables and listings describing disposition of subjects, analysis sets and discontinuation as well as listings for subject demographics, and time schedules.

The following title will be used for all generated tables, listings, and graphs:

ALA-BCC-CT013: Phase III trial with BF-200 ALA/BF-RhodoLED in the treatment of sBCC Page # of #

<Table/Listing/Graph NNN: Description of contents>
<Subtitle for description of contents - if applicable>
<Analysis set>

The numbering NNN of the tables/listings/graphs will be stated in the detailed description (Appendix A).

The following footnote will be used for all generated tables, listings, and graphs:

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

The statistical evaluation will be performed using SAS/STAT software, Version 9.4 or higher of the SAS System for Windows, SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, NC, USA.

5 Changes from Protocol

- The protocol (version 3.0 of 17Jul2018) states: '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.'. Local skin reactions are not separately evaluated using a 4-point scale by visit and illumination field. Local skin reactions are documented as AEs and are included in analysis of AEs defined as local reactions. No separate frequency tables with the respective CIs of local skin reactions will be created.
- The protocol (version 3.0 of 17Jul2018) states: '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).'. 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 intensity).
  - wrong assignment to TEAE, due to allowed per protocol time window for Visit 4 and Visit 7, respectively.

  The adapted TEAE definition is: 'TEAEs are defined as all AEs with time of onset on or after the time of treatment with IMP within 4 weeks (28 days) after each PDT cycle. If time of onset of AEs is not within 4 weeks (28 days) after each PDT cycle but is identified to be at least possibly related to IMP or medical device, AEs will be assumed as TEAEs.'.
- Small wording adaptions were performed within this SAP to be consistent in the analyses, e.g. 'patient' vs. 'subject', etc.
- The protocol (version 3.0 of 17Jul2018) states: "… subjects' overall satisfaction with the treatment will be assessed …using a 4-point scale…". Subjects' satisfaction with treatment was not evaluated on a 4-point scale, they were asked if they would choose the PDT treatment again in the future.

6 Literature

1. Morton CA, Dominicus R, Radny P, Dirschka T, Hauschild A, Reinhold U, et al. A randomized, multi-national, non-inferiority, phase III trial to evaluate the safety and efficacy of BF-200 ALA gel versus MAL cream in the treatment of non-aggressive basal cell carcinoma with photodynamic therapy (PDT). Br J Dermatol. 2018.
2. Geisse JK, Rich P, Pandya A, Gross K, Andres K, Ginkel A, et al. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: a double-blind, randomized, vehicle-controlled study. J Am Acad Dermatol. 2002;47(3):390-8.

7 Signatures

Statistician:
[redacted]
Date (ddmmmyyyy) Signature

CRO acting on behalf of sponsor:
[redacted]
Date (ddmmmyyyy) Signature

Sponsor:
[redacted] Biofrontera Bioscience GmbH [redacted] Hemmelrather Weg 201 51377 Leverkusen Germany
Date (ddmmmyyyy) Signature