

COVER PAGE

STATISTICAL ANALYSIS PLAN

Study ALA-ACV-CT014

NCT05080764

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

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**Statistical Analysis Plan
for
Final Analysis
Version 3.0**

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

Study-ID: ALA-ACV-CT014

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CRO acting on behalf of Sponsor: Biofrontera Discovery GmbH

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Revision History

Version	Author	Date	Reason for Revision
1.0	PPD	20Nov2024	Final version 1.0
2.0	PPD	28Apr2025	Second final version 2.0: - Changes due to new protocol version 4.0 - Further small changes in SAP sections 2, 4.1, 4.2, 5.3, 5.4.1, 5.6.4, 5.7.2, 5.7.6, 5.11, and 6 - Description of subgroup analyses of co-primary efficacy variables added in sections 3 and 5.6.3 and in SAP Appendix - Additional exploratory endpoint added in sections 4.4, 5.6.5, and 6 - Further minor changes in SAP Appendix
3.0	PPD	18Dec2025	Third final version 3.0: - TEAE definition adapted (section 5.7.1) - Analysis of application site skin reactions and application site discomfort adapted (section 5.7.6) - Analysis of protocol deviations added (section 5.9) - Handling of missing data slightly adapted (section 5.11) - Small changes in SAP section 5.122 - Appendix: Selected tables and listing for primary or secondary efficacy variables split; Further minor changes in SAP Appendix

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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
ADaM	Analysis data model
ALA	5-aminolevulinic acid
ATC	Anatomical therapeutic chemical
BDRM	Blind data review meeting
BMI	Body mass index
eCRF	Electronic case report form
FAS	Full analysis set
IMP	Investigational medicinal product
H_0 , H_0	Null hypothesis
H_1 , H_1 , H_A , H_A	Alternative hypothesis
LOCF	Last observation carried forward
MedDRA	Medical dictionary for regulatory activities
N	Number of subjects
PD	Protocol deviation
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
SDTM	Study data tabulation model
SOC	System organ class
TEAE	Treatment emergent adverse event
TLG	Tables, listings, graphs

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 upon the Study Protocol (version 4.0 of 09Dec2024) and contains detailed description of the statistical methods described therein.

The SAP describes prospectively the analyses to be performed on study data. It was finalized before data base lock and unblinding.

1.1 Study Objectives

Primary Objective

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

Secondary Objectives

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

1.2 Study Design

This is a Phase IIb, multicenter, randomized, parallel group, double blind study comparing BF-200 ALA with two incubation times with vehicle. Each subject will receive either BF-200 ALA or vehicle treatment for inter-individual comparison. Subjects will be randomized at a ratio of 2:2:1:1 to BF-200 ALA (1 hour incubation), BF-200 ALA (3 hours incubation), vehicle (1 hour incubation), and vehicle (3 hours incubation). The study will be conducted in a double blind (with respect to vehicle) manner.

Multiple sites in the United States of America (US) will participate in this study. Each site should randomize between 12 and 24 subjects. No site should enroll more than 24 subjects unless prior approval of the Sponsor/CRO acting on behalf of Sponsor is obtained. The maximum number should not exceed 36 subjects.

The clinical study will consist of:

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

- Subjects who received a 3rd PDT will receive a 3rd phone call (PC-3) for safety assessment 1 week (± 2 days) after PDT-3, at which safety and tolerability assessments will be performed.
- PDT-3 will be followed by **Visit 5b** (4 weeks (± 1 week) after PDT-3) and **Visit 6** (8 weeks (± 1 week) after PDT-3) which will be the final visit for all subjects.

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

1.3 Sample Size Justification

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

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

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

This estimate was based on the following quantities and assumptions. The complete references for the cited literature (Pariser et al., Wiegell et al., and Hörfelt et al.) can be found in the study protocol.

Absolute change:

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

Percentage change:

- Percentage changes in active group in Pariser et al. is reported with -37% (after 4 PDTs), in Wiegell et al. with -68% (median values), in Hörfelt et al. -54% (median values). The standard deviation in the active group is reported being 40 in Pariser et al.
- Percentage changes in vehicle group in Pariser et al. is reported with -16% (after 4 PDTs), in Wiegell et al. with 0% (median values), in Hörfelt et al. with -20% (median values). The standard deviation in the vehicle group is reported being 54 in Pariser et al.

- Overall a maximum placebo effect of -20% can be expected. The active effect is assumed being 50%. An SD of 50 is assumed.

1.4 Randomization and Blinding

Randomization

Subjects will be randomized for treatment with PDT with either vehicle (control group) or BF-200 ALA (Ameluz®, test group) with respective incubation times of either 1 or 3 hours. A randomization ratio of 2:2:1:1 to BF-200 ALA (1 hour incubation), BF-200 ALA (3 hours incubation), vehicle (1 hour incubation), and vehicle (3 hours incubation) will be applied. Thus, the chance of receiving verum will be 66%. Randomization numbers will be blocked to facilitate attainment of a homogeneous distribution of treatment groups. The block size will not be revealed but a detailed description of the randomization including block size will be provided in a separate randomization plan (not provided to sites). The IMP is packed in tubes, each containing 2 g gel. A minimum of 12 to a maximum of 36 subjects should be randomized per study site but no site should randomize more than 24 subjects unless prior approval of the Sponsor/CRO acting on behalf of Sponsor is obtained.

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

Blinding

The randomization schedule and the allocation to treatment groups will not be known by the Sponsor/CRO acting on behalf of Sponsor until completion of the clinical study, except in case of an emergency. There is no apparent reason to break the randomization code in the event of an adverse drug reaction. Therefore, no immediate unblinding is foreseen during this study.

2 Statistical Analysis Sets

Set	Definition	Treatment used for analysis
Consented set	All subjects who provided informed consent.	Actual treatment
Randomized set	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). If IMP application is uncertain, the subject will be included in the SAF.	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 deviation (PD). PDs will be identified and classified for each subject during a blind data review meeting (BDRM) (see section 5.12). The following PDs 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 visit) • Other forbidden medication will be decided on a case-by-case basis • Meeting an exclusion criterion throughout the treatment period of the study • All other protocol deviations (including violation of timelines) will be handled on a case by case manner.	Actual treatment

The FAS will be considered the primary analysis set. It will be the analysis set applied to the evaluation of primary and secondary endpoints. The PPS will be used for supplementary analysis of the primary endpoints and may also be used for selected analysis of secondary endpoints.

The SAF will be the analysis set for all safety analyses except for pain during illumination, which will be analyzed for the FAS.

SAF, FAS, PPS, Consented set and Randomized set will be used for tables of subjects per visit as well as discontinuation. Corresponding listings will be presented for the Consented Set only.

Demographic data and other baseline covariates will be presented for SAF, FAS and PPS in tables, whereas only the Randomized Set will be used for corresponding listings (Consented Set for demographic listing and listing of Fitzpatrick skin type).

Medical history as well as medication will be presented for SAF.

3 Subgroup Analysis

The following subgroups will be considered for the co-primary endpoints:

- Subjects who did not switch any cleanser. This subgroup also includes subjects who used any cleanser at Screening/ Visit 1 and then later stopped using any cleanser, or vice versa.
- Subjects treated with vehicle 1 hour incubation time vs. 3 hours incubation time.

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

In addition, treatment-emergent adverse events (TEAEs) will be summarized for the SAF stratified by age group (16 to 17; 18 or older), sex and Fitzpatrick skin type at Baseline (I-III and IV-VI).

4 Efficacy and Safety Variables

4.1 Primary Efficacy Variable

The co-primary efficacy variables are:

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

4.2 Secondary Efficacy Variables

1. Absolute and/or percentage change from baseline in the number of lesions as assessed by investigator:
 - a. Inflammatory lesions - 4 weeks after the last PDT
 - b. Inflammatory lesions - 8 weeks after the last PDT
 - c. Non-inflammatory lesions - 4 weeks after the last PDT
 - d. Non-inflammatory lesions - 8 weeks after the last PDT
 - e. Inflammatory & non-inflammatory lesions - 4 weeks after the last PDT
 - f. Inflammatory & non-inflammatory lesions - 8 weeks after the last PDT
2. Absolute and percentage change from baseline in the number of lesions as assessed by investigator:
 - a. Inflammatory lesions - 4 weeks after PDT-1
 - b. Non-inflammatory lesions - 4 weeks after PDT-1
 - c. Inflammatory & non-inflammatory lesions - 4 weeks after PDT-1
 - d. Inflammatory lesions - 4 weeks after PDT-2
 - e. Non-inflammatory lesions - 4 weeks after PDT-2
 - f. Inflammatory & non-inflammatory lesions - 4 weeks after PDT-2
 - g. Inflammatory lesions - 4 weeks after PDT-3
 - h. Non-inflammatory lesions - 4 weeks after PDT-3
 - i. Inflammatory & non-inflammatory lesions - 4 weeks after PDT-3
 - j. Inflammatory lesions - 8 weeks after PDT-3
 - k. Non-inflammatory lesions - 8 weeks after PDT-3
 - l. Inflammatory & non-inflammatory lesions - 8 weeks after PDT-3
3. Absolute and percentage change from baseline in the number of lesions as assessed by investigator, only for responders at Visit 3 /4 weeks after PDT-1:
 - a. Inflammatory lesions - 4 weeks after PDT-1
 - b. Inflammatory lesions - 8 weeks after PDT-1
 - c. Non-Inflammatory lesions - 4 weeks after PDT-1
 - d. Non-Inflammatory lesions - 8 weeks after PDT-1
 - e. Inflammatory & non-inflammatory lesions - 4 weeks after PDT-1
 - f. Inflammatory & non-inflammatory lesions - 8 weeks after PDT-1
4. Absolute and percentage change from baseline in the number of lesions as assessed by investigator, only for responders at Visit 4b /4 weeks after PDT-2:
 - a. Inflammatory lesions - 4 weeks after PDT-2
 - b. Inflammatory lesions - 8 weeks after PDT-2
 - c. Non-Inflammatory lesions - 4 weeks after PDT-2
 - d. Non-Inflammatory lesions - 8 weeks after PDT-2
 - e. Inflammatory & non-inflammatory lesions - 4 weeks after PDT-2
 - f. Inflammatory & non-inflammatory lesions - 8 weeks after PDT-2
5. Absolute and percentage change from baseline in the number of lesions as assessed by investigator, only for responders at Visit 5b /4 weeks after PDT-3-:
 - a. Inflammatory lesions - 4 weeks after PDT-3
 - b. Inflammatory lesions - 8 weeks after PDT-3
 - c. Non-Inflammatory lesions - 4 weeks after PDT-3
 - d. Non-Inflammatory lesions - 8 weeks after PDT-3

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

4.3 Safety Variables

Safety analysis variables include:

- Frequency and severity of adverse events (AEs), serious AEs (SAEs), AEs of special interest (AESI) and treatment-emergent adverse events (TEAEs).
- Application site skin reactions assessed by the investigators.
- Application site discomfort reported by the subjects.
- Pain during illumination reported by the subjects (pain will be assessed on an 11-point numeric rating scale).
- Vital signs data
- Safety laboratory data
- Physical examinations data

4.4 Exploratory Variables

Exploratory analysis variables include:

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

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 ADaM dataset. Based on the ADaM datasets and the specification documents a define.xml will be created.

All subject data that are mapped to SDTM will be listed and statistically summarized as appropriate. For laboratory, vital sign, and physical examination assessments clinically significantly abnormal values will be listed additionally.

Data will be summarized by treatment group and overall. Treatment groups are 'BF-200 ALA (1 h incubation)', 'BF-200 ALA (3 h incubation)' and 'Vehicle'. This combined presentation of vehicle (1 h incubation) and vehicle (3 h incubation) is standard presentation. If separate presentation of vehicle is used for an analysis, it is stated explicitly below.

For qualitative variables, the number and percentage in each category will be calculated. Percentages will be presented to one decimal place. The calculation of percentages will be based on the number of non-missing values, if not stated otherwise. Missing values (including user-defined missing values as "not done", "unknown", "not applicable", "not documented") will not be presented and not be included in the calculation of percentages.

For quantitative variables, unless otherwise stated, the number of subjects, 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". Preliminary rounding of eCRF entries will not be performed, derived or standardized values will be rounded to a reasonable number of digits. Mean, median, SD, and quartiles will be presented with one decimal place 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 decimal places (i.e., 0.xxxx). In summary statistics tables the overall number of missing values will not be given.

Inferential assessments will be performed for the two co-primary endpoints, see section 5.6. Further secondary efficacy variables will be tested in an exploratory manner.

Subjects who withdraw from study participation before randomization or whose eligibility cannot be confirmed at Visit 2 will be considered as screening failures. The demographic data from screening failures are entered into the clinical database and will not be passed through the data cleaning process. Their data are listed separately from data of treated subjects.

Listings will always be sorted by treatment group and subject. If a different sorting order should be used for some listings, this will be remarked separately. The variables for the specific listings are explicitly given in the description of listings. All listings will be presented for the safety analysis set, if not stated differently. Indicator variables for further analysis sets, e.g. FAS, will be added for the subject disposition listing and selected listings only, where informative. Dates and times will be displayed in data listings using the format yyyy-mm-dd or yyyy-mm-ddThh:mm or hh:mm, respectively.

5.2 Specifications and Definitions

- ☐ Baseline is defined as the value measured at PDT-1/ Visit 2 (Baseline). If this value is missing, the last measurement taken before PDT-1/ Visit 2 (Baseline) will be considered as baseline value.
- ☐ Absolute change from Baseline at visit X is calculated as follows:
post-baseline value at visit X - Baseline value
- ☐ Percentage change from Baseline at visit X is calculated as follows:
(post-baseline value at visit X - baseline value) / baseline value
- ☐ Unscheduled visits will only be listed and not included in any tables except table "Subjects per visit".

- Calculation of a duration (length of time or time interval) is performed as follows:
stop (last observation) date - start (first observation) date + 1 day.
- To convert days to months the following rule will be applied: 1 month = 30.44 days
- To convert days to years the following rule will be applied: 1 year = 365.25 days
- Study day related to PDT-1, PDT-2, or PDT-3 is defined as given below. Please note that there is no study day 0.
if study date < PDT date, then study day = study date – PDT date;
if study date ≥ PDT date, then study day = study date – PDT date + 1 day
- Visit terminology:

Notation used in the protocol	Notation used for tables, listings and graphs
Screening/ Visit 1 (≤ 6 weeks prior to PDT-1)	Screening
PDT-1/ Visit 2 (Baseline)	Baseline/PDT-1
	Baseline ¹
Phone call 1 (1 week ± 2 days post PDT-1)	1 week post PDT-1
Visit 3 (4 weeks ± 1 week post PDT-1) or PDT-2/ Visit 3 (4 weeks ± 1 week post PDT-1)	4 weeks post PDT-1/PDT-2
Visit 4a (8 weeks ± 1 week post PDT-1)	8 weeks post PDT-1
Phone call 2 (1 week ± 2 days post PDT-2)	1 week post PDT-2
Visit 4b (4 weeks ± 1 week post PDT-2) or PDT-3/ Visit 4b (4 weeks ± 1 week post PDT-2)	4 weeks post PDT-2/PDT-3
Visit 5a (8 weeks ± 1 week post PDT-2)	8 weeks post PDT-2
Phone call 3 (1 week ± 2 days post PDT-3)	1 week post PDT-3
Visit 5b (4 weeks ± 1 week post PDT-3)	4 weeks post PDT-3
Visit 6 (8 weeks ± 1 week post-PDT-3)	8 weeks post PDT-3 ²
	4 weeks after last PDT ³
	8 weeks after last PDT ⁴

¹ This artificial visit called 'Baseline' will be used in tables only (except for Table 1.1.2: Subjects per Visit).

² Data collected at Visit 6 as premature termination visit will only be included in listings.

³ Visit 3 will be used for responders after PDT-1, Visit 4b will be used for responders after PDT-2, and Visit 5b will be used for all subjects that underwent PDT-3.

⁴ Visit 4a will be used for responders after PDT-1, Visit 5a will be used for responders after PDT-2, and Visit 6 will be used for all subjects that underwent PDT-3.

- Terminology for treatment groups:

Notation used in the protocol	Notation used for tables, listings and graphs
BF-200 ALA (1 h incubation)	1h BF-200 ALA
BF-200 ALA (3 h incubation)	3h BF-200 ALA
Vehicle (1 h incubation) or Vehicle (3 h incubation)	Vehicle*
Vehicle (1 h incubation)	Vehicle 1h *
Vehicle (3 h incubation)	Vehicle 3h *
* Combined presentation of vehicle (1 h incubation) and vehicle (3 h incubation) is standard presentation. Separate presentation only used for supplementary analysis (stated explicitly).	

5.3 Disposition of Subjects and Analysis Sets

The number and relative frequencies of subjects in each analysis set such as the consented set, the randomized set, the SAF, the FAS, and the PPS will be presented overall, by treatment (1h incubation time BF-200 ALA, 3h incubation time BF-200 ALA, vehicle, vehicle 1h and vehicle 3h) and study site.

Subjects per visit as well as inclusion and exclusion criteria will be presented overall and by treatment.

Premature discontinuation from the study and completion of the study will be summarized as well as the reasons for discontinuation.

5.4 Demographics and Other Covariates

5.4.1 Demographic Data

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

Demographic data (sex, age at inclusion, age categories (16-17, ≥18 years), race, ethnicity), body weight [kg] as well as skin type assessment at Baseline using Fitzpatrick skin type scale (I to VI) and category (I-III / IV-VI) will be tabulated by treatment (1h incubation time BF-200 ALA, 3h incubation time BF-200 ALA, vehicle, vehicle 1h and vehicle 3h).

A summary table for body weight will be displayed. Body height will be listed only.

5.4.2 Prior and Concomitant Medical Conditions

Prior and concomitant medical conditions (medical history) entries will not be coded and will be listed only.

5.4.3 Prior and Concomitant Medication

Any medication/treatment taken by a subject at study or treatments the subject is undergoing at the time of study entry or throughout the study that are not related to any study-specific procedures (PDT with IMP) are considered concomitant medications or treatments. All medications or treatments continuing or with stop date after or at date of written informed consent are regarded as concomitant.

Medications will be coded by WHO-Drug Global. Medications with stop date before date of written informed consent are regarded as prior medication.

To assign a medication to be prior/previous or concomitant, the following rules will be applied to impute incomplete end dates (imputed dates will not be displayed in listings):

yyyy	mm	dd	Imputation
available	available	missing	last day of yyyy-mm
available	missing	missing	yyyy-12-31
missing	missing	missing	no imputation

If the allocation to prior or concomitant is still unclear, medications/treatments will be assumed to be concomitant.

Concomitant medication will be tabulated separately by Anatomic Group (Anatomical therapeutic chemical classification [ATC] level 2), ATC level 3, and preferred name. Prior medication will only be listed.

5.5 Exposure

For analysis of exposure, the following treatment groups will be displayed: 1h incubation time BF-200 ALA, 3h incubation time BF-200 ALA, vehicle 1h, vehicle 3h, and vehicle (both incubation times combined).

The number and relative frequency of subjects treated and re-treated with PDT will be presented by treatment group, side of the face and visit. PDT details as documented in the eCRF (duration of incubation [min], duration of illumination [min], number of interruptions) will be tabulated by treatment group, side of the face and visit.

5.6 Efficacy Analysis

5.6.1 Estimands

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

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

The following possible intercurrent events are considered:

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

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

Co-primary estimand I is defined by:

- **Population:** The population targeted by the clinical questions will be represented by the entire trial population defined through inclusion / exclusion criteria (FAS). The target population of this trial are subjects suffering from moderate to severe acne. As severity increase among others with pubertal age and lasts until adulthood, subjects of 16 years of age will be included (Heng and Chew, 2020; Note: The complete reference for the cited literature can be found in the study protocol). A minimum of 20 inflammatory and 20 non-inflammatory lesions are required per subject to enable a profound assessment. No further demographic factors influencing acne development are considered.
- **Variable:** Continuous response variable defined as the percent change from Baseline in number of inflammatory lesions 8 weeks after the last PDT.
- **Intercurrent event:** The occurrence of all intercurrent events will be handled using the treatment-policy strategy. All values will be used regardless of occurrence of the above mentioned intercurrent events prior 8 weeks after the last PDT. Before data base lock the occurrence of any other, not pre-defined intercurrent event will be reviewed.
- **Population-level summary:** The median of percent changes from Baseline in number of inflammatory lesions 8 weeks after the last PDT will be calculated for the treatment groups. BF-200 ALA, 1h or 3h incubation will be compared to vehicle (all subjects treated with vehicle independent from incubation time) using the difference in median values. Two one-sided Wilcoxon rank-sum tests will be applied to test on superiority of BF-200 ALA vs vehicle. An estimate of the location shift will additionally be used to quantify the treatment effect.

Co-primary estimand II is defined by:

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

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

The estimands target to estimate the effect of initiating the treatment regimen in the population of interest and compares the benefit of the initially randomized treatments as they are taken. As the treatment policy strategy is used for all types of intercurrent events, all available data will be used for the co-primary estimands, regardless of the use of medications with immunomodulating properties, the use or change of cleansers and soaps, refusal of 2nd or 3rd PDT treatment due to pain, any other type of treatment discontinuation, or postponement of 2nd or 3rd PDT treatment.

The co-primary estimands are based on clinical assessments 8 weeks after the last PDT. If a subject dropped out before the planned visit 8 weeks after the last PDT, or the variable value on this is missing, the results based on the last available visit before the planned visit 8 weeks after last PDT with a non-missing variable value will be used for the primary analysis (see section 5.11).

5.6.2 General Efficacy Analysis Considerations

All primary and secondary parameters will be analyzed using descriptive methods.

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

If a subject with at least one assessment after first PDT dropped out before the planned visit 8 weeks after the last PDT, or the variable value on this is missing, the results based on the last available visit before the planned visit 8 weeks after last PDT with a non-missing variable value will be used for the primary analysis (last observation carried forward) (see also section 5.11).

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

Further secondary efficacy variables will be tested, but the results of these statistical tests will be considered exploratory.

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

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

5.6.3 Analysis of Co-Primary Efficacy Variables

The co-primary efficacy variables will be tested for the following hypotheses. For method of replacement of missing value please see section 5.11.

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

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

Improvement of mIGA:

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

The percentage change from Baseline in the number of inflammatory lesions as assessed by investigator will be described with summary statistics per visit for the FAS and will be repeated as supplementary analysis for the PPS.

The improvement of mIGA (success/ no success) will be tabulated per visit for the FAS and will be repeated as supplementary analysis for the PPS.

Additionally, a supplementary analysis will only include subjects who did not switch any cleanser. As further supplementary analysis, the co-primary efficacy endpoints will be displayed separately for subjects treated with vehicle 1 hour incubation time vs. 3 hours incubation time. Moreover, supplementary analyses are performed for the subgroups as described in section 3.

Please refer to section 5.6.2 for the pairwise comparisons and the hierarchical testing procedure.

5.6.4 Analysis of Secondary Efficacy Variables

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

Secondary efficacy endpoints 1 and 7 will be tested, but the results of these statistical tests will be considered exploratory as described in section 5.6.2. These secondary efficacy endpoints will additionally be analyzed for the PPS.

1. The absolute and/or percentage change from Baseline in the number of inflammatory lesions as assessed by investigator will be described with summary statistics per visit (4 and 8 weeks after the last PDT). The table will be repeated twice: for the number of non-inflammatory and for the number of inflammatory & non-inflammatory lesions.
2. The absolute and percentage change from Baseline in the number of inflammatory lesions as assessed by the investigator will be described with summary statistics per visit (4 weeks after PDT-1, 4 weeks after PDT-2, 4 weeks after PDT-3, and 8 weeks after PDT-3). The table will be repeated twice: for the number of non-inflammatory lesions and for the number of inflammatory & non-inflammatory lesions.
3. The absolute and percentage change from Baseline in the number of inflammatory lesions as assessed by investigator will be described with summary statistics per visit (4 and 8 weeks after PDT-1) for the subgroup of subjects who are responders at Visit 3 /4 weeks after PDT-1 (subjects receiving only 1 PDT). The table will be repeated twice: for the number of non-inflammatory lesions and for the number of inflammatory & non-inflammatory lesions.
4. The absolute and percentage change from Baseline in the number of inflammatory lesions as assessed by investigator will be described with summary statistics per visit (4 and 8 weeks after PDT-2) for the subgroup of subjects who are responders at Visit 4b /4 weeks after PDT-2 (subjects receiving 2 PDTs). The table will be repeated twice: for the number of non-inflammatory lesions and for the number of inflammatory & non-inflammatory lesions.
5. The absolute and percentage change from Baseline in the number of inflammatory lesions as assessed by investigator will be described with summary statistics per visit (4 and 8 weeks after the 3rd PDT) for the subgroup of subjects who are responders at Visit 5b /4 weeks after PDT-3 (subjects receiving 3 PDTs). The table will be repeated twice: for the number of non-inflammatory lesions and for the number of inflammatory & non-inflammatory lesions.
6. The absolute and percentage change from Baseline in the number of nodules & cysts 8 weeks after last PDT assessed by investigator will be described with summary statistics.
7. The improvement of IGA by at least 2 (success/ no success) assessed by the investigator will be tabulated 8 weeks after last PDT.
8. The improvement of IGA (assessed by investigator) will be tabulated 8 weeks after the last PDT.
9. The improvement of mIGA (assessed by investigator) will be tabulated 8 weeks after the last PDT.
10. Improvement of scar severity and overall esthetic appearance assessed by investigator will be tabulated 8 weeks after last PDT.
11. Subjects' satisfaction regarding esthetic outcome (0 = very good to 3 = unsatisfactory) and subjects' satisfaction with treatment (yes/no) will be tabulated 8 weeks after last PDT.

5.6.5 Analysis of Exploratory Variables

The analyses on exploratory efficacy endpoints will be performed on the FAS. Exploratory endpoint 4 will additionally be analyzed for the PPS and will be tested.

1. The absolute and percentage change from Baseline in the number of inflammatory lesions as assessed by the Canfield algorithm will be described with summary statistics per visit (4 and 8 weeks after last PDT). The table will be repeated twice: for the number of non-inflammatory lesions and for the number of inflammatory & non-inflammatory lesions.
2. Treatment success defined by a minimum improvement of the PAS (success/ no success) equivalent to an improvement of IGA by at least 2, assessed by the Canfield algorithm will be tabulated 8 weeks after last PDT.
3. Treatment success defined by a minimum improvement of mPAS (success/ no success) equivalent to an improvement of mIGA by at least 2, assessed by the Canfield algorithm will be tabulated 8 weeks after last PDT.
4. The improvement of mIGA by at least 2 (success/ no success) assessed by the investigator will be tabulated 8 weeks after last PDT.

5.7 Safety Analysis

All parameters as described within this section will be analyzed for the SAF.

5.7.1 Adverse Events

AEs will be coded by using the medical Dictionary for Regulatory Activities (MedDRA).

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

1. all AEs
2. serious AEs
3. AESIs
4. TEAEs
5. serious TEAEs
6. non-serious TEAEs
7. TEAEs leading to death
8. Related TEAEs to IMP
9. Related TEAEs to IMD
10. Related TEAEs to IMP and/or IMD
11. TEAEs resulting in discontinuation of study

Treatment emergent adverse events (TEAEs) are defined as all AEs with onset on or after first treatment with randomized IMP up to study termination of the subject.

To assign an AE to be treatment-emergent, the following rules will be applied to impute incomplete start dates:

yyyy	mm	dd	Imputation
available and = year of treatment start	available and = month of treatment start	missing	treatment start date
available and = year of treatment start	available and ≠ month of treatment start	missing	yyyy-mm-01
available and ≠ year of treatment start	available	missing	yyyy-mm-01

yyyy	mm	dd	Imputation
available and = year of treatment start	missing	missing	treatment start date
available and ≠ year of treatment start	missing	missing	yyyy-01-01
missing	missing	missing	no imputation

Imputed start date will be compared to recorded end date. If imputed start date is after end date, imputed start date will be replaced by end date. If imputation of end dates is necessary (if AE start date is completely missing) the following rules will be applied to impute incomplete end dates:

yyyy	mm	dd	Imputation
available	available	missing	last day of yyyy-mm
available	missing	missing	yyyy-12-31
missing	missing	missing	no imputation

If allocation is still unclear AEs will be assumed to be TEAEs.

An AE is considered related (to IMP or IMD or both, separately), if the relationship is assessed as "definitely related", "probably related" or "possibly related", and as not related, if the relationship is assessed as "unrelated" or "unlikely related". An AE with missing relationship is considered "related".

AEs, serious AEs (SAEs), AESI (as ticked within the eCRF by the investigator) and TEAEs (as well as serious and non-serious TEAEs) will be summarized and tabulated according to primary system organ class (SOC) and preferred term (PT) displaying the number of events as well as number and percentages of affected subjects per treatment arm. Moreover, related TEAEs to IMP, related TEAEs to IMD, and related TEAEs to IMP and/or IMD will be summarized the same way, but stratified by severity. Related severe TEAEs will also be summarized. In addition, TEAEs will be summarized the same way, but stratified by age group (16 to 17; 18 or older), sex and Fitzpatrick skin type at Baseline (I-III and IV-VI).

5.7.2 Vital Signs

Blood pressure (systolic and diastolic) and heart rate will be analyzed descriptively.

Absolute values as well as absolute and percentage changes from Baseline to post-baseline visits will be tabulated descriptively.

A listing of all vital sign values and as well as a listing including only clinically significant abnormal vital sign values will be presented.

5.7.3 Laboratory Parameters

Laboratory parameters include clinical chemistry parameters, hematology parameters as well as urinalysis parameters.

Laboratory findings will be summarized using frequency tables showing clinically significant findings for all numeric laboratory parameters by visit.

A listing including clinically significant abnormal laboratory values will be presented separately.

5.7.4 Pregnancy Test

The result of the pregnancy tests (serum and urine) will be listed for female subjects with reproductive potential.

5.7.5 Physical Examination

Physical examination will be summarized using frequency tables showing clinically significant findings for all body systems by visit.

A listing including only clinically significant abnormal examinations will be presented.

5.7.6 Analysis of Further Safety Variables

Application site skin reactions assessed by the investigators

The frequency of local skin reactions for each category (erosion, erythema, exfoliation, oedema, fissure, induration, vesicles, ulceration, flaking, scabbing, discharge, other) will be presented by illumination area. Only local skin reactions with a start time during illumination will be tabulated. If an AE has started from the beginning of the illumination of the corresponding illumination (same area) up to and including the end of the illumination (same area), then the start of the AE is counted as 'Start during illumination'. If the start time of the AE is missing, the corresponding checkbox of the eCRF 'Start during illumination' will be used for the derivation. In addition, the frequency of local skin reactions for each category will be presented by maximum severity over both illumination areas.

Application site discomfort reported by subjects

The frequency of local discomfort for each category (burning, hyperaesthesia, pain, paraesthesia, pruritus, stinging, warmth, other) will be presented by illumination area. Only local discomfort with a start time during illumination will be tabulated. If an AE has started from the beginning of the illumination of the corresponding illumination (same area) up to and including the end of the illumination (same area), then the start of the AE is counted as 'Start during illumination'. If the start time of the AE is missing, the corresponding checkbox of the eCRF 'Start during illumination' will be used for the derivation. In addition, the frequency of local discomfort for each category will be presented by maximum severity over both illumination areas.

Pain during illumination by the subjects

Pain during illumination will be summarized for subjects of the FAS.

Pain will be assessed on a 11-point numeric rating scale. Summary statistics will be presented for the rating scale by illumination area and visit. The summary table will also be presented overall (i.e. without stratification by illumination area) presenting the maximum pain intensity (rating scale) per visit.

Pain relieving measures taken will be summarized.

5.8 Analysis of Further Variables

Information about the use of facial care products and the change of facial care products during the study will be tabulated as appropriate.

5.9 Protocol deviations

Protocol deviations (PDs) as classified during the (B)DRMs (Section 5.12) will be tabulated and listed.

5.10 Interim Analysis

No formal interim analysis will be performed.

5.11 Missing Values

Co-primary endpoints are based on:

- a. Change from Baseline in number of inflammatory lesions as assessed by investigator
- b. Treatment success defined by an improvement of the mIGA score 8 weeks after the last PDT (combined assessment)

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

Missing data of safety variables will not be replaced.

Incomplete (only partially missing) start and end dates will be imputed for classification to prior and concomitant medication and TEAEs (see section 5.4.3 and 5.7.1 for detailed description). In listings, dates will be presented as recorded.

5.12 Data Base Closure and Data Review

A data base closure will be performed before the analysis. All parameters 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 before 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 [L1.1.1 including number of violated criteria, L2.1, L2.3, L2.4, and L4.1.1]
- ☐ Any noncompliance to study therapy, including incubation period, distance of the lamp, and illumination time [L3.1 and L3.2]
- ☐ Use of forbidden medication [L2.4]
- ☐ Premature discontinuation during the study [L1.2.1]
- ☐ Missing primary efficacy variables [L4.1.1, L4.1.2]
- ☐ Incorrect allocation to treatment group
- ☐ Unblinding within the conduct of the study [L1.1.2]

These evaluations and assessments will be done together and in agreement with the CRO acting on behalf of Sponsor, but FGK will provide the CRO acting on behalf of Sponsor with the appropriate subject listings (as defined in Appendix A). Data review can be done via a telephone conference or in writing.

The assignment of subjects to the analysis sets will be done before 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 assignment of subjects to the treatment groups will be done after unblinding.

5.13 Miscellaneous

All data collected will be presented in subject data listings. Data collected only for data management purposes will not be listed.

A detailed description of the planned tables, listings and graphs 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 and/or quantitative variables (except for shift tables):

<Actual/Planned> Treatment					
		1h BF-200 ALA (N=x)	3h BF-200 ALA (N=x)	Vehicle (N=x)	Total (N=xx)
Qualitative variable	n	x	x	x	xx
Value x	n (%)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
Value y	n (%)	x (x.x)	x (x.x)	x (x.x)	x (x.x)
Quantitative variable [unit]	n	x	x	x	x
	Mean (SD)	x.x (x.x)	x.x (x.x)	x.x (x.x)	x.x (x.x)
	Median	x.x	x.x	x.x	x.x
	Q ₁ , Q ₃	x.x, x.x	x.x, x.x	x.x, x.x	x.x, x.x
	Min, Max	x, x	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 tables, listings, and graphs:

ALA-ACV-CT014

Page # of #

Final analysis

Table/Listing/Graph <x.x>
<Title of table/listing/graph>
<Analysis set>

The numbering x.x of the tables/listings/graphs will be stated in the detailed description (Appendix A). Slight deviations from the description in Appendix A are possible in the tables/listings/graphs but all information as displayed will be included.

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)>

All tables, listings, and graphs 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 following variable has been added to exploratory variables: "The improvement of mIGA by at least 2 (success/ no success) assessed by the investigator will be tabulated 8 weeks after last PDT.
- TEAE definition was slightly adapted to include also AEs recorded after last visit of a patient as TEAE in the analysis.

7 Signatures

Statistician:	
PPD	
FGK Clinical Research GmbH Heimeranstr. 35 80339 München Germany	
_____	_____
Date (ddmmmyyyy)	Signature

CRO acting on behalf of Sponsor:	
PPD	
Biotrontera Discovery GmbH Project Manager ALA-ACV-CT014 Hemmelrather Weg 201 51377 Leverkusen Germany	
_____	_____
Date (ddmmmyyyy)	Signature