# Statistical Analysis Plan

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| Title: | Prospective, evaluator-blind, multicenter study to assess the safety and effectiveness of treatment with the Octave System for improving lines and wrinkles of the décolleté |
| Merz Study Number: | M960101003 / NCT04681352 |
| SAP for | Final Analysis |
| Sponsor: | Ulthera, Inc., a division of Merz North America, Inc. /Merz Aesthetics |
| Version: | 2.0 |
| Date: | 27-Apr-2022 |
| Author: | PPD, Biostatistician, PPD<br>PPD |

## SIGNATURE PAGE

I confirm that this Statistical Analysis Plan accurately describes the planned statistical analyses to the best of my knowledge and was finalized before database close.

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# List of Abbreviations

| | |
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| AE | Adverse event |
| ATC | Anatomical Therapeutic Chemical classification system of the World Health Organization |
| BMI | Body mass index |
| CI | Confidence interval |
| COVID-19 | Coronavirus disease 2019 |
| CRO | Contract Research Organization |
| CCI | [redacted] |
| DRM | Data Review Meeting |
| FST | Fitzpatrick skin type |
| CCI | [redacted] |
| ITT | Intent to treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N | Number of non-missing observations |
| PP | Per Protocol |
| PROC MI | SAS multiple imputation procedure |
| PT | Preferred term |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAS | Statistical Analysis System® |
| SD | Standard deviation |
| CCI | [redacted] |
| SOC | System organ class |
| SP | Safety population |
| SSQ | Subject Satisfaction Questionnaire |
| TEAE | Treatment Emergent Adverse Event |
| TESAE | Treatment-emergent serious adverse event |
| TFL | Tables, Figures, Listings |

# 1 General and Technical Aspects

The objective of this statistical analysis plan (SAP) is to specify the final statistical analyses with appropriate detail and precision to serve as a guideline for statistical programming and creation of tables, figures, and listings for clinical study protocol M960101003, dated 22-Jul-2021, version 5.0 (Amendment 4).

All programs will be written using SAS version 9.4 or higher. A preferred font size of 9 points, minimum font size of 8 points with a unique font size for the whole document required will be used for the tables and figures in Section 14. For listings, a standard font size of 9 points above will be used to produce the output in A4 format. Individual SAS programs will be written for all tables, figures, and listings. All outputs will be transferred into PDF files. These PDF files will be generated as needed to populate the subsections of Section 14 and Section 16.2 for the clinical study report. Each output file will include the corresponding table of contents, preceding the content of the file.

The Merz standard Tables, Figures, and Listings (TFLs) for medical devices, version 2.0, dated 18-Feb-2020, will be applied and adapted to study specific requirements as laid down in the clinical study protocol and any amendments. These mock TFLs will serve as study-specific output specifications for statistical programming.

Special attention will be paid to planning and performance of quality control measures. Risk scores based on assessments of complexity and impact of errors and quality control measures for statistical programming (including analysis datasets and TFLs) will be documented in the quality control plan for the creation of statistical output.

# 2 Clinical Trial Design and Objectives

## 2.1 Clinical Study Design

This is a 180-day, prospective, evaluator-blind, multicenter, staged, confirmatory study designed to evaluate the safety and effectiveness of the Octave System for improving lines and wrinkles of the décolleté. Approximately 90 subjects will be enrolled at up to ten investigational sites in the United States. All Fitzpatrick skin types (FST) will be eligible for study enrollment. It is estimated that approximately 90% of the total sample size will consist of subjects with FST I, II, or III, and approximately 10% of subjects will be FST IV, V, or VI. Subjects enrolled will be healthy females, aged 35 to 65 years at the time of screening, with moderate to severe fine lines, wrinkles, laxity, and crepiness of the décolleté that is amenable to improvement with non-invasive intervention and is not severe enough for surgical intervention.

In this non-comparative, staged, confirmatory study, investigators and subjects will not be blinded to treatment, subjects will not be randomized, and all enrolled subjects will receive a single Octave-Ultherapy treatment of the décolleté tissue with two transducers at energy level 4 [redacted] and one transducer at energy level 3 [redacted] In Stage 1, an initial cohort of subjects will be enrolled, safety data will be assessed up to Week 2, and subjects will participate until Stage 1 study end at Day 90. In Stage 2, all enrolled subjects will be followed for 90 days or 180 days if reconsented for extended participation. In addition, to reduce potential bias associated with using only treated-subject photographs for evaluation, photographs of approximately 30 untreated individuals, who meet selected appearance criteria, will be collected at two different time points and subsequently paired for evaluation by the independent, blinded evaluators. Using this 3:1 ratio of treated subjects to untreated individuals, image sets of these untreated individuals will be randomly distributed among the pre- and post-treatment image sets of the treated subjects and presented to the blinded evaluators. For the primary effectiveness endpoint, the “baseline” photograph will be identified as “Photograph 1”, and the independent evaluators will be blinded

to the randomly distributed treated versus untreated status of the comparator Photograph 2 (i.e., Day 90 post-treatment among treated subjects or post-baseline for untreated individuals). The same photographic assessment will be used for the secondary effectiveness endpoint with the comparator Photograph 2 collected at Day 180 post-treatment.

Study subjects will have approximately 4 in-office study visits, including screening, baseline/treatment, a Day 90 (± 7 days) post-treatment visit, and a Day 180 (± 14 days) post-treatment visit. Up to five follow-up telephone calls will occur at 3 days (± 1 day), 14 days (± 3 days), 28 days (+ 3 days), 120 days (± 7 days), and 150 days (± 7 days) after Octave-Ultherapy treatment. The primary effectiveness endpoint, the proportion of treated subjects with improvement in lines and wrinkles of the décolleté, will be evaluated using a blinded, independent assessment of photographs at post-treatment Day 90 compared to baseline. Improvement is concluded if at least two of three independent, blinded evaluators assess the Day 90 standardized, photographic images as improved compared to baseline photographic images.

Standard safety evaluations, including the incidence of adverse events (AEs) and serious adverse events (SAEs), will be assessed.

### 2.2 Clinical Study Objectives

The objective of this study is to demonstrate the safety and effectiveness of the Octave System for improving lines and wrinkles of the décolleté.

## 3 Determination of Sample Size

A responder rate of 70% is assumed for the proportion of subjects with improvement from baseline to Day 90, as defined by the correct selection of the Day 90 standardized, photographic images by two of three independent, blinded evaluators. Monte-Carlo simulations were conducted to obtain sample sizes of evaluable subjects required to achieve an improvement rate of ≥ 65% and lower bound of 1-sided 95% confidence interval (CI) above 50%. To achieve this threshold with ≥ 85% power, a sample size of 80 evaluable subjects will be required. Assuming a maximum attrition of 10 subjects, approximately 90 subjects will be enrolled. In Stage 1, 10 subjects will be enrolled, while all other subjects will be enrolled in Stage 2. Because a sample size of 80 subjects who complete the full Ultherapy treatment session is required, study enrollment will continue until the required number of treated subjects is achieved.

## 4 Analysis Sets

The following analysis sets will be defined for the statistical analysis of this clinical study:

### 4.1 Safety Population (SP)

The Safety Population (SP) includes all subjects who are enrolled and are treated with the Octave System.

### 4.2 Intent-to-Treat (ITT) Population

The Intent-to-Treat (ITT) population consists of all subjects who are enrolled.

### 4.3 Per Protocol (PP) Population

The Per Protocol (PP) population consists of all subjects in the ITT population who complete the full Ultherapy treatment session using the Octave System and do not have a major protocol violation. Major protocol deviations will be defined during the Data Review Meeting (DRM).

# 5 Endpoints for Analysis

## 5.1 Effectiveness Endpoints

The effectiveness of the Octave System to improve lines and wrinkles of the décolleté will be evaluated using several methods, including qualitative assessment of photographs by three blinded evaluators.

### 5.1.1 Primary Effectiveness Endpoint

The primary endpoint of the study is the proportion of treated subjects with improvement in lines and wrinkles of the décolleté by comparing photographs taken at Day 90 (post-treatment) with baseline (pre-treatment) photographs. If the subject's screening photograph (Visit 1) is deemed acceptable upon review by the central photography vendor, it will default to the baseline (pre-treatment) photograph and will be used for reference throughout the study.

- Improvement is concluded if at least two of three independent, blinded evaluators assess the Day 90 standardized, photographic images as improved compared to baseline photographic images.
- The success criterion is defined by achieving simultaneously a point estimate ≥ 65% and a lower bound of the one-sided 95% Wilson confidence interval > 50% for the proportion of treated subjects with improvement.

### 5.1.2 Secondary Effectiveness Endpoint

- Proportion of treated subjects with improvement in lines and wrinkles of the décolleté by comparing photographs taken at Day 180 (post-treatment) with baseline (pre-treatment) photographs.

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## 5.2 Safety Endpoints

### 5.2.1 Secondary Safety Endpoint

Incidence of treatment-emergent adverse events (TEAEs) related to Octave-Ultherapy treatment, as reported throughout the study.

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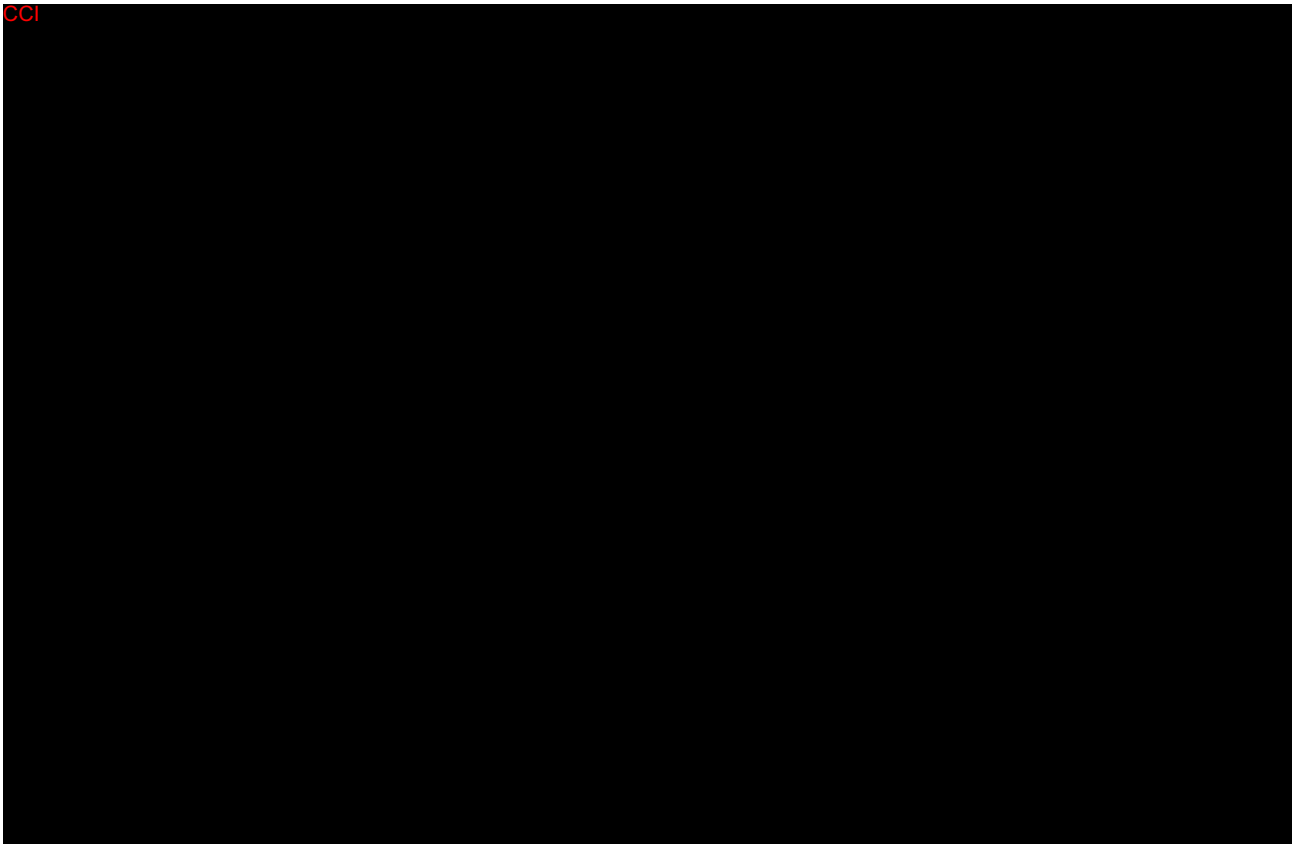

# 6 Statistical Analysis Methods

Adequate descriptive statistics will be provided for each effectiveness and safety evaluation. Continuous variables (values and changes from baseline) will be summarized by number of observed values (n obs), number of missing values (n miss), number of imputed values (n imp, where applicable), mean, standard deviation, median, quartiles, minimum and maximum (i.e., metric statistics). Mean, quartiles, and median will be reported to one decimal place more than the data were collected, for the standard deviation two decimal places more will be displayed; for derived data, the number of decimal places will explicitly be given in the sections below.

Categorical variables will be summarized by frequencies and percentages (n, %) per category where the denominator will be chosen according to the adequate analysis population (i.e., frequency statistics). Frequency tables will include the number of missing values. Percentages will be calculated using the denominator of all subjects in a specified population. Percentages will be calculated using the number of subjects with non-missing data at the corresponding visit as denominator (observed cases). The denominator will be specified in a footnote to the tables for clarification if not otherwise obvious. Percentages will be reported to one decimal place.

Ordered categorical data will be summarized by quantitative and frequency statistics.

Shift tables, confidence limits (95%, two-sided), and descriptive p-values, where appropriate will be given, where appropriate.

Due to the COVID-19 pandemic outbreak, onsite visits might not be performed or only performed as virtual contact. In such cases, quantitative evaluations/assessments will not be performed.

## 6.1 Effectiveness Endpoints

Unless otherwise specified, all effectiveness endpoints will be summarized for the ITT population.

### 6.1.1 Primary Effectiveness Endpoints

#### 6.1.1.1 Primary analysis

The primary endpoint of the study is the proportion of treated subjects with improvement in lines and wrinkles of the décolleté by comparing photographs taken at Day 90 (post-treatment) with baseline (pre-treatment) photographs.

Each independent evaluator will assess "Improvement" or "No Improvement" between Photograph 1 (baseline) and Photograph 2 (post-baseline). Photograph 1 will be identified, and the independent evaluators will be blinded to the random distribution of treated versus untreated status of the comparator Photograph 2 (i.e., Day 90 post-treatment among treated subjects or post-baseline for untreated individuals). If photographs are declared as not assessable during the Day 90 assessment session, the evaluators will be instructed to rate the corresponding Photograph 2 as "No Improvement".

Improvement will be declared if at least two blinded evaluators indicate "Improvement" for the comparator photograph. In case at least two evaluators declare a photograph as not assessable, the corresponding improvement score over all evaluators will be set to missing for the primary analysis.

The point estimate for the proportion of subjects fulfilling the primary endpoint will be described by frequency statistics for the ITT subset.

Effectiveness is established if:

A. the point estimate is ≥ 65% and

B. the lower bound of the one-sided 95% Wilson CI is > 50%.

Missing data, including a missing primary endpoint assessment in subjects with unacceptable or missing photographs at baseline or Day 90, will be imputed by multiple imputation. In case of complete data, no multiple imputation will be performed and the primary analysis is based on complete data for the ITT.

Imputation is done 50 times using a fully conditional specification logistic regression method, as implemented in SAS PROC MI with statement FCS LOGISTIC, and will use the investigational site and the baseline characteristics age and BMI as independent variables.

In a first step a total of m=50 imputed datasets will be generated, where missing data in the primary endpoint (improvement over all evaluators) is modelled via logistic regression based on input variables site, age and BMI at baseline. CCI [redacted]

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CCI [redacted] response is coded as (0=no response ("no improvement"), 1=response ("improvement")). The two-sided 90% Wilson CI ([WL, WU]) will be calculated using the following steps, as detailed in [1]:

1. The mean sample response $\hat{p}_{Imp}$ and sample variance $\widehat{U}_{Imp}$,

$$\widehat{U}_{Imp} = \frac{\hat{p}_{Imp}\,(1-\hat{p}_{Imp})}{n},$$

will be calculated for each of the $m=50$ imputed datasets with sample size $n$.

2. The overall mean $\bar{p}_m$ and variance $\overline{U}_m$ over all imputed datasets will be calculated:

$$\bar{p}_m = \frac{1}{m}\sum_{Imp=1}^{m} \hat{p}_{Imp},$$

$$\bar{U}_m = \frac{1}{m}\sum_{Imp=1}^{m} \hat{U}_{Imp}.$$

These will be used to obtain $B_m$,

$$B_m = \frac{1}{m-1}\sum_{Imp=1}^{m} (\hat{p}_{Imp} - \bar{p}_m)^2,$$

the between-sample variance.

3. The two boundaries of the 90% Wilson CI (WL and WU) will be calculated as

$$\left[ \frac{2\bar{p}_m + \frac{t^2}{n} + \frac{t^2 r_m}{n}}{2\left(1 + \frac{t^2}{n} + \frac{t^2 r_m}{n}\right)} \pm \sqrt{\frac{\left(2\bar{p}_m + \frac{t^2}{n} + \frac{t^2 r_m}{n}\right)^2}{4\left(1 + \frac{t^2}{n} + \frac{t^2 r_m}{n}\right)^2} - \frac{\bar{p}_m{}^2}{1 + \frac{t^2}{n} + \frac{t^2 r_m}{n}}} \right],$$

where $t$ denotes the 0.95 quantile of the t-distribution with degrees of freedom $v$,

$$v = (m-1)\left(1 + \frac{1}{r_m}\right),$$

and with

$$r_m = \left(1 + \frac{1}{m}\right)\frac{B_m}{\bar{U}_m}.$$

4. The study is considered successful, and consequently effectiveness is established, if the parameter estimate $\bar{p}_m \geq 65\%$ (condition A), and the lower limit of the 90% Wilson CI as given above, which is equivalent to the lower limit of a one-sided 95% Wilson CI exceeds the margin of 50% (condition B).

#### 6.1.1.2 Sensitivity analyses

To assess sensitivity of the results, the primary analysis will be repeated for:

- PP population with observed cases,
- ITT with observed cases, and
- ITT with missing value treated as no improvement (worst case analysis).

Observed cases are those not missing on primary analysis.

Additionally, further sensitivity analyses will be performed with regard to image quality as assessed by the central photography vendor. The following analyses will be performed, treating assessments that are based on photographs with not approved image quality as missing:

- PP population with observed cases,
- ITT with observed cases, and
- ITT with missing values imputed by multiple imputation.

For the sensitivity analysis using multiple imputation approach, similar methods as described in section 6.1.1.1 will be performed.

For all other sensitivity analyses, results can be taken directly from the SAS proc freq output:

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, where response_data is the dataset with overall improvement data per subject. The point estimate for the proportion of responders and the lower limit of the two-sided 90% Wilson CI will be used to assess sensitivity.

A sensitivity analysis will not be done, if identical to any other analysis.

#### 6.1.1.3 Subgroup analyses

Gain or loss of ≥ 2 BMI units from screening to Day 90 will be considered a major protocol deviation. Subjects with gain or loss of ≥ 2 BMI units from screening to Day 90 will be excluded from PP population. The following subgroups will be defined by the change in body weight from screening to Day 90:

- Subjects in ITT population with gain of ≥ 2 BMI units;
- Subjects in ITT population with loss of ≥ 2 BMI units; and
- Subjects in ITT population with change of < 2 BMI units.

The primary endpoint with observed cases will be analyzed in all subgroups, as defined above, with more than five subjects. For all subgroup analyses, the improvement score over all evaluators will be treated as missing, if at least two evaluators declare a photograph as not assessable.

Frequency tables for the proportion of treated subjects with improvement in lines and wrinkles of the décolleté (primary endpoint) will be provided by age categories (≤ median age, > median age), by BMI at baseline in categories (<18.5, 18.5 – 24.9, 25 – 29.9, ≥30.0) and by site.

### 6.1.2 Secondary Effectiveness Endpoint

The secondary endpoint will only be assessed among subjects reconsented for extended study participation.

The secondary endpoint of the study is the proportion of treated subjects with improvement in lines and wrinkles of the décolleté by comparing photographs taken at Day 180 (post-treatment) with baseline (pre-treatment) photographs.

Each independent evaluator will assess “Improvement”, “No Improvement” or “Cannot Evaluate” between Photograph 1 (baseline) and Photograph 2 (post-baseline). Photograph 1 will be identified, and the independent evaluators will be blinded to the random distribution of treated versus untreated status of the comparator Photograph 2 (i.e., Day 180 post-treatment among treated subjects or post-baseline for untreated individuals). If photographs are declared as not assessable during the Day 180 assessment session, the evaluators will be instructed to rate the corresponding Photograph 2 as “Cannot Evaluate”.

Improvement will be declared if at least two blinded evaluators indicate “Improvement” for the comparator photograph. In case at least two evaluators declare a photograph as not assessable (i.e., “Cannot Evaluate” is ticked), the corresponding improvement score over all evaluators will be set to missing for the secondary analysis. In case one evaluator rates a photograph as “Cannot Evaluate” and the other two evaluators disagree, the overall improvement score will be set to “No Improvement”.

The proportion of subjects fulfilling the secondary endpoint will be described by frequency statistics for the ITT subset, including the one-sided 95% Wilson CI.

Missing data, including a missing secondary endpoint assessment in subjects with unacceptable, not assessable or missing photographs at baseline or Day 180, will be imputed by multiple imputation. In case of complete data, no multiple imputation will be performed and the primary analysis is based on complete data for the ITT.

Imputation is done 50 times using a fully conditional specification logistic regression method, as implemented in SAS PROC MI with statement FCS LOGISTIC, and will use the investigational site and the baseline characteristics age and BMI as informing variables. Point estimate and Wilson CI will be calculated with methods as described in Section 6.1.1.1. For implementation, SAS code similar to the statements for the primary endpoint will be used.

Similar sensitivity analyses and subgroup analyses will be performed for the secondary endpoint.

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## 6.2 Safety Endpoints

All safety evaluations will be summarized for observed values in the SP.

### 6.2.1 Adverse Events

All AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at the time the database is closed.

Only treatment-emergent AEs (TEAEs) will be analyzed, which are defined as AEs with onset or worsening at or after the first administration of study treatment. In this regard, an AE, with onset prior to treatment, that worsens at or after first administration of study treatment must be documented as a new TEAE with onset at the time of worsening.

An overall summary of AEs will be provided for the following:

- Any AEs;
- Any non-TEAEs;
- Any TEAEs;
- Any treatment-related TEAEs;
- Any serious TEAEs;
- Any serious treatment-related TEAEs;
- Any TEAEs leading to discontinuation;
- Any treatment-related TEAEs leading to discontinuation;
- Any fatal TEAEs, and
- Any treatment-related fatal TEAEs.

Incidences will be provided for the following classes of AEs:

- TEAEs, subjects with TEAEs and number of TEAEs by MedDRA system organ class (SOC) and preferred term (PT);
- TEAEs, subjects with TEAEs by PT;
- Non-TEAEs, subjects with Non-TEAEs and number of Non-TEAEs by SOC and PT;
- Non-serious TEAEs, subjects with TEAEs and number of TEAEs by SOC and PT;
- TEAEs by maximum severity (mild, moderate, severe), subjects with TEAEs by PT;

- TEAEs by worst causal relationship (related, not related), subjects with TEAEs by PT;
- TEAEs by worst outcome, subjects with TEAEs by PT;
- TEAEs by affected treatment area, subjects with TEAEs by PT;
- TEAEs by maximum duration (1-3 days, 4-7 days, 8-14 days, ≥15 days), subjects with TEAEs by PT;
- TEAEs by maximum duration and maximum severity, subjects with TEAEs by PT;
- Related TEAEs, subjects with TEAEs and number of TEAEs by PT and SOC;
- Serious TEAEs, subjects by SOC and PT;
- Related serious TEAEs, subjects by SOC and PT;
- Serious TEAEs, listing of subjects (in case of more than 15 serious TEAEs respective table by PT and SOC will be provided); and
- Related serious TEAEs, listing of subjects (in case of more than 15 related serious TEAEs respective table by PT and SOC will be provided).

All tables will be sorted by descending frequencies in Preferred Terms (within SOCs).

The duration of AEs will be calculated by the difference of start and stop day plus 1.

If a subject has more than one outcome within a PT only the worst outcome in the respective time period will be used in the frequency tables. Also on subject level, only the worst outcome category per subject in the respective time period will be counted in the frequency table. The worst outcome is defined in the following order (from best to worst):

- recovered/resolved
- recovered/resolved with sequelae
- recovering/resolving
- not recovered/not resolved
- unknown
- fatal

Moreover, incidences of TEAEs, by PT and SOC, will be provided for the following subgroups:

- Race
- Fitzpatrick Skin Types (I, II, III versus IV, V, VI).

Listings for all AEs, as well as subsets including AEs leading to discontinuation, related SAEs, and deaths, will be provided. Treatments discontinued due to pain and device deficiencies will also be listed.

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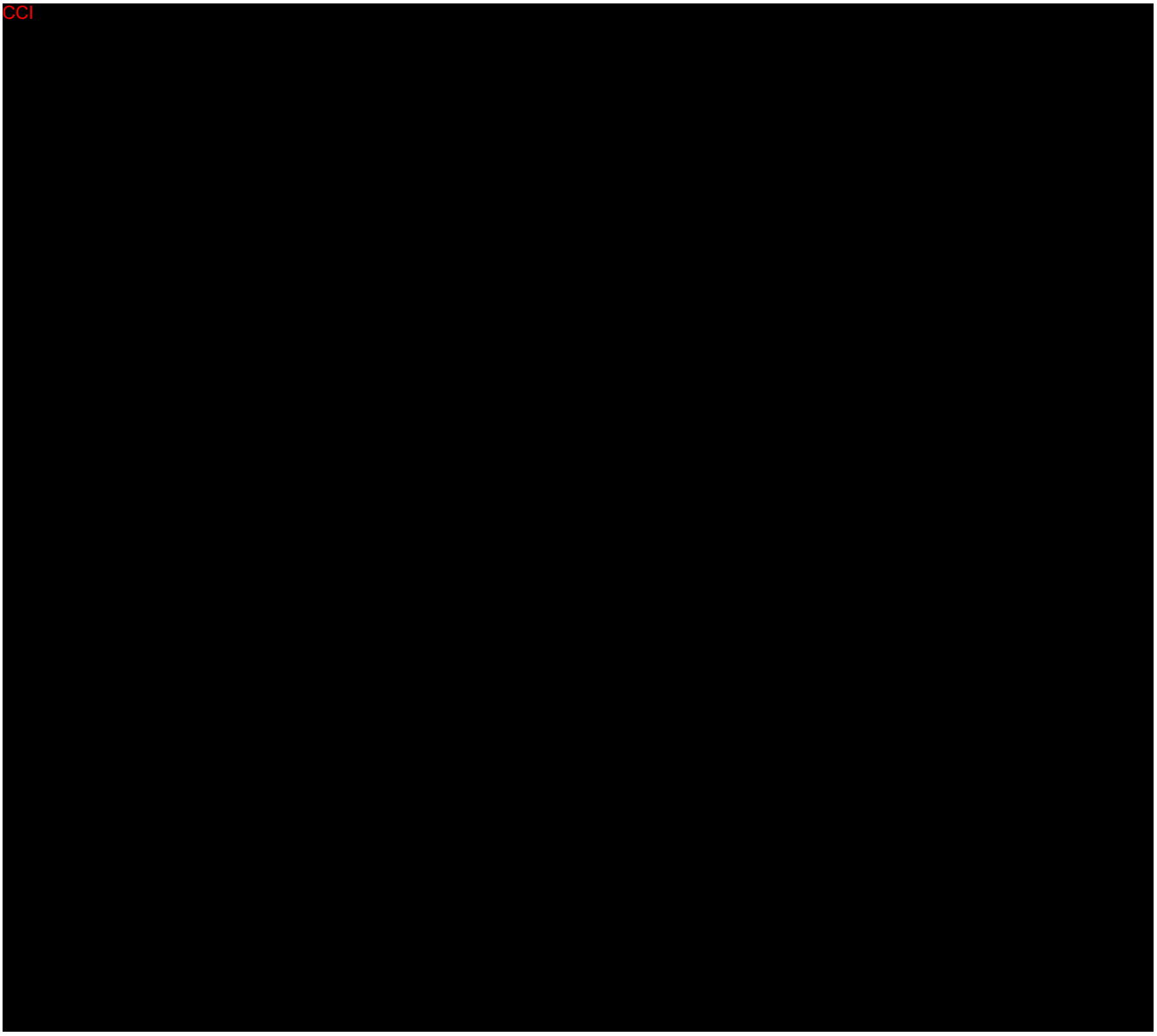


**Disposition of subjects**

The absolute and relative frequencies for subjects' main reason for premature study discontinuation will be tabulated, based on all treated subjects. Furthermore, the number of subjects screened, the number of subjects treated, and the number of subjects in respective analysis sets will be tabulated.

Visit attendance will be presented in a frequency table for all treated subjects. For 'Subjects expected at visit', the following visits are defined as expected for all treated subjects: Screening, Day 1 (Baseline). For subjects without reconsent, all following telephone contacts and visits are expected until Day 90 or premature study discontinuation, whatever occurs first. For subjects with reconsent, all following telephone contacts and visits are expected until regular study completion at Day 180 or premature study discontinuation, whatever occurs first. In case of premature study discontinuation at a regular visit or telephone contact, not the regular visit or telephone contact is expected but either Day 90 visit (for subjects without reconsent) or Day 180 visit (for subjects with reconsent).

Percentages of 'Subjects expected at visit' will be calculated relative to the total number of subjects treated for Screening visit until Day 90 visit and relative to the number of subjects with reconsent from TC (Day 121) until Day 180 visit.

Percentages relating to 'Visit performed' and 'Visit not performed' will be calculated relative to the number of subjects expected at the respective visit. For study discontinuations, only absolute numbers will be displayed.

### Protocol deviations

The absolute and relative frequencies of subjects with protocol deviations and other reasons for exclusion from analysis sets will be tabulated, based on all treated subjects.

### Demographic data and baseline characteristics

Demographic data will be summarized for the SP, the ITT, and the PP. Fitzpatrick skin type will be presented by original value as well as by categories type I-III and type IV-VI.

### Previous and concomitant medications and non-drug treatments

Separation of previous from concomitant medications will be done according to the start and stop date of the medication in comparison to the date of treatment. Each medication will be allocated unambiguously either to previous medication or to concomitant medication.

- Previous medication: If stop date is before start of treatment.
- Concomitant medication: If the start date is at or after start of treatment or if the stop date is at or after start of treatment or ongoing is ticked.

Previous and concomitant medications will be coded by use of the World Health Organization (WHO) whereby the version in effect at the time the database is closed will be used.

Frequencies of previous and concomitant medications will be given on the basis of various Anatomical Therapeutic Chemical classification system of the World Health Organization (ATC) code levels for the SP. Indications for concomitant medications will not be coded and will only be listed.

Non-drug treatments will be coded using MedDRA version which is in effect at the time the database is closed. Non-drug treatments will be reported by SOC and PT levels for the SP.

### Medical history and concomitant diseases

Separation of medical history from concomitant diseases will be done according to the stop date of the finding in comparison to the day of treatment. Each finding will be allocated unambiguously either to medical history or to concomitant diseases.

- Medical history: If stop date is before start of treatment.
- Concomitant disease: If the stop date is at or after start of treatment or ongoing is ticked (even if it refers to a cut-off point before start of treatment).

Rules for separation of medical history and concomitant diseases for missing or incomplete dates are given in the Appendix.

Medical history and concomitant diseases will be coded using the MedDRA dictionary and reported by SOC and PT levels for the SP.

### Pain pre-treatment medication

Frequency tables of pre-treatment pain medication (initial, additional, and/or administration of nitrous oxide / oxygen mixture) will be given for the SP.

#### Extent of exposure

A descriptive table for the number of lines by transducer, energy level, and treatment region will be produced for the SP, containing number of observed values (n obs), number of missing values (n miss), mean, standard deviation, median, quartiles, minimum, and maximum.

Frequency tables for premature treatment discontinuation and areas treated (right, left, and overall) will be given for the SP.

#### Vital Signs

A descriptive summary table will be presented for weight, height, and BMI by visit (i.e., Visits 1, 2, and 3 only; height will be collected at Visit 1 only).

#### Urine pregnancy test

Results of urine pregnancy tests will be listed.

#### Device deficiencies

All device deficiencies including device deficiencies for screening failures will be listed.

## 6.4 Special Statistical/Analytical Issues

### 6.4.1 Discontinuations and Missing Data

#### Primary and secondary effectiveness endpoints

For analysis of the primary and secondary effectiveness endpoints the following conventions will be applied: if data from the independent evaluators is completely missing (e.g., for all 3 evaluators), the multiple imputation method will be employed as described above for the primary and secondary analysis. For the worst case analysis, the subject will be analyzed as having “no improvement”.

The following procedure for incomplete data from the independent evaluators will be applied:

- If the result of two out of three evaluators is missing, the outcome of the subject will be set to missing and the multiple imputation technique will be applied for the primary analysis. The subject will not be included in the observed case analysis and for the worst case analysis, the subject will be analyzed as having “no improvement”.

- If the result of one evaluator is missing and the other two evaluators agree on the assessment “improvement” then the outcome of the subject is set to “improvement” for all analyses.

- If the result of one evaluator is missing and the other two evaluators agree on the assessment “no improvement” then the outcome of the subject is set to “no improvement” for all analyses.

- If the result of one evaluator is missing and the other two evaluators disagree, then the outcome of the subject will be set to missing and the multiple imputation technique will be applied for the primary analysis. The subject will not be included in the observed case analysis and for the worst case analysis, the subject will be analyzed as having “no improvement”.

All other effectiveness data will be analyzed as observed with no imputation of missing values. The denominator for percentages will be all subjects in the respective analysis set or population

(i.e., missing data for binary or categorical variables will be presented as a separate possible category 'Missing').

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**Adverse events**

For any missing data of adverse events, a worst case strategy will be applied for all analysis tables. The intensity will be imputed by the worst intensity "severe", the causal relationship will be imputed by the worst relationship "related". Missing data of the outcome will be imputed by "unknown".

### 6.4.2 Interim Analyses

In Stage 1, an initial cohort of 10 subjects will be enrolled. An interim database close and interim safety analysis of the first 10 subjects treated in Stage 1 will be conducted. This Stage 1 analysis will contain Week 2 safety data for the first 10 subjects treated. Safety analyses will be performed on the SP. Effectiveness data will not be included in the interim analysis.

Continuation to Stage 2 will be paused during evaluation of the Week 2 safety data from the first 10 subjects treated. All 10 subjects enrolled in Stage 1 will participate until Stage 1 study end, for a maximum duration of 90 days (± 7 days).

The interim analysis is only intended to obtain safety data for the first 10 subjects treated before starting recruitment for Stage 2. The interim analysis is not proposed to modify the study design, statistical analyses, or sample size, or for study termination, as this is not an adaptive study design. Since no effectiveness data are analyzed at interim, the interim analysis will not compromise the integrity of the study's effectiveness data, and it will not bias the final effectiveness analysis.

A separate statistical analysis plan for the interim analysis will be written.

### 6.4.3 Multiple Comparisons/Multiplicity

Primary analysis consists of two conditions which both need to be fulfilled to be able to claim effectiveness, therefore no adjustment of the type-1 error is needed.

### 6.4.4 Examination of Subgroups

The primary endpoint of observed cases will be additionally analysed by the different subgroups as described in section 6.1.1.3.

The safety endpoints for incidences of TEAEs using the SP will be descriptively summarized by Fitzpatrick skin type (I-III versus IV-VI) and race.

One subject might be present in multiple subgroups for race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander).

No statistical comparison of subgroups is planned.

### 6.4.5 Pooling of Sites

Analysis will be performed on pooled data across all sites.

Treatment site will be used as explanatory variable for the multiple imputation model. In case it turns out that convergence of the model cannot be accomplished, the two smallest sites will be merged and a new model will be calculated. This process will be repeated until convergence is established.

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[redacted]

# 8 References

[1] Anne Lott & Jerome P. Reiter (2018): Wilson Confidence Intervals for Binomial Proportions With Multiple Imputation for Missing Data, The American Statistician, DOI: 10.1080/00031305.2018.1473796