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Merz Pharmaceuticals GmbH

Statistical Analysis Plan

Open-label, multicenter, uncontrolled, rater-blinded, post-market clinical follow-up [PMCF] study to confirm performance and safety of RADIESSE® (+) Lidocaine in the treatment of nasolabial folds, marionette lines, and/or cheek volume loss

Post Market Clinical Follow-Up

M900391005

Version 1.0, Final

Date: 30-JUL-2019

Author: [redacted]

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 interim analysis.

[redacted]		
Author (print name)	Date (dd-mmm-yyyy)	Signature
[redacted]		
Peer Reviewer (print name)	Date (dd-mmm-yyyy)	Signature
[redacted]		
Study Medical Expert Merz (print name)	Date (dd-mmm-yyyy)	Signature

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1 LIST OF ABBREVIATIONS

AE	Adverse event
ATC	Anatomical Therapeutic Chemical classification system of the World Health Organization
CRF	Case report form
DRM	Data review meeting
FAS	Full analysis set
iGAIS	Investigator Global Aesthetic Improvement Scale
MedDRA	Medical Dictionary for Regulatory Activities
MMLS	Merz Marionette Lines Scale
MNLFS	Merz Nasolabial Folds Scale
MUCFS	Merz Upper Cheek Fullness Scale
n	Number of non-missing observations
PDF	Portable document format
PMCF	Post-market clinical follow-up
PPS	Per protocol set
PT	Preferred term
Q1	First quartile
Q3	Third quartile
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS®	Statistical Analysis System software
SD	Standard deviation
SES	Safety evaluation set
sGAIS	Subject Global Aesthetic Improvement Scale
SMD	Study medical drug
SOC	System organ class
TC	Telephone contact
TFLs	Tables / figures / listings
TEAE	Treatment emergent adverse event
V	Visit
VAS	Visual Analogue Scale
WHO	World Health Organization

2 GENERAL AND TECHNICAL ASPECTS

The objective of this statistical analysis plan (SAP) is to specify the 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 M900391005, dated 18-Jun-2018.

All programs will be written using Statistical Analysis System Software (SAS®) version 9.4. A font size of 10 points with a unique font size for the whole document required will be used for the tables and figures in section 14, corresponding to a linesize of 111 digits and a pagesize of 42 lines for an output in A4 landscape format. For listings, a standard font size of 10 points with the linesize and pagesize as defined 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 portable document format (PDF) files using the Merz internal SAS macro LST2PDF. 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 PDF file will include the corresponding table of contents, preceding the content of the file.

The Merz standard Table, Figures, and Listings (TFLs) for medical devices, version 1.0 will be applied and adapted to study specific requirements as laid down in the clinical study protocol and any amendments.

3 CLINICAL STUDY DESIGN AND OBJECTIVES

3.1 Clinical Study Design

This study is an open-label, multicenter, uncontrolled, post-market clinical follow-up (PMCF) study with a rater-blinded live evaluation. There will be no control group as the objective is to confirm safety and performance in "real-life". Approximately 175 subjects per indication seeking for dermal filler/volumising treatment in the face, who agree to participate by signing the written informed consent form and who are fulfilling inclusion/exclusion criteria will be enrolled at approximately 15-20 sites.

Since subjects must be treated for at least two and up to three indications, selected out of nasolabial folds, marionette lines and cheek volume loss, and since it is planned to collect and analyze data from about 175 subjects per separate indication, about 210 subjects in total are planned to be enrolled.

Assuming that 50% of subjects will be treated for two and 50% for three indications respectively, at least 105 subjects will be treated in all of the three indications (i.e. nasolabial folds, marionette lines, and cheek volume) and 35 subjects will be treated in one of the possible treatment combinations:

- Nasolabial folds + marionette line;
- Nasolabial folds + cheek volume;
- Marionette lines + cheek volume.

If the number of subjects treated in all of the three indications is higher than 105, the number of subjects treated for only two indications may be reduced so that the total number of all treated subjects will be 210 but the aim to treat 175 subjects for each of the indications will be reached.

The duration of the study per subject is approximately 18 months (in case of no touch-up performed at Visit (V) 2) and 19 months (in case of touch-up performed at V2).

The study medical device (SMD) is CE-marked in Europe since 02-JUN-2016 and will be injected as per its current approved labelling and investigator's usual practice at Day 1 with an optional touch-up treatment after 4 weeks.

The subject will be injected at Day 1 with volume for each area to be treated, using injection techniques based on investigator's judgement, skin condition, safety and subject's expectations. A minimum of two and a maximum of three indications (nasolabial folds, marionette lines, cheeks) per subject can be treated. An optional touch-up can be performed after four weeks at V2 in the indications that were treated at Day 1, to obtain an optimal aesthetic outcome, as appropriate.

If the subject fulfills the inclusion criteria and agrees to participate, he/she will attend six visits (if no touch-up is performed), six visits plus one telephone contact (TC) (if touch-up is

performed in all indications that were treated at Day 1), or seven visits plus one TC (if partial [i.e. in at least one, but not in all indications that were treated at Day 1] touch-up treatment is performed) in total. If any serious adverse event (SAE) related to the injection or the SMD is not resolved by the end of the study, the subject will be followed until the resolution of the SAE by the Merz Pharmaceuticals Department of Product Safety.

An interim analysis report is planned on 6 months data (Week 24/28 respectively, depending on touch-up).

Level and method of blinding

Assessments that will be used for the primary variable and some other variables will be performed by a blinded rater who is not otherwise involved in study procedures.

End of study

The end of study will be defined as the last visit of the last subject.

3.2 Clinical Study Objectives

Primary objective(s)

The primary objective of this PMCF study is to collect clinical data to confirm performance and safety for the injectable medical device RADIESSE® (+) Lidocaine, when used in accordance with its labelling in the treatment of nasolabial folds, marionette lines and/or cheek volume loss. The primary objective time point will be at Week 12/16 (depending on touch-up).

Secondary objective(s)

The secondary objective is to analyze performance at all objective time point(s) other than the primary ones.

4 DETERMINATION OF SAMPLE SIZE

The sample size estimation is based on the primary performance analyses, i.e., on three one-sided exact one-sample binomial tests (one test for each indication). Under the following assumptions 140 subjects are required per indication to reach a global power of 80%:

- Global significance level: 0.025 (one-sided)
- Local significance levels for tests per indication: α_1 =0.0083, α_2 =0.0125, α_3 =0.025 (Bonferroni Holm adjusted alpha)
- Proportion of responders under the null hypothesis 0.6
- Expected responder rate under test treatment: 0.75
- Power for each single test: 89.6% (for α_1), 92.6% (for α_2), 96.6% (for α_3)
- Global power for all tests under independence 80.1%

In order to have sufficient subjects for safety analysis the sample size is increased to 175 subjects per indication so that a minimum of 161 subjects per indication will complete the study. In 161 subjects per indication an adverse event (AE) with a true incidence of 1% will be observed at least once per indication with a probability of 80%. The total number of 210 subjects to be treated was chosen to have approximately 175 subjects treated per indication.

5 ANALYSIS SETS

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

Safety Evaluation Set (SES)

The SES is the subset of all subjects who were exposed to the SMD at least once.

Full Analysis Set (FAS)

The FAS is the subset of subjects in the SES for whom at least one of the primary performance variables is available (i.e., all subjects who have a baseline and a post-baseline MAS value of at least one treated indication).

Per Protocol Set (PPS)

The PPS is the subset of subjects in the FAS without major protocol deviations whereby subjects with missing primary performance variable will be excluded from PPS. Major protocol deviations will be defined during the Data Review Meeting (DRM).

6 VARIABLES FOR ANALYSIS

6.1 Performance Variables

For the analysis of the performance variables the following analysis visits will be defined, since the primary evaluation of response shall be done 12 weeks after the last treatment or touch-up of the specific facial area. In Table 1 analysis visits for the responder analysis of Merz Nasolabial Folds Scale (MNLFS), Merz Marionette Lines Scale (MMLS) and Merz Upper Cheek Fullness Scale (MUCFS) are shown. All other performance variables will be analysed by the visits as specified in the case report form (CRF).

Table 1 Definition of the analysis visits for the response

Indication /Merz Aesthetic Scales	Analysis Visit	CRF Visit
All	Visit 2 (Week 4)	V2 (follow-up / optional touch-up)
Nasolabial folds / MNLFS	Week 12/16	• V3 (week 12)/Primary endpoint visit if no touch-up at Visit 2 was done for neither left nor right nasolabial folds • V3a (week 16)/ Primary endpoint visit if touch-up at Visit 2 was done for left and/or right nasolabial folds but not for all other indications treated at V1 • V3 (week 16)/ Primary endpoint visit if touch-up at Visit 2 was done for all indications treated at V1
Marionette lines/ MMLS	Week 12/16	• V3 (week 12)/Primary endpoint visit if no touch-up at Visit 2 was done for neither left nor right marionette lines • V3a (week 16)/ Primary endpoint visit if touch-up at Visit 2 was done for left and/or right marionette lines but not for all other indications treated at V1 • V3 (week 16)/ Primary endpoint visit if touch-up at Visit 2 was done for all indications treated at V1
Cheek fullness / MUCFS	Week 12/16	• V3 (week 12)/ Primary endpoint visit if no touch-up at Visit 2 was done for neither left nor right cheek fullness • V3a (week 16)/ Primary endpoint visit if touch-up at Visit 2 was done for left and/or right cheek fullness but not for all other indications treated at V1 • V3 (week 16)/ Primary endpoint visit if touch-up at Visit 2 was done for all indications treated at V1
All	Visit 4 (Week 24/28)	V4/Follow-up (12 weeks after previous visit)
All	Visit 5 (Week 48/52)	V5/Follow-up (24 weeks after previous visit)
All	Visit 6 (Week 72/76)	V6/Final study visit (24 weeks after previous visit)

6.1.1 Primary Performance Variable(s)

The primary performance variables of this study are:

- Responder rate for **nasolabial folds** after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the MNLFS. Response defined as improvement of ≥ 1 point in both folds (left and right) from Day 1 pre-injection to Week 12/16 (depending on touch-up).

- Responder rate for **marionette lines** after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the MMLS. Response defined as improvement of ≥ 1 point in both marionette lines (left and right) from Day 1 pre-injection to Week 12/16 (depending on touch-up).

- Responder rate for **cheek fullness** after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the MUCFS. Response defined as improvement of ≥ 1 point in both cheeks (left and right) from Day 1 pre-injection to Week 12/16 (depending on touch-up).

6.1.2 Secondary Performance Variables

The secondary performance variables are defined as follows:

- Responder rate for nasolabial folds after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the MNLFS prior to optional touch-up at V2 (Week 4), at Week 24/28, at Week 48/52, and at Week 72/76 (depending on touch-up performed). Response for nasolabial folds defined as improvement of ≥ 1 point in both folds (left and right) compared to Day 1 pre-injection.

- Responder rate for marionette lines after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the MMLS prior to optional touch-up at V2 (Week 4), at Week 24/28, at Week 48/52, and at Week 72/76 (depending on touch-up performed). Response for marionette lines defined as improvement of ≥ 1 point in both marionette lines (left and right) compared to Day 1 pre-injection.

- Responder rate for cheek fullness after treatment with RADIESSE® (+) Lidocaine based on the blinded rater's evaluation on the MUCFS prior to optional touch-up at V2 (Week 4), at Week 24/28, at Week 48/52, and at Week 72/76 (depending on touch-up performed). Response for cheek fullness defined as improvement of ≥ 1 point in both cheeks (left and right) compared to Day 1 pre-injection.

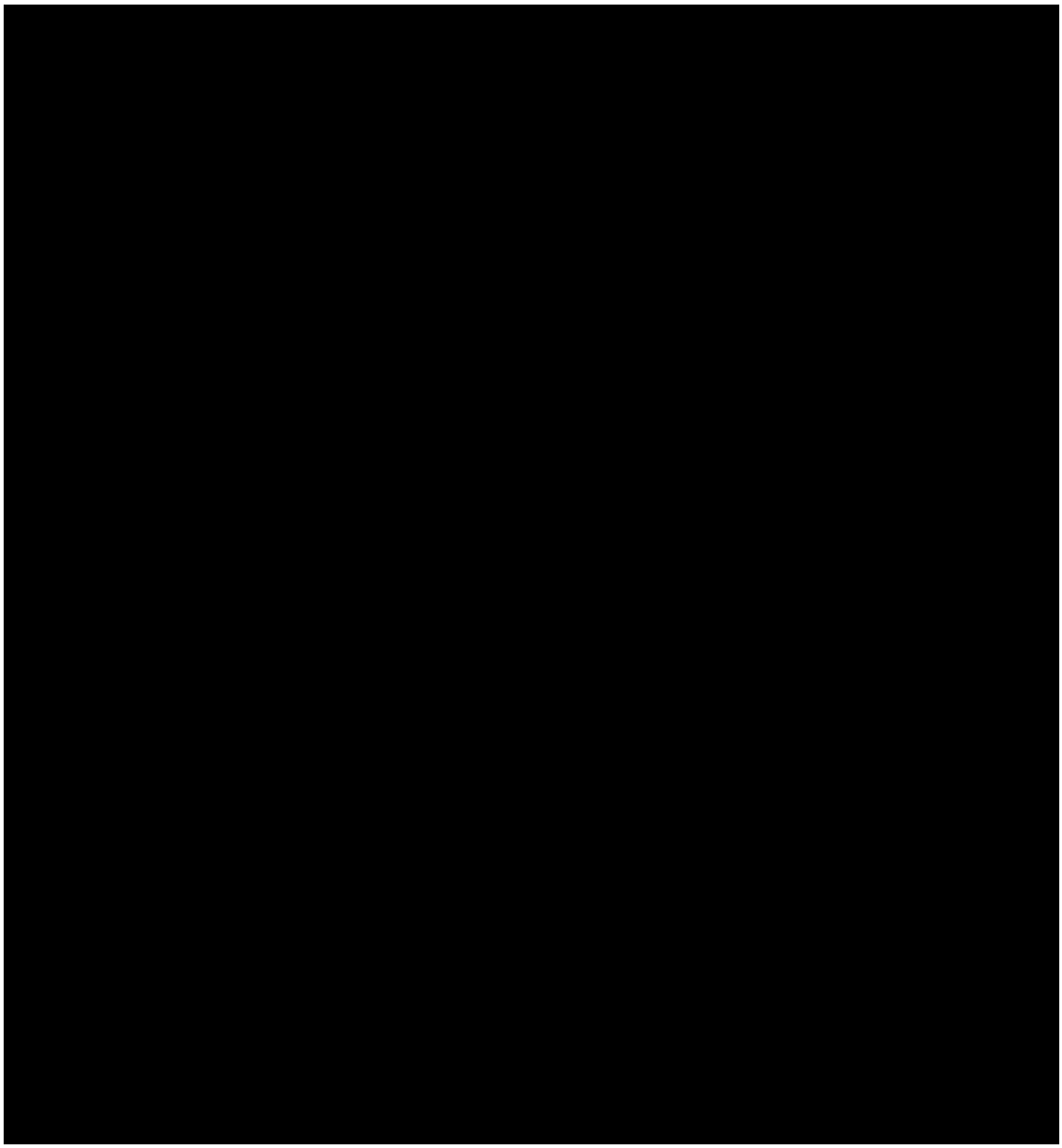
- Treating investigator's evaluation of the global aesthetic improvement on the Investigator Global Aesthetic Improvement Scale (iGAIS) from Day 1 pre-injection photos to V2 (Week 4) prior to optional touch-up, to Week 12/16, to Week 24/28, to Week 48/52, and to Week 72/76 (depending on touch-up performed).

- Subject's evaluation of the global aesthetic improvement on the Subject Global Aesthetic Improvement Scale (sGAIS) from Day 1 pre-injection photos to V2 (Week 4)

prior to optional touch-up, to Week 12/16, to Week 24/28, to Week 48/52, and to Week 72/76 (depending on touch-up performed).

[redacted]

[redacted]



6.2 Safety Variables

6.2.1 Primary Safety Variable(s)

The primary safety variable is:

- Occurrence of treatment emergent adverse events (TEAEs).

6.2.2 Secondary Safety Variables

Not applicable.

[redacted]

7 STATISTICAL ANALYSIS METHODS

7.1 Performance Variables

All performance analyses will be based primarily on the FAS and additionally for primary performance analyses on the PPS. Where applicable, subgroup analyses will be performed on the following subpopulations “nasolabial folds”, “marionette lines” and “cheek volume loss”. Statistical tests will be one-sided hypothesis tests for responder rates. The Bonferroni Holm alpha correction will be used for three statistical testes to adhere to the global significance level of 0.025.

Continuous variables (values and changes from baseline) will be summarized by number of non-missing values (n), mean, standard deviation (SD), median, quartiles, minimum, and maximum. For qualitative variables, absolute and percent frequencies (n, %) will be displayed. The responder analyses the percentage will be based on the number of subjects in respective indication group. The percentage of all other analyses will be based on the number of observed values. Confidence limits and descriptive p-values will be given, where appropriate.

For performance variables the measurement at V1 (Day 1) is defined as baseline value.

P-values will be reported to four decimal places (e.g., p=0.0375). P-values below 0.0001 will be presented as ‘<0.0001’.

Mean, first quartile (Q1), median, and third quartile (Q3) 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, an adequate number of decimal places will be chosen. Percentages will be calculated using the denominator of all subjects in a specified population and treatment group. The denominator will be specified in a footnote to the tables for clarification if necessary. Percentages will be reported to one decimal place.

7.1.1 Primary Performance Variable(s)

For the primary performance analyses, responder rates for nasolabial folds, for cheek volume loss, and for marionette lines will be summarized as absolute and percent frequencies (n, %). The denominator for each response will be the number of subjects in the analysis set treated in the indication. Only the subjects of the FAS treated for the corresponding indication will be included into the analyses of responder rates. Any subject with missing assessment will be evaluated as non-responder in the FAS. Subjects with missing assessments with respect to the primary performance variables will be excluded from the PPS.

The aim of primary performance analyses is to show that there are:

- significantly more than 60% of responders in treatment of nasolabial folds

- significantly more than 60% of responders in treatment of marionette lines
- significantly more than 60% of responders in treatment of cheek volume loss

A confirmatory exact one-sample binomial test will be used to test probability of being a responder (p) is above 60% separately for each indication:

- $H_{0\ nasolabial\ folds}: p \leq 0.6$ vs. $H_{1\ nasolabial\ folds}: p > 0.6$
- $H_{0\ marionette\ lines}: p \leq 0.6$ vs. $H_{1\ marionette\ lines}: p > 0.6$
- $H_{0\ cheek\ volume\ loss}: p \leq 0.6$ vs. $H_{1\ cheek\ volume\ loss}: p > 0.6$

Using the Bonferroni Holm alpha correction with global significance level of 0.025 for the test with lowest p-value the local significance level α_1 is 0.0083. For the test with the second lowest p-value α_2 is 0.0125. For the test with the highest p-value α_3 is 0.025. If the lowest p-value of a single (one-sided) hypothesis is below 0.0083 it is shown that the responder rate lies significantly above 60% for this indication. In this case performance is shown for this indication. If additionally the second p-value of a single (one-sided) hypothesis is below 0.0125 it is shown that the responder rate lies significantly above 60% also for this indication. If additionally the highest p-values of the single sub-hypothesis are below 0.025, the primary objective regarding performance (i.e., performance shown for all three indications) can be concluded. The procedure is stopped if a p-value is higher than the corresponding local significance level. In this case no subsequent null hypothesis will be rejected.

Point estimates of the rates will be provided with exact one-sided 97.5% Clopper-Pearson confidence intervals. The following SAS code will be used:

```
proc freq data = dataset order = freq;
      tables response / binomial (p=.6) exact cl alpha=.05;
      exact binomial;
run;
```

Confirmatory testing will be performed on the FAS with missing response imputed as non-responder. Furthermore, sensitivity analysis on PPS (observed case) will be performed.

7.1.2 Secondary Performance Variables

No additional secondary hypotheses will be tested. All secondary variables will be treated as exploratory and will be analyzed descriptively for FAS as follows:

Responder rates for nasolabial folds, for marionette lines, and for cheek fullness of the remaining visits will be summarized as frequency tables with absolute and percent frequencies (n, %). The denominator at each analysis visit will be the number of subjects in FAS (worst cases).

iGAIS and sGAIS will be displayed using descriptive summary statistics for continuous variables and as frequency tables with absolute and percent frequencies (n, %). In addition to total population, subgroup analyses for iGAIS and sGAIS will be done per indication (subjects treated for nasolabial folds, for marionette lines, and for cheek volume loss). The denominator at each visit will be the number of subjects evaluated at this visit (observed cases).

[redacted]

7.2 Safety Variables

All safety analyses will be performed on the SES in total and by the subpopulations of each indication (subjects treated for nasolabial folds, for marionette lines, and for cheek volume loss).

7.2.1 Primary Safety Variable(s)

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). For interim and final analysis the MedDRA version in effect at the time the database is closed will be used. Only TEAEs will be analyzed, which are defined as AEs with onset or worsening at or after the first administration of SMD(s). Each documented worsening of an AE will be counted and presented as separate AE. The start date of the AE will be the date of worsening. If an AE worsens between start and end of this AE it will be considered as new AE entry starting with the date of the worsening (start of new AE = worsening date, stop date of milder AE Episode= date of AE worsening).

The main analysis for the primary safety variable will be:

- Overall incidence of TEAEs.

Further the following AE summary tables will be created displaying incidences of:

- TEAEs, subjects with TEAEs and number of TEAEs by system organ class (SOC) and preferred term (PT).
- TEAEs, subjects with TEAEs by PT.
- TEAEs by worst intensity, subjects with TEAEs by SOC and PT.
- TEAEs by worst causal relationship to RADIESSE® (+) Lidocaine, subjects with TEAEs by SOC and PT.
- TEAEs by worst outcome, subjects with TEAEs by SOC and PT.
- TEAEs by affected area, subjects with TEAEs by SOC and PT.
    - TEAEs occurred outside treatment area, subjects with TEAEs by SOC and PT.
    - TEAEs affected right nasolabial fold, subjects with TEAEs by SOC and PT (only for subjects treated at right nasolabial fold).
    - TEAEs affected left nasolabial fold, subjects with TEAEs by SOC and PT (only for subjects treated at left nasolabial fold).
    - TEAEs affected both nasolabial folds, subjects with TEAEs by SOC and PT (only for subjects treated at both nasolabial folds).
    - TEAEs affected right marionette line, subjects with TEAEs by SOC and PT (only for subjects treated at right marionette line).
    - TEAEs affected left marionette line, subjects with TEAEs by SOC and PT (only for subjects treated at left marionette line).

- TEAEs affected both marionette lines, subjects with TEAEs by SOC and PT (only for subjects treated at both marionette lines).
- TEAEs affected right cheek volume, subjects with TEAEs by SOC and PT (only for subjects treated at right cheek volume).
- TEAEs affected left cheek volume, subjects with TEAEs by SOC and PT (only for subjects treated at left cheek volume).
- TEAEs affected both cheeks volume, subjects with TEAEs by SOC and PT (only for subjects treated at both cheeks volume).

Time to onset and duration of TEAEs will be listed.

Calculation of time to onset/duration of AEs (days):

- Time to onset of an AE is defined as start date of AE - date of first administration of study drug [+ 1 for AE starting after start of treatment]
- The duration will be calculated as stop date - onset date + 1.

Incomplete AE start and/or end date will not be replaced. Rules for separation of TEAE from non-TEAEs for missing or incomplete start dates are given in the Appendix M900391005-sap-appendix-v1.0.

In case of missing intensity or missing causal relationship of an AE the worst case principle will be applied, i.e. a missing intensity will be set to “severe” and a missing causal relationship will be set to “related”. Missing data of the worst outcome will be imputed by “unknown”. If a subject has more than one outcome within a PT only the worst outcome will be used in the frequency tables. Also on subject level, only the worst outcome category per subject will be counted in the frequency table. The worst outcome is defined in the following order:

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

In case of a subject with affected left and right nasolabial folds, with affected left and right marionette line or with affected left and right cheek volume within a PT the subject will be counted once under both nasolabial folds, under both marionette lines or under both cheeks, respectively. In case of a subject with at least one affected treatment area and one AE outside

treatment area within a PT the subject will be counted once under the respective affected treatment area.

7.2.2 Secondary Safety Variables

Not applicable.

[redacted]

Disposition of subjects

The absolute and relative frequencies for subject's main reason for premature study discontinuation will be tabulated, based on all enrolled subjects. Main reason "death" will be mapped to adverse event(s). Furthermore, the number of subjects screened, the number of subjects enrolled, the number of subjects enrolled and treated and the number of subjects in respective analyses sets will be displayed. For this study all enrolled subjects will be treated. Therefore, the number of subjects enrolled and the number of subjects enrolled and treated will be the same and screening failures are defined all as not treated subjects. The analysis will be performed in total and by the subpopulations of each indication.

Demographic data

Demographic data will be summarized in total and by subpopulations of each indication for the SES, the FAS, and the PPS. The following age categories will be analyzed:

- 18 - 64 years
- 65 - 84 years
- ≥85 years

Prior and concomitant medication and non-drug therapies

Separation of previous from concomitant therapies will be done according to the start and stop date of the therapy in comparison to the date of first injection. Each therapy will be allocated unambiguously either to previous therapies or to concomitant therapies.

- Previous therapy: If stop date is before start of treatment.
- Concomitant therapy: 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.

Rules for separation of previous and concomitant medication for missing or incomplete dates are given in the Appendix M900391005-sap-appendix-final v1.0-2019-07-30.

Previous and concomitant medication 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 for interim and final analysis.

Frequencies of previous and concomitant medication will be given on the basis of various Anatomical Therapeutic Chemical classification system of the World Health Organization (ATC) code levels for the SES, the FAS and the PPS. The analysis will be performed in total and by the subpopulations of each indication. Indications for concomitant therapies 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 displayed by SOC and PT levels for the SES, the FAS and PPS. The analysis will be performed in total and by the subpopulations of each indication.

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 start of study 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 (even if it refers to a cut-off point before start of treatment) is ticked.

Rules for separation of medical history and concomitant diseases for missing or incomplete dates are given in the Appendix M900391005-sap-appendix-final v1.0-2019-07-30.

Medical history and concomitant diseases will be described on the basis of MedDRA SOC and PT levels for the SES, the FAS, and the PPS. The analysis will be performed in total and by the subpopulations of each indication.

Extend of exposure

Data of injection technique, depth of injections, volume and needles and cannulas will be analyzed separately for each indication for the corresponding subpopulation per treatment area (side) and in total for SES.

7.4 Special Statistical/Analytical Issues

7.4.1 Discontinuations and Missing Data

Discontinued subjects will not be replaced.

For responder analyses, missing values will be evaluated as non-responder (worst case replacement) for FAS. PPS will be used only for the primary performance analyses. Subjects with missing assessments with respect to the primary performance variables will be excluded from the PPS. Therefore no missing value replacement is needed for PPS.

[redacted]

Missing values for all further variables will not be imputed. All analyses except responder analysis [redacted] will be performed on observed cases only.

7.4.2 Interim Analyses

An interim analysis for the SES and the FAS will be performed including all data (safety, performance and other data) up to Week 24/28 respectively, depending on touch-up. The analyses of the subpopulations “nasolabial folds”, “marionette lines” and “cheek volume loss” is also part of the interim analysis. The PPS analysis is not part of the interim analysis and will be done for the final analysis at the end of the study in addition to SES and FAS. All tables and listings planned for the final analysis in the appendix will also be done for the interim analysis

up to the Visit V4 Week 24/28 except for the PPS tables and the table and listing for "Protocol deviations and other reasons for exclusion from analysis sets".

The interim analysis will be done for obtaining the performance and safety data up to Week 24/28 as early as possible. Therefore, the purpose of this interim analysis is not to perform any adaptions on the study design, statistical analysis, sample size or for stopping the study, as this is not a study with an adaptive design.

Since this is an open label study, the interim analysis will not have any influence on the integrity of the study data and it will not bias the data collected after interim analysis.

7.4.3 Data Monitoring Committee

Not applicable.

7.4.4 Multiple Comparisons/Multiplicity

Three confirmatory tests will be performed in the primary analysis, one for each primary performance variable of the corresponding indication. Bonferroni Holm correction will be used to counteract the problem of multiple comparisons. For the three statistical test the local significance levels α_1=0.025/3, α_2=0.025/2 and α_3=0.025 will be applied to obtain the global significance level of 0.025.

7.4.5 Examination of Subgroups

The subpopulation "nasolabial folds" will contain all subjects treated for nasolabial folds, regardless if they have been treated for one or both other indications as well. The subpopulation "marionette lines" will contain all subjects treated for marionette lines, regardless if they have been treated for only one or for two other indications as well. The subpopulation "cheek volume loss" will contain all subjects treated for cheek volume loss, regardless if they have been treated for one or both other indications as well. Each of these three subpopulations will contain approximately 175 subjects. Each subject will belong to at least two of these subpopulations. At least 50% of the subjects will be treated in all of the three indications and as consequence these subjects will belong to all of these three subpopulations (i.e. nasolabial folds, marionette lines, and cheek volume loss).

For the performance variables iGAIS, sGAIS, [redacted] for subject dispositions, [redacted], and for all safety analyses (analysis of TEAEs), subgroup analyses will be performed for each indication (subjects treated for nasolabial folds, for marionette lines and/or for cheek volume loss) in addition to the total population.

Responder analysis of MNLFS, MUCFS, and MMLS will only be performed for the subpopulations and not for the total population. [redacted]

[redacted]™ – Satisfaction with Cheeks will only be analysed for the subpopulation "cheek volume loss".

[redacted]

7.4.6 Pooling of sites

Not applicable.

8 CHANGES IN THE PLANNED ANALYSES

Not applicable.

9 REFERENCES

Appendix 1: [redacted]

[redacted]

Appendix 2: [redacted]

[redacted]